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Development of new technologies for the home monitoring and treatment of patients with chronic respiratory disorders

Leonardo Govoni — Ph.D. Dissertation

Tutor:
Prof. Antonio Pedotti

Advisor:
Prof. Raffaele Dellacà

Supervisor of the Ph.D. program:
Prof. Maria Gabriella Signorini

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"Se il solo strumento che possedete è un martello,
vedrete in ogni problema un chiodo"

Abraham Maslow, 1908-1970, psicologo statunitense.

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INTRODUCTION

Telemedicine (TM) has been defined as the use of information and communication technologies (ICTs), to deliver health services and transmit health information at distance for the purpose of improving, maintaining, or assist patient's care and education (1). Recent and considerable advances in ICTs led to the development of new techniques able to electronically acquire, process, store and transmit health information.

Starting from aged visions (Figure 1) and passing through recent and more serious possibilities (2), telemedicine has become a reality and is spreading widely in all healthcare fields. The first interactive telemedicine system, operating over standard telephone lines, for remotely diagnosing and treating patients requiring cardiac resuscitation was developed and marketed by MedPhone Corporation in 1989. Telemedicine includes a growing variety of applications and services and uses two-way video, email, mobile phones, portable electronic monitoring equipment (spirometer, glucometer, pulse oximeter…) (3), and other forms of telecommunications technology. Telemedicine is most widely associated with populations living in isolated communities and remote regions and is currently being applied in virtually all medical domains such as congestive heart failure (4), diabetes (5), psychiatric (6) and other chronic illnesses (7), for tele-consulting and second opinion delivery, to provide expert-based health care to understaffed remote sites (8), for medical education (9), and many other fields. Thanks to its clinical effectiveness and costs saving capabilities (10), telemedicine has become a standard methodology for monitoring and treating patients directly at home, especially those with chronic pathologies and in particular the respiratory disorders (11;12), and is in daily use across different countries (13;14).

Figure 1: On the "Radio News" magazine cover of April 1924 is showed a possible application of the use of the radio for Telemedicine.

Telemedicine is a rapidly developing application of clinical medicine where medical information is transferred through the Internet and other networks for the purpose of consulting and remote medical procedures or examinations. Its spread and development can

meet the needs of a growing and ageing population which is affected by chronic pathologies, the most expensive condition in terms of health care services.

Over the last 50 years, the number of people age 60 years or over has tripled, and is expected to triple again to almost two billion by 2050 (15). The proportion of older people is projected to reach 21% in 2050 (16). Population ageing is profound, having major consequences and implications for all facets of human life, including health and health care. Indeed the incidence and prevalence of chronic diseases, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), and diabetes, continue to increase (17). Chronic diseases are the main cause of death in almost every developed country, and deaths from chronic respiratory diseases are second only to those from cardiovascular diseases (18). Chronic pathologies like COPD, which WHO (World Health Organization) has predicted to become the third leading cause of death throughout the world by 2030 (19), determine a serious burden on patients and health care systems because of low quality of life and frequent and expensive hospitalizations. The need to reduce this burden brought health care providers to rely on telemedicine services, which on one hand can perform a better follow up of the patient at home, on the other it aims to provide health services at home and to be able to prevent acute events that can lead to the hospitalization of the patient.

In the last few years many projects, clinical trials and tests involving telemedicine have been performed, some of them are now incorporated in standard clinical practice, but most of them only showed a lot of potentialities and possibilities, and did not developed further because of some problems and difficulties involving the use of telemedicine (20).

The architecture of the conventional telemedicine systems is based on a complex informatics structure managed by external providers and centralized computer servers which operates through a call center (21). This structure requires complex and expensive agreements among the hospitals, the telemedicine service providers and the communication line providers and is the main obstacle to the wide application of the ICTs in the medical routine. The existing telemedicine services usually are dedicated and aimed to specific illnesses and are characterized by a rigid structure, not able to be configured nor adapted to the necessities of different kinds of chronic pathologies. Moreover a dedicate person, a physician or a nurse, must periodically actively interact with the telemedicine system, through a computer or calling the patient by phone to ask him to perform some actions or answer some questions.

Home tele-monitoring, in most of the cases, is performed by means of the administration of phone or telematic questionnaires and, when it's possible, depending on the pathology, some physiological parameters are reported to the clinicians. In any case the present practice is to use

the same technologies and devices used in the hospital to achieve significant measures of patient's conditions at home, limiting the quality and reliability of the acquired data because of the absence of the physician during the performing of the tests. The absence of specific devices and technologies designed to be used at patient's home without the presence of the physician is another factor limiting the spread of telemedicine.

However more than logistic difficulties, nowadays the Telemedicine concept is limited and not implementable both because of cost and feasibility issues. The present telemedicine architectures aim to create a direct connection between the health care professional and the patient in order to monitor patient's conditions from the hospital, that is virtually bringing the physician at home.

Such an approach entails the production of an enormous amount of raw data provided continuously from every patient, and a physician, beyond his standard clinical activities in the hospital, should also examine and evaluate all these data in order to perform the optimal home monitoring.

This strategy evidently cannot be pursed. A new Telemedicine concept must be properly designed, planned and realized, an approach able to handle the healthcare system's and patient's needs, to face the constant growing number of chronic patients and their complex and articulate management. The new Telemedicine approach that addresses a set of strategies and tools comprehends some key points that at the present day are still missing or not properly developed.

The first necessity is the to development of new technologies and methods that allow the patient itself to perform significant physiological tests in a domestic environment, without the supervision of a healthcare professionals.

The automatic intervention directly at patient's home for therapy adjustments by means of "intelligent" and trained devices, would both relieve physician's burden and, for some aspects would better perform on patient's care.

Moreover, the physician should be able to easily and instantly connect to the patient's house to be able to interact with the patient and better perform the monitoring task and, if needed, to modify the previously prescribed treatment.

These points, together with the use of both edge cutting informatics and information and communication technologies, should help healthcare professionals to better manage every single patient and to address the growing health care requirements.

The purpose of the project of the doctorate program is to define and design a new Telemedicine approach and to realize the technological platform that implements it.

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CHAPTER 1

PHYSIOLOGY AND PATHOLOGIES OF THE RESPIRATORY SYSTEM

1.1 Physiology of the Respiratory System

The respiratory system thanks to the combined action with the circulatory system provide gas exchange from and into the blood, creating around all cells an environment rich in oxygen, and in carrying carbon dioxide out of the body. The role of the respiratory system is to move atmospheric air in and out of the body, to and from a suitable place (i. e. the alveoli of the lungs), where O_2 can enter the blood flow and CO_2 exit it. At the same time, a sufficient amount of blood must reach as well the alveoli and this is provided by the pulmonary circulation (Figure 1.1). Concerning the respiratory process, therefore, we distinguish three actions known as:

- Ventilation, the movement of atmospheric air in and out the lungs
- Diffusion, oxygen and carbon dioxide passing from the air to the blood stream and vice versa
- Circulation or perfusion, blood pervading the area where diffusion occurs.

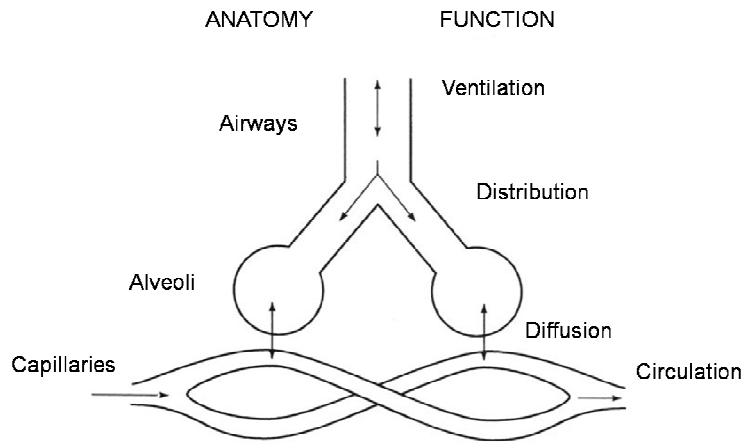

Figure 1.1: An overview of the ventilation - diffusion - perfusion process

All of these three actions must be accomplished efficiently for the whole respiratory process to be successful. Different diseases may affect their performance, therefore it is useful to find ways for assessing how well each of them is performed.

1.1.1 Physiological structures

The Airways

The function of the airways is to conduct air from the outside of the body to as close as possible to the blood stream, so that gases can diffuse in and out of the blood, renewing its content of oxygen and removing carbon dioxide. The airways start from the mouth and the nose, have the pharynx in common with the digestive system and continue in the trachea, whose first tract is called larynx (or voice box) and hosts the vocal cords. There is a muscular flap, called epiglottis that, folding over the glottis, the opening of the larynx, seals the airways, to prevent intrusion of food or liquids while swallowing.

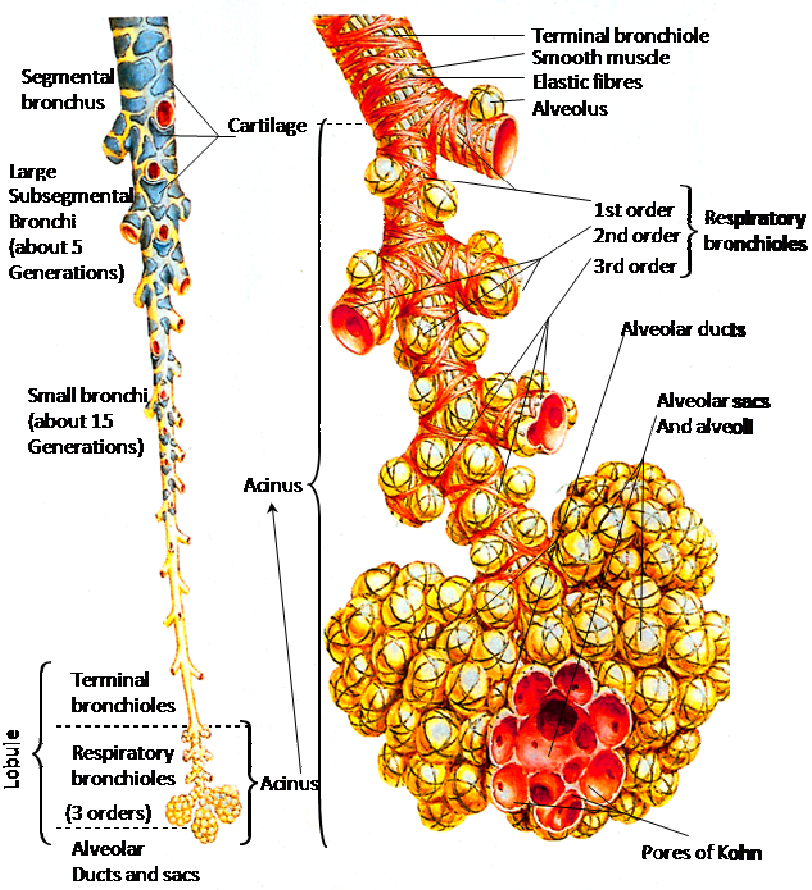

Figure 1.2: Subdivisions and structure of intrapulmonary airways

The trachea leads the air to the level of the lungs, where it departs in two main bronchi, one for each lung. After this first bifurcation each bronchus divides further in

two sub-bronchi, which in turn divide into two and so on. The global structure therefore looks like a reversed tree, whose branches split into two each time. The smallest bronchi are called terminal bronchioles and in adults 23 levels of branching have been estimated, which means something like more than 4 millions terminal bronchioles. Terminal bronchioles end up in grapelike clusters of microscopic air bags, called alveoli (Figure 1.2).

The walls of the bronchi, until the alveolar ducts, contain muscle fibres able to control their diameter and, therefore, the airflow inside them. The walls of the airways are crossed by numerous blood vessels and are lined with mucus, which contains a lot of water. In this way the air coming from outside (at Ambient Temperature and Pressure, Saturated, ATPS) passing through them is warmed up to body temperature and moistened until water saturation (Body Temperature and Pressure, Saturated, BTPS).

The alveoli

The alveoli represent the most important part of the respiratory system because they are the only place, along all airways, where gas exchange can take place effectively, between atmospheric air and blood. The wall of the alveoli is made up by a very thin and delicate layer of epithelial cells, which on one side are in contact with the air, on the other side are surrounded by a dense net of pulmonary capillaries (Figure 1.3).

Therefore inside the alveoli the air is brought the closest to the blood, which remains separated only by a two cell layer membrane, the respiratory membrane; it is constituted by the capillary wall and the wall of the alveolus itself. The average thickness of the respiratory membrane is about 4 μm, consequently gases can diffuse through very quickly. Indeed the transit time for blood in the pulmonary capillaries has been computed as somewhat less than 1 second in normal conditions and can reduce to less than half during exercise. During this short time the respiratory gases must get through the respiratory membrane. In the adult lung there are 250 to 350 millions of alveoli. Their large number confer the lungs the typical spongy appearance and feel, besides it makes available an enormous surface for gas exchanging; the total alveolar surface is quantified as about 75 m^2, depending on the degree of lung inflation.

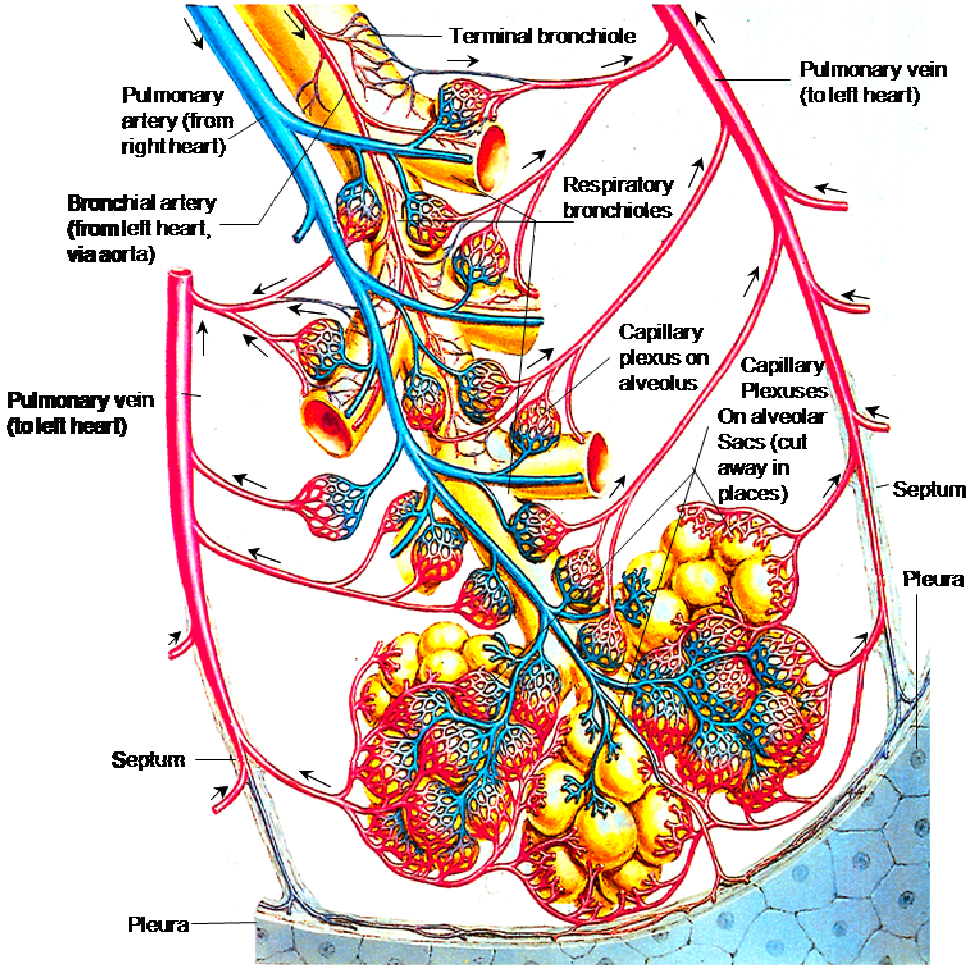

Figure 1.3: Intrapulmonary blood circulation.

The dead space

Not all the inspired air reaches the terminal bronchioles. The air entering the mouth (or the nose) the last remains far from the areas where gas exchange occur and cannot reach them even by diffusion, in the short time between inspiration and expiration. This air is not participating to the respiratory process at all. The volume of the airways having just the function of conducing the air, without providing means of gas exchange is called *dead space*. The normal volume of the dead space in a young man is about 150 ml, a significant portion of the air inspired during normal quiet respiration, and it increases slightly with age. On occasion, some of the alveoli themselves are non-functional or partially functional because either there is no blood flow through adjacent pulmonary capillaries, or it is poor. From a functional point of view, these alveoli must also be considered dead space. When this functional alveolar dead space is included in the total measurement of the dead space, we use the term *physiological dead space*.

1.1.2 Ventilation mechanics

The ventilation of the lungs is accomplished alternating phases in which air is flowing into the lungs (inspiration) and phases in which air exits the lungs (expiration). The mechanics of these air movements are strictly related to the peculiar anatomy of the chest.

The pleura

The lungs and the internal wall of the thoracic cavity are covered with two sheets of membranous tissue called *pleura;* the sheet wrapping the lungs is called *pulmonary pleura* while the sheet covering the inside of the thorax is called *parietal pleura*. The space in between these two membranes *(intrapleural cavity)* is filled with a very thin layer of fluid, the *intrapleural fluid*, having excellent lubricating properties (Figure 1.4). The excess of this fluid is continuously removed through the lymphatic system, in order to maintain a slight suction in the *intrapleural cavity*, that is, the pressure of the fluid in the space between the two pleura is lower than atmospheric. This is very important, because, although the lungs don't touch the internal walls of the chest (a part the hilium, where they are suspended) they are like glued to the internal wall of the thoracic cavity. The negative intrapleural pressure makes the lung volume to follow closely volume changes of the thoracic cage but, at the same time, thanks to the intrapleural space and to the intrapleural fluid, the lungs and the thoracic cage are allowed to slide with respect to each other well lubricated. Figure 1.4 shows the relative position of the lungs and the thoracic cage in the resting position, at the end of a quiet expiration, and at the end of the inspiration. We can notice that the lungs slide into the comer of the thoracic cavity, to fill the room left empty when the diaphragm contracts.

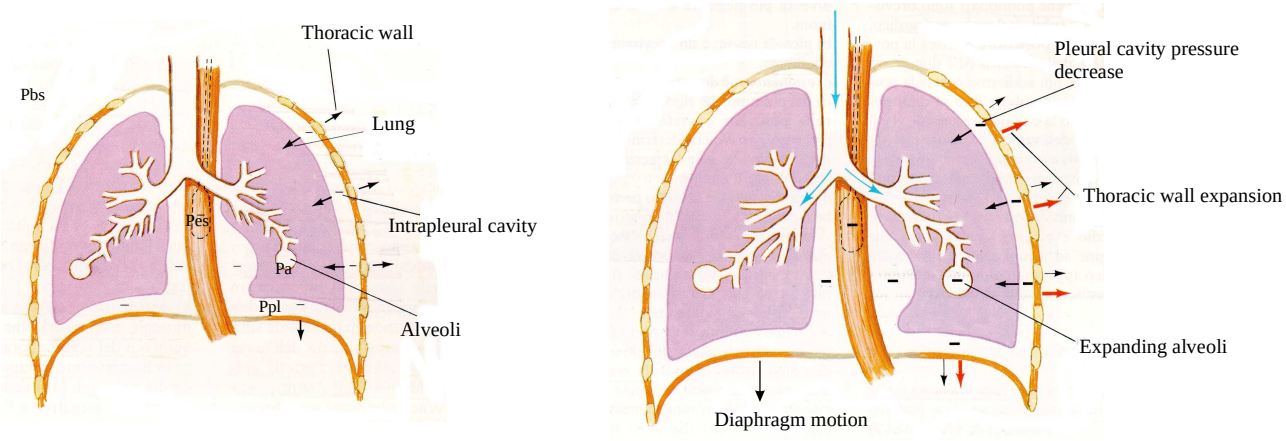

Figure 1.4: Both the lungs and the internal wall of the thoracic cavity are covered by a membraneous sheet of tissue called pleura. Left: the two pleura are folded in such a way to create two distinct intrapleural cavities

(their dimensions are here exaggerated). Right: at inspiration, when the diaphragm contracts, the lungs slide along the thoracic cavity to fill the freed space.

Inspiration

Inspiration is determined by the contraction of the inspiratory muscles, which are basically the diaphragm and the external intercostal muscles. The diaphragm represents the lower closure of the chest; when relaxed it is dome shaped while when it contracts it moves downward and it flattens. (Figure 1.4). In this way the bowels are pressed down and the volume of the thoracic cavity increases. During quiet respiration the diaphragm alone is responsible for the 75% of volume expansion of the thoracic cavity.

External intercostal muscles are located in between the ribs, elongated forward and downward, as it is shown Figure 1.5. The same figure shows the forces acting on the ribs when they contract, and the moments of these forces around the pivot points at the spinal cord. Accordingly to the third principle of dynamics, each muscle exerts the same force on both ribs it is attached to. The force it exerts on the lower rib, however, has a greater arm than the force acting on the upper rib, due to the physiological leaning of the muscles. The imbalance of the two moments makes the rib to rotate upward. Since ribs normally slant downward, when rotating, they push the sternum in front.

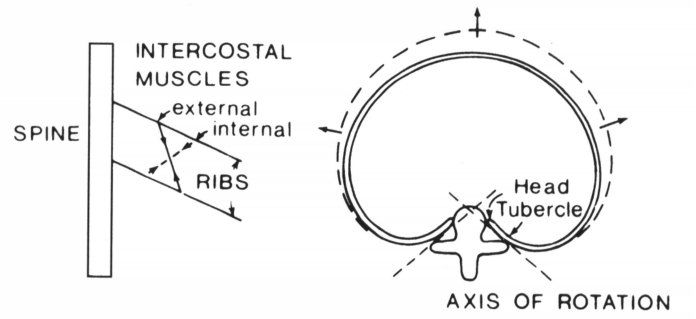

Figure 1.5: When the external intercostal muscles contract, the ribs are pulled upward and forward, and they rotate on an axis joining the tubercole and head of rib. As a result, both the lateral and anteroposterior diameters of the thorax increase. The internal intercostals have the opposite action.

This increases the antero-posterior diameter of the thoracic cage and therefore the volume of the thoracic cavity enlarges (Figure 1.5). The expansion of the thoracic cavity produces negative pressure in the intrapleural space, which induces the lungs to expand. The alveoli, the alveolar ducts and the bronchioles in their turn enlarge, creating a negative pressure (with respect to atmospheric) inside them, which recalls air from the outside.

Expiration

Expiration in quiet breathing occurs passively, without the recruitment of any muscle. When the diaphragm and external intercostals muscles stop contracting, the weight of the thoracic cage and its own elasticity bring it to its resting position. At the same time the compressed bowels push back the relaxed diaphragm as well and the volume of the thoracic cavity resumes its smaller dimensions. Decreasing the volume of the lungs, the pressure inside them rises, becoming greater than the atmospheric pressure. This forces the air out, through the airways.

When expiration needs to be faster, as during exercise or for coughing for instance, the expiratory muscles are recruited as well to provide greater ventilation. Expiratory muscles are mainly the abdominal muscles and the internal intercostals muscles. When contracting the abdominal muscles squeeze the viscera, which in turn push up the diaphragm. Internal intercostals muscles work similarly to external intercostals muscles (inspiratory muscles); they are also located in between the ribs but they are turned symmetrically, that is the expiratory muscles lean backward and downward. When these muscles contract, the ribs are pulled down, so that the sternum and the rib cage regain fast their resting position. Expiratory muscles, besides, are able to force the thoracic cavity to a smaller volume than at the end of a passive expiration. Nevertheless, whatever effort is placed in forcing the expiration, it is not possible to empty completely the lungs, which physiologically will always contain some amount of air.

The parenchyma

The tissue of the lungs is called parenchyma, it is very elastic and can easily distend. It contains elastin and collagen fibres. The collagen fibres normally are folded and they distend as the lungs expand; the elastin fibres, when the lungs expand, stretch. Both fibres, however, exert a force to regain their initial condition. In every healthy human being even at the end of the deepest expiration, when the lungs contain the minimum amount of air, the fibres of the parenchyma always remain stretched to a certain extent, and they exert an elastic recoil. The thoracic cage, in fact, cannot follow lung volume contraction indefinitely because of mechanical constraints and, when the volume of the thoracic cavity reaches its lower boundary, the lungs could actually shrink further. This is what they do if they are taken outside of the rib cage.

1.1.3 Mechanical Properties of the Respiratory System

Pressure, airflow, and volume are related to the fundamental mechanical properties of the respiratory system - compliance (Crs), resistance (Rrs), and inertance (Irs)- and indirectly to other parameters, such as work of breathing, by the equation of motion of the relaxed respiratory system:

$$Pao = \frac{1}{Crs}V + Rrs\dot{V} + Irs\ddot{V} \qquad (1.1)$$

In this equation Pao is the pressure at the airway opening, and V, $\dot{V}$, and $\ddot{V}$ are the volume of the lung above its relaxed equilibrium end-expiratory volume and its time derivatives, flow and acceleration, respectively. This equation is the three-dimensional, respiratory equivalent of Newton's equation of motion of a mechanical, rectilinear system.

Compliance

Under static conditions in completely relaxed patients, airway pressure is equal to the elastic recoil pressure of the respiratory system. Thus, compliance is measured as the change in lung volume per unit change in applied static pressure (elastic recoil pressure). The units are liters per cmH_2O or milliliters per cmH_2O. Compliance is the mathematical inverse of elastance, the amount of pressure required to change the volume of the lung by a given amount. Although both terms are useful, the clinical practice and refers to compliance more frequently than elastance will be followed.

The lung and chest wall are said to be aligned in series, since pressure applied to the airway is first transmitted to the lung. From the lung, a reduced amount of applied pressure is transferred to the chest wall. Because of this series relationship, the pressure to distend the respiratory system is the sum of the pressures required to distend the lung and the chest wall. Thus the elastance of the respiratory system (Ers) is the sum of the lung elastance (E_L) and chest wall elastance (E_{CW})

$$Ers = E_L + E_{CW} \qquad (1.2)$$

or

$$\frac{1}{C_{rs}} = \frac{1}{C_L} + \frac{1}{C_{CW}} \qquad (1.3)$$

The lung and the chest wall display different pressure-volume relationships (Figure 1.6). The resulting pressure-volume relationship of the respiratory system is sigmoidal in shape, and compliance is greatest in the midvolume range, where breathing normally occurs. At the completely relaxed static equilibrium volume of the respiratory system, elastic recoil of the lung and the chest wall exactly balance each other. Also at this point, compliance of the lung and chest wall are approximately equal in normal subjects. In this midvolume range, the elastic work of breathing and fluctuations in transpulmonary pressure will be minimized.

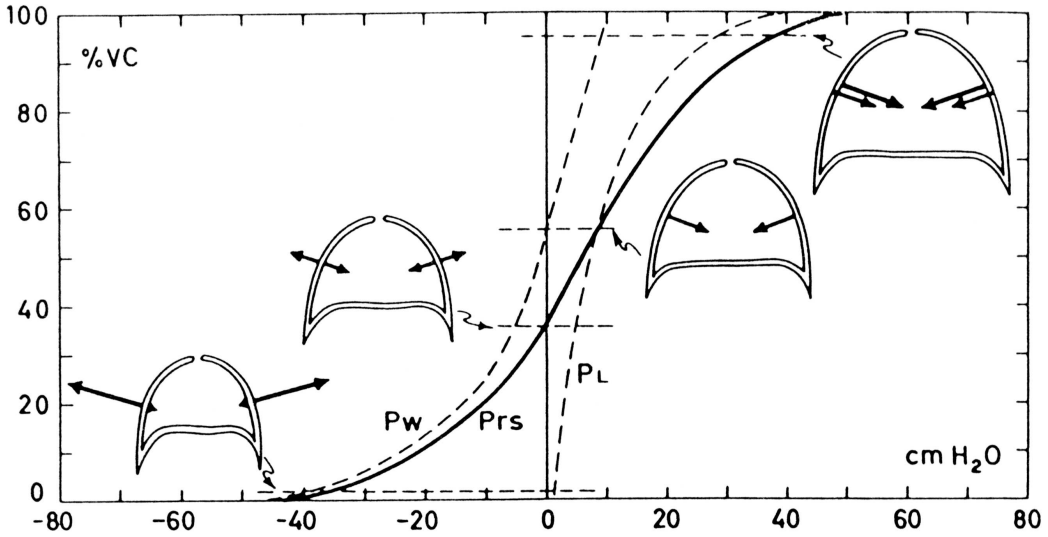

Figure 1.6: Static curves of the lungs (P_L), of the chest wall (P_W) and of the lungs-plus-chest wall (Prs). The slope of these curves is related to the compliance of the systems.

Resistance

The second fundamental property of the respiratory system in the equation of motion is resistance to airflow. Resistance is the opposition to the flow of gases due to frictional forces within the respiratory system. The energy required to overcome resistance is dissipated as heat within the system. Increased resistance to airflow is common in ventilator-supported patients. Resistance is quantified as the amount of pressure required to cause a unit rate of gas flow. It is calculated according to the following equation:

$$Resistance = \frac{driving\ pressure}{flow\ rate} \qquad (1.4)$$

Thus, the airway pressure (Paw) needed to maintain a constant flow across a resistive element is given by:

$$Paw = R\ Fao \qquad (1.5)$$

The customary units of respiratory resistance are $cmH_2O/(liter/s)$. The mathematical inverse of resistance is conductance, but this term is seldom used.

The resistance of the respiratory system can itself be subdivided into elements that are in series and hence additive. These elements include pulmonary resistance (R_L) and resistance of the chest wall (R_{CW}). Pulmonary resistance is itself further subdivided into airway resistance (Raw) and a lung tissue component. Each of these components is determined by measuring the net pressure required to produce flow of the component.

The relationship between driving pressure and airflow depends on whether flow is laminar, turbulent, or a mixture of both.

As is the case with compliance, resistance also varies significantly throughout the respiratory cycle. In addition to turbulence associated changes in resistance, there are also changes associated with lung volume and, particularly in patients with chronic obstructive pulmonary disease, with the phase of respiration. Resistance tends to decrease as volume increases, although this effect is usually small and often ignored. Resistance also tends to be greater during expiration than inspiration, especially when elastic recoil is lost, as in patients with emphysema.

Inertance

The last fundamental mechanical property of the respiratory system and component of the equation of motion is inertance. Inertance of the respiratory system is the analog of inertia and is a measure of the tendency of the respiratory system to resist *changes* in flow. For example, when flow is absent, inertial elements resist the onset of flow. At frequencies normally encountered during spontaneous and mechanical ventilation, the effects of inertance are usually insignificant and are customarily ignored. The pressure generated by inertance is in the opposite direction to that generated by the elastance of the respiratory system. Hence, inertial forces tend to slightly offset the impedance to flow provided by the stiffness of the respiratory system.

The sum of the elastic and inertial forces is referred to as the *reactance* of the respiratory system. Forces due to inertance increase with increasing frequency, and since they are opposite in direction to those forces produced by elastance, reactance is reduced. At a sufficiently high frequency, reactance will vanish. At this frequency, only resistance impedes flow and ventilation. This frequency, the *natural resonance frequency* (f_0) of the respiratory system, is given approximately by the expression:

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{1}{I_{rs}C_{rs}}} \qquad (1.6)$$

Usually f_0 ranges between 5 to 10 Hz in normal adults. With pressure ventilation at frequencies near f_0, resonance can substantially increase tidal volume. At frequencies greater than that of f_0, inertance of the lung becomes the predominant component of reactivity.

The frequency-based analysis of the respiratory system has been termed *oscillatory mechanics*. This approach has the advantage of permitting the determination of resistance and compliance during the course of spontaneous breathing and without the cooperation of the patient. Oscillatory mechanics also permits analysis of elements of the respiratory system that are otherwise not directly observable.

1.2 Screening and assessing the pulmonary function

Lungs function can be assessed under different points of view, elastic properties, airway function, respiratory muscle function, blood gases, etc. The techniques that are significant in this work are described below.

1.2.1 Pulmonary Function Testing (PFT)

In standard clinical practice, a sequence of tests is performed in order to detect, characterize and quantify the severity of lung disease. Inspired and expired air flows and lung volumes of the respiratory system are measured by means of a spirometer inside a total body plethysmographic cabin during respiratory maneuvers executed forcefully.

A spirometer is mainly constituted by a pneumotachograph and is used to measure the flow rate passing through the airway opening. During the measurement the subject breathes through a mouthpiece connected to the pneumotachograph with the nose close by a nose clip. Inspired and expired air volumes are derived by numerical integration of the flow data.

The plethysmographic cabin is a rigid airtight chamber in which the subject sits and breathes through a mouthpiece connected to a pneumotachograph. Mouth pressure, pressure variation inside the box and airway opening flow are measured by sensors placed inside the box.

Measurements of absolute lung volume are based on Boyle's Law, which states that, under isothermal conditions, when a constant mass of gas is compressed or decompressed, the gas volume decreases or increases and gas pressure changes such that the product of volume and pressure at any given moment is constant. During the measurement, airway opening is blocked at the end expiration by a shutter placed after the mouthpiece and the subject is asked to pant against the closure. The compression and decompression resulting from this maneuver are used to estimate the volume of gas contained into the lung (1). In Figure 1.7 is shown the volume trace during a standard lung function test performed in a plethysmographic cabin.

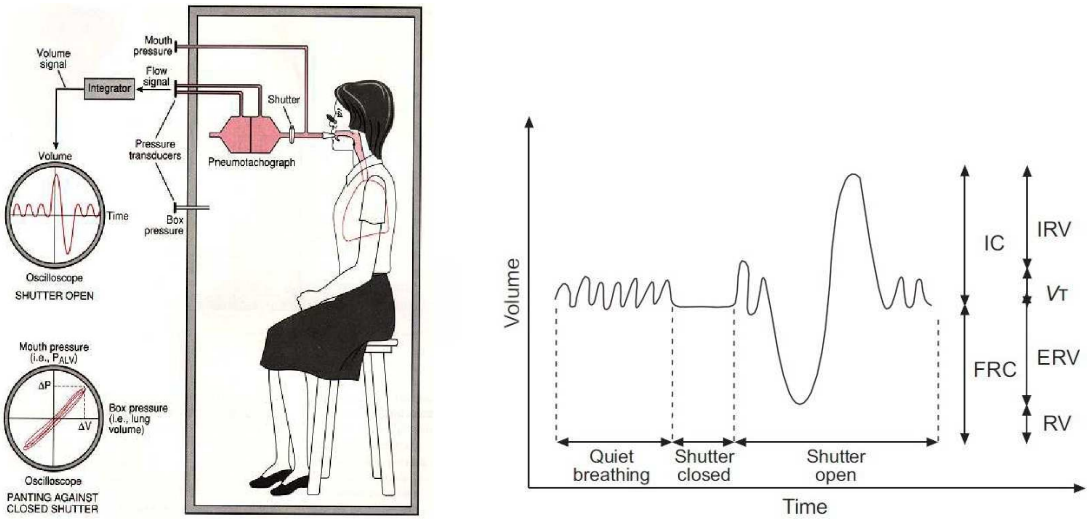

Figure 1.7: Lung function test in a plethysmographic cabin on the left and the resultant volume trace on the right.

To perform the test, the subject is asked to breathe normally through the mouthpiece of the equipment until a stable end-expiratory level is achieved. Then, after a short period when a shutter is closed for determination of the thoracic gas volume, the subject inhales maximally until his maximal chest wall volume and then to exhale as completely as he can. All volumes are determined without the patient coming off the mouthpiece, in a "linked" maneuver in order to measure simultaneously air flow and absolute lung volumes. Lung function is examined by

evaluating both the time course of the lung volumes and the shape of flow-volume curves as the one reported in Figure 1.8.

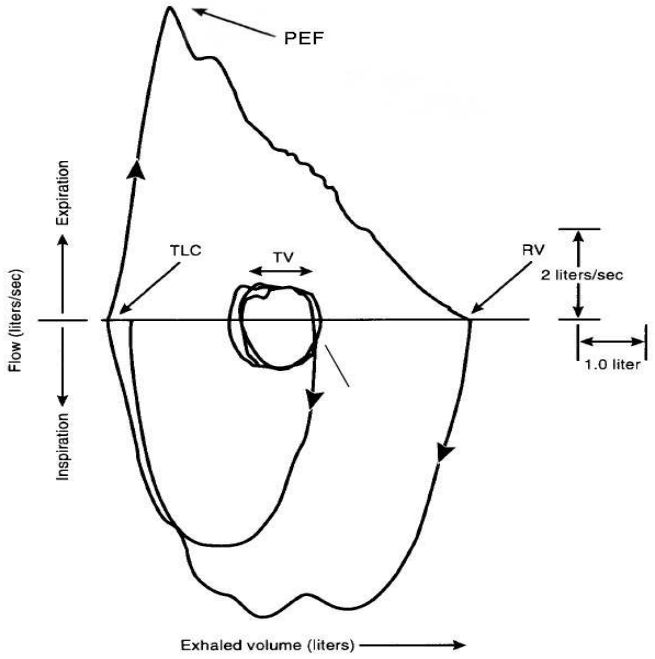

Figure 1.8: Flow - Volume curve obtained during a plethysmographic lung function test.

In clinical practice the following quantities are taken into account:

- Total lung capacity (TLC): pulmonary volume at the end of a maximal inspiration
- Residual volume (RV): pulmonary volume at the end of a maximal expiration
- Functional residual capacity (FRC): pulmonary volume at the end of a normal expiration
- Inspiratory capacity (IC): volume difference between volume at the end of a normal expiration and that at the end of a maximal inspiration
- Vital capacity (VC): volume difference between the volume at the end of a maximal inspiration and the one at the end of a maximal expiration. The maneuver may be performed in a forceful manner to generate a forced vital capacity (FVC) or in a slower manner to generate a slow vital capacity (SVC)
- Tidal Volume (Vt): volume of air moved during a spontaneous breath
- FEV1: volume of gas exhaled in the first second by a forced expiration from full inspiration
- PEF: peak of expiratory flow

1.2.2 Pulse Oximetry

Pulse oximetry is another parameter that is taken into consideration during patient screening and in successive visits. The pulse oximeter is a device that applies to the patient's skin, through two Light Emitting Diodes (LED) that emit light at two different wavelengths, a red light (660nm) and an infrared light (910nm) at low power. As blood hemoglobin and oxyhemoglobin have two different light absorption curves, using a photodiode that receives the LED emissions after they passed through the patient's tissues, it is possible to measure the ratio of oxyhemoglobin over the total amount of hemoglobin. This way the pulse oximeter provides mainly two parameters, relative arterial blood oxygen concentration (SpO_2) expressed as a percentage (%), and heart rate (HR) expressed as beats per minute (BPM).

Pulse oximeters can operate in two different modes, transmission and reflectance. The first operation mode transmits the radiations of the LEDs from one side of the patient tissues and collect them with the photodiode on the other. Typically is mounted on a clip that can be applied on patient's fingers or earlobes. Reflectance pulse oximeters can be applied virtually on every place on patient's skin because the photodiode is positioned next to the emitting LEDs, in order to recover the radiations reflected by the internal tissues. The best placement can be done on skin parts with near bones underneath, the forehead is the best sampling spot.

1.2.3 Arterial Blood Gas Measurement

The arterial blood gas (ABG) test The test is used to determine arterial oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), and acidity (pH) of the blood, and the bicarbonate level, that are indicators of the conditions and efficiency of the respiratory system. The test is performed on a small amount of blood sampled typically from the wrist artery or from the earlobe.

1.2.4 Six-Minute Walk Test

A pulmonary function test aimed to the objective evaluation of functional exercise capacity is the Six-Minute Walk Test (6MWT). It is a practical simple test that requires a 30m hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance

that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.

It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

The 6MWT is performed as follows. The patient is asked to walk back and forth along the 30m hallway during 6 consecutive minutes, without running nor jogging. If the patient feels breathless or tired can slow down, stop for resting or finish the test. Before starting and at the end of the test the physician samples blood pressures and the grade of shortness of breath. Every minute SpO_2 and heart rate are sampled together with the grade of shortness of breath declared by the patient on the basis of the Borg scale, which is shown in the table below (2).

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

The distance covered by the patient during the 6MWT is the first outcome that can be used to determine patient's exercise tolerance. Pulse oximetry provides another significant parameter in order to better understand respiratory system efficiency. The test can be

evaluated by itself or by comparison with previously performed 6WMT in order to assess disease evolution.

1.3 Restrictive and Obstructive Lung Diseases

The pathologies of the respiratory system can be divided into two categories, restrictive and obstructive lung diseases.

In their widest sense, the restrictive lung diseases are all conditions that restrict complete filling of the lungs with air. This definition includes diseases of the chest wall, pleura and lungs. The impairment of the structures of the respiratory system results in a consequent reduction of lung volumes, an increased work of breathing and inadequate ventilation and/or oxygenation. Diseases of the chest wall and diaphragm include respiratory muscles and neuromuscular disorders, rigid or deformed chest wall. Diseases of the pleura include space-occupying lesions, stiff pleura due to fibrosis, malignancy, etc. Diseases of the lung including chronic interstitial lung diseases. The lung function test in restrictive lung disorders typically shows the reduction of FEV1 and FVC parameters (Figure 1.9).

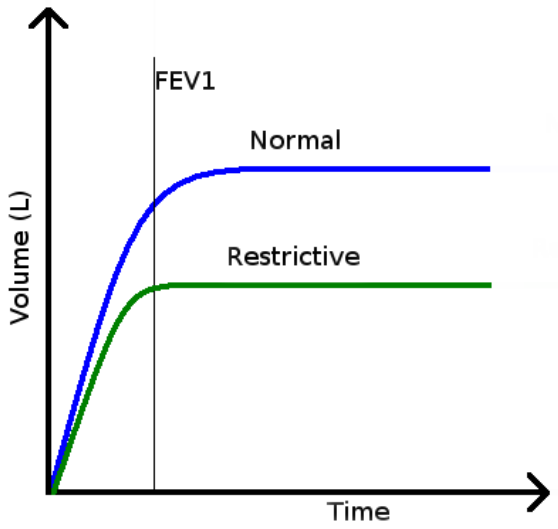

Figure 1.9: Typical lung function test result of a restrictive patient, in which FEV1 and FVC are reduced compared to a healthy subject.

Among a great number of restrictive lung diseases, some of them have a chronic nature leading to the necessity of home treatments and constant monitoring of patient's conditions. Telemedicine is a tool that can effectively help to fulfil the functions of monitoring and remote intervention and nowadays only few feasibility studies have been reported, most of them

involving home monitoring of patient's rehabilitation (3) and only one very recent test on mechanical ventilation monitoring (4).

Obstructive lung diseases cause reduced air flow due to temporary or permanent obstruction of the airways, which are inflamed and easily collapsible, thus determining air trapping into the lungs and increased lung volumes. The lung function test in obstructive lung disorders typically shows the reduction of FEV1, FVC and PEF parameters (Figure 1.10).

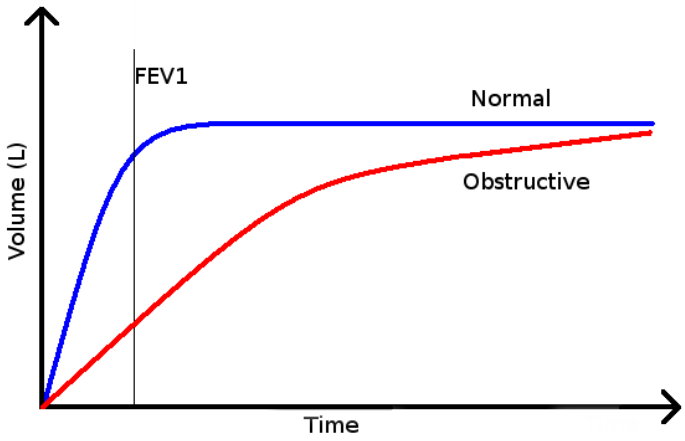

Figure 1.10: Typical lung function test result of an obstructive patient, in which FEV1 and FVC are reduced compared to a healthy subject.

The two primary types of obstructive lung diseases are asthma and chronic obstructive pulmonary disease and one of its significant complications, the obstructive sleep apnea syndrome.

1.3.1 Chronic Obstructive Pulmonary Disease (COPD)

Also called chronic obstructive lung disease COPD is a pathology characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. A diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnoea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post bronchodilator FEV1<80% of the predicted value in combination with an FEV1/FVC<70% confirms the presence of airflow limitation that is not fully reversible.

Pathologic changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. In the central airways — the trachea,

bronchi, and bronchioles greater than 2 to 4 mm in internal diameter — inflammatory cells infiltrate the surface epithelium (5). In the peripheral airways—small bronchi and bronchioles that have an internal diameter of less than 2 mm—chronic inflammation leads to repeated cycles of injury and repair of the airway wall (6). The repair process results in a structural remodeling of the airway wall, with increasing collagen content and scar tissue formation, that narrows the lumen and produces fixed airways obstruction Destruction of the lung parenchyma in patients with COPD typically occurs as centrilobular emphysema. This involves dilatation and destruction of the respiratory bronchioles (7) with consequent air trapping that promotes hyperinflation of the lungs and the presence of an Intrinsic Positive End Expiratory Pressure (PEEPi), which leads to respiratory muscle inefficiency, patient discomfort and reduced exercise tolerance.

The causes can be various, but the major part have in common the introduction in the airways of harmful gases and substances (8).

- *Tobacco smoke*: cigarette smokers have a higher prevalence of lung-function abnormalities and respiratory symptoms, a greater annual rate of decline in FEV1, and higher death rates for COPD than nonsmokers. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particulates and gases (9).
- *Occupational dusts and chemicals*: When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapours, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking (8).
- *Outdoor and indoor air pollution:* High levels of urban air pollution are harmful to persons with existing heart or lung disease. The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with cigarette smoking (10).

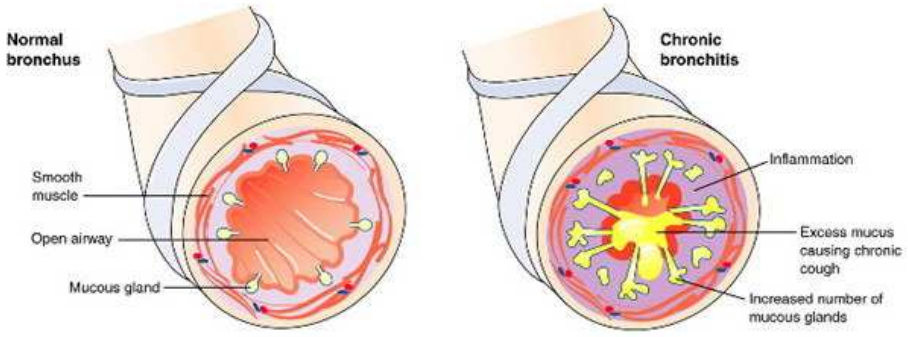

Figure 1.11: Normal bronchus and bronchus affected by chronic bronchitis. The lumen is considerably reduced due to inflammation and mucus excess.

Classification of Severity

The management of COPD is largely symptom-driven, and there is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms. The staging, therefore, is a pragmatic approach aimed at practical implementation and should only be regarded as an educational tool, and a very general indication of the approach to management. All FEV1 values refer to post bronchodilator FEV1.

- *Stage 0: At Risk*. Characterized by chronic cough and sputum production. Lung function, as measured by spirometry, is still normal (11).
- *Stage I: Mild COPD*. Characterized by mild airflow limitation (FEV1/FVC<70% and FEV1>80% of the predicted value) and usually, but not always, by chronic cough and sputum production. At this stage, the individual may not even be aware that his or her lung function is abnormal (11).
- *Stage II: Moderate COPD*. Characterized by worsening airflow limitation (FEV1/FVC<70% and 50% ≤FEV1<80% of the predicted value) and usually the progression of symptoms, with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical attention because of dyspnoea or an exacerbation of their disease (11).
- *Stage III: Severe COPD*. Characterized by severe airflow limitation (FEV1/FVC<70% and 30%<FEV1<50% of the predicted value) or the presence of respiratory failure or clinical signs of right heart failure. Patients may have severe COPD even if the FEV1 is >30% predicted, whenever these complications are present (11).
- *Stage IV:* Very severe COPD. Characterized by severe airflow limitation (FEV1/FVC<70% and FEV1<30% of the predicted value or FEV1<50% plus chronic respiratory failure). At this stage, quality of life is appreciably impaired and exacerbations may be life-threatening (11).

COPD is a chronic regression of patient's conditions, which starts with shortness of breath and production of sputum, it worsens determining reduced exercise capability and increased dyspnea. Exacerbations, temporary acute conditions which entail hospitalization, have an impact on patient's quality of life and can lead to the shift to a worse stage of the disease and in stage IV there is a progressive inability to perform daily activities, and exacerbations can lead to death. To avoid fast worsening of COPD and exacerbations, it is necessary to remove the harmful substances like smoke, even if it is not anymore possible to recover the normal lung functions (Figure 1.12) because some lung damage cannot be reversed.

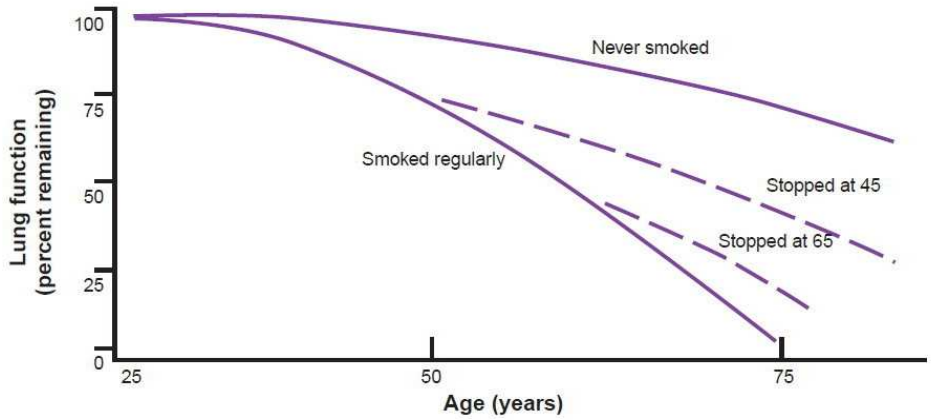

Figure 1.12: Age related change in the lung function and effect of smoking and smoking cessation.

Exacerbations

Acute exacerbations of COPD are defined as a worsening of COPD symptoms caused by a rapid deterioration of the underlying respiratory function. Exacerbations represent a further amplification of the inflammatory response in the airways of COPD patients, and may be triggered by infection with bacteria or viruses or by environmental pollutants. During an exacerbation there is increased hyperinflation and air trapping, with reduced expiratory flow, thus accounting for the increasing dyspnea. There is also the worsening of the ventilation to perfusion ratio abnormalities, resulting in severe hypoxemia.

Moderate to severe exacerbations represent a major cause of hospital admissions (12). Indications for hospitalization are the inadequate response to outpatient management, the inability to perform activities of daily living owing to increased dyspnea, the development of respiratory failure, the association of comorbidities, or inadequate home care resources. For these patients, admission to an intensive care unit (ICU) is common and average hospital lengths of stay are long (12). Exacerbations can lead to a consistent and permanent worsening of the conditions of the patient, thus determining the change of the classification to a worse stage, and sometime to the death. The mean number of exacerbations per person per year ranges from 0.6 to 3.5 according to the disease stage and the age group (13). The number of exacerbation can be reduced by treatment. Exacerbations are usually categorized as mild (symptoms treated at home or easily tolerated), moderate (treatment in a hospital or affecting daily activity) or severe (specialist treatment or inability to work). More severe disease stages

are associated with more severe exacerbations. the average frequencies of severe exacerbations are 0.01 and 0.33 per patient per year at GOLD stage 1 and GOLD stage 4, respectively (13).

Expiratory Flow Limitation

Expiratory flow limitation (EFL) is a common phenomenon in COPD patients and depends on the altered mechanical characteristics of the airways. EFL is visible, during the PFTs in the flow-volume curve: after the peak of expiratory flow, the curve depends only on the mechanical properties of the parenchyma and on the expiratory effort.

In Figure 1.13 flow-volume relationship during a series of inspiratory and expiratory VC maneuvers performed with graded muscular effort are reported. The red line represents the curve obtained with maximal expiratory effort. Increasing inspiratory efforts produce increasing inspiratory flows; in contrast, during expiration the flow first increases with the muscular effort but, once the maximum value is reached, all the curves follow the same course, that is the maximal expiratory flow-volume (MEFV) curve. Therefore, for each lung volume there is a maximum value of the expiratory flow independent from the driving pressure. This phenomenon is known as Expiratory Flow Limitation and it is present in healthy subjects during maximal expiratory effort but it can be present also during quiet breathing in patients affect by obstructive diseases. The mechanism by which expiratory flow limitation occurs is complex. The airways are compliant structures: their caliber depends on transmural pressure (Ptm) that is the difference between the lateral pressure inside the airways (Pa) and pressure outside the airways (peribronchial pressure (Pbr)). The pressure distribution along the tracheobronchial tree depends on lung volume,

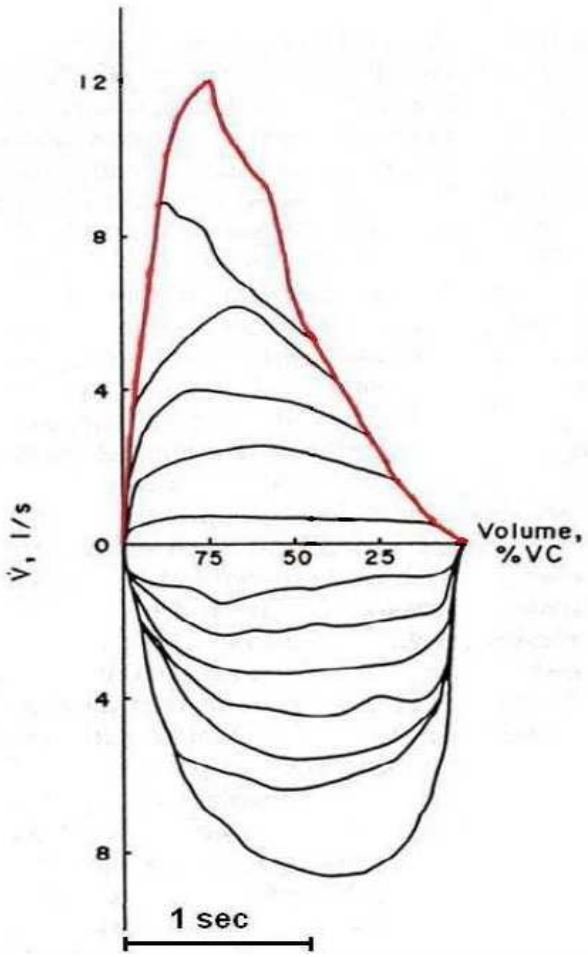

Figure 1.13: Flow-volume relationship during a series of inspiratory and expiratory VC maneuvers performed with graded muscular effort until maximal expiratory effort. The red line represents the MEFV curve

gas properties, and flow. Therefore, the mechanics of the airways and the mechanics of the flow are coupled, thus causing the onset of the so called *choke points*, flow limiting points inside the lungs, the which location changes with lung volume, and cannot be determined.

Dynamic Hyperinflation

Pulmonary hyperinflation is defined as an increase in end expiratory lung volume (EELV) above the predictable value. This can be due either to a loss of elastic recoil of the lung (as it occurs in emphysema), or to dynamic hyperinflation (DH).

Dynamic hyperinflation exists if the expiration time is not long enough to allow the lung to deflate to FRC before the next inspiration starts. The presence of EFL at rest is the principal cause of DH. This produces several important consequences. First of all, hyperinflated lung flattens the diaphragm and stretches the rib cage. This altered geometrical configuration of the system worsens the efficiency of the contraction of the respiratory muscles.

At higher volumes lungs and rib cage are stiffer; therefore breathing at higher volumes implies a bigger work of breathing.

In addition, patients affected by dynamical hyperinflation, since they cannot deflate completely, at the end of expiration have still air trapped inside their lung, and therefore the pressure in the alveolar space is not zero but a positive value known as PEEPi (intrinsic Positive End Expiratory Pressure). Increased breathing frequency, as during exercise, worsens hyperinflation. Because the expiratory time decreases, the PEEPi increases and the respiratory work increases causing dyspnoea and insofar shortens the exercise time duration. The presence of PEEPi hinders the intrathoracic venous return and the cardiac output as well.

DH commonly occurs in COPD, where the presence of expiratory flow-limitation (EFL) requires the patient to breath at higher lung volumes to produce the necessary expiratory flow. In these patients PEEPi provides a substantial threshold load that must be counterbalanced by respiratory muscles: the inspiratory flow starts only when the pressure developed by the inspiratory muscles exceeds PEEPi. In these conditions the inspiratory efforts required by the patient may be excessive.

Sleep related disorders in COPD

A great number of patients have both Sleep Disordered Breathing (SDB) and COPD. This is called the overlap syndrome, even if this definition is primarily for the presence of both obstructive sleep apnea (OSA) and COPD (14), and causes more severe nocturnal hypoxemia than either disease alone (15). This has important implications for diagnosis, treatment, and outcome. Patients with COPD and OSA have a substantially greater risk of morbidity and mortality, compared to those with either COPD or OSA alone.

SDB cause recurrent episodes of nocturnal arterial oxyhemoglobin desaturation, especially during REM (rapid eye movement) phase sleep (16). Generally, patients who experience hypoxemic state when awake, are the ones which most severely desaturate during sleep, however patients classified as non hypoxemic, during the night have severe hypoxemic events, suggesting the need for complete screening also during the sleep (17).

It has been suggested that nocturnal desaturations occurring in patients without significant daytime hypoxemia could lead to permanent pulmonary hypertension precipitating the development of cor pulmonale. Moreover it has been demonstrated that patients with nocturnal desaturation had a lower survival rate than those who did not desaturate (18).

The development of nocturnal desaturation in COPD patients has been related to several causes, including changes in respiratory mechanics, worsening of ventilation/perfusion mismatch, increased airflow resistance, and progressive respiratory muscles weakness. Hypoventilation during sleep is the most important cause of hypoxemia and the presence of ventilation/perfusion alterations and reduced functional residual capacity probably also plays a significant role (19).

While imperfect, there exist reasonable estimates of the prevalence of OSA and COPD. Furthermore, as the major risk factors for each disorder are known, the expected incidence and future prevalence can also be predicted. Unfortunately, such prevalence data are not available for the overlap syndrome. In part this deficiency reflects the lack of a standardized definition, and a lack of a unique diagnostic code. Additionally, both OSA and COPD have undergone revisions in diagnostic techniques and/or criteria in the last 25 years.

Because both COPD and OSA occur on a spectrum of severity, it is unclear at what level of severity the combined diseases begin to have additive or synergistic clinical relevance. It is also unknown if patients with severe COPD and mild OSA should be evaluated and treated similarly to those with mild COPD and severe OSA. Regardless, given the high prevalence of

both COPD and OSA, it would be expected a large cohort of patients affected with both of these common diseases.

COPD prevalence and mortality

WHO estimates that 210 million people have COPD worldwide. This number could be higher because many people with COPD often do not seek medical help until the disease worsens (8).

COPD prevalence in Europe is not a simple numerical data, it varies depending on many factors as there is still not a standard and clear procedure to diagnose COPD. Its prevalence data can be categorized into four types according to the criteria used to define the disease, symptoms, physician reports, spirometry and models (13).

The symptoms based data (cough and expectoration on most days for as much as three months per year and for at least two successive years) shows a range from 0.7% to 9.7% (20). The prevalence of chronic bronchitis is reported to be significantly lower among women than among men in all countries (2.8% versus 3.7%; $P < 0.001$) (20). The prevalence increased gradually from nonsmokers to "moderate-heavy" smokers (≥15 packs-yrs) and from higher socioeconomic classes to the unemployed and blue-collar workers.

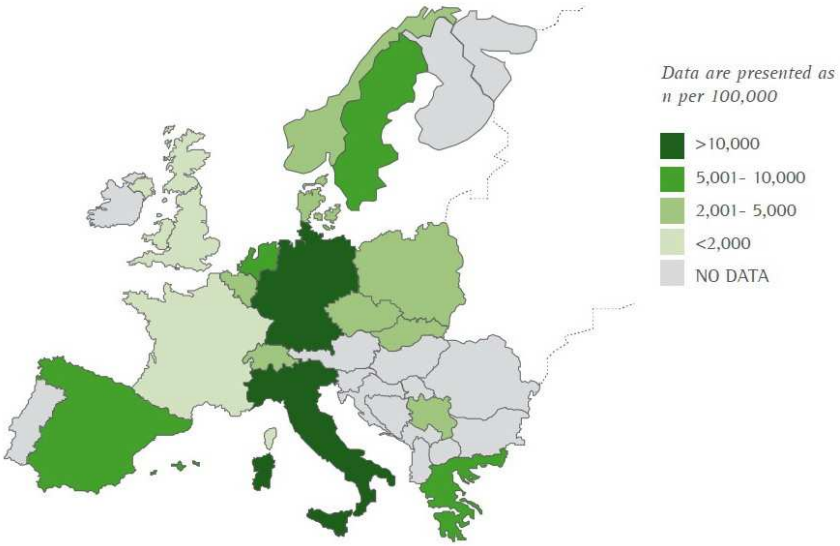

Figure 1.14: COPD prevalence around Europe according to the Organization for Economic Co-operation and Development (www.oecd.org). Data are presented as n per 100,000 inhabitants (21).

Studies (22) based on diagnoses of chronic bronchitis by healthcare professionals have produced less varying results, with prevalence rates ranging from 3.7% to 5.6% among adults. In studies based on respiratory function, such as the ratio of the maximum expiratory volume

in 1 second (FEV1) over forced vital capacity, or the difference between measured and predicted FEV1, the prevalence ranged from 2.1% (23) to 26.1% (24;25).

Several authors have proposed model-based approaches for estimating COPD prevalence (26). These models combine demographic data with smoking rates, data on respiratory function in the general population and other risk factors such as air pollution and low socioeconomic status. In these studies, the prevalence varied from 1.5% to 15% in the general population.

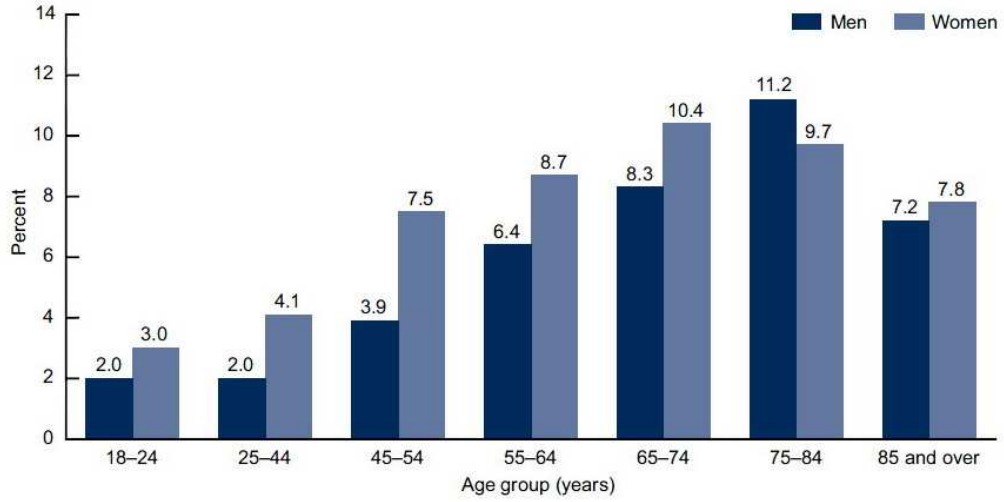

Figure 1.15: Prevalence of COPD among adults aged 18 and over, by age gropu and sex in U.S., annual average 2007-2009.

In the United States in 2007-2009 11.8 million of adults (5.1%) aged 18 and over had COPD, among which prevalence was higher in older age groups, and women had higher COPD prevalence than men, 6.1% of women compared with 4.1% of men (27) (Figure 1.15). The prevalence of COPD did not change significantly from 1998 through 2009, following a period (1980-1996) during which COPD increased for women but not for men, and during which there were greater increase in COPD hospitalizations and deaths among women compared with men (27).

A wide and reliable estimation of the burden of COPD in the Arabian states is not available, however recent studies shows that prevalence is 3.7% (29) with no significant difference between genders, but the causes can be due more to biomass rather than to smoke exposure (29).

In China the overall crude prevalence of COPD was 2.9% based on self-report (30). The prevalence among men was significantly higher than among women (3.4% vs. 2.4%, $p < 0.001$), rural area higher than urban area (3.1% vs. 2.5%, $p < 0.001$), and western areas (3.7%) higher than central (2.7%) and eastern (2.2%) areas. The prevalence increased with age, from 0.8% in the youngest age group (15-29 years) to 7.5% in the eldest age group (60-69 years). Former

smokers had a higher prevalence of COPD (9.0%) compared to current smokers (3.3%) and never smokers (2.3%) (30).

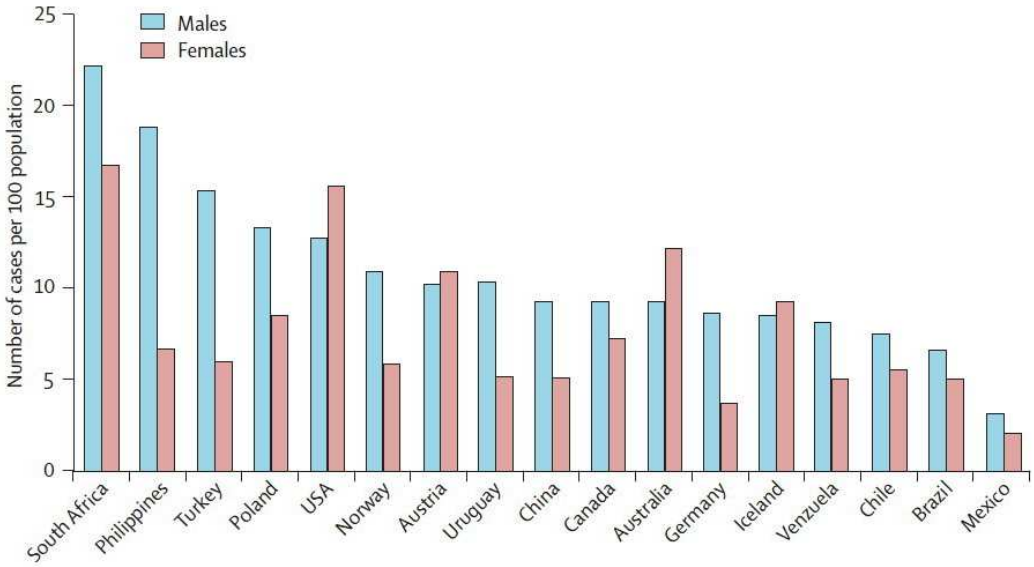

Figure 1.16: Estimated prevalence of GOLD stage 2 or higher COPD around the world (28).

Besides all these data, nevertheless, it is estimated that there is a widespread of underrecognition and underdiagnosis of COPD (31;32) (Figure 1.17).

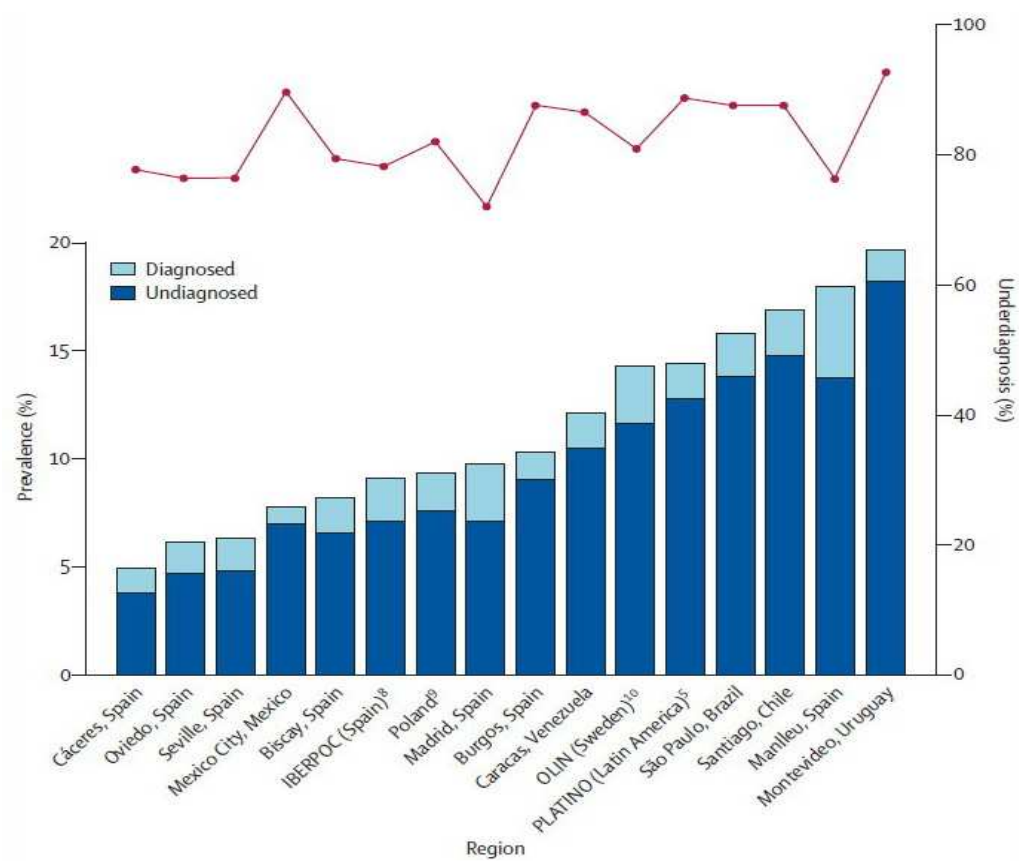

Figure 1.17: Reported prevalence of COPD divided by region and relative underdiagnosis in selected population studies (32) (upper red line).

COPD is one of the most important causes of death in most countries, the WHO estimates that in 2000, 2.74 million people died of COPD worldwide. COPD, which was ranked sixth as the cause of death in 1990, will become the third leading cause of death worldwide by 2020 (11). This increased mortality is driven by the expanding epidemic of smoking and the changing demographics in most countries, with more of the population living longer. However data on COPD mortality must be interpreted cautiously because of inconsistent use of the terminology, as prior to about 1968 the terms "chronic bronchitis" and "emphysema" were used extensively. During the 1970s the term "COPD" increasingly replaced those terms in some but not all countries, making COPD mortality comparisons in different countries very difficult.

At present in Europe, the fairest comparison between countries should be made with 2007 European COPD-related mortality estimates issued by Eurostat (33) (Figure 1.18). The estimates ranged from 7.2 per 100,000 inhabitants in France to 36.1 per 100,000 inhabitants in Hungary, and mortality was between 1.3 (Sweden) and 13 (Malta) times higher in men than in women (33-35).

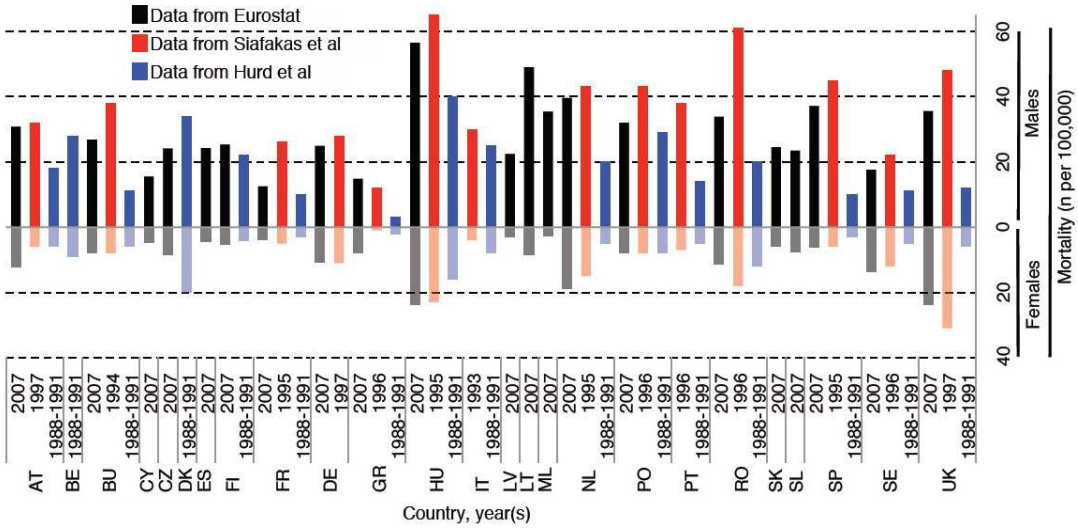

Figure 1.18: COPD age-standardized mortality rates (n per 100,000). Abbreviations for countries: AT, Austria; BE, Belgium; BU, Bulgaria; CY, Cyprus, CZ, Czech Republic; DK, Denmark; ES, Estonia; FI, Finland; FR, France; DE, Germany; GR, Greece; HU, Hungary; IR, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; ML, Malta; NL, Netherlands; PO, Poland; PT, Portugal; RO, Romania; SK, Slovakia; SL, Slovenia; SP, Spain; SE, Sweden; UK, United Kingdom.

COPD is the 3rd leading cause of death in the United States and it kills more than 120,000 Americans each year (36). In USA COPD in 2007 caused the death of nearly 60,000 men and nearly 65,000 women, with death rates of 63.5 per 100,000 population for men and 46.8 per 100,000 for women (27).

COPD mortality can vary considerably depending on the age and sex of the patient considered, in China for example in varies from 10 to 1,000 deaths per 100,000 inhabitants

depending on age, as shown in Figure 1.19, where mortality is displayed per year and age, both for men and women (37).

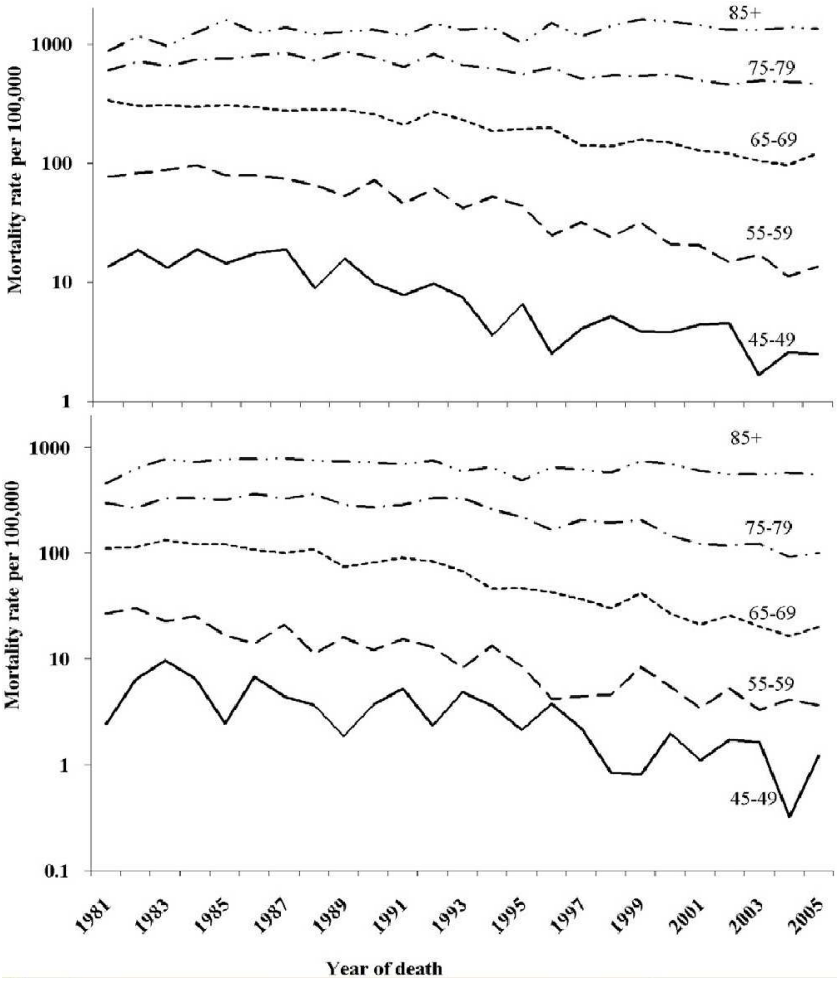

Figure 1.19: Age specific mortality rates from COPD in men (above) and women (below) by year of death in Hong Kong, 1981-2005.

COPD-related mortality is probably underestimated because of the difficulties associated with identifying the precise cause of death. COPD is a disease associated with high and increasing worldwide mortality, however, COPD-related mortality is probably underestimated because it can be difficult to attribute death to a single cause, even when the patient dies in a clinical setting. Contrary to common opinion, respiratory failure is not the only major cause of death in end-stage COPD; moreover, cardiovascular disease and lung cancer are common causes of death earlier in the disease progression of COPD (38).

COPD management and treatments

As COPD is a disease not fully reversible it is necessary to prevent or otherwise to treat and manage the course of the disease. Given the intrinsic characteristics of the pathology, an effective COPD management plan includes the assessment and monitoring of the disease, reducing the risk factors, managing the stable states and the acute states, i.e. the exacerbations.

In mild and moderate COPD patients (stages I and II), in order to prevent the disease progression, it is necessary to avoid the exposure to the risk factors and to start a pharmacotherapy that usually is composed of bronchodilators (help airways opening), corticosteroids or steroids (lessen inflammation of the airways walls), antibiotics (counteract infection), expectorants (help loosen and expel mucus secretions from the airways), diuretics (excrete excess fluid), digitalis (heart support), and other drugs like tranquilizers, pain killers, cough suppressant and sleeping pills.

Severe and very severe COPD (stages III and IV) often require the integration of many different disciplines and treatments, such as patient education, health advice, instruction in physical exercise, nutritional advice, continued nursing support, and in more serious conditions also oxygen therapy and ventilatory support.

Non-invasive Positive Pressure Ventilation (NPPV) is a standardized practice that was initially used in patients with hypercapnic respiratory failure secondary to COPD. Small, handy and easily portable machines provide pressure-cycled ventilation, during which a preset pressure level is applied during inspiration and expiration. The ventilation can be either Continuous Positive Airway Pressure (CPAP), which provide a fixed pre-set pressure level throughout the whole respiratory cycle, or Bi-level Positive Airway Pressure (BiPAP). The latter is the preferred one for COPD patients. It provides airflow positive airway pressure, which cycles between high and low positive pressures, where a breath by the patient triggers the transition from the Expiratory Positive Airway Pressure (EPAP) to the Inspiratory Positive Airway Pressure (IPAP), initiating the next breath. The patient is connected to the ventilator through a tight-fitting oronasal or nasal mask, which is held in place by straps. The choice of mask depends upon comfort and compliance of patient as well as operator choice.

The benefits of the employment of NPPV on COPD patients is to offload the respiratory muscles and reduce the respiratory work load, leading to improvement in the imbalance. Further, an increase in the tidal volume, alongside a reduction in respiratory rate with consequent augmentation of the alveolar ventilation, and improvement in the hypercapnia and its consequent

adverse effects. In addition, EPAP delivered through NPPV helps in counteracting the PEEPi.

It has been shown both in physiologic and clinical studies that application of an positive external pressure et end expiration (PEEP) equal to PEEPi reduces the work of breathing, normalizes the pattern of breathing, improves blood gases and reduces patient-ventilator asynchrony (39). On the other hand, if the externally applied PEEP is greater than the PEEPi it results in an increased EELV (and, thus, in an increase of work of breathing) and in adverse effects on hemodynamics, as it may severely decrease venous return and cardiac output, depending upon intravascular volume status, myocardial function and other factors (40;41).

A large number of clinical trials have clearly established the role of NPPV in acute management of patients with COPD. It has been found to reduce the incidence of requirement of endotracheal intubation, as well as improving ICU and hospital survival (42). The use of NPPV shows good level of evidence for clinical efficacy in the treatment of acute condition on chronic respiratory failure due to acute exacerbations of COPD and it is also an alternative to invasive ventilation for symptom relief in end stage COPD (43).

NPPV showed to be effective also in non acute settings, in hypercapnic COPD patients and in COPD patients with the overlap syndrome, that is the coexistence of COPD and SDB. Long term treatment provide a better ventilation-perfusion match and hence better blood gases and lung function (44). Moreover, there are several theoretical reasons and clinical evidences to use NPPV in home setting in patients with severe hypercapnia and symptoms of hypoventilation, in individuals who failed long-term oxygen therapy (LTOT) treatment and in subjects with recurrent exacerbations. Moreover, NPPV in acute and chronic setting was recognized as a cost-effective treatment (45).

Economic burden of COPD

COPD is a costly disease with both direct costs (value of health care resources devoted to diagnosis and medical management) and indirect costs (monetary consequences of disability, missed work, premature mortality and caregiver or family costs resulting from the illness). In developed countries, exacerbations of COPD account for the greatest burden on the health care system.

In the European Union the total direct costs of respiratory disease per year are estimated to about 6% of the total health care budget, with COPD accounting for 56% (38.6 billion Euros) (11), and a total of 14 billion Euros for time off work (Figure 1.20) (46).

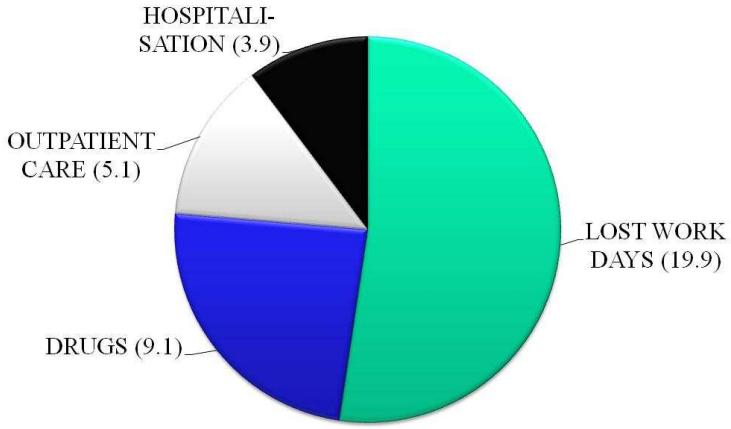

Figure 1.20: Total costs (billions of Euros) of COPD and Asthma in Europe. in 2009.

Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care (47), and the distribution of costs changes as the disease progresses.For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases, as illustrated by data from Sweden shown in Figure 1.21.

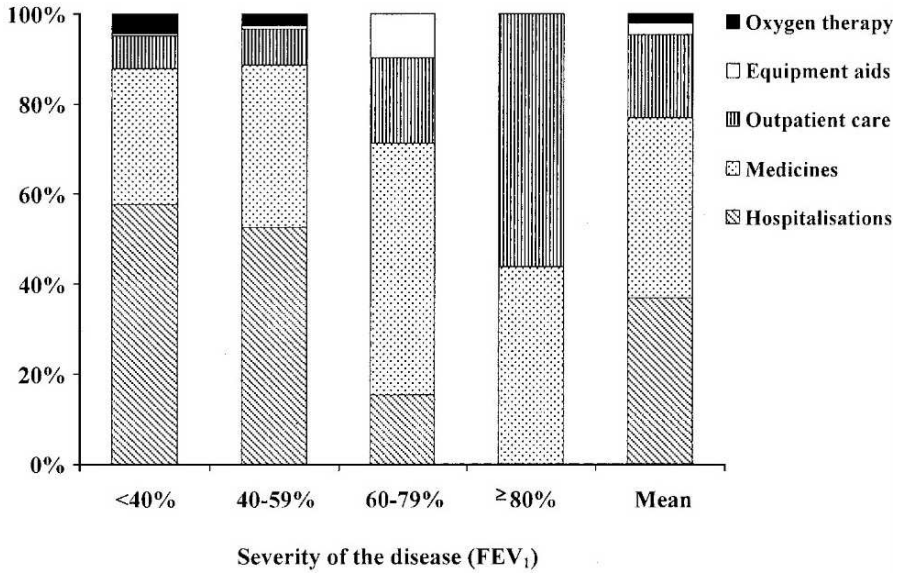

Figure 1.21: The percentage distribution of direct costs in the different groups of severity.

COPD exacerbations and the consequent hospitalizations play an important role in the economic burden, as shown in Figure 1.22 under. COPD is the most costly disease among lung pathologies in terms of hospital stays, as a matter of fact in 2009 the cost to the health services were 2.7 billion of Euros (46).

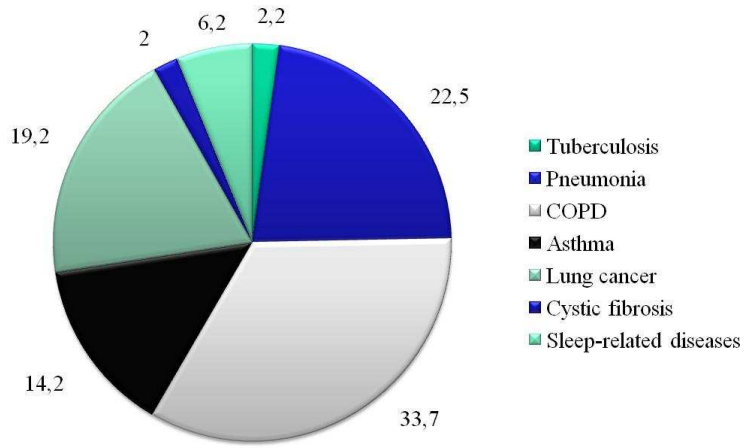

Figure 1.22: Distribution of costs (%) for hospitalizations in 2009 in Europe.

In a recent international (Brazil, China, Germany, Turkey, US, UK) survey (48) it has been shown that the annual cost of healthcare utilization (excluding treatment costs and diagnostic tests) per individual was estimated to be 2,364$. For those remaining in active employment the lost time from work costs the individual an average of 880$ per year. The working population that had retired prematurely because of COPD, incurred in individual estimated lifetime income losses of 316,000$.

In the US the estimated costs of a COPD patient per year ranged around 2382$ in 2007 to 3339$ in 2009, comprised the majority of total costs (49). In 2010, the cost to US for COPD was projected to be approximately $49.9 billion, including $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs (50).

1.3.2 Obstructive Sleep Apnea Syndrome (OSAS)

Sleep apnea is a sleep disorder characterized by pauses in breathing during sleep. These episodes, called apneas (literally, "without breath"), each last long enough so one or more breaths are missed, and occur repeatedly throughout sleep. The standard definition of any apneic event includes a minimum 10 second interval between breaths, with either a neurological arousal, or a blood oxygen desaturation of 3-4% or greater, or both arousal and desaturation. Clinically significant levels of sleep apnea are defined as 5 or more events of any type per hour of sleep time.

There are three distinct forms of sleep apnea, central (0.4% of cases), obstructive (84% of cases) and complex (15% of cases), a co presence of both the first two. In central sleep apnea there is a lack of the respiratory drive, thus meaning that the muscles don't receive the stimulation to start a new breath.

Sleep-disordered breathing, which can occur at any age, corresponds to a continuous clinical spectrum from snoring, upper airway resistance episodes, to obstructive hypopneas and apneas according to the severity of upper airway collapsibility (51). The common characteristic is a repetitive partial or complete collapse occurring during sleep at the pharyngeal level, a region lacking rigid support. Thus, pharyngeal patency is dependent on both its anatomy (caliber) and on the activity of pharyngeal dilator muscles. Factors predisposing to upper airway collapse include anatomical narrowing and/or their abnormal collapsibility. Patients with obstructive sleep apnea have anatomically small upper airways, even during wakefulness. This may be due to obesity through fat deposition in the neck area, small mandible, jaw position, soft-palate elongation and thickness, tonsil or tongue hypertrophy.

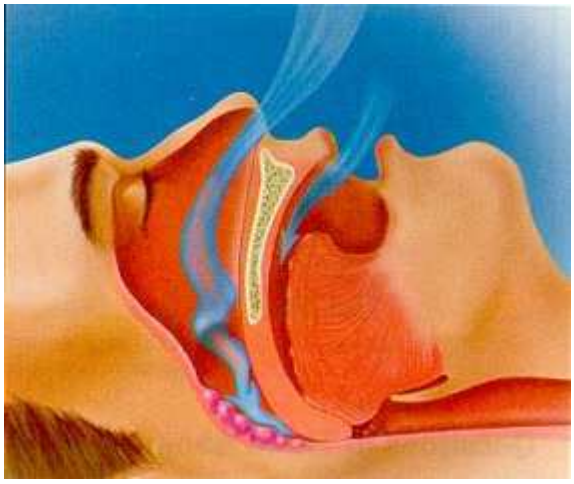

Figure 1.23: Obstruction occurring during an apnea in sleep disordered breathing.

The occurrence of apneas and hypopnoeas, an average of 40 to 60 events every hour is not uncommon, leads to a reduction in oxygen levels in the blood, sleep fragmentation, confusion and nocturnal restlessness, nocturnal gastro-esophageal reflux, dry mouth, nocturnal sweating. When blood oxygen levels fall, or the physical exertion to breathe is too great, neurological mechanisms trigger a sudden interruption of sleep, called a neurological arousal. These events may or may not result in complete awakening, but can have a significant negative effect on the restorative quality of sleep. In significant cases of obstructive sleep apnea, one consequence is sleep deprivation due to the repetitive disruption and recovery of sleep activity.

This sleep interruption can interfere with normal growth patterns, healing, and immune response, especially in children and young adults.

All these symptoms cause daytime sleepiness, cephalalgia, irritability, car driving danger, libido reduction, anxiety and depression. Furthermore recent studies state that OSAS seems to play a role in the onset of relevant cardiovascular diseases (52).

Mild OSAS patients show less than 10 events per hour, moderate between 10 and 30 events per hour, while severe OSAS experience more than 30 events per hour.

Polysomnography

Sleep apnea is diagnosed with an overnight sleep test called full polysomnography (PSG), a multi-parametric test that allows to notice the apnea periods during the sleep and the relative physiological values. The test is performed at the hospital and the parameters measured are (Figure 1.24):

- Electrooculogram (EOG), to pick up the activity of the eyes
- Elecrtoencephalogram (EEG), to monitor the brain activity
- Electromyogram (EMG), used to measure muscle tension in the body
- Electrocardiogram (ECG), to monitor heart activity
- Oral and nasal airflow
- Thoracic and abdominal movements
- Blood oxymetry, to determine changes in blood oxygen levels
- Sleeping position
- Snoring
- Legs movements

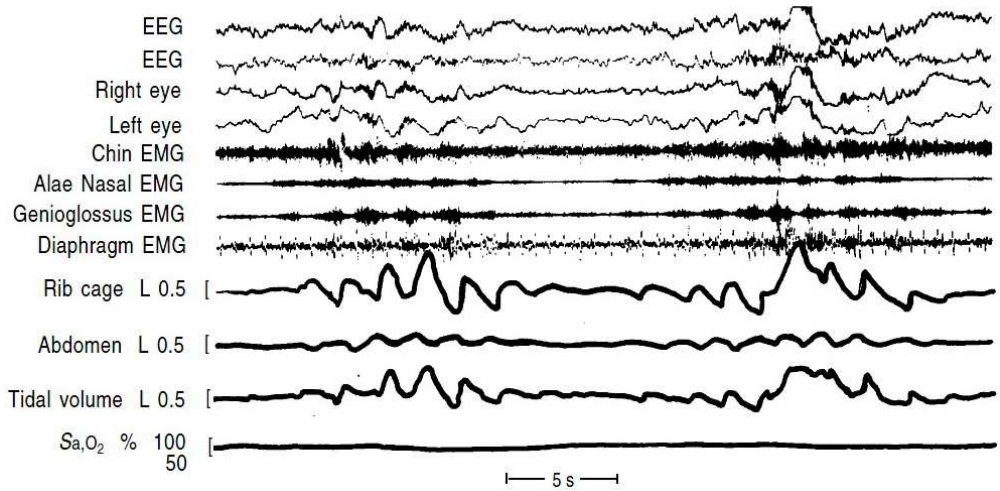

Figure 1.24: Example of PSG exam in which is possible to see a 5s apnea followed by a burst of EMG activity.

In obstructive sleep apnea the polysomnography shows pauses in breathing. As in central apnea, pauses are followed by a relative decrease in blood oxygen and an increase in the blood carbon dioxide. Whereas in central sleep apnea the body's motions of breathing stop, in obstructive sleep apnea the chest not only continues to make the movements of inhalation, the movements typically become even more pronounced. Monitors for airflow at the nose and mouth show the dynamics of airflow, but efforts to breathe are not only present, they are often exaggerated. The chest muscles and diaphragm contract and the entire body may thrash and struggle.

As PSG is long and expensive exam it is possible to diagnose OSAS also with a simplified version called polygraphy. It is performed by portable devices that can be used at home, and that acquired a reduced set of parameters.

OSAS prevalence

Obstructive sleep apnea is a common condition in many parts of the world and is very diffused. The prevalence of OSAS is increasing worldwide, in part linked to the epidemic of obesity (53). The estimated prevalence is 2-4.4% in women and 4-11% in men (54;55). Approximately 1 in 5 adults has at least mild OSA, and 1 in 15 adults has at least moderate OSA (56). Relative prevalence of OSAS as a comorbidity increases up to 80%, as shown in figure.

The prevalence of pediatric obstructive sleep apnea syndrome is approximately 1-3% in children (57;58). Adenotonsillar hypertrophy is the most common cause of OSAS in children,

and obesity, hypotonic neuromuscular diseases, and craniofacial anomalies are other major risk factors (58).

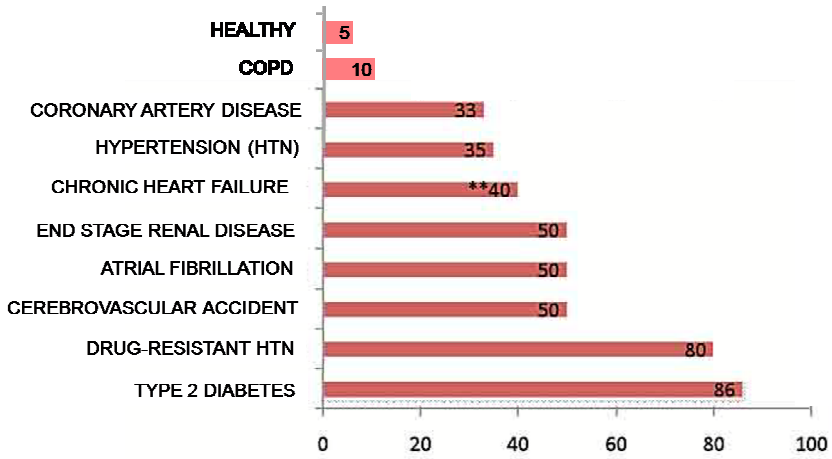

Figure 1.25: OSAS prevalence in healthy subjects and as a comorbidity. (Gami et al, J cardiovasc electrophysiol, vol 19, 997-1003, 2008. West et al, Thorax, 61:945-250, 2006. Sim et al, Chest epub, Nov 24 2008. Foster et al, Diabetes Care, 32: 1017-1019, June 2009)

OSAS management and treatments

OSAS can be treated in several ways, depending on the origin and severity of the disease. The first intervention should be done on predisposing factors, which include positional therapy, weight loss, addressing poor sleep hygiene, treating nasal obstruction, avoiding sedatives and alcohol, increasing exercise, and smoking cessation. Positional maneuvers attempt to keep patients with mild positionally dependent apnea or snoring off their back (where disordered breathing is often worse) or alter head position. A multitude of snore pillows, alarms, or mechanical devices have been offered as positional therapy. Positional therapy can seldom be dependably maintained. Medical treatment of nasal disease, and nasal dilators may successfully treat mild apnea and snoring complaints.

Treatment of obesity is important in all obstructive sleep apnea patients. Rarely weight loss alone may be curative. Moderate weight loss, nonetheless, may significantly improve OSAS or snoring. In severe apnea, definitive treatment (medical or surgical) is necessary in conjunction with weight loss.

Surgery treatments comprehend mandibular advancement, bariatric surgery (surgical weight loss) which may be indicated in morbidly obese patients, adequate thyroid replacement or treatment of acromegally by removal of pituitary adenomas (benign tumors). Obstructive apneas and periodic breathing may reverse with treatment of the heart failure. The main

treatment for children with OSAS is surgery, with removal of the child's enlarged tonsils and adenoids (tonsillectomy and adenoidectomy).

Oral appliances may be either mandibular repositioning devices or tongue retaining devices. Many patients report discomfort of teeth, gums, and temporo-mandibular joint complaints following prolonged use.

Drug therapies like protryptyline, a non-sedating anti-depressant, increases upper airway muscle tone, reduces rapid eye movement (REM) related apnea by decreasing REM sleep, and acts as mild respiratory stimulant.

All these treatments cannot be applied on all the patients, and sometime are too delicate and hazardous, like surgery, to be accepted. The common therapy prescribed is the continuous positive airway pressure (CPAP).

CPAP applies positive pressure to the upper airway and effectively acts like a pneumatic splint to maintain airway patency. Physiologically, nasal CPAP increases intraluminal pressure to keep airway pressures above collapsing pressures during both inspiration and expiration. Effective nasal CPAP pressure to treat OSAS varies depending on sleep state, body weight, head and body position, nasal patency, and sedative use. CPAP pressure must be individually titrated (determine the amount to be used for a given result) and may need periodic adjustments if signs of symptoms warrant. Incorrect pressure settings may under-treat apnea resulting in arousal and movement, which may dislodge the device. Alternately, too high pressure increases spontaneous arousal, central apnea, and patient intolerance.

The reasons for failure vary but successful nasal CPAP requires: 1) a correct machine pressure setting, 2) a comfortable and air tight patient/mask interface, 3) patient tolerance, and 4) patient compliance. Poor patient mask interface may result in face or mouth air leaks. High air flow is often intolerable and also results in loss of effectiveness. Chin straps, nasal prongs, better fitting face masks may decreases air leaks. Other factors influencing patient tolerance and compliance include lifestyle, mask claustrophobia, rhinitis, nasal obstruction, and the level of positive pressure.

A variety of CPAP machines have been developed to minimize patient intolerance. For example, patients who have difficulty initiating sleep on nasal CPAP can utilize "ramped" CPAP devices which gradually increase applied pressure so that maximum pressure is achieved after sleep onset. Advances and applied pressure may include "smart machines" that self titrate the pressure to the patient. Warm or cool humidity may help improve comfort and reduce nasal symptoms. Many patients, who don't tolerate high expiratory pressures, use CPAP machines that apply a lower pressure value during expiration.

1.4 Telemedicine for the Pathologies of the Respiratory System

Proactive and consistent primary care for chronic diseases of the respiratory system can reduce hospitalizations. Optimal chronic disease management requires focusing on maintenance rather than merely acute rescue (59). Continuous monitoring of patient's conditions and treatment adjustment should be performed in order to assure the best treatment to the patient, follow disease evolution, avoid acute episodes and optimize the delivered therapy, both pharmacological and ventilatory.

Telemedicine can be an effective tool for patient home monitoring of disease progression, avoid acute episodes, treatment optimization, and to improve patient's self management and self awareness of disease evolution. Telemedicine can also be used as a diagnostic tool, for example home oximetry is an effective practical method for screening sleep hypoxia in COPD patients (17).

Furthermore Telemedicine can be employed in case an acute condition has not been avoided. Early assisted discharge of exacerbated patients can be implemented in order to reduce costs (60) and to allow the patient recover in a familiar environment, useful for a quicker healing. A Telemedicine platform at patient's home can better monitor patient's in such a condition.

Nowadays only standard clinical devices are used at patient's home without healthcare professionals support, thus trying to gain specific measurements of significant physiological parameters. This approach showed its intrinsic limits, as the devices used are designed only for the use under strict supervision in a clinical ambient. Therefore the measurement taken at home cannot be considered reliable, hence providing not significant information.

There is no such thing as automatic intervention at patient's home, but autotitrating CPAP devices, which are used once for patient and are intended only as burden relievers for hospital PSG waiting lists, not for real continuous monitoring and constant intervention for automatic therapy adjustments directly at patient's home.

The infrastructure needed to connect the physician with the patient is very complex a requires particular agreements between the hospital, the telemedicine service provider and the communication line provider, making it difficult to implement rapidly at cheap costs.

Although few studies showed the efficacy of the use of Telemedicine applied to the respiratory pathologies, they're still based on very primitive technologies and architectures, such as the constant telemonitoring of COPD patients, based on the periodic administration of telephonic questionnaires and voice reporting of SpO_2 measurements (61) showed to be

effective in reducing exacerbations and consequently hospitalizations and patient's symptoms relieve.

Current Telemedicine projects have highlighted some difficulties involving patient and clinical board acceptance, infrastructures, economic and clinical effectiveness (62;63), but they also showed its potentialities that can be expressed addressing properly all these issues.

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CHAPTER 2

A NEW TELEMEDICINE APPROACH

In the last fifteen years the technology advancement, informatics development and ICTs expansion and improvement, brought to the wide availability and extended diffusion of cheap and functional technological instruments and communication services in the health care environment.

New, small and easy-to-use sensors based on old and edge-cutting techniques and methods have been realized to simply acquire specific physiological parameters, moreover broad and efficient communication services have been implemented.

Taking advantage of the use and the combination of these technologies it is possible to support the realization of a tool that is complex and articulate but also practical and easy to use, and that is able to assist the physician managing, monitoring and treating chronic patients, and that provides easy access to all patient's clinical information.

The Doctorate project is aimed to realize a Telemedicine platform based on a new Telemedicine model, a new approach able to face the increasing number of chronic patients that are treated at home, in an ageing population.

The proposed model accounts on the use of an approach on three different levels, tightly bonded among them by a feedback structure (see Figure 2.1).

The new model is based on one side on the development and use of new technologies to measure patient's significant parameters in a domestic environment. The acquired data are fused and computed by an artificial intelligence in order to perform the automatic intervention on therapy adjustments directly at patient's home.

On the other side the new model comprehends the possibility of a remote intervention by an automatic central decision server. The server is a concentrator that is able to collect, cross, analyse and evaluate all the data coming both from patient's house instruments, both from results of clinical exams and visits, and from previous patient's clinical history. Moreover the server can intervene in modifying the provided therapy to the patient with automatic and autonomous decision tools.

Finally the architecture modelled allows the simple and quick connection between the patient and the physician, thus to permit the clinical supervision and the possible remote intervention of the physician for therapy optimization.

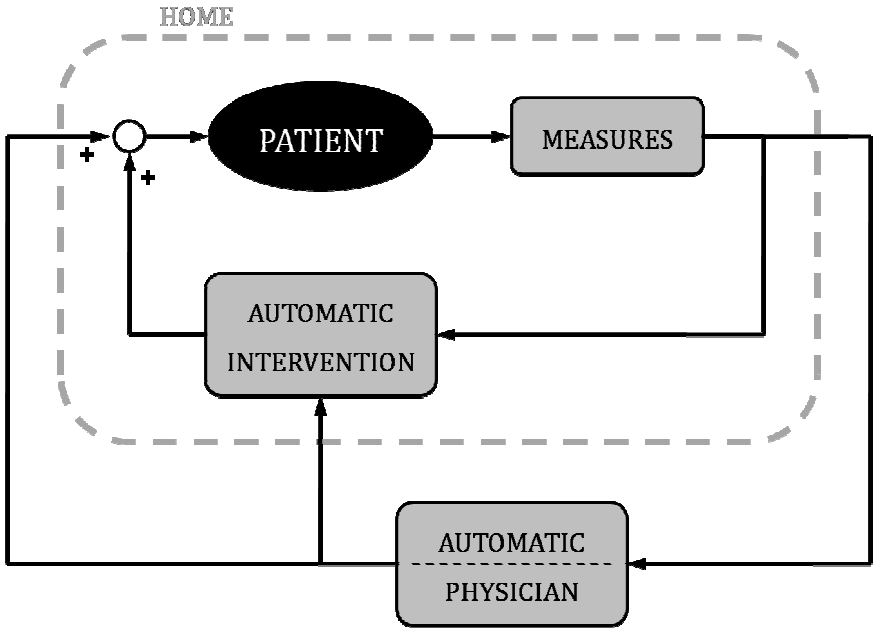

Figure 2.1: The model of the new Telemedicine approach.

The first fundamental step for the project development and the composition of the architecture, is the acquisition of the physiological significant parameters. This task can be carried out by the devices devoted to patient's treatment, like the mechanical ventilator, or by means of new instruments and sensors provided at patient's house able to sample the appropriate parameters.

The acquisition devices are designed expressly for domestic use by the patient himself and without physician supervision. These instruments are able to gain the necessary information in a non-invasive way and with the minimal patient cooperation. They must be simple, easy to use and adaptable to different conditions of the patient involved (Figure 2.2).

All the information collected must be catalogued, synchronized and conveniently stored by a device that acts as a centralizer.

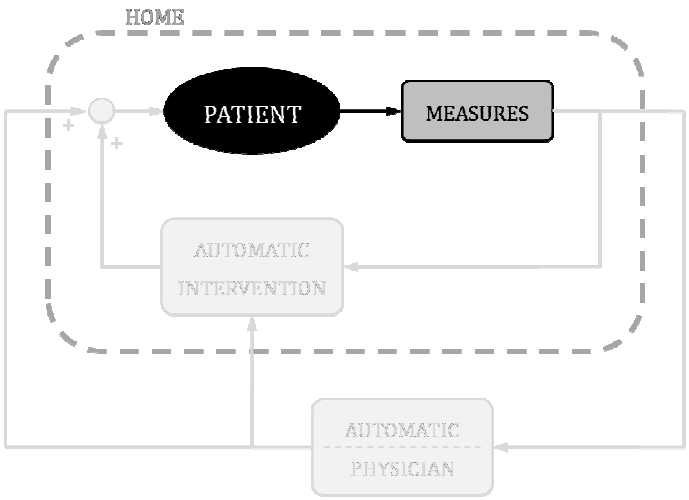

Figure 2.2: The new Telemedicine model highlighting the first block, Measures.

The collected information are analysed through the use of intelligent functions implemented inside the systems that provide the therapy, and inside the centralizer, in order to perform the continuous monitoring of patient's conditions.

Thanks to the use of particular procedures, the intelligent tools implemented inside the devices are able to monitor certain parameters in order to perform the automatic intervention on the therapy delivered to optimize it according to the conditions and necessities of the patient, without the supervision of any health care professional.

Moreover the monitoring function can be oriented to the identification of sudden alterations of particular parameters or life threatening conditions in order to alert the physician at the right time (Figure 2.3).

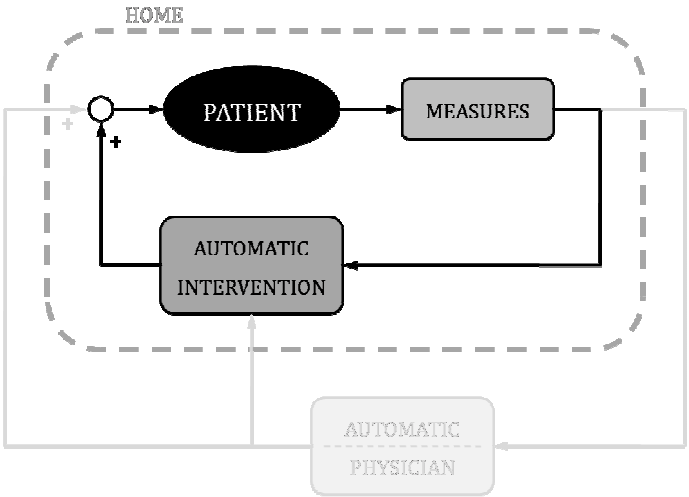

Figure 2.3: The new Telemedicine model highlighting the first ring, Automatic Intervention.

The designed architecture allows the physician to have access quickly and simply both to the previously acquired and stored data of a single patient and also to the real time traces of particular parameters. This consents the physician to perform complete monitoring of patient's conditions, to view and evaluate both the raw data and the pre-analysed, classified and summarized data, therefore more manageable and interpretable.

As the physician can monitor and evaluate patient conditions, he is also provided with tools that allow him to modify the patient's therapy at distance in order to optimize the treatment directly at patent's house from the hospital (Figure 2.4).

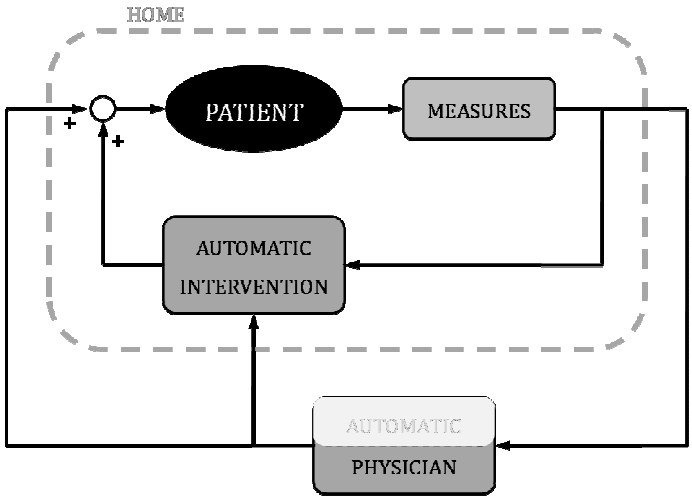

Figure 2.4: The new Telemedicine model highlighting the third ring, the remote physician's intervention

Finally, thanks to an Internet connection all the information acquired at patient's house are collected and stored by a remote central server, which also concentrate information and results of clinical exams originating from the hospital, about test and clinical history of the patient.

The central remote system is endowed of an intelligence for the evaluation of the acquired information. In this case the central system performs a deeper and more detailed analysis crossing and fusing the available information thanks to use of new procedures, data mining techniques and new developed clinical guidelines. It takes into account both data coming from patient's house, and considering their variation, evolution and clinical variability and data originated by the progress of clinical exam results, of specialist visits.

As the central system is able to perform such detailed analysis, very wide in terms of time and parameter's diversity, it is provided with decisional intelligence able to connect to the devices at patient's house in order to intervene and, automatically and conveniently, modify the provided therapy with the purpose of the optimization of the therapy itself (Figure 2.5).

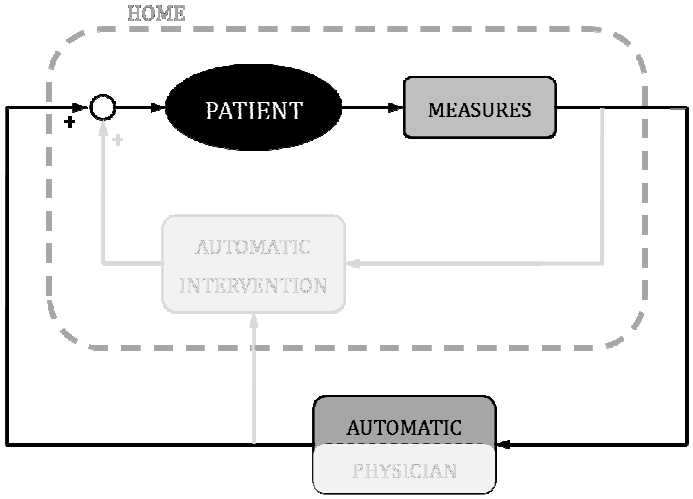

Figure 2.5: The new Telemedicine model highlighting the second ring, the remote automatic intervention.

The new Telemedicine system designed and realized during the Doctorate program is thought to be composed of an architecture simple but robust, realized on different levels.

It is provided with new methods and technologies for sampling significant physiological parameters at patient's home. It has automatic intervention capabilities for the optimization of the delivered therapy. Data pre-analysis capabilities, and telemonitoring services together with availability of services for remote control and changes of the administered therapies, allow the physician to perform complete monitoring and therapy optimization.

It is a complex system but simple to be applied and easy to be used, and it is able to provide a valid support to the health care professionals managing a growing number of chronic respiratory patients.

CHAPTER 3

PATIENT'S PHYSIOLOGICAL PARAMETERS ACQUISITION

Nowadays Telemedicine project and devices mainly rely on parameters acquired at patient's home by means of readapted standard medical devices, and often under the supervision of health care professionals by phone connection (telespirometry, SpO_2…), or on telephonic administered questionnaires.

The absence of specific devices and technologies designed to be used at patient's home without the presence of the physician is a factor limiting the spread of telemedicine.

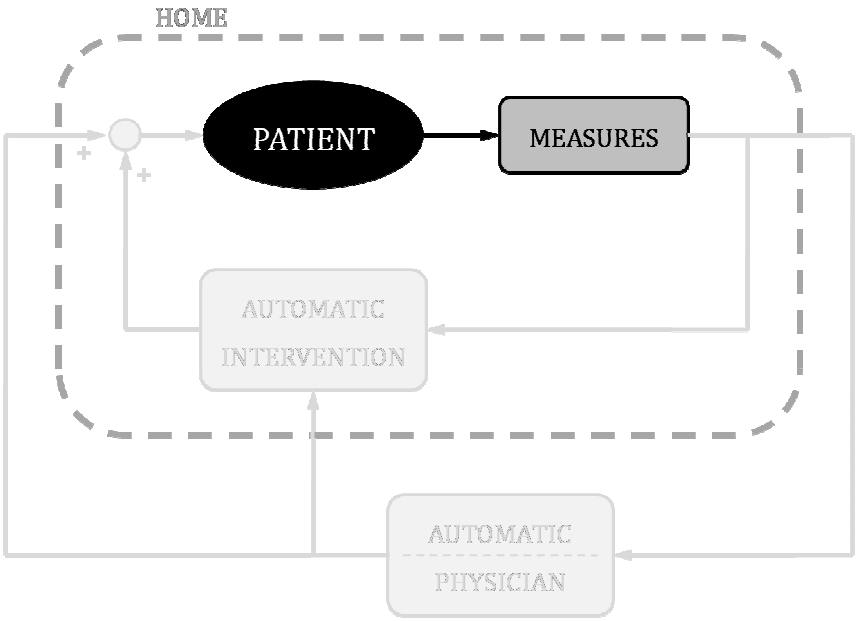

Figure 3.1: The new Telemedicine model highlighting the first block, Measures.

In the Doctorate project we designed and developed devices in order perform signals acquisition at patient's home Figure 2.2. A number of specific and generic parameters can be automatically acquired or by means of minimal collaboration of the patient. The parameters acquired are the basic health care parameters, common to most of the diseases, however we focused the ones that are related to respiratory diseases.

The first part of this Chapter is aimed at the presentation of the work carried out in the context of a European project called CHRONIOUS, in which we addressed the development of a wearable system in order to continuously acquire patient's vital parameters.

The second part describes the development of a technique for the measurement of new specific parameters for the assessment of the respiratory system, inside a home mechanical ventilator.

3.1 CHRONIOUS: The Patient Sensing Framework

CHRONIOUS is a FP7 European Community project that aims to create a platform for a generic health status monitoring schema, addressing people at risk or with chronic health conditions. The use of a multidisciplinary, sophisticated, and adaptive chronic disease platform that integrates state of the art sensors and services allows to cover both patients and healthcare professional's needs.

CHRONIOUS addresses a smart wearable platform, based on multi-parametric sensor data processing and fusion for monitoring people suffering from chronic diseases in long-stay setting. It is constantly monitoring parameters using audio observation methods and selected environmental and social context sensors while at the same time tracking their medical condition via vital signs sensors. In addition, the proposed platform offers interfaces for monitoring drug intake, dietary habits, weight and glycamia values, through the use the so called home patient monitor (HPM).

All data are stored in the system's repositories where CHRONIOUS has foreseen data exchange with healthcare facilities external legacy systems using well known and established standards, taking into account privacy and ethical issues concerning patient information. Healthcare professionals are provided with full access to the patient's information and data continuously stored from the patient's wearable devices, in order to perform the offline monitoring of patient's conditions at distance (Figure 3.2).

The wearable platform is composed of many different sensors and devices aimed to measure physiological parameters at patient's home. The aim of this first in vitro test is to test the feasibility and reliability of the sensors and to define methods and procedures to calibrate them, moreover to test the usability of the wearable system.

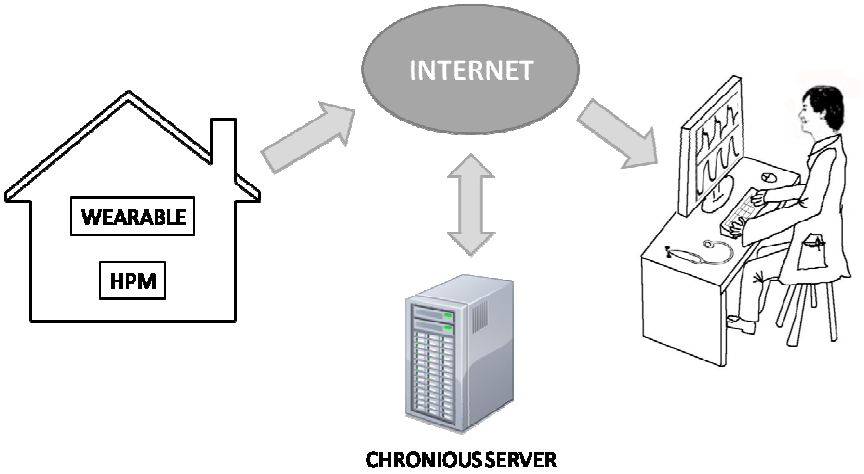

Figure 3.2: CHRONIOUS architecture schematic representation. The collected data at patient's home are stored in a server through the connection to the Internet. The physician can access to the server through a secure connection and monitor patient's conditions.

3.1.1 Setup: the Wearable Platform

The wearable platform is composed of a shirt, made of washable stretch-material, into which are sewn four electrocardiographic (ECG) electrodes, to continuously acquire three ECG leads, and two bands for respiratory inductive plethysmography (RIP) to acquire respiratory movements and volumes. A reflectance pulse oximeter is kept in contact with patient's skin by a special holder connected to the shirt that allows the sampling of arterial blood oxygen saturation (SpO_2) and heart rate (HR). A microphone for cough counting, a posture sensor with a step counter, a skin temperature, ambient temperature and humidity sensors are also included.

All the sensors are connected to a microcontroller based concentrator called Data Handler (DH). This device collects and transmits all data coming from the sensors via a Bluetooth wireless connection to a PDA or a personal computer (Figure 3.3).

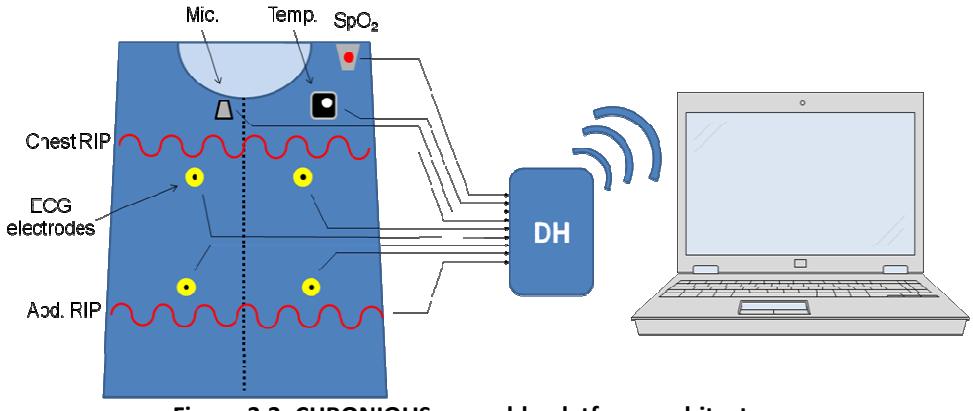

Figure 3.3: CHRONIOUS wearable platform architecture.

A device external to the shirt, that is a commercial flowmeter, is used for the calibration procedure of the RIP bands.

In the CHRONIOUS architecture the data coming from the data handler are collected by a small portable device, or PDA, which transmits the data to the central server thanks to the Internet connection provided by the SIM of the PDA itself, through a data communication contract via UMTS/GPRS. In order to test the wearable system the data sent by the DH are collected by a personal computer on which a program developed in Labview® allows the visualization in real-time and storing off the incoming data (see a screenshot of the developed software in Figure 3.4).

Figure 3.4: Labview® software interface for the acquisition of data transmitted by the data handler via Bluetooth for testing purposes.

The Shirt

The first version of the shirt was a commercial device called Lifeshirt® from VivoMetrics, but as it became unavailable another device has been developed. The new shirt is composed mainly of elastan, a synthetic fiber known for its exceptional elasticity and strength. A lateral zip is used to wear the shirt and an additional elastic band on the back at middle height assures tighter wear ability to guarantee ECG electrodes contact with patient's skin. A posterior pocket is used in order to contain the data handler and two different connectors assure cable connection with it.

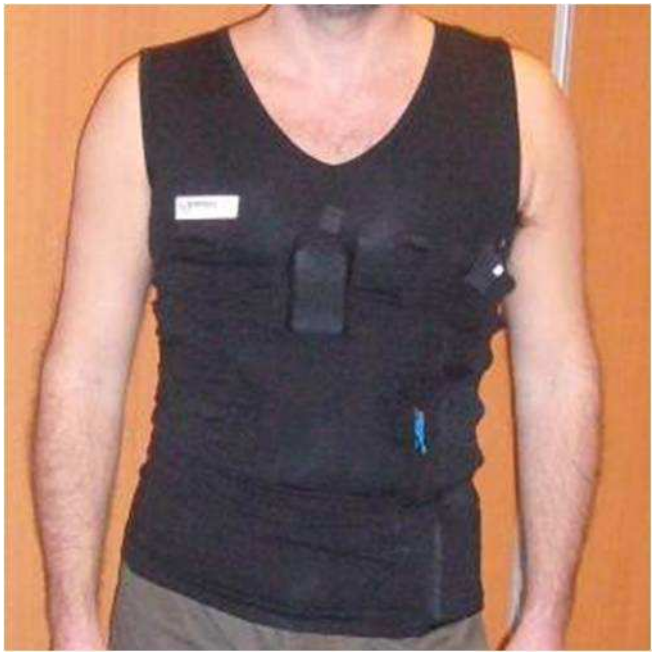

Figure 3.5: CHRONIOUS shirt, the second version.

The Pulse Oximeter

The shirt includes the measurement of pulse oximetry, a fundamental parameter for COPD patients because it provides the relative arterial blood oxygen concentration, which is indicative on patient's respiratory system functionality.

The sensor used is a reflectance pulse oximeter, which allows sensor placement on numerous body locations such as the chest, cheek, or forehead. Placement of the sensor on the forehead has shown greater sensitivity to SpO_2 changes during low perfusion situations compared to other peripheral body locations (1). Moreover, a thin skin layer coupled with a prominent bone structure helps to direct light back to the photodiode of the pulse oximeter, providing stronger reflex of emitted radiations (2). There are two significant problems involving the use of a reflectance pulse oximeter, one is measurement error due to motion artefacts (3), the second is that the signal is affected by pressure disturbances acting on the pulse oximeter probe, which can lead to the inability to measure relative blood oxygen concentration (SpO_2) and heart rate (HR) (2;4).

As the sensor must be inside the shirt, it has been chosen as placement site the shoulder. The position chosen reduces movements artefacts between the shirt and the sensor, due both to patient's movements and breathing, guarantees the right pressure between the skin and the sensor, and provides sufficient reflex to the emitted radiations by the sensor itself, thanks to the shoulder's bones (clavicle and acromion).

The standard attachment method for the used sensor, Nonin (Plymouth, MN) 8000RTM, secures the sensor by means of a medical adhesive.

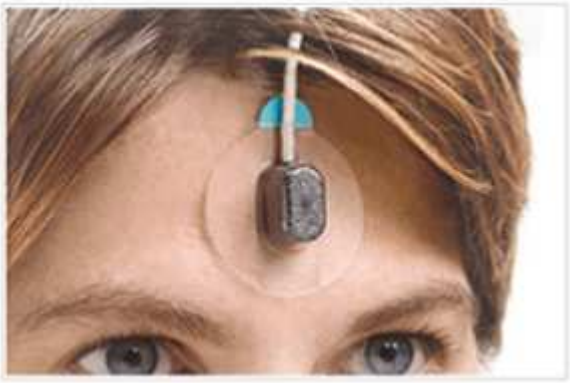

Figure 3.6: The NONIN reflectance pulse oximeter assured by means of an adhesive holder on the forehead.

The pulse oximetry data (SpO_2 and HR) are sampled at a frequency of 1Hz by the data handler from a NONIN sensor. Furthermore five service bits used to assess the status of the sensor, are collected and transmitted by the data handler:

- *Sensor Disconnect:* Sensor is not connected or sensor is inoperable
- *Out Of Track:* An absence of consecutive good pulse signals
- *Low Perfusion:* Amplitude representation of low signal quality
- *Marginal Perfusion:* Amplitude representation of medium signal quality
- *Artefact:* A detected pulse beat didn't match the current pulse interval

This control bits are displayed and can be used by the physician to monitor sensor status and reliability of data received.

Electrocardiographic Electrodes

The wearable system includes ECG signals in order to allow the physician to better understand patient's conditions. As it is not possible to gain a complete and exhaustive 12 leads ECG acquisition at patient's home without the supervision of trained personnel, it was necessary to make a compromise and this brought to the choice of using four electrodes in order to acquire the three basic leads, the Einthoven's triangle derivations (5) (see Figure 3.7).

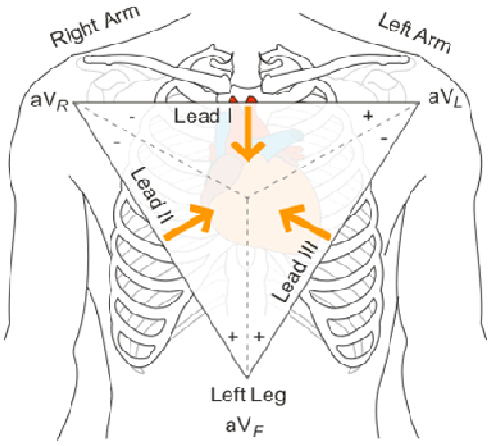

Figure 3.7: Einthoven triangle with the three ECG leads.

The ECG electrodes are directly sewn into the shirt and are made of a texture of silver and cotton. The electric signal is brought to the Data Handler through wires made on the same way, that is a binding of silver and cotton (see Figure 3.8).

Figure 3.8: ECG electrodes. On the left the sewn silver electrode, on the right the silver bindings that bring the signal to the data handler.

The optimal contact between the electrode and the patient skin is guaranteed only though the use of a conductive gel, which needed to be renewed every 30 minutes.

The four ECG electrodes have been positioned into the shirt in order to guarantee three ECG derivations taking into account patient's sex, BMI and shirt's shape characteristics that may affect electrodes to skin contact during some patient's movements (see Figure 3.9).

Each ECG lead is sampled at a frequency of 256Hz by the data handler, the which, with a computing algorithm, provides also the heart rate frequency value. Information about electrodes disconnection is provided with three status bits.

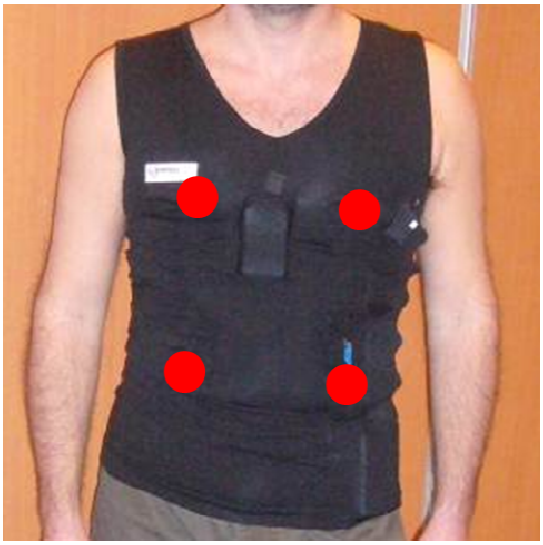

Figure 3.9: The position of the four ECG electrodes in shown in the figure by the red spots.

The Respiratory Inductive Plethysmography

Respiratory Inductive Plethysmography (RIP) is a technique that is able to measure lung volume changes and various respiration parameters (6). It is composed of two inductive coils of insulated electric wire sewn into the shirt and placed around the thorax and abdomen. The coils are connected to the Data Handler, through the which are supplied with an oscillator module that produces a sine wave of approximately 20mV of amplitude and 930 kHz and 850 kHz of frequency, respectively for thorax and abdomen coils. This module is in turn connected to a demodulator unit which outputs signals proportional to the cross-sectional area of each coil. Changes in cross-sectional area of each compartment produce variations in self-inductance of the wire, thereby changing frequency.

The frequency change is demodulated to produce an analogue voltage corresponding to the waveforms of ribcage and abdomen compartmental volumes as they change during respiration (7). A microcontroller performs the acquisition of the volume displacement traces continuously and an analysis software can be used to calculate volume changes and breathing rate. (see Figure 3.10).

The weighted sum of the ribcage and abdomen volume displacement signals is therefore proportional to the tidal volume (VT). Whereas uncalibrated RIP is a valuable means of assessing both respiratory timing and various qualitative aspects of ribcage and abdomen asynchrony, calibration is essential if quantitative changes in ventilation are to be assessed.

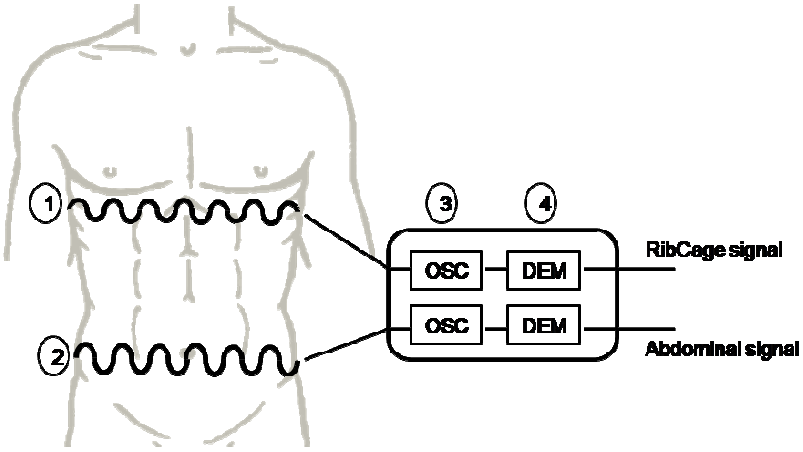

Figure 3.10: The respiratory inductive plethysmography system including the rib cage (1) and abdominal (2) sensor bands, the oscillator (3), and the signal demodulator (4).

In addition to the calibrated tidal volume the Data Handler also provides some computed breathing parameters, such as breath amplitude, minute ventilation, breathing rate, labour breathing index, breathing rate and inspiratory and expiratory times. Furthermore the data handler transmits RIP bands status information, that is if the bands are disconnected.

The Spirometer

In order to perform the calibration of the RIP a commercial spirometer used as a calibrated flowmeter, provided the calibrated mouth flow of the breathing subject. The spirometer, Sibelmed DATOSPIR MICRO C (Barcelona, Spain), is a battery powered stand alone device that transfers data through a Bluetooth connection. After the pairing process with a personal computer for the connection with the device, a software developed on purpose using Labview®, sends to the spirometer the start command that initiates the sampling of the calibrated flow signal, which is transmitted and stored on the computer.

Figure 3.11: The spirometer (DATOSPIR MICRO, Sibelmed, Barcelona, Spain).

The Data Handler

The Data Handler is a microcontroller based device developed by the Fraunhofer Institute that collects data coming from all the devices that compose the wearable system.

The Data Handler is connected to the SpO_2 sensor, the RIP bands, the ECG electrodes, the microphone, the temperatures and humidity sensors, and to the activity sensor through a multiple cable (see Figure 3.12).

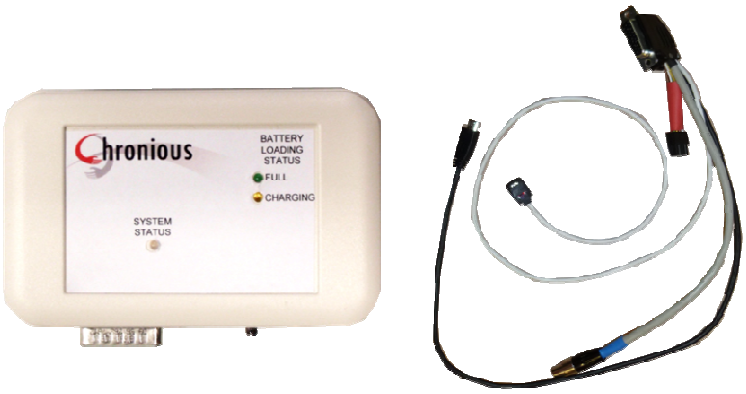

Figure 3.12: CHRONIOUS Data Handler, on the left, and the connecting cable on the right.

All the signals coming from the sensors are collected and stored in a very short buffer, in order to be sent via a Bluetooth connection to a PDA or a personal computer. After Bluetooth connection and pairing, the data handler starts sampling the signals as soon as it receives the "start" command from the connected device, and stops sampling after the special command is received. All incoming data are bundled in packets containing timestamp information, and error debugging headers. The communication protocol is proprietary and has been used to develop the interface software for the personal computer. The data handler is powered by a Li-ION cells battery that guarantees an autonomy of 16 consecutive hours of data acquisition and transmission.

Each parameter is acquired at a different sampling frequency, see Table below.

Data Type	**Sampling Frequency**
ECG	256 Hz per lead
ECG Heart Rate	0.5Hz
RIP	12.5Hz
SpO_2	1Hz
Cough Counts	On event

Temperature and Humidity	0.1Hz
Activity report data	On demand
Activity change data	On event
Event status	On demand
Sensor status	1Hz
Acknowledge	Response to each PDA command

Table 3-1: Parameters nnd the relative sampling frequency used to acquire signlas by the Data Handler.

3.1.2 Methods: the Experimental Setup

The Data Handler is used to acquire simultaneously the signals coming from the shirt: ECG, RIP, SpO_2 and temperature sensors. The data are temporarily stored and sent to a computer via a Bluetooth connection.

The spirometer (SP) provided by Sibelmed transmits via a Bluetooth connection to a second computer. A preheated pneumotachograph (PNT) signal is acquired by a third computer. In this phase the SP is connected in series of a PNT, thus the air breathed by the patient passes through both the devices.

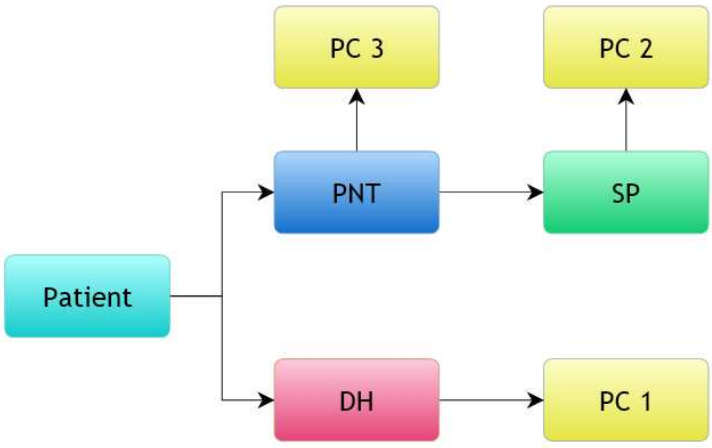

Figure 3.13: Scheme of the experimental setup.

The sampling rate is set to 50 Hz for both SP and PNT, while the sampling rate for the RIP of the Chronious wearable is set to 16 Hz.

The software used for data acquisition from the Data Handler and from the spirometer have been realized in LabVIEW.

3.1.3 Methods: experimental protocol

Before every measurement the PNT was calibrated as described in the previous section. The subject was asked to wear the t-shirt during the whole day, without changing normal day operations, movements nor habits. Every two hours the subject underwent a measuring session. During these sessions, the subjects were asked to breathe through the PNT connected in series to the handheld spirometer in both seated and supine positions. In this way, thoracic and abdominal volume changes were measured by RIP and simultaneously at the mouth by SP and PNT. Before each acquisition, in order to acquire the three electrocardiographic signals we put conductive gel on the electrodes, Even if ECG electrodes embedded in the t-shirt were dry electrodes, conductive gel was used to improved the signal since the contact area between the skin and the electrodes was not large enough to provide a good signal to noise ratio.

During all the experiments, the subject was asked to perform the following respiratory manoeuvres in sequence:

1) One inspiratory capacity (IC)
2) Four minutes of normal breathing
3) Increasing and decreasing breaths volume manoeuvre
4) Few seconds of normal breathing

The IC is used for the synchronization of the signals collected during the data analysis phase, from SP, PNT and the RIP. The increasing and decreasing volumes manoeuvre was performed by asking the subject to breath at increasing and then decreasing tidal volumes.

The calibration was computed at the first acquisition, and then applied in the following acquisitions during the day.

3.1.4 Methods: Data Analysis

Four healthy subjects were studied. In this phase we collected respiratory parameters from the Data Handler expressed in digits, from the Spirometer (SP) and the Pneumotachograph (PNT). The SP and PNT measured the air flow at the subject's mouth in litres per second.

As we described in the section of the respiratory inductive plethysmography, the RIP data are not calibrated. In order to calibrate the RIP of the CHRONIOUS wearable we adopted

two different methods. Both methods are based on the two-compartments model for motion of the respiratory system.

Calibration Method 1

The identified and validated calibration procedure (7;8) involves a two-stage process composed of a phase used for determining the relative contributions of ribcage and abdomen to each breath and then computing a proportionality coefficient in order to scale the weighted sum to actual tidal volume (8).

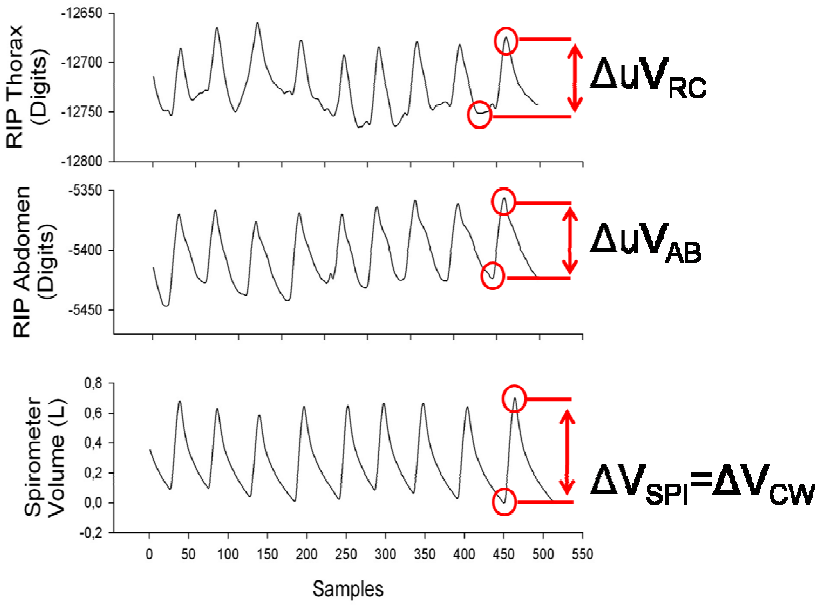

Figure 3.14: RIP calibration signals. From the top uncalibrated Thorax signal ($u\Delta V_{RC}$), uncalibrated Abdomen signal ($u\Delta V_{AB}$) and the reference calibrated signal coming from a spirometer (ΔV_{SPI}).

The ribcage (ΔuV_{RC}) and abdominal (ΔuV_{AB}) uncalibrated volume signals are composed in a single total contribution and compared to the calibrated volume (ΔV_{SPI}) trace obtained through the integration of the calibrated flow trace provided by the spirometer.

Assuming that the subject is breathing with a constant tidal volume, for every breath, ΔuV_{RC}, ΔuV_{AB} and ΔV_{SPI} are computed and inserted into the following equation:

$$\Delta V_{CW} = M[K(\Delta uV_{RC}) + \Delta uV_{AB}]$$

Where ΔuV_{CW} is ΔuV_{SPI}. The calibration coefficients K, M and Q are computed using a Linear Least Squares algorithm and sent to the Data Handler in order to provide calibrated volumes.

Calibration Method 2

In this case, instead of taking into consideration only the tidal volume values, we considered the whole dataset of the acquired traces, and we applied the following equation:

$$\Delta V_{cw} \cong M[K(\Delta V_{RC}) + \Delta V_{AB}] + Q$$

The calibration coefficients M, K and Q are computed using a Linear Least Squares algorithm.

3.1.5 Results

The respiratory parameters are evaluated on four healthy subjects by comparing the data collected from the acquisition system with the measurements provided by the spirometer (SP) and the pneumotachograph (PNT) as references. The respiratory parameters coming from the RIP have been calibrated with two methods, and evaluated by a linear regression analysis.

In Figure 3.15 are shown the results of the tidal volume of RIP, calibrated using SP as a reference, of four subjects obtained with the first calibration method applied on the acquisitions following the calibration acquisition. The Tidal volumes computed from the wearable system (RIP) versus tidal volumes computed from the SP traces of the whole working day in seated and supine positions are shown in Figure 3.15. The regression line showed poor correlation between the two sets of data: r^2=0.10, m=0.318 q=0.317. The regression varies significantly with posture, as in sitting and supine position respectively we obtained sitting: m=-0.897, q=1.025; supine: r^2=0.92, m=0.332, q=0.274.

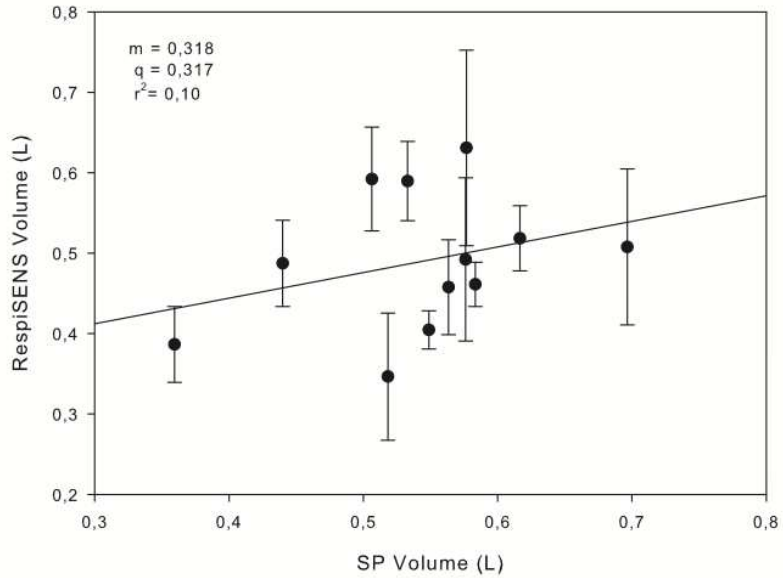

Figure 3.15: Results of calibration by SP, with the first method.

We performed the linear regression analysis also on the tidal volume of RIP calibrated using as a reference data of the PNT. In Figure 3.16 are shown the results of four subjects obtained with the first calibration method applied on the acquisitions following the calibration acquisition. The data used to plot the Figure are tidal volumes computed from the wearable system (RIP) versus tidal volumes computed from the PNT traces of the whole working day in seated and supine positions. The regression line showed no correlation between the two sets of data: r^2=0.004, m=0.087, q=0.483.

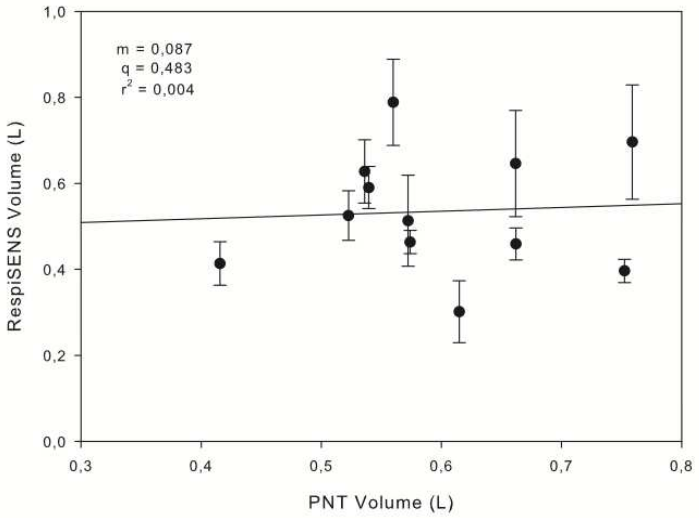

Figure 3.16: Results of calibration by PNT, with the first method.

The second method of calibration shows better correlation between the volume signals produced by RIP and the volume measured by SP and PNT. The second method uses the whole data of the traces of uncalibrated RIP, the flow trace of the SP and of the PNT. In Figure 3.17 are shown the results of the tidal volume of RIP calibrated by SP obtained with the second calibration method.

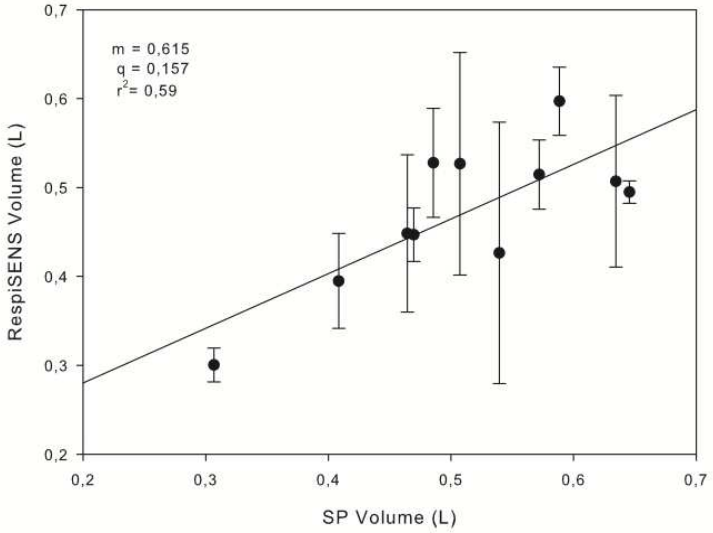

Figure 3.17: Results of calibration by SP, with the second method.

The data used to plot Figure 3.17 are tidal volumes computed starting from the wearable system (RIP) versus tidal volumes computed starting from the SP traces of the whole working day in seated and supine positions. The regression line showed still poor correlation between the two sets of data: r^2=0.59, m=0.615, q=0.157

In Figure 3.18 are shown the results of the tidal volume of RIP calibrated using PNT as a reference, obtained with the second calibration method applied on the acquisitions following the calibration acquisition. The data used to plot the figure are tidal volumes computed starting from RIP versus tidal volumes computed starting from the PNT traces of the whole working day in seated and supine positions. The regression line showed poor correlation between the two sets of data: r^2=0.14, m=0,573 q=0,171.

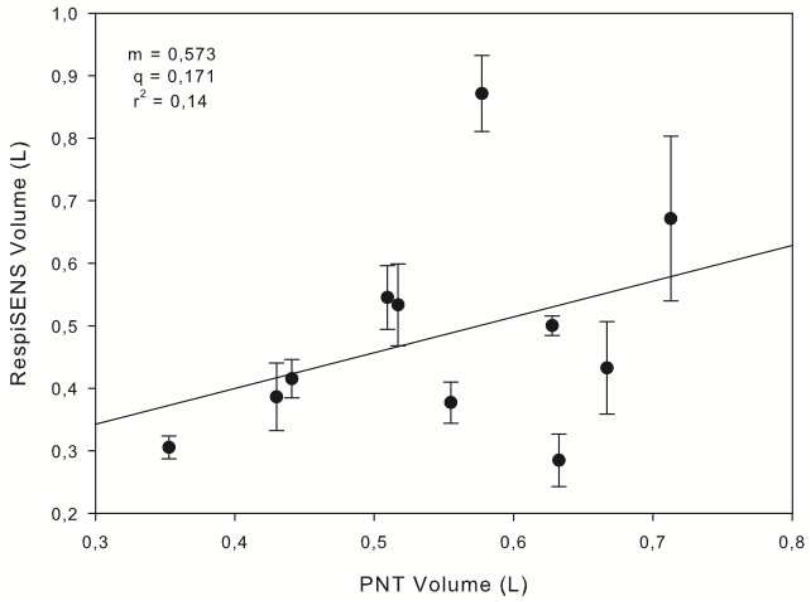

Figure 3.18: Results of calibration by PNT, with the second method.

During the tests we registered also the electrocardiographic signals, the oxygen saturation and the heart rate. We identified PQRST waves within the three derivations in all subjects, and values of oxygen saturation and heart rate compatibles with the subjects studied.

This test phase allowed us to develop the procedures and functions to compute the calibration of the system by the spirometer. Moreover, this phase of test allowed us to assess the set up for the clinical validation on COPD patients and to test the wearable system. In fact, we observed that the on the females the shirt wasn't tight enough, even if we used the new shirt designed to be more adherent on the thin people, and the signals of the two respiratory bands weren't satisfactory. Moreover the ECG signals were not still satisfactory, especially during any kind of movement, and we had to continuously put the conductive gel on them to guarantee skin contact.

3.2 Respiratory System Measurements: the Forced Oscillation Technique

Expiratory flow limitation (EFL) in COPD patients promotes dynamic hyperinflation, leading to respiratory muscle inefficiency, patient discomfort and reduced exercise tolerance (see Chapter 1). The identification of the presence of the flow limitation and its level is an important tool to understand patient's conditions.

Forced oscillations technique is an instrument able to detect and quantify the EFL condition. The implementation of the FOT inside the home mechanical ventilator used by the patient for therapy, would allow the identification of the degree of obstruction in COPD patients breath by breath.

3.2.1 Expiratory Flow Limitation Assessment

The currently available techniques to detect the presence of expiratory airflow limitation (EFL) can be divided into two categories, invasive and non-invasive techniques. This work is focused on two techniques that are the Mead and Whittenberger method, part of the first category and the forced oscillation technique which is a non-invasive technique.

The Mead and Whittenberger method

In 1953 Mead and Whittenberger (M&W) proposed a method for the measurement of the physical properties of the lungs during spontaneous respiration (9). We refer to the motion equation of the respiratory system that during quiet breathing, since the inertance of the system can be neglected, can be rewritten as:

$$Ptp(t) = EV(t) + R\,\dot{V}(t)$$

where, Ptp is the transpulmonary pressure (Ptp = Pm-Ppl) and V is the volume relative to FRC. The elastance E is the reciprocal of the compliance of the respiratory system. R is the resistance of the air flowing in the airways.

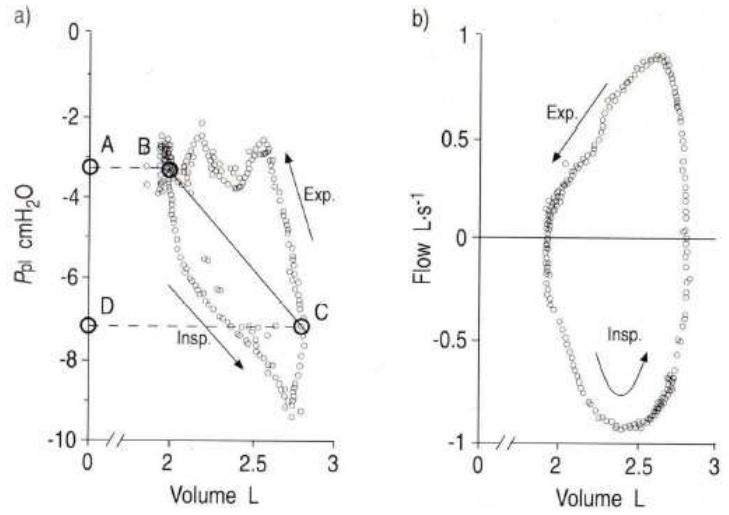

Figure 3.19: Pressure-volume curve: it is used to estimate the elastance E. B and C are the points where the flux is zero (a); flow-volume curve (b).

The Pm and flow are measured at airway opening and the pleural pressure is estimated by measuring the oesophageal pressure. To establish the elastic component, the volume–pressure curve (Figure 3.19) is considered: in the points where the flow is zero (B e C) the transpulmonary pressure expresses only the elastic properties of the lungs. The elastance is estimated as:

$$E = \frac{\Delta Ptp}{\Delta V}$$

Where ΔPtr and ΔV are, respectively, the pressure and volume difference between the end-inspiration and the end-expiration points (B and C). To measure the resistive term R, the hypothesis is that the elastance is independent of the lung volume: it's plausible during normal breathing. From the pressure-curve we get the elastic component:

$$\text{Pel}\,(t) = \text{E}\,\text{V}\,(t)$$

The resistive component of Ptp (Pfr) is obtained as difference between Ptp(t) and Pel(t). Because $\text{Pfr} = Flow \cdot R$, plotting Pfr versus flow we can obtain R by the slope of this curve.

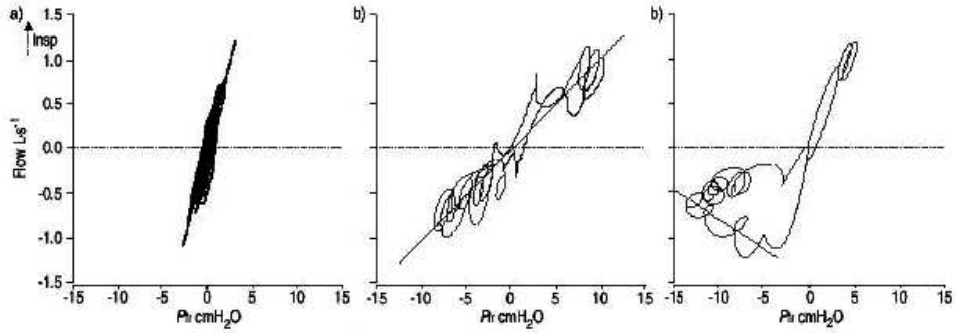

Figure 3.20: M&W. Flow versus Pfr: health breath (a); non_EFL breath (b); EFL_breath. The slope of the curve is the reciprocal of R.

In patients who are flow limited at rest, the curve presents a typical shape, with the linear relationship preserved during inspiration and a clockwise loop during expiration in which the decrease in pressure is followed by a decrease in flow, clearly demonstrating the flow limitation (see Figure 3.20). Therefore this technique allows classifying each breath as flow limited or non flow limited on the basis of the graphical examination of the above-said curves. However, this method presents the disadvantage of the invasive character, the measure of pleural pressure, which is sampled thanks to an oesophageal balloon inserted through the nose, into the oesophagus and properly inflated, and connected to a pressure sensor.

The forced oscillation technique

The respiratory impedance can be measured using the forced oscillation technique (FOT). The FOT which was proposed in the 1950s (10), is based on applying a small-amplitude oscillation pressure at the mouth. A possible instrumentation set-up needed for the FOT is showed in Figure 3.21.

The stimulus is generated by a loudspeaker and applied to the subject either by a mouthpiece or by a nasal mask. In the first case, the subject wears a nose clip and an operator firmly supports his cheeks in to limit the art factual role of the upper airways shunt.

In order to measure the $\dot{V}ao$, the mouthpiece (or the nasal mask) is connected to a pneumotachograph. The pressure is measured immediately after the mouthpiece or directly to the nasal mask.

The pneumotachograph is in turn connected to a T-piece with one side connected to the loudspeaker, the other one to a low-resistance high-inertance tube that allows the subject to breathe without significant loss of the forcing signal. However this tube greatly increases the

equipment dead space. Therefore, the system is connected to a vacuum generator that extracting the expired air reduces the dead space of the equipment.

To record the data and control the loudspeaker, an A/D-D/A board connected to a personal computer can be used.

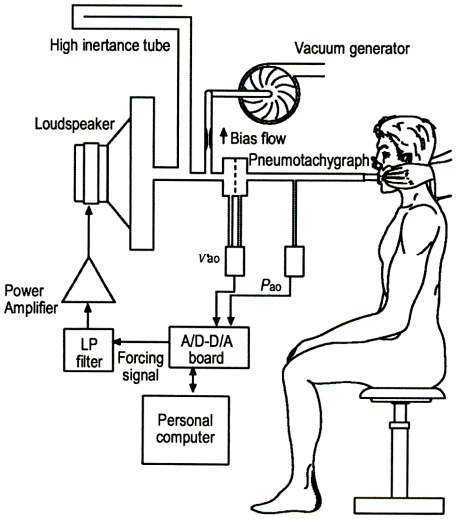

Figure 3.21: Instrumentation setup for the measurement with the forced oscillation technique.

Using the FOT the patient's respiratory impedance can be determined by simply fitting of the mechanical response on a model of the respiratory system and the definition of the mechanical properties of the system can be determined by identifying of the model parameters.

The model the method refers to is the T-network model proposed by DuBois et al (10). In this specific two-port model (Figure 3.22):

- The lung and chest wall are modelled by an inertance-resistance-capacitance series: their impedance is Zt;
- The compressibility of the alveolar gas is modelled by a capacitance Cg;
- The airways compartment is represented by an inertance-resistance series: Zaw.

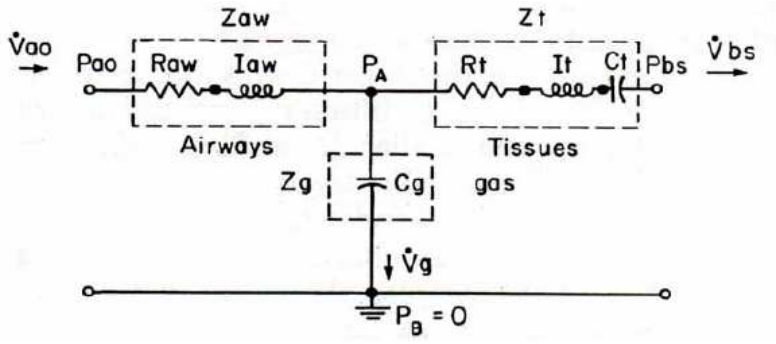

Figure 3.22: Model of T network accounting for airway impedence (*Zaw*), tissue impedance (*Zt*) and gas compression (*Zg*). (Raw), airway resistance; (*Iaw)*, airway inertance; (*Rt)*, tissue resistance; (*It)*, tissue inertance; (*Ct)*, tissue compliance (lung + chest wall); (*Cg)*, gas compressibility; *Pb* atmospheric pressure; ($\dot{V}$ *g*), alveolar gas flow; (*Pbs)*, body surface pressure; ($\dot{V}$ *bs*), body surface flow; (*Pao)*, airway opening pressure; ($\dot{V}$ *ao*), airway opening flow.

The oscillation frequency is much higher than the breathing rate to exclude the muscle activity. The ratio between the pressure (Pao, measured either at the mouth or at the nose) and flow ($\dot{V}$ ao) signals at the mouth is the input impedance of the respiratory system (Zrs):

$$\text{Zrs} = \frac{Pao}{\dot{V}ao}$$

By stimulating this system at the airway opening, assuming Pbs = Pb and considering that Zt is smaller that Zg (i.e Zg can be neglected), we can simplify the circuit (Figure 3.23(a)). If we define Rrs = Raw + Rt, Irs = Iaw + It and Crs = Ct, the circuit becomes as in Figure 3.23(b). It is a second order system: several data demonstrate that, in healthy subjects, the respiratory system approximately behaves as a second order system (10).

Thus the impedance of the respiratory system (Zrs) has two components: respiratory resistance (Rrs) and reactance (Xrs):

$$\text{Zrs} = Rrs + \text{j}\left[\omega Irs - \frac{1}{\omega Crs}\right]$$

In a simple interpretation, Rrs is attributed to airways and tissue resistances, whereas Xrs is determined by the inertial and compliant properties of the respiratory system (11).

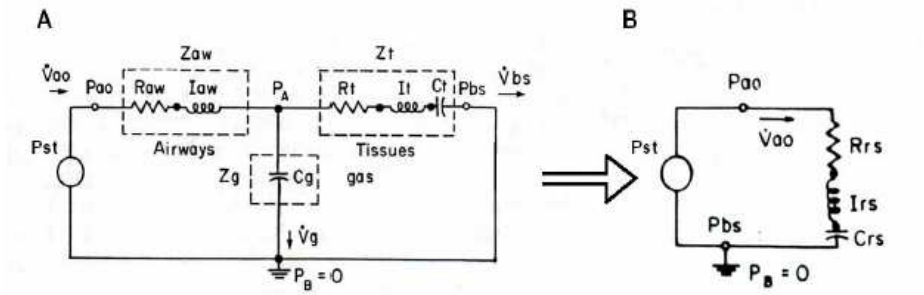

Figure 3.23: A**. Model of T-network with a stimulus generator applied to the airways opening.** B: **Equivalent model by neglecting Cg.**

The FOT and EFL assessment

In 2004 for the European Respiratory Journal (ERJ), Dellacà et al. (12) presented interesting novel data showing that FOT can be useful for no invasively detecting EFL during spontaneous breathing. The method is based on the measurement of the respiratory impedance

at the frequency of 5 Hz and on the examination of the changes of Rrs and Xrs during tidal breathing. At this low frequency, the term representing the inertance can be neglected so that, the reactance can be considered as depending only on the compliance on the respiratory system.

In healthy subjects both the resistance and the reactance show an oscillating time-course depending on the volume-dependence of both the resistance and the compliance. Flow limited subjects still present these swings, but they are wider than in healthy subjects. Particularly, they show large differences between the inspiratory and the expiratory reactance, whereas the resistance differences, although greater than in healthy subject, does not (Figure 3.24).

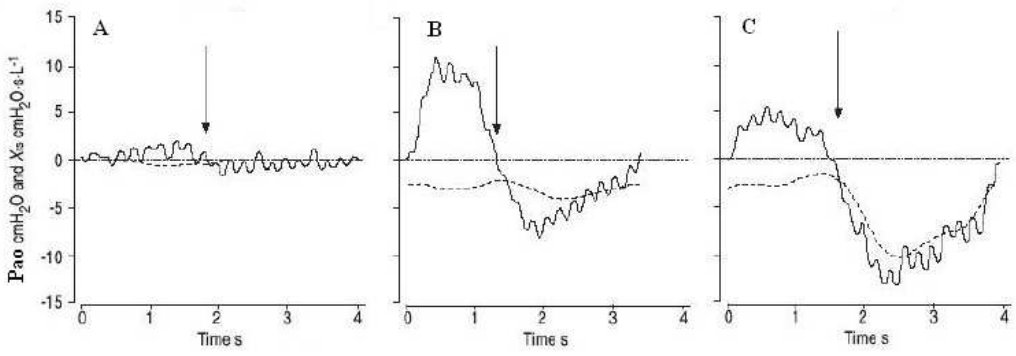

Figure 3.24: Pao versus time (continuous line), Reactance versus time (dot line): health breath (a); no_EFL breath (b); EFL_breath. Arrow indicates end of inspiration

Patients who are flow limited, develop choke points somewhere in their airways. Thus the impedance measured by FOT is only a measure of the mechanical properties of airways downstream from the choke points. This is because a change in pressure cannot be transmitted upstream through the choke points and thus only the downstream airways are oscillated (13). Furthermore, the mechanical properties of the airways are not homogeneous along the treachobronchial tree, with the resistance becoming smaller as we proceed toward the alveoli and the compliance bigger.

Therefore, since the choke points develop only during expiration, the respiratory impedance will express the mechanical properties of overall system only during inspiration, whereas during expiration only that part of the tracheobronchial tree prior to the choke points can be assessed. This implies that, because of the exclusion of the more compliant peripheral airways that greatly contribute to lower the total compliance, the value of the expiratory reactance will become more negative than during inspiration. The same mechanism happens for the resistance but, since the peripheral airways, because of their very low resistance, give a little contribute to the total resistance, the swing between its value during inspiration and the one during expiration is less evident.

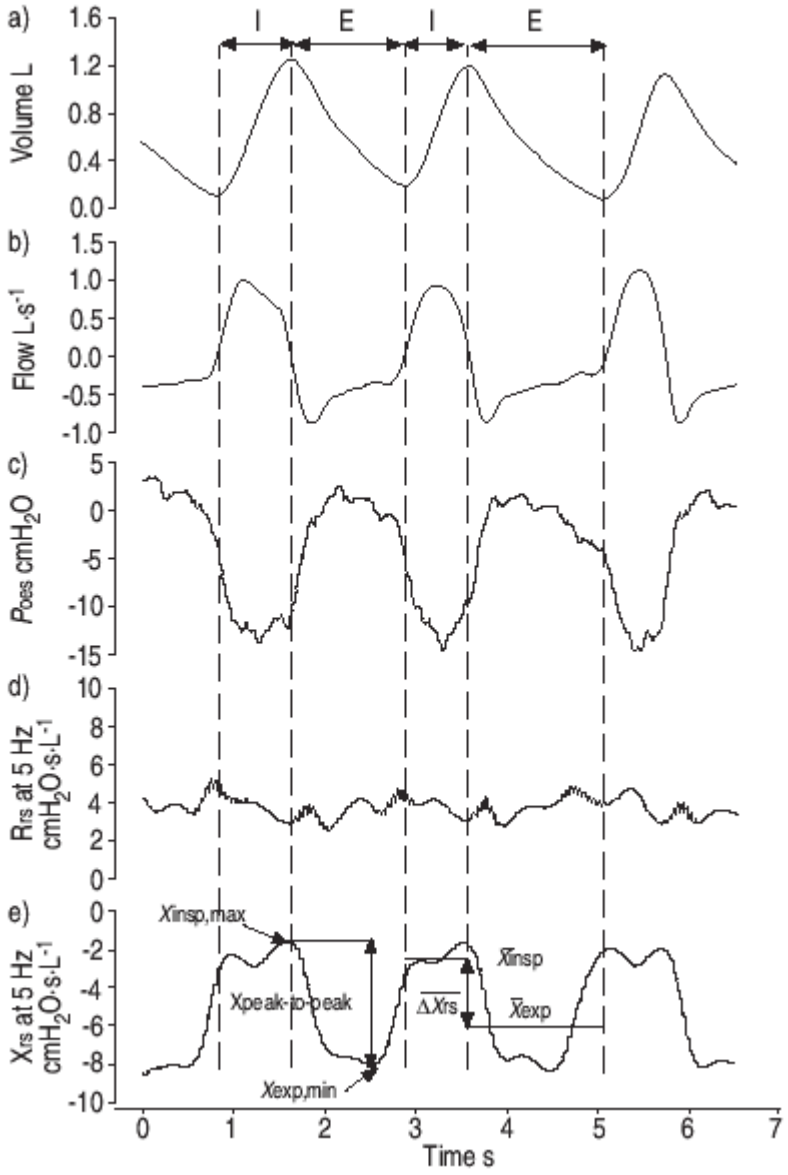

Figure 3.25: Experimental tracing from a representative flow-limited patient and definition of the indices used to characterise the respiratory system reactance time course during a single breath

Four different indices (Figure 3.25) based on the anticipated reactance change are used to detect EFL (12):

- *Xexp*: the mean value of Xrs during expiration;
- *Xexp, min*: the minimal value of Xrs during expiration;
- ΔXrs the difference between the mean value of Xrs during inspiration (Xinsp) and expiration (Xexp);
- *Xpeak-to-peak*: the difference between the maximal value of Xrs during inspiration (Xinsp, max) and Xexp, min.

Different thresholds were applied to the values of each index (Xexp, Xexp_min, ΔXrs and Xpeak-to-peak) computed breath-by-breath. Thus a breath is considered EFL if:

- *Xexp* is less than -5.4 cm $H_2O \cdot s \cdot L^{-1}$;
- *Xexp,min* is less than -7.1 cm $H_2O \cdot s \cdot L^{-1}$;
- ΔXrs is bigger than 2.8 cm $H_2O \cdot s \cdot L^{-1}$;
- *Xpeak-to-peak* is bigger than 6 cm $H_2O \cdot s \cdot L^{-1}$;

ΔXrs seems more suitable to be used as a clinical tool to individuate EFL. It's so because it is based on a relative change rather than on an absolute value, it is less dependent on the intra-subject variability than the other indices. In fact, whatever the condition of the patient, the difference between the impedance of the shunt pathway due to the airway wall compliance (measured by expiratory Xrs when EFL is present) and the open lung (measured by Xrs during inspiration) is so high (approximately one order of magnitude) that even differences in airway wall mechanical properties due to intra-subject variability and to disease should only marginally affect the change in Xrs during expiration.

These parameters should not be used only as inclusion-exclusion criteria, but also as quantitative indices of the degree of EFL. In fact, Xrs should fall as each new choke point develops by an amount dependent on the elastic properties of that part of the trecheobronchial tree subtended by the airways in which the choke point occurs.

3.2.2 FOT and Impulse Oscillometry

Impulse oscillometry is a non-invasive technique based on the same principle of the FOT, the application of low amplitude pressure stimuli at the mouth of the patient, superimposed the spontaneous breathing, used to assess respiratory system impedance. IO stimuli is a pressure impulse (a rectangular waveform) at 5Hz, very different in terms of frequency domain from a single sinusoidal waveform.

A commercial device, the Jaeger impulse oscillation system, is based on this method and it provides data-analysis and an elaborate report, containing total respiratory system resistance (Rrs) and reactance (Xrs) at a wide range of frequencies. It also contains estimations of central

and peripheral pulmonary mechanics based on a simple model. However, only limited data have been published on this technique and it have never been validated for EFL detection.

In order to understand which would be the better and more reliable technique to use for EFL detection, we performed a clinical test on COPD patients with the two systems, FOT and IOS, both the which performances were evaluated.

3.2.2.1 Materials and Methods

Patients

We recruited clinically stable and hospitalized COPD patients in accordance with the standard diagnostic guidelines (14) who were ex-smokers. They omitted their short- or long-acting bronchodilators for at least 12/24 hours, as appropriate, before the study. The study was approved by the institutional research ethics committee, and written informed consent was given by each subject.

Measurements

Pulmonary function tests were performed in a constant volume body plethysmograph (Masterlab, Jaeger, Würzburg, Germany). We report FEV_1, FVC, FEV_1/FVC, inspiratory capacity (IC), peak expiratory flow (PEF) both as absolute values and % predicted, before and after the administration of a broncodilator. Predicted values for flows and volumes were those recommended by the European Respiratory Society (15).

We measured breathing parameters using a commercial system (Jaeger, MasterScreen IOS, Hoechberg, Germany), which provided calibrated data of mouth pressure (P_{AO}) and flow (V'_{AO}) sampled at a frequency of 200Hz and recorded onto a personal computer.

Experimental setup: sinusoidal and impulse oscillations

Patients were subjected to two different pressure forcing signals: 1) a pulse pressure waveform and 2) a sinusoidal 5Hz pressure signal, both having a the peak to peak pressure amplitude measured at the mouth of ~1-2 cmH_2O and being over imposed the normal breathing of the patient.

In order to maintain the same tubings and connections to the patient both the pressure signals were transferred from the generating device to the subject's mouthpiece using the MasterScreen IOS system. Impulse oscillations (IO) were provided by the standard voice-coil device composing the IOS which was used alternatingly with a home-made device, also based on voice-coil technology, able to provide sinusoidal pressure waveform stimulation (S) (see Figure 3.26).

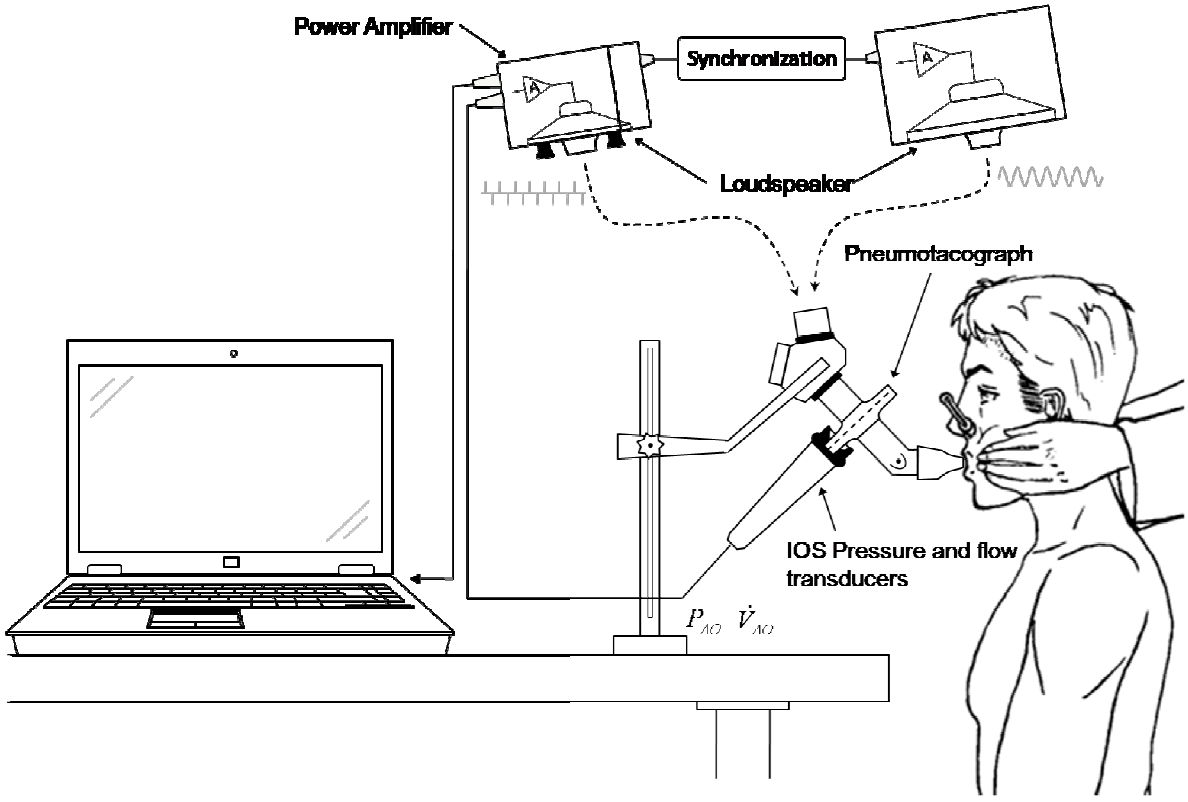

Figure 3.26: Experimental setup.

Experimental protocol

Patient's pulmonary function tests were performed at first. Afterwards patients were connected to the mouth piece of the IOS MasterScreen device, in sitting position, wearing a nose clip and firmly supporting their cheeks to reduce upper airways shunt. Pressure and flow at the patient's mouth were recorded continuously during two minutes of normal breathing with IO and for other two minutes with the S, in a randomized order. The same measurements were performed in the same order after the administration of Albuterol (BD, 400mcg) delivered by a metered-dose inhaler.

Data Analysis

Raw data were computed separately for S and IO. The main parameter taken into account is the ΔXrs (see below), in addition to inspiratory (R_{IN}) and expiratory (R_{EX}) resistance at 5Hz, mean value of resistance (R) and inspiratory (X_{IN}) and expiratory (X_{EX}) reactance at 5Hz.

S: The imaginary part of the impedance (Xrs) was computed breath by breath starting from P_M and V'_M as previously described (12). In order to identify the condition of expiratory flow limitation it has been previously defined a parameter (12), ΔXrs=Xinsp-Xexp, computed as the difference of the mean value of Xrs during inspiration (Xinsp) and expiration (Xexp). The ΔXrs parameter is used to classify every breath as flow-limited (FL) if ΔXrs is greater than 2.8cmH_2O*s/L or non-flow-limited (NFL) if smaller. This threshold was identified in a previous study (12) and demonstrated to be able to identify expiratory flow limitation condition with 100% sensitivity and specificity when compared to Mead and Whittenberger method (9).

For every acquisition session the breaths in which the Xrs trace showed spikes or oscillations due to swallowing or glottis closure were discarded. The mean value of ΔXrs was computed for all the remaining breaths in order to classify the session as FL or NFL.

IO: The traces of P_{AO} and V'_{AO} were computed automatically by the MasterScreen software which provided all the needed parameters for every session.

Significance of differences in physical characteristics, spirometric data, ΔXrs and breathing patterns between IO and S use were tested by paired T-test. Values of $p>0.05$ were considered nonsignificant (NS). The agreement of IO and S in classifying a given patient as flow-limited or not flow-limited was evaluated by the kappa statistic.

The regression analysis between S and IO parameters was computed on FL and NFL tests.

Finally we applied the paired T-test between FL and NFL tests, taking into account the absolute value of the difference between the measurement performed by IO and the measurement performed by S.

3.2.2.2 Results

	Pre-BD	Post-BD
Age yrs	69±10	
Sex M/F	17/4	
Weight Kg	79.2±16.1	
Height cm	166.3±7.9	
BMI Kg/m^2	28.6±5.7	
FEV_1		
L	1.34±0.64	1.53±0.92
% pred	53.74±24.90	57.57±27.36
FVC		
L	2.83±0.72	3.22±0.78
% pred	86.33±19.91	96.20±20.30
FEV_1/FVC	0.47±0.18	0.46±0.21
PEF		
L/s	3.59±1.68	3.88±2.18
% pred	50.97±23.28	53.10±24.56
IC		
L	2.28±0.67	2.31±0.66
% pred	67.70±18.62	66.74±18.22

Table 3-2: Patients data pre and post the administration of a bronchodilator.

We studied 17 COPD patients before and after the administration of broncodilator and 3 patients with no administration of broncodilator. Patient's characteristics and spirometric data are shown in the table above. An example of pressure and flow traces of a patient breathing while the S and IO stimuli are applied at the patient's mouth is shown in Figure 3.27.

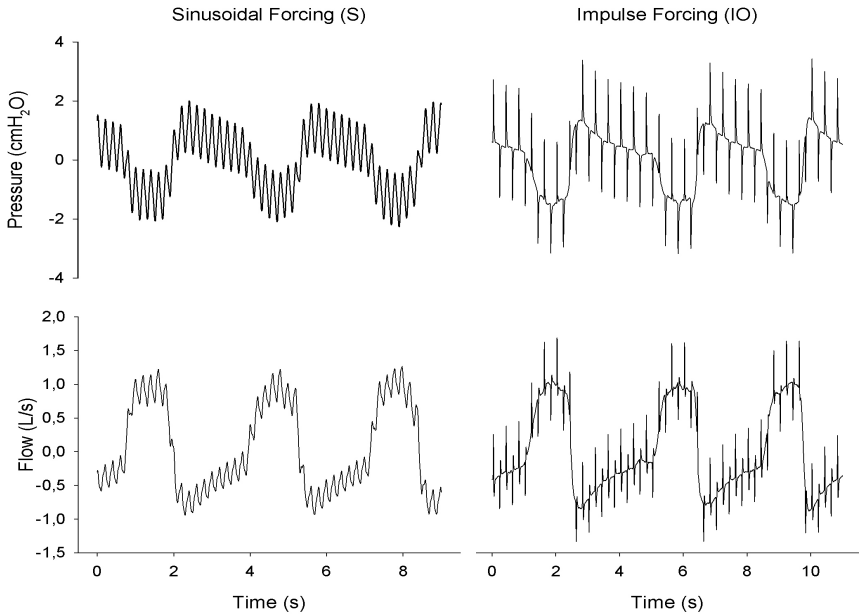

Figure 3.27: Acquired signals example. On the left pressure and flow from sinusoidal forcing, on the right with impulse forcing.

The T-tests performed on breathing pattern (respiratory frequency, tidal volume, inspiratory time, total time, duty cycle) of patients showed that there is no significant difference in the modality of breathing whilst applied IO or S stimulus to the patients' mouth during the acquisition sessions.

	q	m	r^2	p		q	m	r^2	p
R_{IN}					**R_{EX}**				
NFL	-0,36	1,06	0,81	<0,001		-0,24	1,07	0,89	<0,001
FL	0,26	0,82	0,73	<0,001		-0,04	0,81	0,75	<0,001
X_{IN}					**X_{EX}**				
NFL	0,02	0,96	0,84	<0,001		0,16	1,08	0,81	<0,001
FL	-2,32	0,33	0,27	<0,001		-5,24	0,64	0,60	<0,001
ΔXrs									
NFL	0,06	1,04	0,84	<0,001					
FL	3,38	0,53	0,47	0.003					

Table 3-3: Regression analysis parameters computed from impedence values.

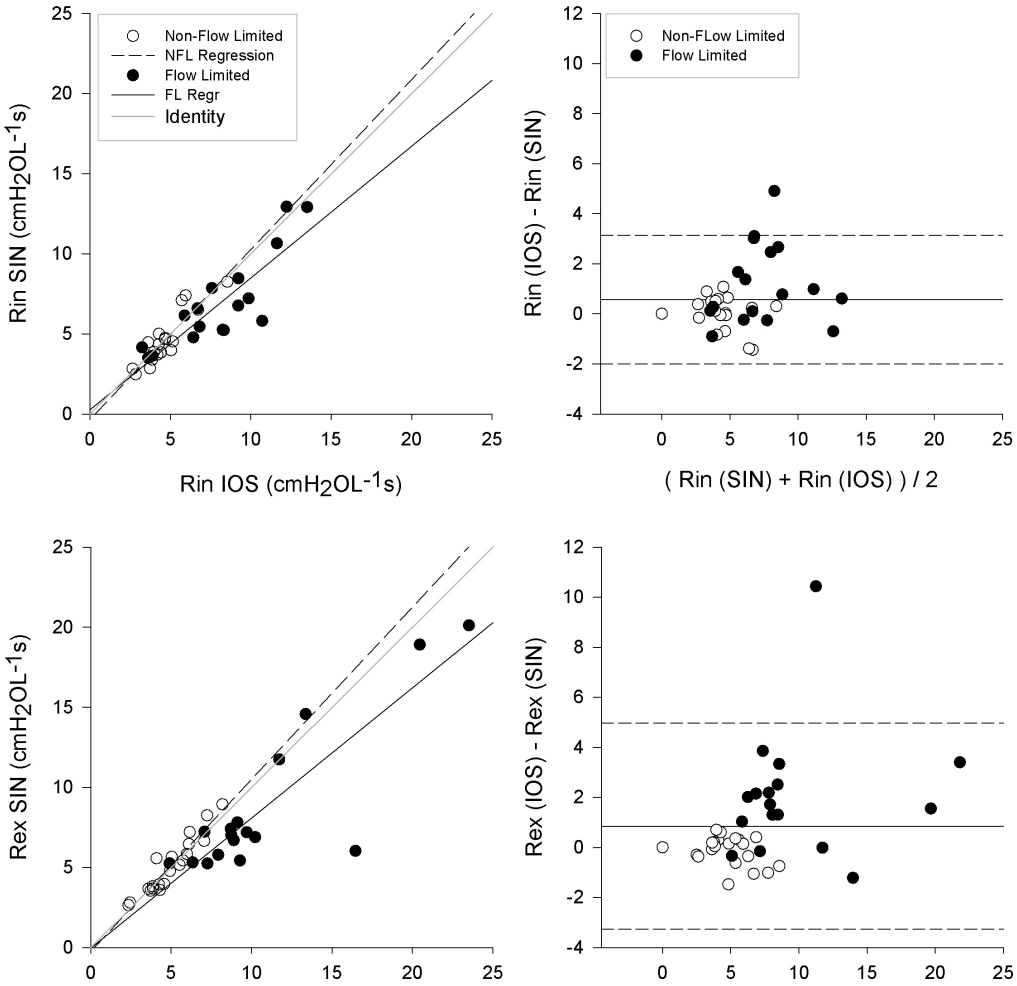

Figure 3.28: Regression analysis graphs (on the left) and Bland-Altman analysis (on the right) of Rin and Rex parameters.

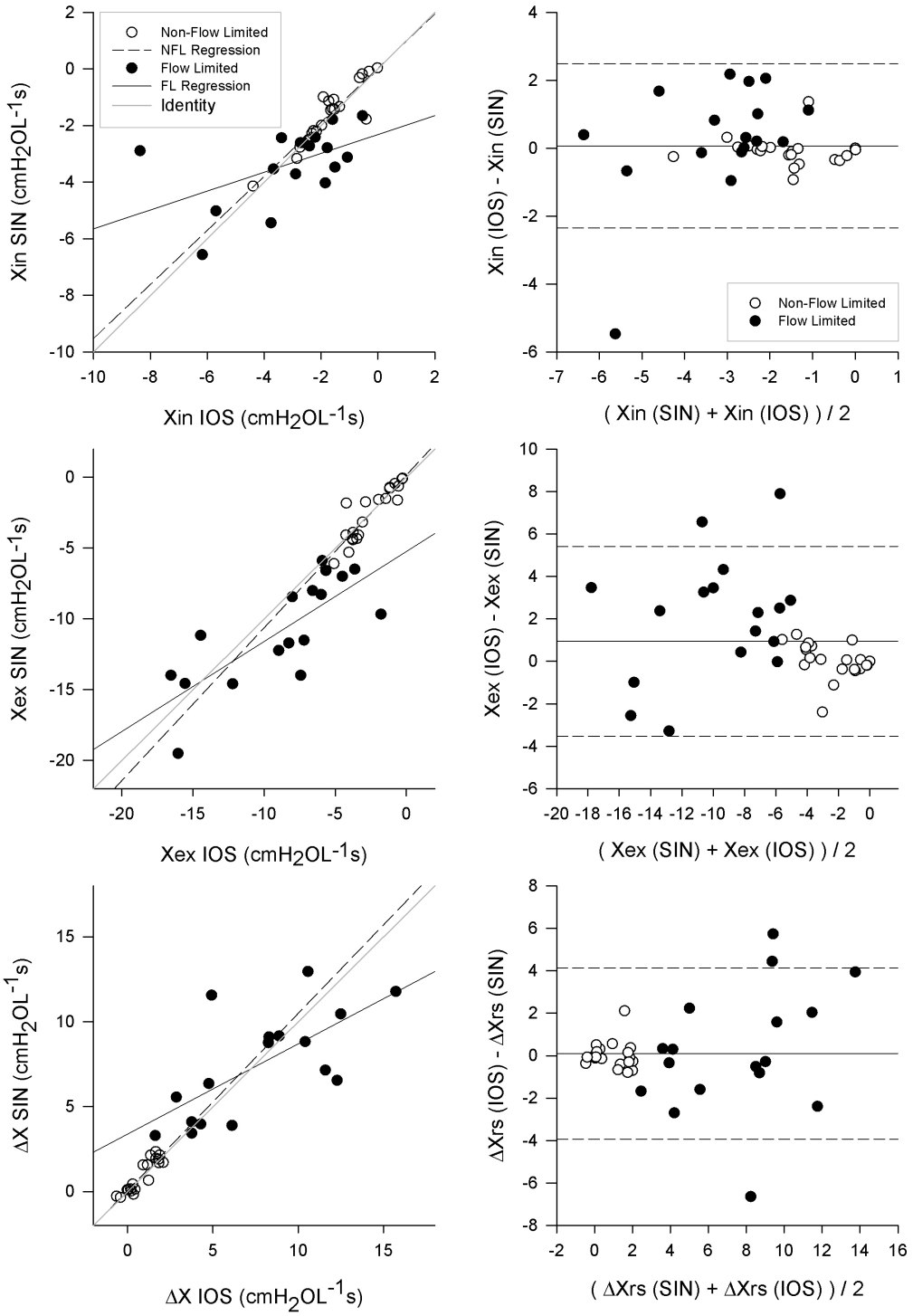

Figure 3.29: Regression analysis graphs (on the left) and Bland-Altman analysis (on the right) of Xin, Xex and ΔX parameters.

For both methods we classified COPD patients as FL or NFL if ΔXrs was respectively greater or lower than 2.8cmH_2O*s/L. The Kappa statistic showed an almost perfect agreement of the classification of the two methods (k=0.95).

For every measured parameter (R_{IN}, R_{EX}, X_{IN}, X_{EX} and ΔXrs) we performed the regression analysis between IO and S values both for FL and NFL classified data. All the plots are

reported in Figure 3.28 and Figure 3.29. The parameters of the regressions are reported in the table below subdivided into FL and NFL. Bland-Altman analysis was computed between IO and S values for the previously mentioned parameters, and the relative plots are visible in Figure 3.28 and Figure 3.29.

For every measured parameter (R_{IN}, R_{EX}, X_{IN}, X_{EX} and ΔXrs) we performed a paired T-test between FL and NFL patients, considering the absolute value of the difference between a parameter measured with IO and S. All the tests showed statistically significant difference between FL and NFL patients.

3.2.2.3 Conclusions

Expiratory flow limitation is a phenomenon that introduces non-linearity characteristics to the frequency response of the respiratory system. Using broadband signals for the stimulation provides the development of a great number of harmonics that superimpose each other and mainly with the stimuli of interest, 5Hz. This promotes the generation mainly of noise that affects the computing of impedance but most important of reactance, from which is gained the ΔX parameter, which is significant for EFL assessment. As we can see in Figure 3.30 this is confirmed by the fact that below the EFL threshold the two measurements with IO and S are much more correlated than the measurements over the EFL threshold of 2.81cmH_2O/L/s.

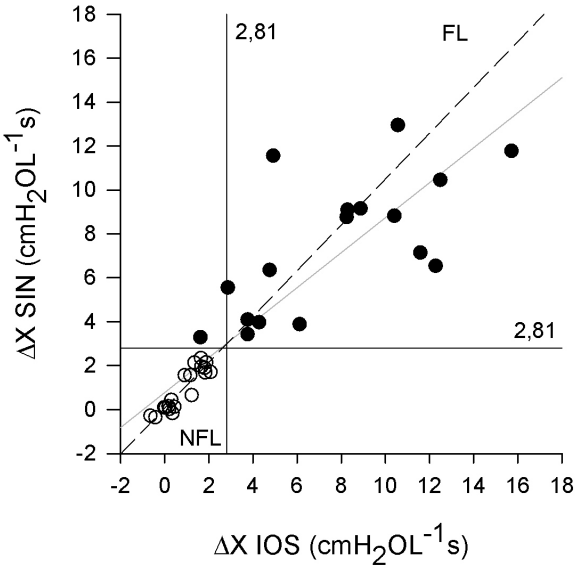

Figure 3.30: DX measurements comparison. Under EFL limit (2.81) the measurements are well correlated, over EFL threshold the measurements are poorly correlated.

As EFL assessment is very important and it is necessary to be the most accurate possible, we chose to use the single sinusoidal FOT at 5Hz to be implemented inside a home mechanical ventilator, in order to detect the EFL condition.

3.2.3 Implementation of the FOT in a Home Mechanical Ventilator

Forced oscillation technique has been shown to be effective in the EFL detection in COPD patients during nasal CPAP (13). The aim of this section is to show how we developed the same technique inside a BiPAP home mechanical ventilator without the need of any external device.

In order to implement the FOT into a home mechanical ventilator it is necessary to take into account the measurement setup which is totally different from the standard one, described in paragraph 3.2.1.

The system that provides the pressure oscillation is the ventilator itself, together with the ventilatory therapy. A sliding valve, connected in series with the turbine that provides high pressures, generates the 5Hz sinusoidal pressure oscillations that are superimposed the ventilatory pressures.

The FOT oscillations are provided to the patient, together with the ventilation, through a tube and a nasal mask. Air rebreathing is avoided thanks to a little hole next to the nose of the patient, called whisper swivel, through the which exhaled air is expelled. New and fresh air come again from the ventilatory tube for the next inspiration.

Pressure and flow sensors are located inside the ventilator, at the beginning of the hose. This means that the impedance computed from the outlet of the ventilator includes also the impedance of the tubings and the mask. To be able to detect EFL it is necessary to compute the respiratory system impedance alone, that's why an impedance model of the connection devices has been developed.

3.2.3.1 The tubing compensation model

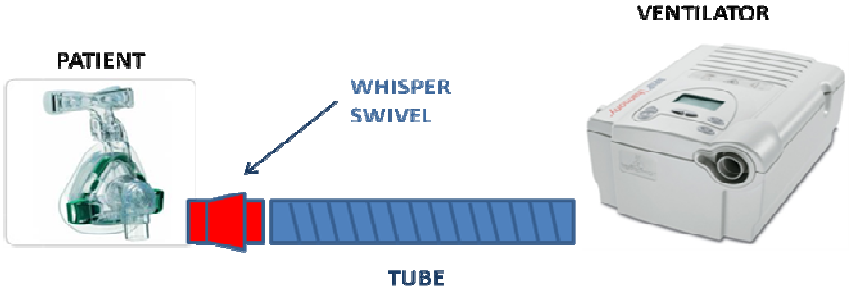

Figure 3.31: Ventilator - patient connection scheme

The ventilator, as shown in Figure 3.31, is connected to a tube which has a length of Len=1.8m and a diameter of Di=0.02m. After the tube there is a whisper swivel, the mask and finally the patient. Each one of these elements is characterized by its own impedance (see Figure 3.32) and the aim of this section is to show how to compute patient's impedance starting from impedance measured at the outlet of the ventilator.

The model used to correct for the presence of tubings and leaks has been developed starting from a previous study and is (16) depicted below.

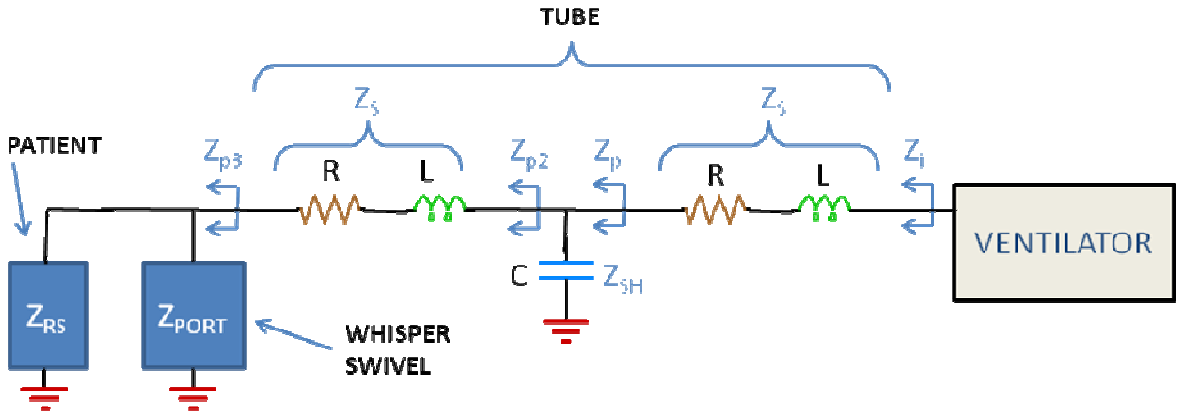

Figure 3.32: Electrical equivalent scheme of the total impedance seen by the ventilator.

Tube

The impedance of the tube is modeled as a series of a resistance R:

$$R = \frac{8 \cdot \pi \cdot \mu \cdot Len}{A^2} \cdot \frac{1}{2} \cdot \frac{1}{10^5} \text{ cmH}_2\text{O*s/L}$$

and an inductance L:

$$L = \frac{n \cdot \rho \cdot Len}{A} \cdot \frac{1}{2} \cdot \frac{1}{10^5} \text{ cmH2O*s}^2\text{/L}$$

Where

- μ=0.000018369Pa*s is air viscosity
- $A = \pi * \left(\frac{D_i}{2}\right)^2$ m² is the tube section
- n=1 is dependent on the velocity profile of air into the tube and in this case is considered blunt (turbulent)
- ρ=1.204Kg/m³ is the air density

Therefore impedance for this first branch (R-L series) results in:

$$Z_S = R + i \cdot 2\pi f \cdot L \text{ cmH}_2\text{O*s/L}$$

A shunt capacitor C is used to model gas compressibility:

$$C = \frac{V}{\beta \cdot P_{atm}}$$

Where

- $V = A \cdot Len \cdot 1000$ is the tube volume in Liters
- β=1 is the compressibility constant, equal to 1 for isothermal conditions
- Patm=1013.25cmH_20 is atmospheric pressure
- f=5Hz is the frequency of the stimulus

The impedance of the shunt capacitor C is defined as follows:

$$Z_{SH} = -\frac{i}{2\pi f \cdot C}$$

Finally another R-L series is connected after C.

If we define Z_i as the impedance measured at the ventilator, to compute the impedance after the tubing, we have to eliminate the terms defined above. Since Z_i and Z_s are in series the impedance after the first part of the tubing (Z_p) is computed:

$$Z_p = Z_i - Z_S$$

As Z_p is defined by the parallel of Z_{sh} (capacitor impedance) and Z_{p2} (the rest of the circuit):

$$Z_p = \frac{Z_{p2} \cdot Z_{sh}}{Z_{p2} + Z_{sh}}$$

To compute Z_{p2} we have to reverse the formula and find the impedance after the first part of the tubing without shunt effect:

$$Z_{p2} = \frac{Z_p}{1 - \frac{Z_p}{Z_{sh}}}$$

Finally the impedance at the end of the tubing is computed by a subtraction, because Z_{p2} and Z_s are in series:

$$Z_{p3} = Z_{p2} - Z_s$$

Whisper Swivel

The whisper swivel impedance has been calculated by using the pressure - flow relationship of a generic orifice and takes its origin from the Bernoulli's law (17):

$$Q = C_f A_0 \sqrt{\frac{2P}{\rho}}$$

Where Q is the flow, C_f is the flow coefficient, A_0 is the section area of the orifice, P is the pressure difference at the orifice and ρ is the fluid density. This equation can be written in another way:

$$Q = a \cdot P^{0.5}$$

Where a is a constant that takes into account the previously described constants. As we have:

$$Z_{port} = \frac{\partial P}{\partial Flow}$$

By differentiation we can obtain the impedance of the whisper swivel:

$$Z_{port} = b \cdot P^{c}$$

Where P is the circuit pressure as measured by the vent and with oscillations filtered out.

Unintentional Leaks

In parallel with the intentional leaks orifice and the patient it is also necessary to consider the contribute to the unintentional leaks between the mask and the face of the patient.

The equations that describe these kind of leaks are the same as for the whisper swivel, and as they're in parallel we can modify the previous equation taking into account for the contribution of unintentional leaks:

$$Z_{port} = g \cdot P^{\gamma}$$

However the total contribution for leaks is electrically in parallel with patient's impedance. For this reason we set a threshold for leaks over the which the patient's impedance cannot considered reliable.

Patient's Impedance

The impedance of the last part of the system is composed of the parallel of two contributions, exhalation port and patient's impedances:

$$Z_{p3} = \frac{Z_{port} \cdot Z_{rs}}{Z_{port} + Z_{rs}}$$

To compute patient's impedance we have to reverse the equation above and find the impedance after correcting for the presence of the exhalation port:

$$Z_{rs} = \frac{Z_{p3}}{1 - \frac{Z_{p3}}{Z_{port}}}$$

The procedure and computings for tubings, leaks and masks impedance compensation has been implemented inside the ventilator. This allows the ventilator to correctly and accurately measure the impedance of the respiratory system of the patient breathing through the ventilator. At this point the ΔX value can be computed breath by breath, therefore the ventilator autonomously can use this parameter to classify each breath as flow limited or not.

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CHAPTER 4

AUTOMATIC INTERVENTION AT HOME

The devices and methods described in Chapter 3 are able to collect information that can be analysed through the use of intelligent functions implemented inside the systems that provide the therapy, and inside a centralizer, in order to perform the continuous monitoring of patient's conditions.

Thanks to the use of particular procedures, the intelligent tools implemented inside the devices are able to monitor certain parameters in order to perform the automatic intervention on the therapy delivered to optimize it according to the conditions and necessities of the patient, without the supervision of any health care professional (Figure 2.3).

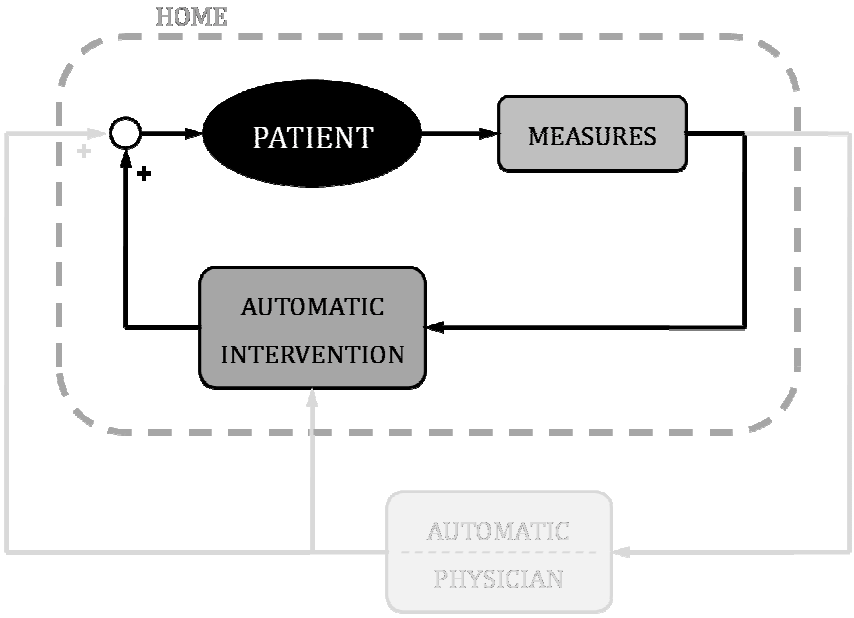

Figure 4.1: The new Telemedicine model highlighting the first ring, Automatic Intervention.

During the Doctorate program it has been developed an important automatic function inside an home mechanical ventilator delivering BiPAP ventilation in order to optimize the delivered ventilation therapy. This chapter describes the clinical study for the validation of the method and the development of the automatic function.

4.1 Detection and abolishment of EFL during NPPV ventilation

One of the treatments provided to COPD patients is the BiPAP home mechanical ventilation, a bilevel ventilation which provides a Positive end expiratory pressure (PEEP) over the which an inspiratory pressure (IPAP) is provided at patient's trigger for a new breath.

Positive end expiratory pressure (PEEP) is used in COPD patients to counteract the intrinsic PEEP (PEEPi), which represents the end expiratory recoil pressure of the total respiratory system due to the presence of dynamic hyperinflation (DH).

DH commonly occurs in COPD, where the presence of expiratory flow-limitation (EFL) requires the patient to breath at higher lung volumes to produce the necessary expiratory flow. To be effective, the PEEP level applied to the patient should be equal to PEEPi.

The continuous monitoring of EFL could be a useful tool to select the minimum PEEP level required to abolish it.

EFL can be detected using the forced oscillation technique (FOT) by an index which quantifies, for each breath, the within-breath variations of respiratory reactance (ΔXrs) at 5Hz (see Chapter 3).

The aim of this work was to test the implemented FOT measurement (see Chapter 3) in a commercial bilevel mechanical ventilator and to evaluate its specificity and sensitivity in detecting EFL in COPD patients submitted to NPPV.

4.1.1 Material and Methods

Patients

Measurements were performed on a group of COPD patients that met the following inclusion and exclusion criteria:

Inclusion Criteria

- Age $\leq$ 80 years
- Moderate – Severe COPD diagnosed by spirometry (according to the GOLD criteria)
- Free from any exacerbation in the 6 weeks preceding the study

Exclusion Criteria

- Any co-existing cardio-pulmonary conditions which may result in a picture of ventilatory failure such as congestive cardiac failure, chest wall or neuromuscular disease, bronchopneumonia, pulmonary fibrosis, bronchiectasis, cystic fibrosis or obesity-hypoventilation syndrome
- Clinically unstable; exacerbation within the preceding 6 weeks
- The presence of pulmonary or extra-pulmonary neoplasia that is still active
- The presence of a bleeding diathesis
- Unstable coronary artery disease
- Presence of tuberculosis, current infection or potentially infectious pathogen
- Inability to provide informed consent to the study

Measurements

Patients were measured while subjected to nasal BiPAP. A commercial ventilator (Synchrony, Respironics, USA) specifically modified to provide a 5Hz pressure stimulus over imposed on the ventilation waveform was used. A nasal mask without exhalation port coupled with a whisper swivel valve was used in the study.

To evaluate the influence of the breathing circuits and the exhalation port on the impedance measurements performed by the ventilator, two additional sets of pressure and flow measurements were collected simultaneously with the ventilator data (Figure 4.2). Nasal pressure (Pn) and flow ($\dot{V}_p$) at the inlet of the mask were measured by a differential pressure sensor (Honeywell, Minnesota USA, SURSENSE precision very low pressure sensors, DCXL30DS, 75cmH2O) and a mesh type pneumotacograph connected to a differential pressure sensor (Honeywell, Minnesota USA, SURSENSE precision very low pressure sensors, DCXL30DS, 2.5cmH2O).

An additional identical set of sensors was placed at the outlet of the ventilator to measure ventilator pressure (Pv) and flow ($\dot{V}_v$). An anti-bacterial filter was placed between this last set of sensors and the ventilator.

Oesophageal pressure (Poes) was measured using a differential pressure sensor connected to a balloon-catheter system placed in the central third of the oesophagus. Transpulmonary pressure (Pl) was then derived as the difference between nasal pressure and oesophageal pressure (Pl = Pn – Poes).

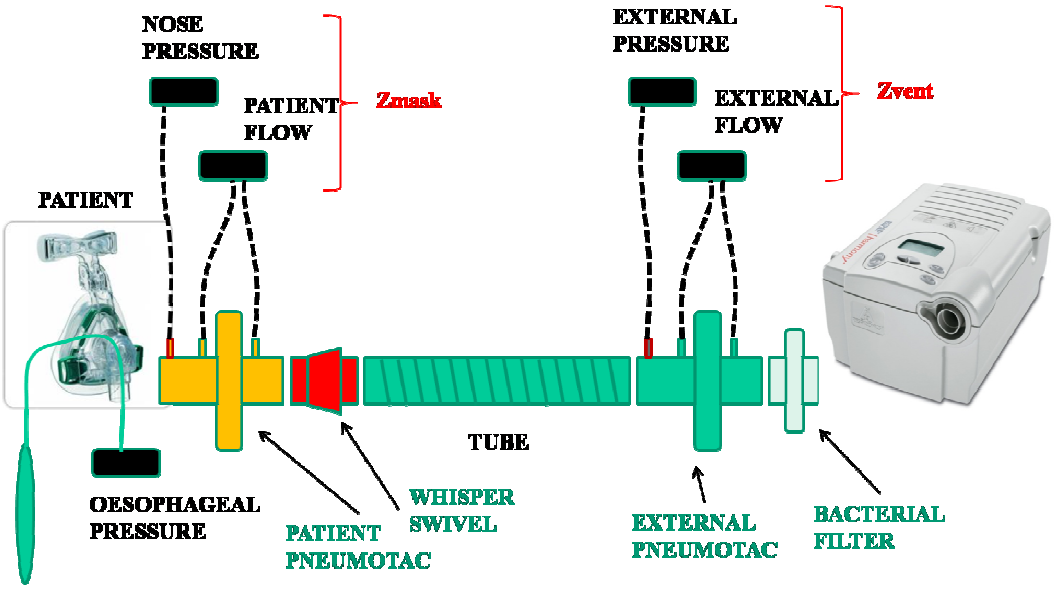

Figure 4.2: The system for patient's impedance measurements.

Data from the two sets of external sensors were sampled by a commercial AD/DA board (National Instruments DAQ Card 6062E, and BNC-2110 connector block). Data measured by the ventilator's sensors were acquired by the RASP Utility program (PHILIPS® Respironics).

Protocol

After recruitment each patient was screened by means of standard pulmonary lung function test. Pulmonary flow and volumes were assessed in a full body pressure type plethysmographic cabin. Before placing the oesophageal balloon, the patients underwent a first 5 minutes measurement period in sitting position at EPAP=3cmH_2O (Expiratory Positive Airway Pressure) and IPAP=9cmH_2O (Inspiratory Positive Airway Pressure). Patients were classified as flow limited (ΔXrs > 2,8cmH_2O·s/L ➔ FL) of non flow limited (ΔXrs < 2,8cmH_2O·s/L ➔ NFL) according to their ΔXrs value derived as described in the data analysis section. Depending by his comfort and value of ΔXrs, the patient was studied in seated position if classified as FL and supine otherwise. After administration of nose and throat local anesthesia, the oesophageal balloon was inserted.

Ventilator was set at EPAP=3cmH_2O and IPAP=9cmH_2O and both pressures were increased by 1cmH_2O every 6 minutes of normal breathing up to 3 steps above the pressure able to abolish EFL (EPAP max 10cmH_2O). Pn, $\dot{V}_p$, Pe, $\dot{V}_E$, Pv, $\dot{V}_V$, Poes were all recording for the duration of the whole trial.

Data Analysis

For each patient and pressure level at least 10 breaths were manually selected in the last three minutes of each pressure step excluding those where swallowing, oesophageal spasms, or cough were present.

FOT

Using pressure and flow data patient impedance (Zn), external impedance (Ze) and ventilator impedance (Zv) were computed as follows: $Z_N = \frac{P_N}{\dot{V}_P}$, $Z_E = \frac{P_E}{\dot{V}_E}$, $Z_V = \frac{P_V}{\dot{V}_V}$. Three corresponding values of ΔXrs (ΔXrs_N, ΔXrs_E, ΔXrs_V) were calculated for each breath as difference between the mean value of reactance during inspiration and expiration.

External and ventilator sets of sensors data were compensated for the presence of the impedance of the tube and of the whisper swivel valve.

Mead and Wittenberger (M-W)

The Mead and Wittenberger method (see Chapter 3) was used as a reference technique to score each breath as Flow-Limited (FL), Non-Flow-Limited (NFL) (see Figure 4.3).

Briefly for each breath the flow-resistive pressure drop (Pfr) was estimated from Pl by subtracting the elastic recoil pressure of the lung and plotted against $\dot{V}_p$. If Pfr-$\dot{V}_p$ plot showed a loop during expiration where flow decreased while Pfr increased, the breath was classified as FL. If the relationship between Pfr and $\dot{V}_p$ had little or no loop with a quasi-linear dependency, the breath was classified NFL.

When:

- The inspiratory pressure-flow curve was looped or
- The expiratory pressure-flow curve showed a loop characterized by a phase which flow decreased but Pfr didn't simoultaneously increase

The breath was considered undetermined (I) and excluded from the analysis.

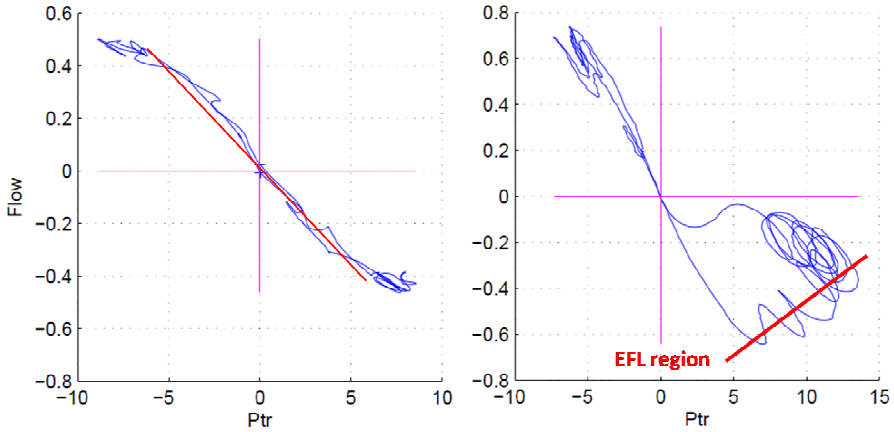

Figure 4.3: Mead and Wittenberger method example. The graphs show Airway Opening Flow plotted vs Resistive Pressure Drop during a single breath. On the left is show a breath of a COPD patient without flow limitation. On the right is show a single breath of a COPD flow limited patient.

Sensitivity and specificity of ΔXrs_N, ΔXrs_E, ΔXrs_V with respect to the M-W method were computed as follows:

$$Sensitivity = \frac{\#\text{of FL breaths detected by FOT}}{\#\text{of FL breaths detected by M \& W}} \cdot 100$$

$$Specificity = \frac{\#\text{of NFL breaths detected by FOT}}{\#\text{of NFL breaths detected by M \& W}} \cdot 100$$

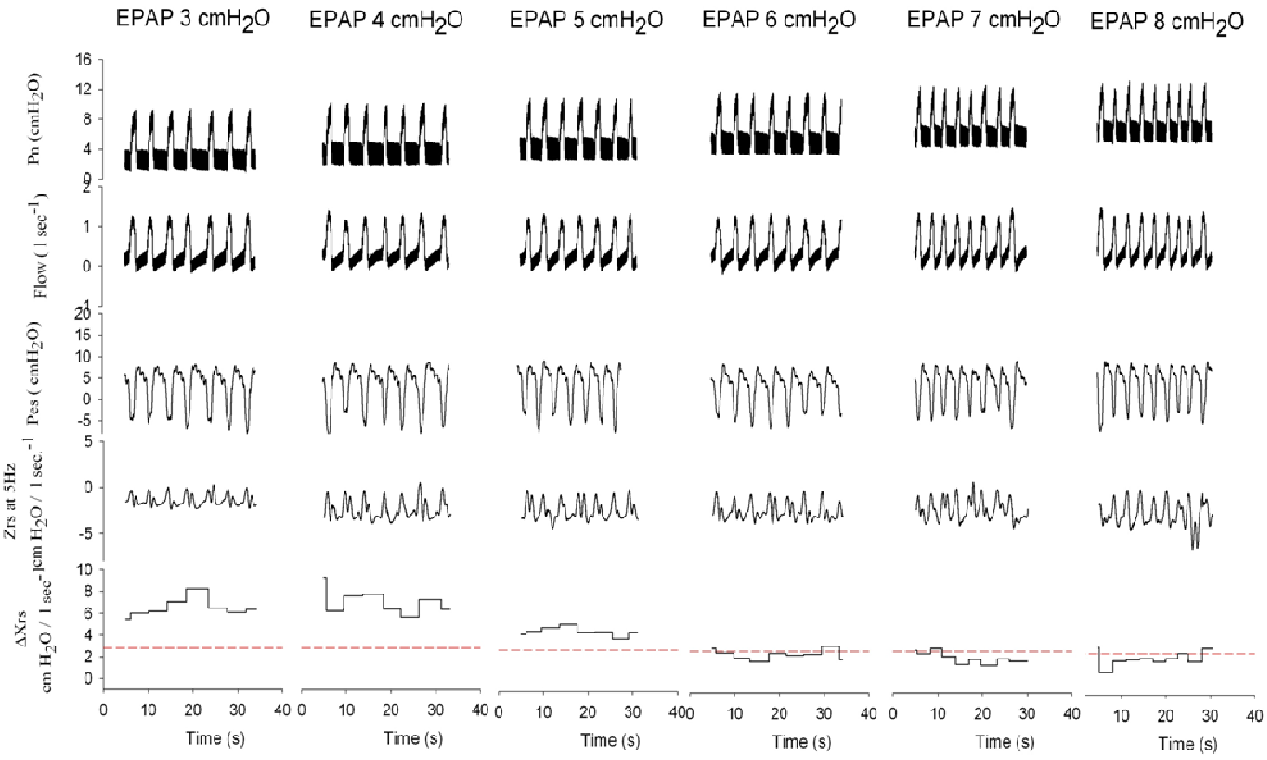

Figure 4.4: Experimental tracings from a representative patient at different EPAP pressures. From top to bottom: pressure and flow measured at ventilator's outlet, oesophageal pressure, respiratory reactance and ΔXrs. ΔXrs values decreased with increasing EPAP until expiratory flow limitation was abolished (EPAP=6cmH_2O).

4.1.2 Results

Twenty-two patients were recruited for the study. However 7 of them didn't tolerate the oesophageal balloon and 2 had an exacerbation and were excluded from the study. Patient's physical characteristics and spirometric data are reported in Table 4-1 below. Basing on the GOLD classification 7 patients were severe COPD, 5 moderate COPD and 1 mild COPD. According to their value of ΔXrs_N 9 patients were studied supine and 4 in sitting position. A total of 2497 breaths were analyzed. M-W method classified 534 breaths as FL (21,4% of the total) and 567 breaths as NFL (22,7% of the total). According classification criteria 1395 breaths were considered undetermined (55,8% of the total).

	Patients	Age	Weight	Height	FEV1		FVC	
	n	yrs	Kg	cm	L	% pred	L	% pred
COPD								
Mean	13	67,9	169,5	84,8	1,2	44,9	2,4	68,1
SD		6,5	8,8	19,2	0,6	19,7	0,7	17,3
NFL@3cmH2O								
Mean	5	67,4	172,4	90,1	1,7	58,2	2,9	80,0
SD		8,5	10,1	19,8	0,4	20,8	0,4	17,9
FL@3cmH2O								
Mean	8	68,2	167,7	81,5	1,0	36,6	2,0	60,7
SD		5,6	8,1	19,4	0,5	14,5	0,7	13,0

	FEV1/FVC	TLC		TGV		RV	
		L	% pred	L	% pred	L	% pred
COPD							
Mean	50,2	6,2	100,2	4,8	145,2	4,6	192,0
SD	10,5	1,2	21,5	1,3	43,5	1,3	55,5
NFL@3cmH2O							
Mean	56,2	6,1	95,3	4,5	129,7	4,5	183,4
SD	9,6	0,9	21,1	1,2	30,8	1,2	45,5
FL@3cmH2O							
Mean	46,5	6,2	103,3	5,1	155,0	4,6	197,4
SD	9,8	1,4	22,6	1,4	49,2	1,4	63,3

Table 4-1: Physical characteristics and spirometric data of the patients. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; TGV: thoracic gas volume; RV: residual volume; COPD: chronic obstructive pulmonary disease; NFL: non flow limited; FL: flow limited.

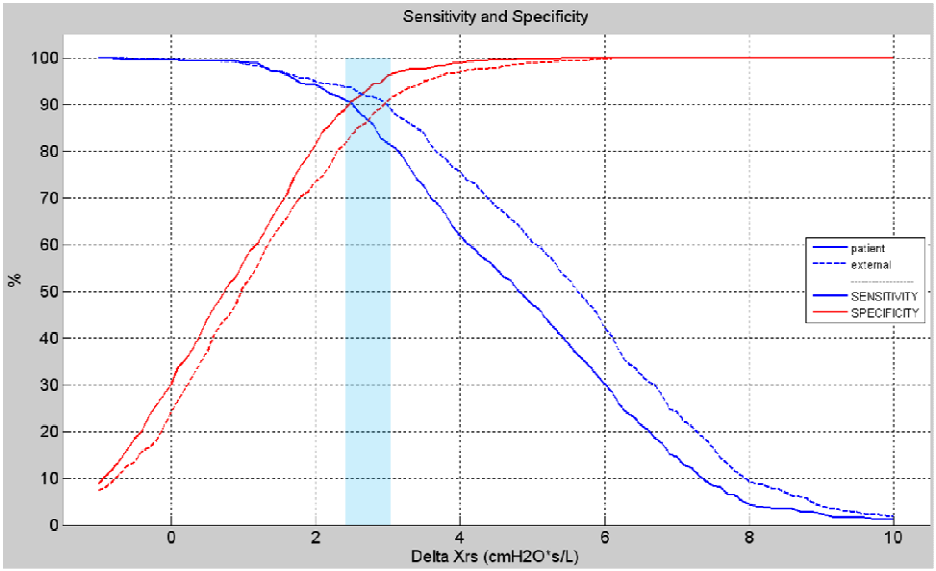

Figure 4.5: Sensitivity and Specifity plots of ΔXrs as calculated from Zmask (continuous lines) and Zvent (dotted lines). In blue is the range of 100% sensitivity and specificity as identified in a previous study (1).

Considering flow and pressure signals measured at the outlet of the ventilator, the computed ΔXrs, after appropriate leak correction, showed a sensitivity and specificity in detecting EFL in respect to M-W method of 90.2% (Figure 4.5).

Considering flow and pressure signals measured at mask, the computed ΔXrs showed a sensitivity and specificity of 90.37% (Figure 4.5).

4.1.3 Conclusions

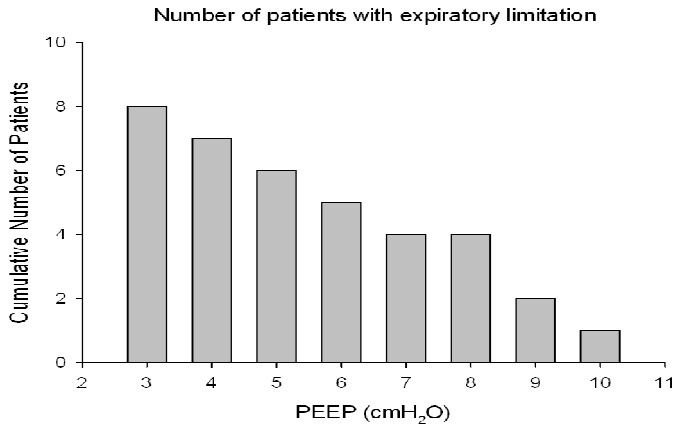

Figure 4.6: Cumulative number of patients showing expiratory flow limitation for increasing EPAP values.

Interestingly we found that the PEEP value able to abolish EFL can range from 3 to 10 cmH_2O and over (see Figure 4.6) and as we can see in Table 4-2 the severity is not an index of the level of PEEP that should be delivered.

Pat.	COPD	EFL@EPAP=3cm H_2O	EPAP EFL abolishment
1	severe	NFL	-
2	moderate	NFL	-
3	severe	EFL	10
4	severe	EFL	>10
5	moderate	EFL	4
6	severe	EFL	9
7	severe	EFL	6
8	moderate	NFL	-
9	severe	EFL	7
10	moderate	NFL	-
11	severe	EFL	5
12	moderate	EFL	9
13	mild	NFL	-

Table 4-2: Severity, presence of flow limitation and relative PEEP value to abolish it in the 13 patients.

The results showed that after the PEEP level that abolish EFL is reached, a further increasing in the PEEP value is not providing better results in term of EFL, as it is already abolished. Increasing further the PEEP value worsens the patient to ventilator adaptation as the BiPAP device is hyperinflating the patient, making him more difficult to breathe.

This suggests that there is an optimal value of PEEP that must be provided and this is the minimum value that abolish EFL.

These data indicate that FOT can be implemented into commercial mechanical ventilators to automatically and reliably detect EFL during NIV. In the patients studied, the minimum pressure needed to abolish EFL was quite variable ranging from 3 to 11 cmH_2O, supporting the potential usefulness of an automatic system to adjust EPAP during NIV in COPD.

4.2 The algorithm for Automatic PEEP Level Adjustment

The new home mechanical ventilator developed is provided with an instrument capable of detecting EFL breath by breath from the COPD patient treated with the BiPAP device.

As shown in the previous paragraph EFL is a condition that occurs more in determinate conditions than others or depending on patient's posture or disease progression.

A continuous adjustment of the PEEP level is therefore needed. To perform this task it has been implemented an algorithm that, thanks to the use of the FOT technique, adapt the provided ventilation to the optimal value for the patient in that moment.

During normal breathing through the mechanical ventilator the patient can cough, swallow, take deep breaths and so on. As FOT works during normal breathing it necessary to implement a set of rules that select the suitable breaths for FOT computings.
The included breaths are those who fulfil the following five rules.

Low unintentional leaks

The unintentional leaks affect the impedance calculations of the respiratory system of the patient, used for obtaining the ΔXrs. This happens because the 5Hz sinusoidal pressure stimuli has to be applied to the nose of the patient, where the input impedance can be quite high, up to 6-10$cmH_2O/L/s$. This means that if the patient impedance has a low parallel impedance provided by the leaks, the amplitude of the provided stimuli lowers. If it lowers under a certain

level the signal to noise ratio is too low to perform any computings of the impedance of the respiratory system.

For this reason we decided to consider only the breaths where the unintentional leak was lower than 0.2L/s.

Tidal volume amplitude

The ΔXrs value is computed from the impedance of the respiratory system, which is a result of the contribution mainly of the compliance of the respiratory system. In the range of the normal breathing the compliance is within the normal range of working and this is the most reliable condition for ΔXrs measurement (see Chapter 1). If the patients breathe at too high of too low volumes the lung stiffen and the ΔXrs measurement is no more reliable.

For this reason are taken into consideration the breaths with volume within:

$$0.1\text{L} < V_T < 2\text{L}.$$

ΔXrs values

ΔXrs is a parameter that is computed starting from the impedance of the respiratory system, for this reason is the patient swallows or cough, as the impedance can suddenly change to very different values, ΔXrs can assume very different values, that in these cases are not significant from a EFL point of view. This is the reason because the accepted values for ΔXrs are the following:

$$-2 < \Delta\text{Xrs} < 20 \ (\text{cmH}_2\text{O/L/s}).$$

Xrs Values

As we said before patient's alterations in normal breathing (cough, swallowing…) can affect only part of the whole breath impedance trace, and this is shown in spikes in the reactance trace. In order to avoid those spikes in ΔXrs calculation we exclude the breaths that fulfil these equations:

$$\left|\frac{X\ \min(\exp)}{X\_mean\_\exp iratory}\right| > 3.5$$

$$\left|\frac{X\ \min(insp)}{X\_mean\_inspiratory}\right| > 3.5$$

Flow Shape Index Filter

This filter is implemented in order to check for signal to noise ratio of the pressure signal stimuli.

If the Flow Shape Index Filter, defined in (2) as the sign-less difference between the measured flow oscillation and the ideal sine wave having the same Fourier coefficients, normalized by the amplitude of the measured oscillation, is above a defined threshold the breath is discarded:

$$\frac{\frac{\sum_{i=0}^{window-1} \left| \dot{V}_{ideal}[i] - \dot{V}_{measured}[i] \right|}{window}}{\sqrt{[Re(\dot{V})]^2 + [Im(\dot{V})]^2}} > 0.2$$

The Automatic algorithm

After the breaths are filtered, and we obtain the ΔXrs values that are actually describing patient's EFL condition, it is possible to implement the decisional algorithm, which actually is very simple:

- The value of ΔXrs is monitored for a sufficient number of breaths.
- If the value is above the flow limitation threshold, that is 2.81 $cmH_2O/L/s$, the ventilator settings are increased by one cmH_2O, PEEP+1cmH_2O, IPAP+1cmH_2O.
- If the value is below the flow limitation threshold, the ventilator settings are decreased by one cmH_2O, PEEP-1cmH_2O, IPAP-1cmH_2O.

This very simple algorithm implemented inside the home mechanical ventilator allows to automatically adapt the ventilation parameters to the present conditions on the COPD patients, in order to optimize the delivered therapy continuously and autonomously.

Reference List

(1) Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PMA. Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 2004;23:232-40.

(2) Global initiative for chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2010.

CHAPTER 5

PHYSICIAN REMOTE INTERVENTION FOR THERAPY OPTIMIZATION

Telemedicine comprehends a great number of applications and different kind of uses in order to provide better and wider health services. Patients with impaired respiratory system have particular needs depending on the specific disease evolution and therapies. In particular COPD patients main exigency is the disease management and maintenance in order to avoid exacerbations and worsening of the conditions.

As shown in the previous chapter, home telemonitoring can be an effective tool to achieve these objectives, however in case the necessity to change the therapy arose, the patient would have to go to the hospital for standard visits and prescriptions.

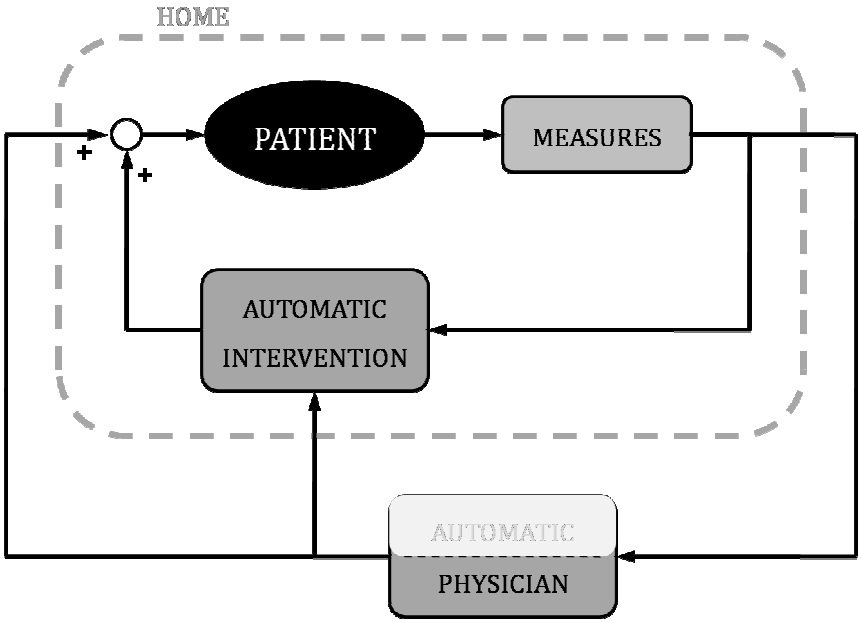

Figure 5.1: The new Telemedicine model highlighting the third ring, the remote physician's intervention

A fundamental element of telemedicine is the intervention of the physician at distance in order to modify the therapy directly at patient's home. In principle the intervention can be done in two different manners, asynchronously or synchronously. The first kind of intervention

involves the exchange of pre-recorded data between two or more individuals at different times, while the second type of intervention takes place in real-time and requires the involved individuals (i.e. patient and health care professional) to be simultaneously present for immediate exchange of information.

Among COPD and SDB patients' treatments, ventilatory therapy is a ticklish issue that must be addressed in the proper way, and telemedicine, through real-time telemonitoring and telecontrol of the ventilatory settings, allows to properly manage the ventilatory support applied.

During the Doctorate program it has been addressed this issue developing a new device able to allow the physician a direct connection to the patient's home mechanical ventilator in real-time. Through the new device the physician is able to tele-monitor and tele-control the ventilator (CPAP or BiPAP) in order to optimize the ventilatory therapy delivered.

5.1 Real-time Monitoring and HMV Adjustment: the first test

Home mechanical ventilation (HMV) is progressively being used to treat patients with severe chronic respiratory failure caused by neuromuscular diseases, chest wall abnormalities or pathologies of the lung parenchyma (1), (2). Treatment with HMV increases the quality of life of the patient because he/she is not hospitalized but lives at home. HMV also has economic advantages for the health system, either public or private, because of the associated cost reduction. The use of HMV has experienced an extraordinary increase in the last decade (1) and its application is expected to rise considerably owing to the progressive increase in chronic respiratory patients in our ageing population (3).

Contrary to application of mechanical ventilation at the hospital ward, HMV is provided with no continuous surveillance by health care professionals. Consequently, quality control and follow-up are key issues for optimizing this therapy (4). Indeed, it is important to ensure a good adaptation of the ventilator to the patient at the home environment, particularly in the first days after discharge. The most conventional clinical procedure when discharging the HMV patient is that the settings of the ventilator are determined at the hospital during a short trial which in some cases does not include a sleep period (5). At home, there are several factors that can contribute to reduce the adaptation of the patient to the ventilator: the patient's clinical status can change, different daily activities, position variations and also the quality of mask fitting can be reduced. Therefore, all these factors can contribute to the reduction of the actual

ventilation that the patient actually receives (6;7). Hence a crucial point is both to monitor the quality of the ventilation provided to the patient at home and to adjust the ventilator's settings accordingly to the needs of the patient. These factors point out the need for suitable quality assessment and show that follow-up of HMV can be enhanced if early discharge protocols are applied.

A crucial point for HMV quality control and follow-up is to monitor the actual ventilation received by the patient at home and to adapt the ventilator settings to the patient's requirement. The main reason why the implementation of tele-health is difficult in this practical application is that the conventional telemedicine approach consists of a complex technological architecture based on centralized server systems, usually requiring commercial agreements between the HMV provider and the company providing the telemedicine platform. Given the complexity of information technologies in health care, these approaches hinder the widespread application of instrumentation telecontrol, particularly in the field of HMV and also prevent further extensive research studies to investigate to what extent HMV telecontrol could be cost-effective.

The aim of this work was to develop and test the feasibility of a novel approach for monitoring and controlling HMV in a straightforward way. Contrary to the most conventional settings, the system designed avoids any high order information technology architecture. It is based on a simple and low cost data transfer server (DTS) that can be connected to most commercially available ventilators. The device captures ventilation signals (e.g. pressure, flows, volume, leaks, oxygen saturation) and controls the ventilator settings. The device operates, via conventional wireless mobile data network, as a web server with its own address and password. With such an approach, an independent point-to-point (from patient home to HMV provider) communication is established. Therefore, the HMV provider (being a hospital service or a private practice physician), can receive real-time or previously recorded ventilation data and modify the settings by simply connecting, via internet, to the individual web address of the DTS at the patient's home.

5.1.1 Methods

Monitoring device.

We developed a low-cost tele-monitoring device assembled in a small and lightweight box that is made of three components: 1) an embedded system board (FOX board LX100,

Acmesystems s.r.l., Roma, Italy) 2) a GPRS (General Packet Radio Service, a data transmission protocol for GSM mobile phone networks) modem (Industrial Modem GPRS Plus, Audiotel, Mozzo (BG), Italy); and 3) a commercial USB flash memory disk used for data logging (512 MB). The FOX board is based on a ETRAX 100LX 100 MIPS RISC microprocessor with 16 MB of RAM and 8 MB of flash memory, 2 USB 1.1 ports, two serial ports and one Ethernet (10/100Mb/s) adapter. The device runs an embedded Linux operating system and the full development system is freely available on Internet. All these devices were assembled in a small and lightweight unit whose external dimensions are 110x106x46 mm.

Given that commercial ventilators have different options for data communications, we developed a flexible software platform for the DTS in which the data acquisition module can be easily adapted to the communication system provided by any mechanical ventilator. An optional 12-bit analog-to-digital and digital-to-analog converter provided analog inputs and outputs that, together with the serial port available on the DTS, allows the connection to any other measuring device (e.g. external pressure, flow transducers or pulse oxymeters).

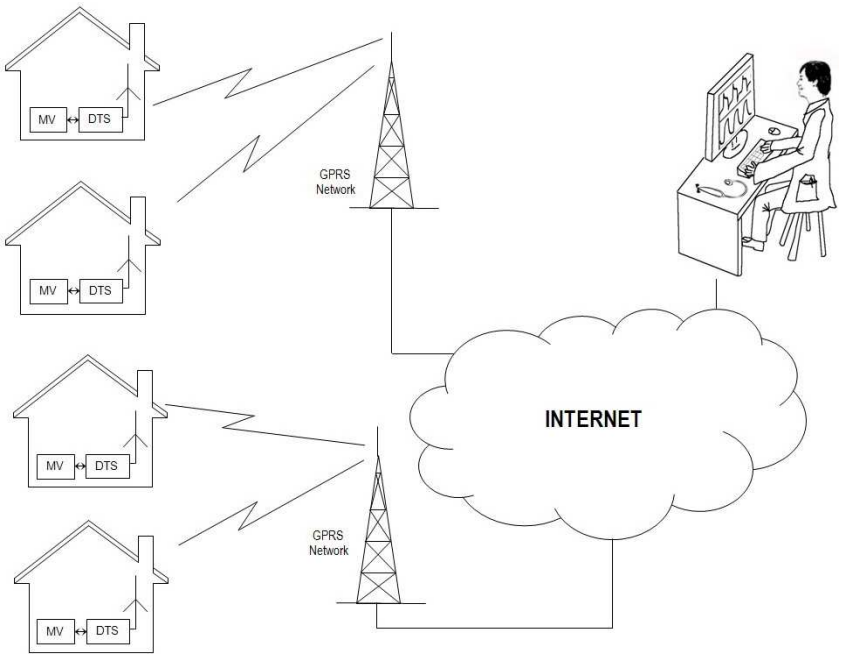

Figure 5.2: Diagram of the network architecture adopted in this study. MV: mechanical ventilator; DTS: data transmission system; GPRS network: General Packet Radio Service, a data transmission protocol for GSM mobile phone networks.

Network architecture

To avoid the need for a centralized network with dedicated servers, we developed a software for the DTS to make the system act as a server itself allowing an authorized personal computer connected to Internet to exchange data with it (Figure 5.2).

The software developed for the DTS runs one program which waits for connection on one specific TCP/IP port. Once connection is established, the client computer is identified by a proper combination of username and password and a TCP/IP socket is opened for data transmission.

As the IP address of the DTS is dynamically assigned from the service provider and it changes for each connection, it is necessary to make the client application aware of the DTS actual IP address to allow the connection. To this purpose, we used a public dynamic DNS service (in our prototype we used the free service provided by No-IP.com, Vitalwerks Internet Solutions, Reno, NV, USA). The DTS runs a software daemon which sends the actual IP assigned by the GPRS network to a DNS server every 5 min. This server updates its name resolution tables accordingly to the actual IP address. With this approach, every single DTS can be identified by assigning it a symbolic name (for example, in our experiments we used the symbolic name "resmon1.zapto.org") without requiring any dedicated server. If the IP of the DTS changes, there could be a short period (5-10 min maximum) during which the DTS cannot be reached from the Internet through its symbolic name.

The system works as follows: when the patient switches on the device the system starts recording the data from the ventilator. At the same time, it connects to Internet through the wireless modem. Once the connection is established, any authorized user can connect to the DTS through Internet by indicating the device symbolic name. When the physician wants to monitor the mechanical ventilation delivered to the patient, he/she connects his/her personal computer (or PDA) to Internet and executes a program which asks 1) which is the device that he/she wants to connect to and 2) which is the period of time of interest (either real-time or data previously recorded, for example referring to the previous night). The program connects to the DTS at the patient's home, requests the proper data and displays them on graphs (an example of the Personal Digital Assistant, or PDA, version of the software is shown in Figure 5.3). The program also allows the physician to change the settings of the mechanical ventilator (in our example the inspiratory and expiratory pressures for bi-level mechanical ventilation). When the physician updates these values on his/her computer, the new settings are transmitted to the DTS and introduced in real-time into the mechanical ventilator, after verifying that the new values are within a previously programmed safety range.

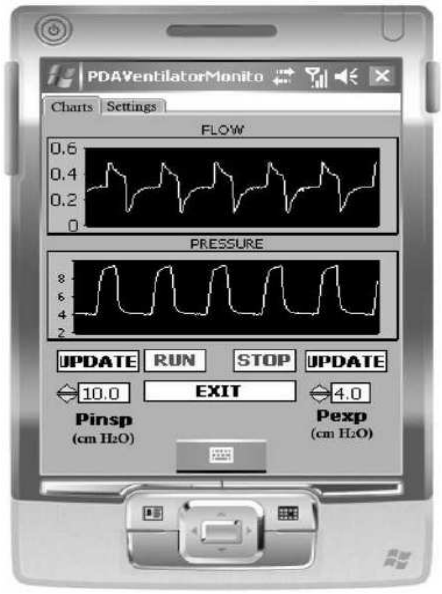

Figure 5.3: Screenshot of the PDA version of the software which allows the physician to monitor the signals from the mechanical ventilator and to modify the settings in real-time. Pinsp: inspiratory pressure; Pexp expiratory pressure.

Consideration on data security and patients privacy

The privacy of the data transmitted by the device used in this work is the same provided by commercial cell phone communications, which are protected by national and international laws. In our prototype the data transmitted over the network were encoded but not encrypted. However, the Linux operating system used by the DTS allows us to add this security feature (for example by using data encryption and user identification by a double combination of public and private keys) with limited efforts. Moreover, it is remarkable that privacy is ensured because no patient personal data are transmitted through the network (each patient device is identified by means of a symbolic name (see section on Data communication).

Validation setting

This approach was tested in two experimental protocols, one in vitro and another in vivo. In both cases the DTS was placed in one laboratory (Universitat de Barcelona, Spain), and was connected to a bi-level mechanical ventilator (BiPAP S/T-D, Respironics, Murrysville, PA, USA) through its analog signals port. The ventilator provided airway opening pressure, flow (both uncorrected and corrected for estimated leaks) and volume signals. The ventilator received also two analog signals for setting the inspiratory and expiratory pressures. The connection to the mobile network was obtained by subscribing a data-only transmission flat-

rate plan for GPRS (General Packet Radio Service) from Vodafone-Spain. The client program was run on a personal computer connected to Internet by an operator from another remote laboratory (Politecnico di Milano, Milano, Italy). Data were sampled and transferred at a rate of 10 samples per second for each of the four input channels used during the experiments.

Reliability study

Our network architecture is based on the concept of an embedded server placed in the patient's home connected to the internet by a wireless link, which is usually less reliable than wired link. To identify how possible GPRS failures may impact the usefulness of our telemedicine system, we developed a program which simulated the activity of a physician by activating the connection every two hours and recording the signals for 1 min. This program was run from Milano and the DTS was connected to the ventilator in Barcelona. This procedure was carried on 24 hours per day for 8 consecutive days, and the data were analyzed to identify any failure in the connection.

In vitro study

A mechanical test lung (resistance=12 $cmH_2O \cdot s/L$, compliance=0.04 L/cmH_2O) was connected to the ventilator to simulate a patient. An operator in Milano blinded to the activity in Barcelona was instructed to monitor the ventilation and, when detecting changes in tidal volume signal appearing in the client program, to change the settings of inspiratory and expiratory pressures in order to maintain the tidal volume. An operator in the Barcelona lab simulated a change in the patient's mechanics by reducing the compliance of the test lung to 0.02 L/cmH_2O.

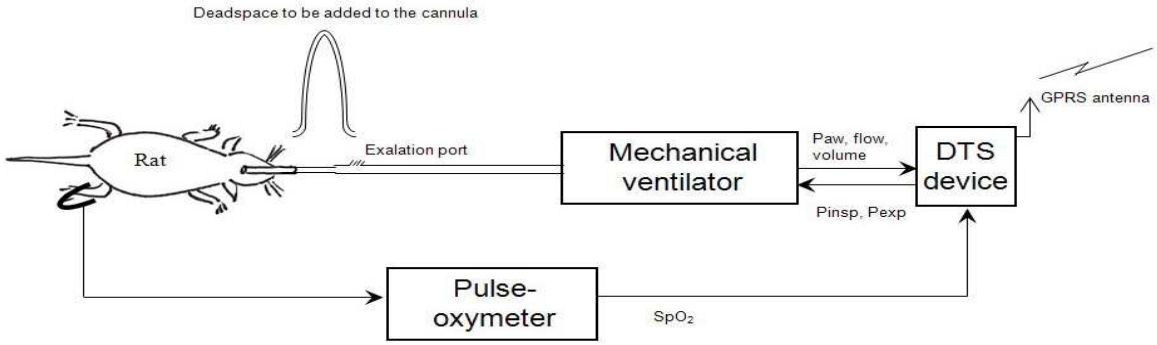

Figure 5.4: Experimental set-up for the in-vivo validation study. A deadspace has been added at a given time to the cannula to reduce alveolar ventilation. Paw: airway pressure. Pinsp and Pexp: inspiratory and expiratory pressures delivered by the ventilator

In vivo study

This part of the study was approved by the local Ethical Committee for Animal Research. An anesthetized and paralyzed and intubated male Sprage-Dowley rat (270g) was connected to the same mechanical ventilator and monitoring device used for the in vitro experiment (Figure 5.4). The oxygen saturation analog output of a commercial pulseoxymeter (504; Critical Care Systems, Inc., Waukesha, WI) connected to the leg of the rat and the pressure signal from the ventilator were connected to the DTS device. The operator in Milano was blinded to the activity of the experimenters in Barcelona and was instructed to modify the ventilator pressures to keep the baseline oxygen saturation along the experiment. At a given time, 1.3 mL of deadspace (made by a tube of internal diameter 3.5 mm and length 135 mm) were added at the entrance of the tracheal cannula to reduce oxygen saturation.

5.1.2 Results

During the reliability study a total of 96 attempts to connect to the DTS were performed. In only three cases it was not possible to get immediate response from the DTS.

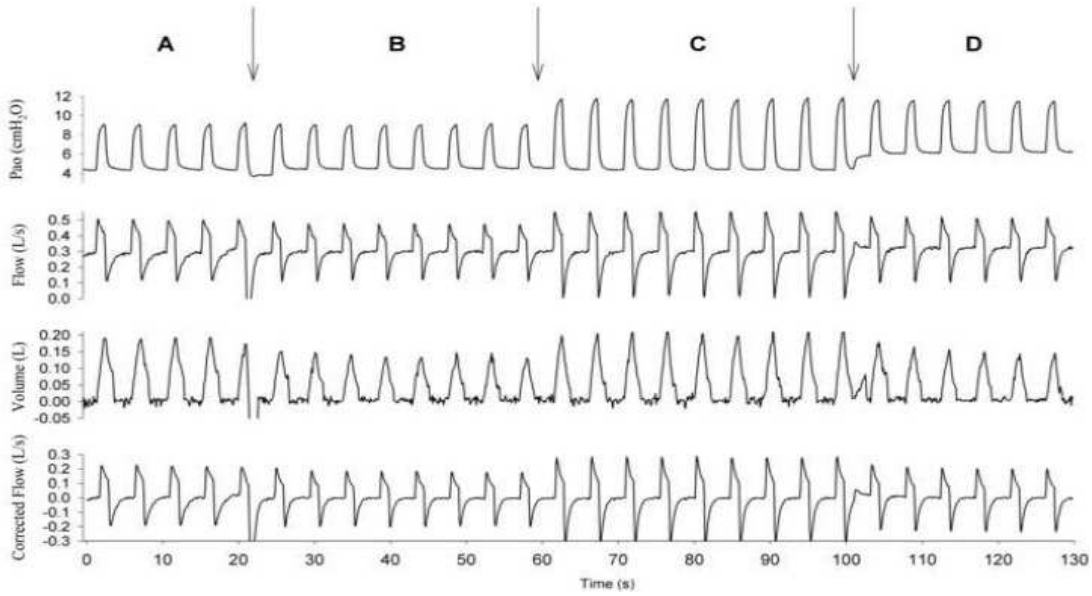

Figure 5.5: Representative experimental tracing recorded during the in-vitro validation study. During period A the ventilator (in Barcelona) was running with baseline parameters. The remote operator (in Milano) was connected to the DTS and visualized the data in real time. At the beginning of period B the test lung compliance was increased. This was immediately noticed from Milano. As a consequence, the operator changed the inspiratory pressure (period C) obtaining an immediate increase in tidal volume. At the beginning of period D, the operator remotely increased also the expiratory pressure, which, as expected, produced an immediate reduction in ventilation.

This can be due to temporary disconnections to the GPRS network or to a change of IP address which causes the impossibility to connect to the DTS for five to ten minutes during which the DNS tables have to be updated.

However, in all these three cases the following attempt to connect to the DTS was always successful. The recorded data were always correct with no missing or corrupted values.

Figure 5.5 shows a representative experimental tracing from the in vitro experiment in Barcelona recorded from Milano. In the first part of the experiment (period A) the ventilator was running with baseline parameters. An increase in the test lung compliance was immediately noticed from Milano (period B). The operator changed first the inspiratory pressure (period C) obtaining an immediate increase in tidal volume. After 40 seconds, he increased also the expiratory pressure, which, as expected, produced an immediate reduction in ventilation (period D).

A representative experimental tracing of the in vivo experiment is reported in Figure 5.6. The operator in Milano was connected to the DTS while the rat was ventilated in Barcelona with baseline settings. At time A the dead space was added to the cannula, resulting in an immediate drop in oxygen saturation. The operator in Milano, unaware of this experimental change, reacted by slowly increasing the inspiratory pressure by steps, with the consequent restoration in alveolar ventilation as evidenced by the oxygen saturation signal (time B).

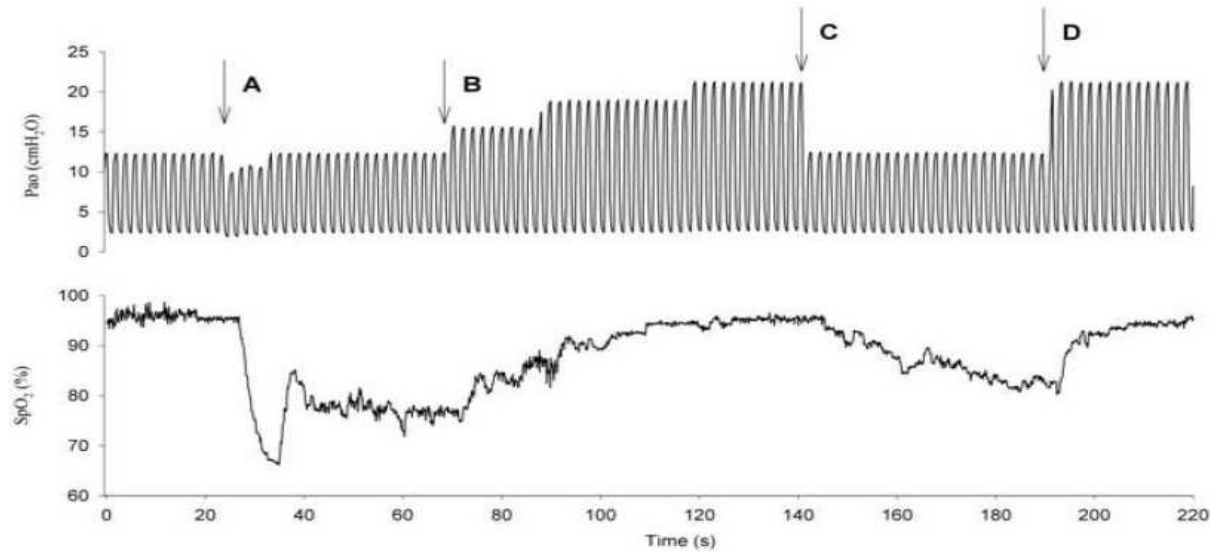

Figure 5.6: Representative experimental tracing recorded during the in-vivo validation study. A rat was ventilated in Barcelona and the ventilator was monitored and controlled from Milano. At time A a deadspace was added to the cannula, resulting in an immediate drop in oxygen saturation. The operator in Milano reacted by slowly increasing the inspiratory pressure by steps and restoring alveolar ventilation (time B). After approximately 20 seconds the operator reduced the inspiratory pressure to see whether the observed reduction of oxygen saturation was transient (time C). As the dead space was still connected to the rat, this procedure resulted in a new drop in saturation and, therefore, the operator restored the high inspiratory pressure (time D).

Given the high values of required inspiratory pressure, the operator reduced it to the baseline value to see whether the observed reduction of oxygen saturation was transient (time C). As the dead space was still connected to the rat, this procedure resulted in a new drop in saturation and, therefore, the operator restored the high inspiratory pressure to normalize blood gases (time D).

5.1.3 Discussion

The approach described in this work is conceptually novel in that the bidirectional link between the patient's home and the physician is carried out in an independent point-to-point communication by the wireless mobile phone network. As far as clinical applicability is concerned, the main advantage of the approach is that the physician or any health professional in charge of mechanical ventilation is able to monitor the ventilation signals and to modify the settings of the ventilator in real time, by connecting to Internet through any personal computer or PDA. The novelty in this rationale is that the procedure proposed avoids the need for any telemedicine network involving complex architectures and contracts with third part companies providing the telemedicine service. Moreover, it is also remarkable that this approach can be applicable to homes of any socio-economic status. Indeed, given that the device communicates via the conventional and cheap cell phone technology, no communication facilities (telephone nor internet) at the patient's home are required.

It is well known that there is a considerable delay between the progress in the information and communication technologies and their medical application, particularly in the field of respiratory medicine. A possible reason to explain this delay is the difficulty to implement these technical advances in the clinical arena. Indeed, the conventional telemedicine approach is based on complex information architectures involving hospitals, call centres and external communication companies providing the tele-health links (8-10). In our opinion, this approach causes a vicious circle that limits a more widespread use of the telemedicine tools technologically available. On the one hand, there are almost no research studies assessing the cost-effectiveness of telemedicine because its application requires a complex and expensive information/technology network, and, on the other hand, companies and hospitals do not implement these networks because there are not enough previous data demonstrating their cost-effectiveness. By incorporating the simple and cheap communication technology currently available, this work provides a proof of concept of the feasibility of an alternative paradigm in the communication architecture in telemedicine.

The most simplified procedure for off-line monitoring of HMV is currently implemented in modern ventilators and consists of built-in memory facilities to store ventilation data for further download and analysis. The approach devised in this work adds the possibility of controlling the ventilator settings to optimize patient ventilation in real time according to the actual ventilation signals.

The safety of the system is warranted by the possibility to change the settings only within a previously defined safe range stored in the DTS. Another important comment concerning safety is that HMV is usually a non life-support system but a therapy to support ventilation in spontaneously breathing patients. In fact, a significant number of HMV devices legally-approved and currently in use do not have a built-in full set of alarms (6).

An obvious potential application of our approach is to help in the adaptation of the HMV to patient in the first days/weeks after discharge. Indeed, during the initiation of HMV, the health professional in charge of it can interact at distance with the patient to help him/her to better adjust the mask to reduce leaks and to improve comfort by adapting ventilator settings. In addition to optimize the treatment, this active and real-time interaction could empower the patient and facilitate tolerance. This system could also be useful to readapt the ventilator settings in the case that, after several weeks/months after treatment initiation and as a result of a change in clinical status, the patient does not feel comfortable or the efficacy of the treatment is reduced.

The telemedicine approach devised in this work could also be useful to better assess the effectiveness of HMV where there is not enough evidence available. For instance, at present there is no consensus in the literature concerning whether patients with chronic obstructive pulmonary disease (COPD), or what specific COPD subpopulation, should be treated with HMV. Given that in absence of detailed monitoring the actual ventilation received by the patient could be clearly different from that prescribed (6;7), it is possible that assessment of HMV effectiveness in some patients is masked by lack of monitoring and ventilator settings adaptation. Finally, real-time telecontrol of ventilators could be applied to the titration of the level of continuous positive airway pressure (CPAP) required by patients with the obstructive sleep apnea syndrome (OSAS). By allowing the simultaneous CPAP titration of several patients at home by one sleep technician who is not necessarily operating in a specialized sleep lab (11), this approach could reduce the large waiting lists for CPAP titration in OSAS (12).

In conclusion, the described telecommunication approach is a potential contribution to initiatives aimed at extending the provision of health services at patient's home such as those promoted by the National Institutes of Health and the European Commission. The system is

easy to implement and can considerably facilitate the application of telemonitoring and telecontrol in the specific field of home mechanical ventilation. It can be useful not only for future routine applications but also to facilitate the performance of research studies to assess the potential effectiveness of telemedicine in home mechanical ventilation.

5.2 Telemetric CPAP Titration at Home in Patients with OSAS

Individual titration of the level of continuous positive airway pressure (CPAP) suitable for treating each patient is commonly indicated after diagnosis of moderate-to-severe obstructive sleep apnea-hypopnea syndrome (SAHS). To this end, the standard procedure is based on the determination of the level of nasal pressure that normalizes the patient's sleep and breathing during a full-night attended laboratory polysomnography (PSG) (13). However, given that PSG titration is expensive and time-consuming, and bearing in mind the long waiting lists in many sleep labs, alternative procedures for simplifying CPAP titration have been proposed (14). In most of these methods CPAP titration only involves the analysis of breathing variables during sleep (15;16).

One widespread simplified procedure for titrating nasal pressure in SAHS patients is based on the use of automatic CPAP devices during sleep in the patient's home. These devices measure various respiratory variables in order to detect breathing abnormalities (apneas, hypopneas, flow limitation and snoring) by means of built-in pressure and flow sensors; the machine then uses proprietary algorithms to modify nasal pressure automatically and normalize breathing. The signals recorded during the titration night are digitally stored by the device and are subsequently downloaded by the sleep lab staff and used to determine the optimal CPAP for treating the patient. Several studies evaluating the performance of automatic CPAP titration at home have shown that this procedure can predict the fixed CPAP that would eliminate all respiratory events (13-16). Unfortunately, automatic CPAP titration at home is not applicable to a non-negligible number of SAHS patients: for instance, in patients with significant comorbidities, such as chronic heart failure, chronic obstructive pulmonary disease, central sleep apnea syndromes, or hypoventilation syndromes (17). In fact, it has been reported that around 20% of consecutive SAHS patients may not be candidates for automatic CPAP titration and therefore require full PSG titration (16;17). Furthermore, it could also be possible that the automatic unattended procedure fails in some eligible patients because a lack of feedback or psychological support from sleep lab staff (18).

In order to improve simplified CPAP titration at home, this study seeks to design and assess the feasibility of a novel procedure for telemetrically titrating CPAP in the patient's home. The approach is based on controlling the CPAP device at home through the simultaneous monitoring of breathing signals and modification of nasal pressure from the hospital in real time.

5.2.1 Methods

Patients

The study was carried out on 20 consecutive patients (age = 56 ± 3 years; body mass index (BMI) = 35 ± 2 kg/m2; mean ± SE) for whom CPAP treatment was recommended, recruited immediately after a diagnosis of SAHS with full polysomnography (apnea-hypopnea index (AHI) = 58.1 ± 5.1 events/h and percentage of sleep time with arterial oxygen saturation below 90% (CT90) = 19.8 ± 4.4 %). The protocol was approved by the Ethical Committee of the Hospital Clinic of Barcelona and informed consent was obtained from the patients.

Device for telemetric home CPAP titration

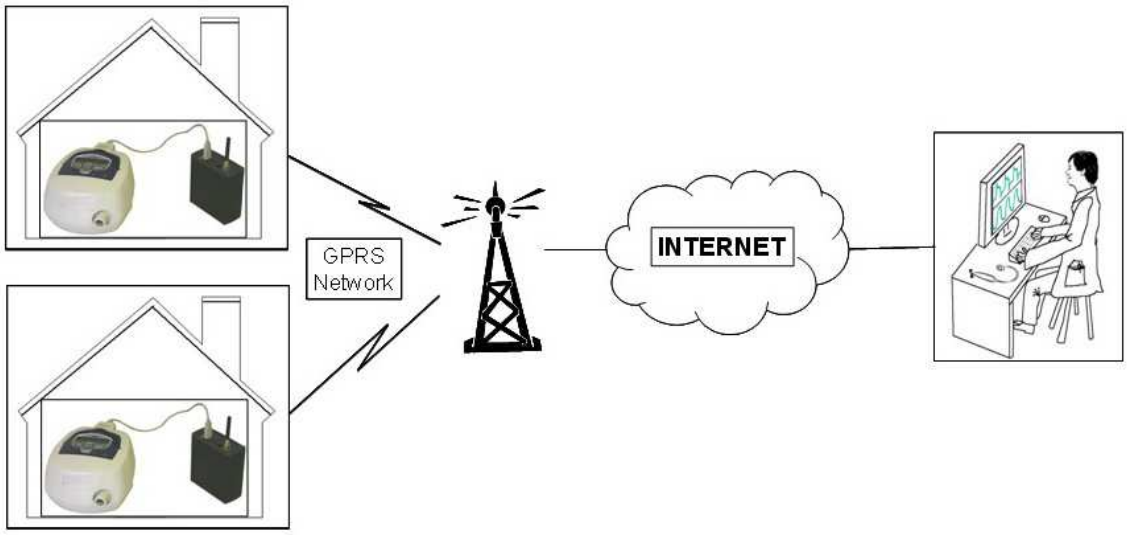

Figure 5.7: Network architecture of the telemetric system for CPAP titration in the patient's home. The telemetric system connected to the CPAP device acts as an individual stand-alone server, allowing an authorized user connected to Internet to obtain flow, pressure and airleak tracings and adjust the CPAP level.

The novel approach used for the titration of CPAP in the patients' homes is shown in Figure 5.7. The system is based on a telemetric unit connected to a commercially available

CPAP device. The telemetric unit, which has recently been developed and technically validated (see Paragraph 5.1) (19), permits two important functions: remote monitoring of the flow, pressure and airleak signals from the CPAP device, and adjustment of the nasal pressure applied to the patient in real time.

Unfortunately, nowadays there are no standardized communication protocols for mechanical ventilators and each manufacturer is free to define its own. For this reason, an appropriate communication software module has to be added to the telemetric unit. To do this, the communication protocol needs to be provided by the manufacturer.

The telemetric unit uses the conventional mobile phone data network (GPRS) via a Class 10 data modem, which uses 3 TDMA time slots for download and 2 for upload, providing a maximum bit rate of 40 Kbps and 60 Kbps, respectively. It operates as a stand-alone, ready-to-use Internet server with its own address and password. The unit establishes an Internet connection throughout the time that the ventilator is used. It acts as a server that collects and stores all the data provided by the ventilator in an internal database. When a physician/technician tries to connect to it, the device verifies the caller ID and starts sending the ventilator signals (flow, pressure, leaks) in real time. The system can also send data previously recorded in its internal database (for example hours or days previously), if requested.

Therefore, when the patient is at home the sleep technician can monitor the breathing signals and modify the patient's nasal pressure in real time by simply connecting to his/her specific device via the Internet. The telemetric unit was set to transfer nasal pressure, breathing flow and airleak signals at a rate of 12.5 Hz each. A low-overhead binary communication protocol was designed to achieve both efficiency when using the limited available bandwidth and reliability in the identification of possible data losses. Custom-made software allowed the technician to observe, store and review the transmitted signals by means of a computer screen similar to those used for conventional polysomnography, thereby allowing the technician to manage several patients at home simultaneously.

Telemetric home CPAP titration.

Before CPAP titration the patient received a 1-hour day-time training session in our laboratory to adapt to the CPAP equipment. During training, the nasal pressure applied was 4-6 cmH2O and the patient was asked to freely alternate both sitting and supine postures. The patient took the CPAP machine (Autoset Spirit, Resmed), mask, tubing and telemetric unit back home with instructions about how to use them during sleep. The technician explained to

the patient that his/her breathing signals during sleep would be remotely monitored from the hospital and that the nasal pressure applied would be optimized accordingly. During the night the technician monitored nasal pressure, breathing flow and air leaks and titrated the optimal CPAP required. The starting pressure was 4 cmH2O, and the pressure was increased by 1 cmH2O every 5 minutes until the apneas disappeared. Thereafter, the pressure was increased by 1 cmH2O every 10 minutes until the hypopneas, flow limitation and snoring disappeared. In the final hour the CPAP pressure was slowly reduced to see whether a lower nasal pressure could be appropriate. The final pressure that normalized breathing was considered to be the optimal CPAP. The following day the patient dropped off the CPAP device and telemetric unit in the sleep lab. No CPAP therapy was applied until the patient was subsequently subjected to full PSG titration in the sleep lab.

Assessment of CPAP titration.

To assess whether the optimal CPAP value telemetrically determined at home was able to normalize sleep, the patient was subjected, one week after home titration, to a nocturnal full PSG in the sleep lab with the fixed CPAP recommended by the telemetric procedure. For the first 4 h CPAP was set to the value titrated telemetrically at home. This procedure allowed us to determine the residual AIH and CT90. To assess whether the CPAP pressure could be optimized, during the final 2 h of the night the technician modified the nasal pressure according to the conventional procedure of polysomnographic CPAP titration (whereby the optimal pressure value eliminates all respiratory events in all sleep stages in the supine position). This final pressure was considered the optimal CPAP. The same technician carried out both the home and PSG titrations for all the patients.

Statistical analysis

Data are shown as mean ± SE. Paired t-tests were used to compare AHI and CT90 during the diagnostic polysomnography and the hospital polysomnography, when the patient was subjected to his/her home-titrated CPAP value. A Bland-Altman analysis (20) was used to compare the CPAP value titrated telemetrically at home and the polysomnographically determined CPAP value.

5.2.2 Results

The average airleak recorded during the home telemetric titration was 0.12±0.03 L/s. The percentage of recording time with airleak lower than 0.4 L/s, which could be considered a reasonable threshold to ensure correct titration from a technical viewpoint, was 7.8±3.1%. Interestingly, in the 5 patients exhibiting a percentage of time with airflow >0.4 L/s greater than the mean value (7.8%), we did not observe any discrepancy between the CPAP value determined at home and the pressure that optimized breathing during hospital PSG, suggesting that the potential technical problems induced by airleaks were similar in both the home and lab CPAP titrations.

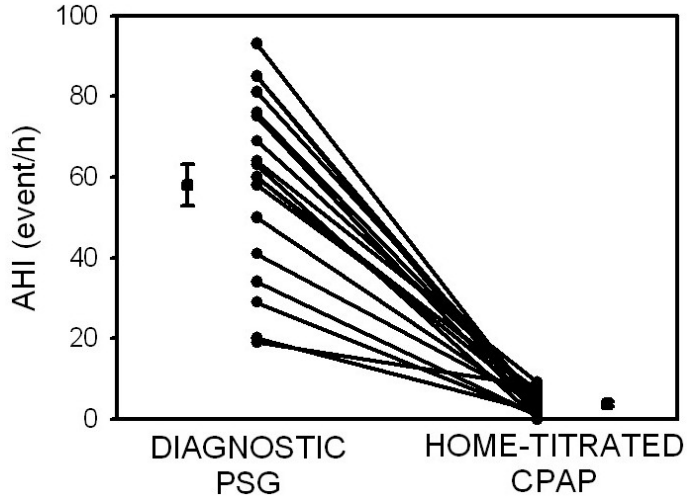

Figure 5.8: Apnea-hypopnea index (AHI) and percentage of sleep time with arterial oxygen saturation below 90% (CT90) during the polysomnography used to diagnose SAHS and during a polysomnography performed when the patient was subjected to the CPAP value titrated telemetrically at home. Circles correspond to individual data. Squares and error lines correspond to the mean±SE.

The CPAP value titrated telemetrically at home proved to systematically improve patients' breathing during sleep when it was applied several days after titration. As shown in Figure 5.8, AHI and CT90 were reduced from 58.1 ± 5.1 events/h to 3.8 ± 0.6 events/h and from 19.8 ± 1.1% to 4.4 ± 0.7%, respectively ($p < .001$ in both cases).

In keeping with this result, the CPAP value determined telemetrically at home (9.15 ± 0.47 cmH2O) was virtually the same as the pressure that optimized breathing during hospital polysomnography (9.20 ± 0.41 cmH2O) one week after telemetric titration at home, Figure 5.9. The mean difference was 0.02 cmH2O and the limits of agreement were ± 1.00 cmH2O.

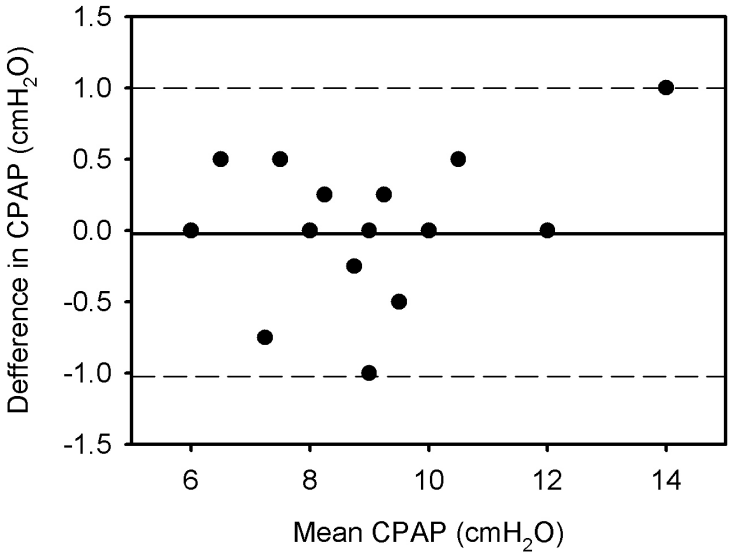

Figure 5.9: Bland-Altman analysis of the optimal CPAP titrated telemetrically at home and under polysomnography in the hospital for each patient. The solid line corresponds to the mean difference and dashed lines are the limits of agreement. A number close to the upper left corner of a data point indicates the number of patients corresponding to this point.

5.2.3 Discussion

The results of this pilot study show that the novel telemetric procedure implemented for CPAP titration in the patient's home was useful for determining the value of nasal pressure for treatment in a population of consecutive SAHS patients with a wide range of SAHS severity (AHI: 18 – 93 events/h).

The CPAP value telemetrically determined at home was shown to reduce the two main indices of sleep breathing disturbance when the patient was polysomnographically evaluated in the sleep lab one week later. The degree of reduction in AHI and CT90 was similar to that reported when CPAP is titrated by the standardized PSG method (16). The difference between home-titrated CPAP and the nasal pressure that optimized sleep and breathing in the sleep lab study was, on average, negligible (0.02 cmH2O). Remarkably, the limits of agreement of this difference (± 1.00 cmH2O) were within the ranges of reproducibility observed from night to night (21), or compatible with the different, widely accepted CPAP titration methods routinely use in clinical practice (16).

This study was conceived to test the feasibility and performance of a new technological approach and was not a conventional randomized controlled trial (RCT). Accordingly, this study has some methodological limitations when compared with RCT designed to compare different procedures for CPAP titration. Firstly, the order in which the patients were studied

was not randomized. Secondly, the technician who carried out the hospital PSG was aware of the value of the CPAP value titrated at home by telemetry. Thirdly, only the final 2 hours of sleep were used in the night in hospital to assess whether this CPAP value could be improved. In fact, we did not even compare the telemetric titration procedure with the conventional one based on PSG. Instead, we tested whether the value of CPAP titrated at home was able to virtually eliminate breathing disturbances during a night on PSG in the sleep lab. Apart from these limitations, which prevent us from drawing any conclusions about the clinical validity of this novel methodology, the results did reveal the practicality of this approach in clinical practice.

The telemetric system used in this study is based on currently available low-cost, miniaturized integrated circuits and works out cheaper than an APAP device. The system has three functions: first, the capture of digital signals from any conventional apparatus (for instance, flow, pressure and airleaks from a CPAP device or arterial oxygen saturation from a pulse oximeter (19)); second, the transmission of signals to control another appliance (e.g. to modify nasal pressure in a CPAP device); and, third, and most importantly, the function of an independent Internet server via a mobile phone SIM card, with its own conventional web address and password. Given the relatively low sampling frequency required for this application, the broad outreach of GPRS provides sufficient communication facilities, although the telemetric unit can also operate on a G3 telephone network or on potential future conventional networks (19).

The use of a wireless network introduces potential problems of data loss and connection breakdowns (as well as problems of data security) that would affect the overall reliability and security of our system. The transmitted data are provided to the telemetry unit by the ventilator in digital format. As data are transmitted via reliable communication protocols capable of identifying possible data corruption, any incorrectly transmitted data are identified and barred from being displayed to the operator.

To improve reliability in the case of a lost connection, our software was designed to detect this problem and automatically redial if required. Temporary interruptions to the connection were occasionally observed (slightly less than 1 per full night study, on average, in keeping with our previous technical study (19)). In these cases, the system performed the automatic redialing procedure and was usually back online in less than 5 min, or at most 10 min.

As regards privacy, only digital signals are transmitted via the GPRS phone line and no personal information on the patient are sent or even stored in the telemetric device, thus

significantly reducing any concerns about data protection. Moreover, digital signals are sent via a proprietary binary protocol, making any kind of data sniffing even more difficult. Finally, in this prototype, we do not protect the transmitted data. However, given that the system is a Linux-based embedded device, the incorporation of an encrypted data transmission channel would be a relatively simple technical improvement.

Previous applications of telemedicine in SAHS were limited to supporting the patient in order to improve treatment compliance or to remotely download previously recorded data (22-26). The novelty of the present approach is that a telemetry unit is connected to a commercially available CPAP device to permit a low-cost (1.5€ per night per device), two-way communication channel in real time between the sleep lab technician and the CPAP device in the patient's home. Accordingly, the approach requires no special telemedicine platform, nor does it require any kind of communication infrastructure (computer or the Internet) in the patient's home or his/her active cooperation. It is therefore applicable to homes from a wide range of socio-economic levels.

This pilot study opens up the possibility of introducing changes to the organizational model and budgeting of sleep labs by providing a way to improve unattended home CPAP titration via automatic CPAP devices. With the approach described in this work, the titration is carried out by a sleep technician instead of by an algorithm operating in the automatic CPAP machine. It seems obvious that the response capability and flexibility of a technician, including his/her capacity to phone the patient to advise on use of the CPAP equipment, could improve the effectiveness of home CPAP titration, at least in a subgroup of patients. In addition to this application, the telemetric system could be used to re-titrate CPAP in patients, to control CPAP performance or to manage patients living far away from the sleep lab. Furthermore, the procedure will be optimized with the incorporation of a pulse oximeter signal and will probably be useful in patients treated with bilevel mechanical ventilation.

5.3 Remote Titration and Optimization of Home Mechanical Ventilation

A new tele-monitoring and tele-control device has been proposed (19) and it suggests a concept of bidirectional link between the patient's home and the physician that is carried out by an independent point-to-point communication provided by the wireless mobile phone network. The main advantage of this new approach is that it allows the physician, or any health professional in charge of mechanical ventilation, to monitor the ventilation signals and to modify the settings of the ventilator in real time, by connecting to Internet through a personal

computer or PDA. Up to now this device has been tested and used to monitor and titrate the ventilator of patients affected by Obstructive Sleep Apnoea Syndrome (see Paragraph 5.2) (27).

The aim of this work was develop and improve the device functionalities to make it able to monitor the breathing pattern of patients affected by chronic respiratory diseases that require different and more complex ventilation monitoring and settings. The device is based on a simple and low cost data transfer server (DTS) that can be connected to most commercially available CPAP and BiPAP ventilators. It acquires different signals (e. g. pressure, flow, volume, leaks, oxygen saturation, heart rate, snoring information), snapshot of the patient through an infrared webcam, also suitable for night vision, and allows to remotely modify the ventilator settings. The device acts as a web server requesting authentication information using a conventional wireless mobile data network. As an independent point-to-point communication is ensured and achievable by this approach, a hospital service or a private practice physician can receive real-time or previously recorded data and modify the settings of the ventilator by simply connecting, via Internet, to the individual web address of the DTS at the patient's home.

5.3.1 Materials and Methods

Monitoring Device

We developed a low-cost tele-monitoring and tele-controlling device assembled in a small and lightweight box (see Appendix for details). The device has a flexible software platform in which the data acquisition module is adaptable to communication system of any mechanical ventilator. The DTS includes a GPRS (General Packet Radio Service) standard modem that allows the Internet connection and a ZigBee (IEEE 802.15.4-2003) module (XBee, MaxStream, DIGI, Minnetonka, Minnesota, USA) that provides a point-to-point wireless serial communication. It also includes a standard SD flash memory card (1Gb) used for data logging. A standard commercially available pulse oxymeter (XPOD Module, NONIN Medical inc., Plymouth, Minnesota, USA) is connected and supplied by a device that through a microcontroller (Microchip, dsPIC30f3013) samples patient oxygen saturation (SpO_2) and heart rate signals. The microcontroller sends the data to a ZigBee module that implement a direct serial communication with the DTS. The device is powered by a 6V 2400mAh battery and enclosed in a small plastic box. The microcontroller and the ZigBee module are held in a power saving functioning modality for about 4 seconds. After this time they activate, sample and send the pulse oximetry data to the DTS in about 0.5 seconds. This procedure is performed

to save power consumption and increase battery life. The DTS exchanges data with a mechanical ventilator connected through a standard USB port: ventilation signals, sampled at frequency of 20Hz, from the ventilator to the DTS, and ventilator control signals from the DTS to the ventilator. DTS is also connected to a webcam (Itry s.r.l., Napoli, Italy) through a second USB port. The webcam is capable of capturing snapshot in daylight and nighttime light thanks to six infrared LEDs. It is used to take pictures of the patient when requested by the operator. A diagram of the described system architecture is shown in Figure 5.10.

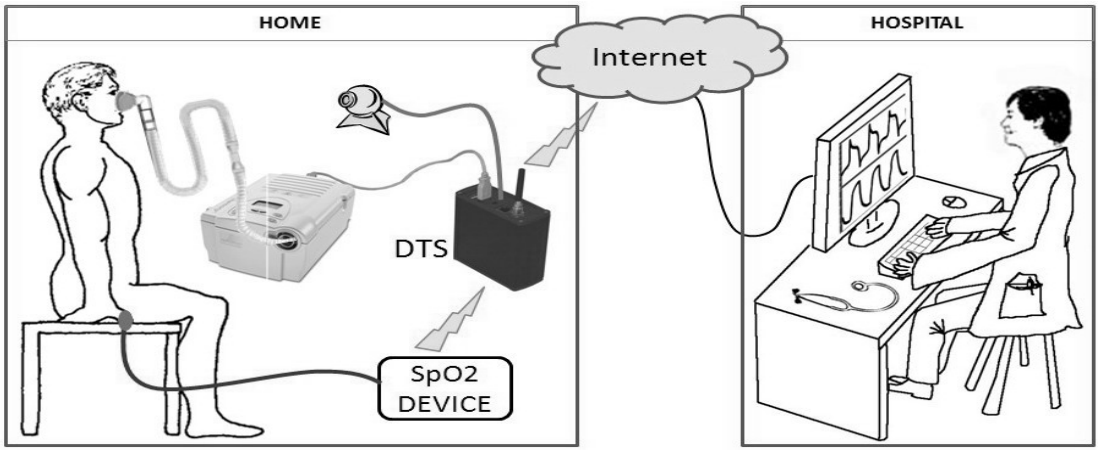

Figure 5.10: Architecture scheme of the whole system. On the left is shown the patient at home, that can be seated or laying. The DTS is connected to his ventilator and to a webcam, and the SpO2 device samples data from the patient. On the right is shown a physician at the hospital who is watching at the real-time data on his computer. The DTS and the computer are both connected to Internet.

When the DTS is switched on, it starts sampling and recording the data coming from the ventilator and from the SpO2 device. At the same time the DTS connects to Internet and activates a server that is ready to accept client connections. When a physician wants a connection to the patient's ventilator, he has to run a program (see Figure 5.11) installed on any computer connected to Internet. The program asks for the symbolic name of the patient's device and for authentication information. Patient's information are not transmitted thus ensuring privacy for patient's data. Once the physician is authenticated he can ask for real-time or previously recorded data. Physician's computer and the DTS are both authenticated through a Public Key based procedure. The DTS starts sending the requested data, which are showed in a graph, encoded through an Open SSL cryptography protocol. In every moment the physician can request a snapshot of the patient just clicking on a button. When the request is done, the DTS takes a frame from the webcam and sends it to the computer that shows the photography in a dedicated window. The program also allows the physician to change the settings of the mechanical ventilator through an apposite menu. When the physician updates these values on his/her computer, the new settings are transmitted to the DTS and sent in real-time to the

mechanical ventilator, after verifying that the new values are within a previously programmed safety range. The operation of the ventilator is not modified, therefore all the alarms and alerts are managed as usual. If the ventilator is used in assisted ventilation mode, the physician can change the settings of inspiratory and expiratory pressures, while if used in timed mode, he can also change the settings for inspiratory time and respiratory frequency.

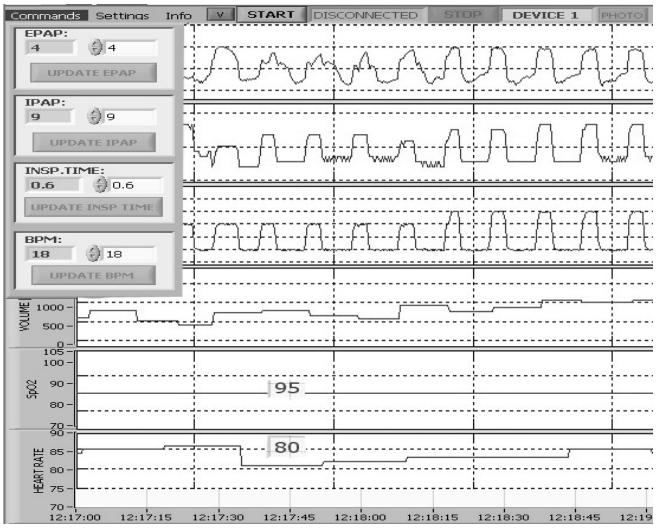

Figure 5.11: Zoom on a screenshot of the software installed on the physician computer that allows to see the traces and to control the ventilator through the menu showed. It is possible to see in the upper right corner the button (PHOTO) used to send the request for a screenshot

Device Testing: Experimental Set-Up

The DTS was placed in a sleep lab room (Hospital Clìnic, Barcelona, Spain) and connected to a bi-level mechanical ventilator (BiPAP Harmony, Respironics, Murrysville, PA, USA) through its first USB port, to the pulsoxymeter through the ZigBee module, and to the webcam through its second USB port. The ventilator provided airway opening pressure, flow, mask leaks, tidal volume, while the pulse oxymeter provided SpO_2 and heart rate. The ventilator was used in assisted ventilation mode, thus allowing to control the settings of inspiratory and expiratory pressures. The connection to the mobile network was obtained by subscribing a data-only transmission flat-rate plan for GPRS from Vodafone-Spain. Data were sampled at a rate of 20 samples per second and down-sampled and transferred at a rate of 10 samples per second for each of the four input channels coming from the ventilator. Pulse oxymetry and hart rate data were sampled every 4 seconds.

Device Testing: Study Protocol

Two patients with chronic obstructive pulmonary disease were studied in sitting position, connected to the ventilator in assisted ventilation modality with the attending physician next to him. The client program was run on a personal computer connected to Internet by an operator in an adjacent room in the same sleep lab, thus to allow the operator to the follow the instructions of the physician. The patient was instructed to breath normally and, when asked, to tell the physician if the current settings of the ventilator were comfortable or not. During the test the physician was periodically telling the operator how to set the ventilator and checking patient's signals. The test lasted about 30 minutes.

5.3.2 Results

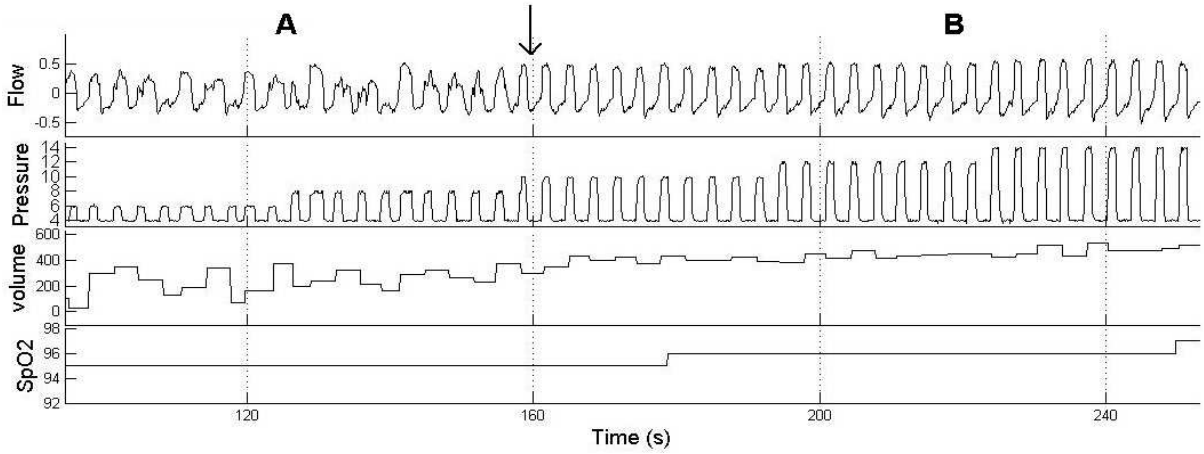

Figure 5.12: In this graph the traces of Flow, Pressure, Volume and SpO_2 acquired during a functioning test are shown. It is possible to appreciate in the first phase (see flow and volume curves), indicated by the letter "A", an irregular breathing pattern, suggesting that the settings of the ventilator in this phase are not the right ones for this patient. In this phase SpO_2 is 95%. After some changing in pressure settings, it is possible to see in phase "B" that the breathing pattern is regularized and the value of SpO_2 is increased to 97%.

A representative experimental tracing of the experiment is reported in Figure 5.12 in which are displayed only four of the six recorded tracks. The test started with the values of inspiratory and expiratory pressures of 6 hPa and 4 hPa, respectively. The operator was told by the physician to gradually increase the inspiratory pressure in steps of 2 hPa till a value of inspiratory pressure of 14 hPa. This protocol was repeated three times. In the first part of the experiment (period A) it is clear that the settings are not optimal for the patient; in fact both flow and volume traces show an irregular breathing pattern. This fact is also highlighted by the

value of the SpO_2 that is 95%. By increasing the inspiratory pressure (period B) the patient breathing pattern became regular and also SpO2 value increased up to 97%.

5.3.3 Conclusions

We designed, developed and tested a system that, once connected to a ventilator, can provide a direct connection between the physician's computer in the hospital and the patient's ventilator. The connection is capable of sending different signals from the ventilator (patient's flow, pressure, tidal volume, mask leaks, oxygen saturation and heart rate) and patient's snapshots to the physician. It also allows the physician to directly control and change the ventilator settings. The improvement that has been done with this work will allow the physician both to titrate the ventilator for patients that require a more complete respiratory parameters analysis, and to periodically verify that the ventilation settings are the best one for the actual conditions of the patient.

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CHAPTER 6

AUTOMATIC REMOTE DECISION SYSTEM

The telemedicine system described up to now is provided with an intelligent function, but still generates a great amount of raw data that cannot be filtered by the physician.

Thanks to an Internet connection all the information acquired at patient's house are collected and stored by a remote central server, which also concentrate information and results of clinical exams originating from the hospital, about test and clinical history of the patient.

The central remote system is endowed of an intelligence for the evaluation of the acquired information. The central system performs a deeper and more detailed analysis crossing and fusing the available information thanks to use of new procedures, data mining techniques and new developed clinical guidelines. It takes into account both data coming from patient's house, and considering their variation, evolution and clinical variability and data originated by the progress of clinical exam results, of specialist visits. This allows the physician to have access to a pre-analyzed and pre-evaluated set data and parameters representative of the conditions of the monitored patient (Figure 2.5).

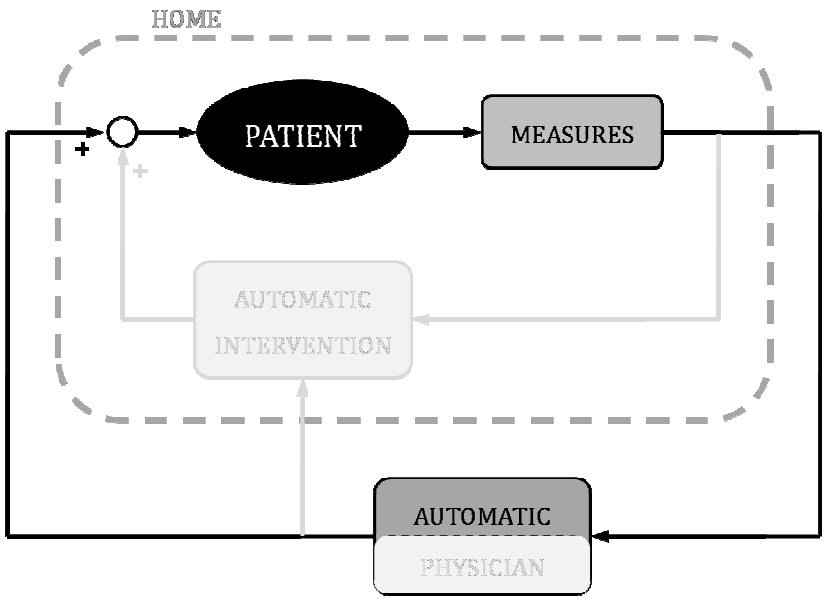

Figure 6.1: The new Telemedicine model highlighting the second ring, the remote automatic intervention.

This task is addressed by the CHRONIOUS system, which acquires data from patient's home with a wearable device and evaluate and filter all the collected data through the use of new coded clinical guidelines, suitable for home monitoring and supporting decisions.

6.1 The European Project CHRONIOUS

CHRONIOUS primary goal is to define a European framework for a generic health status monitoring platform schema, addressing people at risk or with chronic health conditions. This can be achieved by developing a multidisciplinary, sophisticated, and adaptive chronic disease platform that integrates state of the art sensors and services in order to cover both patients and healthcare professional's needs.

CHRONIOUS addresses a smart wearable platform, based on multi-parametric sensor data processing and fusion for monitoring people suffering from chronic diseases in long-stay setting. It is constantly monitoring parameters using audio observation methods and selected environmental and social context sensors while at the same time tracking their medical condition via vital signs sensors. In addition, the proposed platform offers interfaces for monitoring, drug intake, dietary habits and bio-chemical parameters concerning the patient's health situation. All these parameters are being fused by the CHRONIOUS intelligence module in order to reach a decision on the patient's state. This is an advance multi-parametric expert system that fuses information from various sources using intelligent techniques. Any trait of abnormal health status is recognised by the severity estimation component and actions (alerts, reminders etc) are formed and sent to the appropriate recipients (patient, health professional, call centre etc).

Finally all data will be stored in the system's repositories where CHRONIOUS has foreseen data exchange with healthcare facilities external legacy systems using well known and established standards. Of course one of the primary concerns while designing and developing the CHRONIOUS platform will be the provision of a secure platform, taking into account privacy and ethical issues concerning patient information.

For medical professionals several services are being provided by the CHRONIOUS platform. Firstly, healthcare professionals are provided with access to certified healthcare information that is indexed in meaningful and structured way so as to not waste time searching for it. Most of the current browsing and navigation tools use keyword-based search, and when the requested keyword does not match the indexed one of the relevant documents, the system

does not find it. The new approach proposed by CHRONIOUS is to use ontologies for cross-lingual information retrieval systems. Use of domain specific ontologies is an appealing approach to allow users to express information requests at a higher level of abstraction as compared to keyword based access.

Furthermore, CHRONIOUS will offer Decision Support services for Professionals involved in the Chronic Disease Monitoring and Management Process. Different specialties participate in the process of chronic disease management (GPs, specialised doctors, nurses, care givers, dieticians, trainers). They all need to know pieces of the information collected in order to adjust their treatments and plans accordingly. In this process the system should provide decision support, and education support for each specialty involved in the management program. In addition, it is within the project's scope to develop services that exploit the mass amount of data recording (monitoring, patient-system interaction, acute episodes) and information available at different sites of the process (health history, hospitalisation data), in order to discover links between daily activity processes that are not yet known. The system based on previous experience (results, treatment changes and interactions) will periodically provide guidelines for appropriate medical interventions for specific conditions that will be validated by specific medical experts. Medical professionals will also be able to adjust management programmes according to new findings and new knowledge acquired by the system.

In addition, it is within the scope of the proposed project to provide the guidelines and standards of the future generations of "chronic disease management systems" that should be followed by IT professionals when designing and implementing such systems. This is based on the combination of the views of chronically ill people, healthcare professionals and a review of the current technology and standards and their projected trends. Issues such as safety & security, comfort, accessibility and adaptability will be thoroughly examined. The guidelines consist of a set of rules, which describe the implementation aspects of a management system; that measure health, environmental and other activity parameters in order to provide reliable health and life style monitoring. A description of suitable sensors, location, communication technologies and installation procedures will be issues that will be tackled; CHRONIOUS focus its efforts in their standardisation. In addition, CHRONIOUS investigate appropriate procedures for establishing such standard at National and European level.

All these goals and objectives areachieved by integrating existing state of the art sensors and services along with novel services developed by the CHRONIOUS consortium always aiming at providing a complete and universal platform for chronic disease management both

for the patient and the healthcare professional. Our proposed solution is initially applied to chronic diseases of Chronic Obstructive Pulmonary Disease (COPD) and Chronic Kidney Disease(CKD) and Renal Insufficiency.

6.1.1 CHRONIOUS Architecture

The proposed framework's architecture and structure is generic and thus it will enable further expansion to the support of the management of other categories of chronic diseases such as Psychiatric Disorders Management, Diabetes, and Asthma etc. This provides an added value to the proposed solution and a tremendous exploitation potential. We envisage that in its final form CHRONIOUS will be a universal solution to healthcare facilities and professionals for managing all different kind of chronic diseases Figure 6.2.

CHRONIOUS results in the design and development of an open platform for adaptation to the different needs of the above mentioned chronic diseases, exploiting the advantages of new and evolving IT solutions for the different tasks of chronic disease management. Furthermore, CHRONIOUS aims at the metamorphosis of chronic care, by integrating all – among which innovative- disease management procedures through:

- Wearable solution for monitoring not only vital parameter but also environmental parameters and social context parameters
- Multi-fusion from heterogeneous sources decision support system
- Simple, customised and adaptive interfaces that take into account the user's profile, medical history and relating HCI (human-computer interaction) factors.
- Implementation of new algorithms and methods to perform perceptual and evaluation of the subject using information from multiple sensors.
- Research on algorithms that best integrate, analyze and combine data from the different sensors.
- Intelligent mechanisms and decision support tools for both patients and healthcare professionals (medical staff etc) for chronic disease management components.
- Creation of a repository (knowledge base) that aids to derive the most accurate decision of learning process. Multiple repositories of health related material (hospitals, healthcare centers etc).

- Appropriate, certified medical content and personalised views on it exploiting intelligent agent techniques coupled with Flexible search and retrieval of information. Intelligent indexing system for information classification in relation to user profiling.
- Interoperability with existing healthcare legacy systems based on standards such as HL7 etc.
- Alert and reminding mechanisms to inform end-users of several events. Universal, easy access to the system through fixed and wireless devices.
- Standard specifications of personal medical record. All the above over a secure platform, taking into account privacy and ethical issues
- Provision of guidelines and standards of the future generations of "chronic disease management systems"

The CHRONIOUS project involved a great number of partners which developed the whole system. We participated into the project phases of designing, developing and testing the wearable platform and in the editing and developing the clinical guidelines for the Central Decision Support System able to implement a decision intelligence.

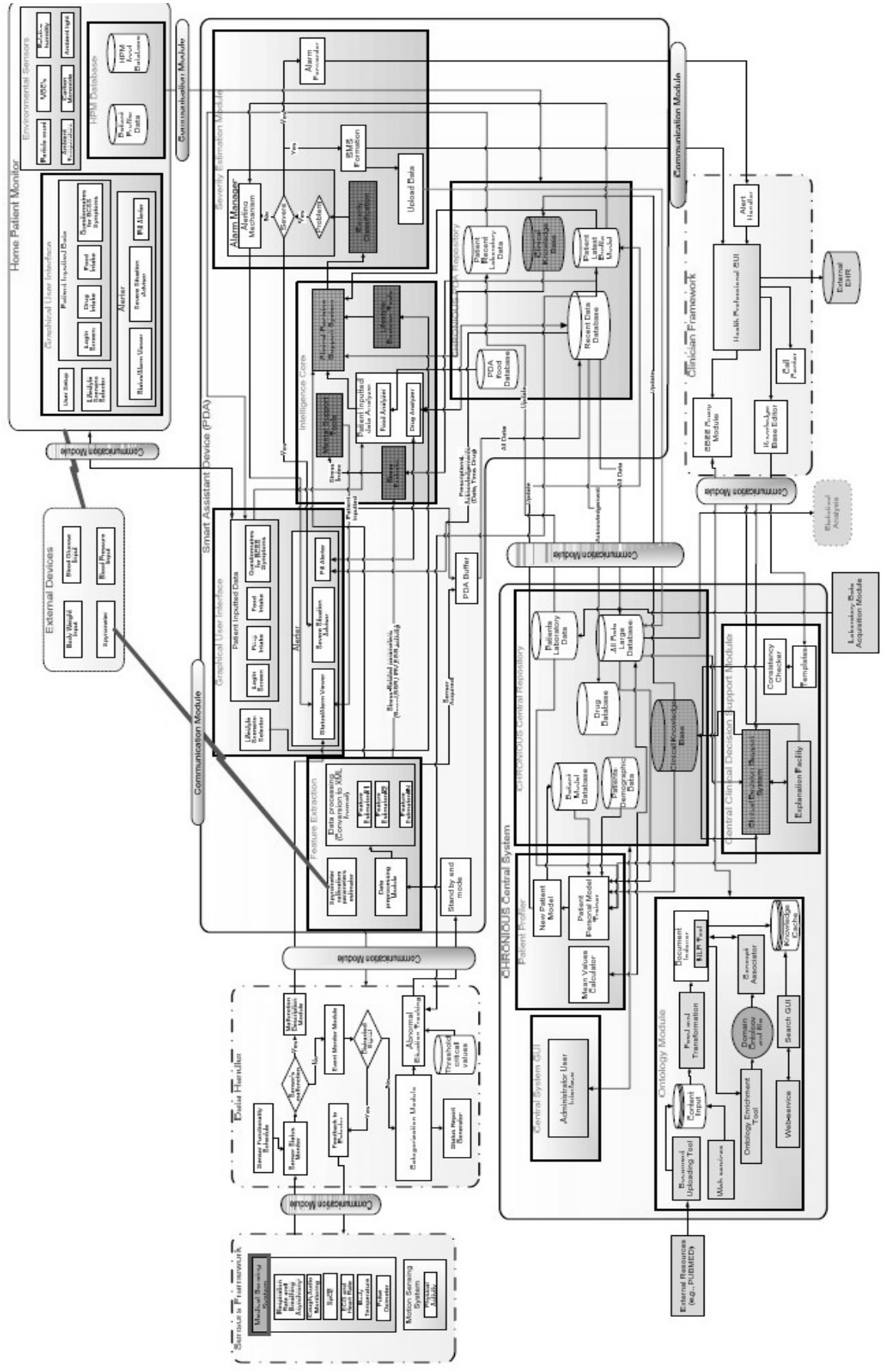

Figure 6.2: CHRONIOUS complete architecture.

6.2 CHRONIOUS: The Patient Sensing Framework - Patient Testing

In this phase the system has to be tested under the supervision on the health care professionals.

In order to evaluate the accuracy and reliability of the signals acquired by the CHRONIOUS wearable platform on patients, the system has been tested in a preserved environment, i.e. the hospital, under the continuous supervision of a physician. The wearable platform has been tested on COPD patients during three acquisition sessions in the Careggi Hospital of Firenze (Italy) and one session into the Hospital of Feltre (Belluno, Italy).

6.2.1 Materials and Methods: the Wearable Platform

After the first in vitro testing phase (see Chapter 3) we developed a new shirt composed of improved sensors that in the first version showed inefficiency and not reliability issues. Here are reported only the devices that has been modified, for complete description refer to Chapter 3.

The Shirt

A final version of the shirt has been designed and realized, it is made of cotton (80%) and elastan (20%) and is normally washable. It is composed of two layers sewn together between the which are sewn the wires for the RIP and the connection wires for the ECG signals.

Figure 6.3: CHRONIOUS shirt, the final version.

It is available in three sizes, M, XL and XXXL, thought for typical COPD patients with a frontal zip for easier wearing.

The sizes are studied in order to guarantee the maximal adherence of the shirt to the body or the patient, thus to allow all the sensors to acquire the physiological signals with the best quality. The shirt has pockets, holes and wires holders for all the devices that must be connected and wired.

The Pulse Oximeter

The standard attachment method for the used sensor, Nonin (Plymouth, MN) 8000RTM, secures the sensor by means of a medical adhesive. As this method showed to be inefficient and after less than 30 minutes the adhesive was no more effective, it has been designed and realized a rubber holder into which the sensor is lodged. The new holder is bigger than the sensor because it must hold steady and firmly the sensor on the skin. On the other side of the holder a Velcro strip allows the connection to the shirt, where, on the internal side, a longer strip is sewn on the shoulder and allows single patient adjusting.

Figure 6.4: On the left the Nonin reflectance pulse oximetry sensor is inserted into the plastic holder, which, on the right, is connected to the internal side of the shoulder of the shirt.

The pulse oximetry data (SpO_2 and HR) are sampled at a frequency of 1Hz by the data handler from a NONIN sensor. Furthermore five service bits used to assess the status of the sensor, are collected and transmitted by the data handler:

- *Sensor Disconnect:* Sensor is not connected or sensor is inoperable
- *Out Of Track:* An absence of consecutive good pulse signals
- *Low Perfusion:* Amplitude representation of low signal quality
- *Marginal Perfusion:* Amplitude representation of medium signal quality

- *Artefact:* A detected pulse beat didn't match the current pulse interval

This control bits are displayed and can be used by the physician to monitor sensor status and reliability of data received.

Electrocardiographic Electrodes

The previous sensors were substituted with dry snap fastener type capacitive electrodes. The electrode chosen is a reusable and designed for continuous recording. It is flat, made of a conductive silicon material connected to a Silver Silver-Chloride (SSC) clip produced and sold from FIAB SpA (IT) (see Figure 6.5). They are circular shaped conductive rubber devices, with a slightly conical shape that facilitates a suction cup effect which helps keeping contact between the electrode and the skin. At the centre of the rubber circle there is a metal contact which is the backside of a snap fastener used to connect the electrode to the shirt. The signal is brought to the Data Handler through normal cupper wires sewn into the shirt.

These kind of electrodes provide the best connection to the patient in dry conditions because the rubber promotes the sweating of the skin and this enhance the conductivity. Furthermore the suction cup effect guarantees optimal signal quality, even during patient's movement.

Figure 6.5: ECG electrodes shown on the upper right corner (back and forward) are connected to the shirt with snap fateners as shown in the lower right corner. The position of the four electrodes in shown in the image on the left by the red spots.

The four ECG electrodes have been positioned into the shirt in order to guarantee three ECG derivations taking into account patient's sex, BMI and shirt's shape characteristics that may affect electrodes to skin contact during some patient's movements (see Figure 6.5).

Each ECG lead is sampled at a frequency of 256Hz by the data handler, the which, with a computing algorithm, provides also the heart rate frequency value. Information about electrodes disconnection is provided with three status bits.

The Data Handler

The Data Handler is a microcontroller based device developed by the Fraunhofer Institute that collects data coming from all the devices that compose the wearable system.

The Data Handler is connected to the SpO_2 sensor, the RIP bands, the ECG electrodes, the microphone, the temperatures and humidity sensors, and to the activity sensor through a multiple cable (see Figure 6.6).

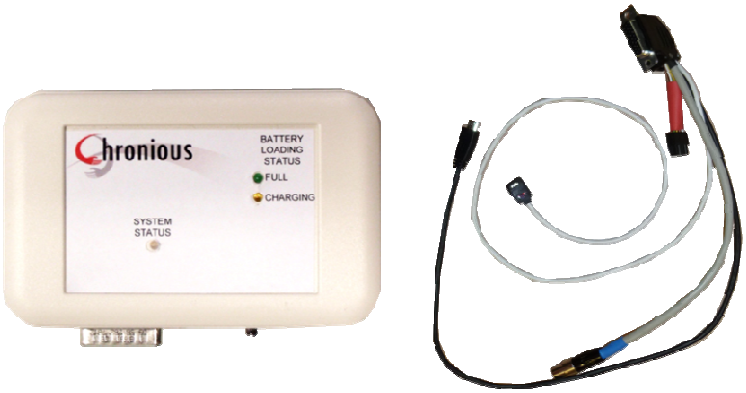

Figure 6.6: CHRONIOUS Data Handler, on the left, and the connecting cable on the right.

All the signals coming from the sensors are collected and stored in a very short buffer, in order to be sent via a Bluetooth connection to a PDA or a personal computer. After Bluetooth connection and pairing, the data handler starts sampling the signals as soon as it receives the "start" command from the connected device, and stops sampling after the special command is received. All incoming data are bundled in packets containing timestamp information, and error debugging headers. The communication protocol is proprietary and has been used to develop the interface software for the personal computer. The data handler is powered by a Li-ION cells battery that guarantees an autonomy of 16 consecutive hours of data acquisition and transmission.

Each parameter is acquired at a different sampling frequency, see Table below.

Data Type	Sampling Frequency
ECG	256 Hz per lead
ECG Heart Rate	0.5Hz
RIP	12.5Hz
SpO_2	1Hz
Cough Counts	On event
Temperature and Humidity	0.1Hz
Activity report data	On demand
Activity change data	On event
Event status	On demand
Sensor status	1Hz
Acknowledge	Response to each PDA command

6.2.2 Materials and Methods: experimental setup

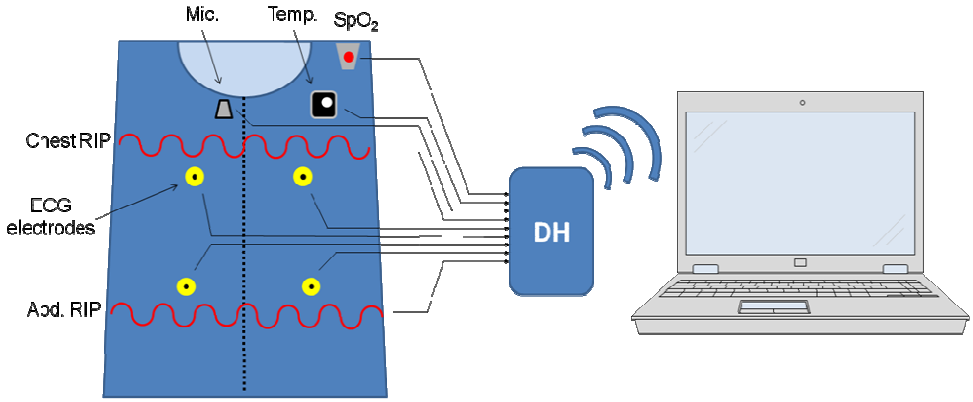

Figure 6.7: CHRONIOUS wearable platform: Experimental setup.

The signals acquired from the shirt worn by the COPD patient was equipped were the ECG, RIP bands, SpO_2, temperatures and humidity, cough counts, posture and steps counter. Using a personal computer connected to the Data Handler via Bluetooth (see Figure 3.3), all the data were collected continuously during spontaneous breathing of the COPD patient for one hour in the seated position and for another consecutive hour in the supine position.

At the beginning and at the end of each hour it was also measured for 5 minutes the flow at the mouth of the patient wearing a noseclip, through the spirometer (Sibelmed, Barcelona, Spain). The initial acquisition was used to perform the calibration of the RIP signals as described in the previous paragraph, while the final one was used to verify calibration accuracy after one hour. During every hour of acquisition, heart rate (HR) and oxygen saturation (SpO_2)

were also measured for 10 minutes by a finger clip pulse oximeter (NONIN, Plymouth, Minnesota, USA) in order to get reference values for comparison.

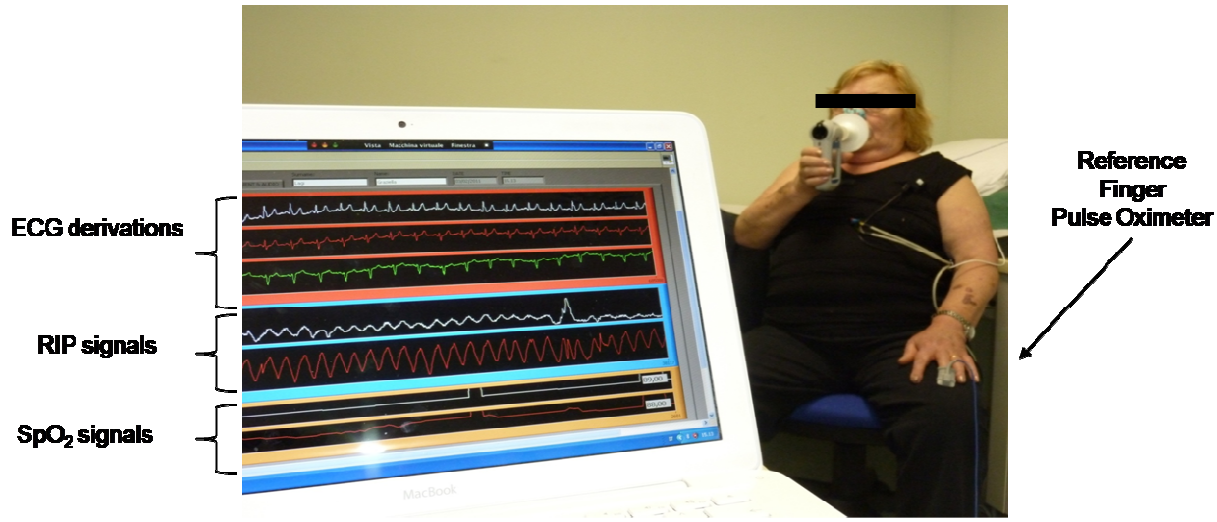

Figure 6.8: A patient during RIP calibration procedure in sitting position with the real-time visualization of the acquired signals on a personal computer.

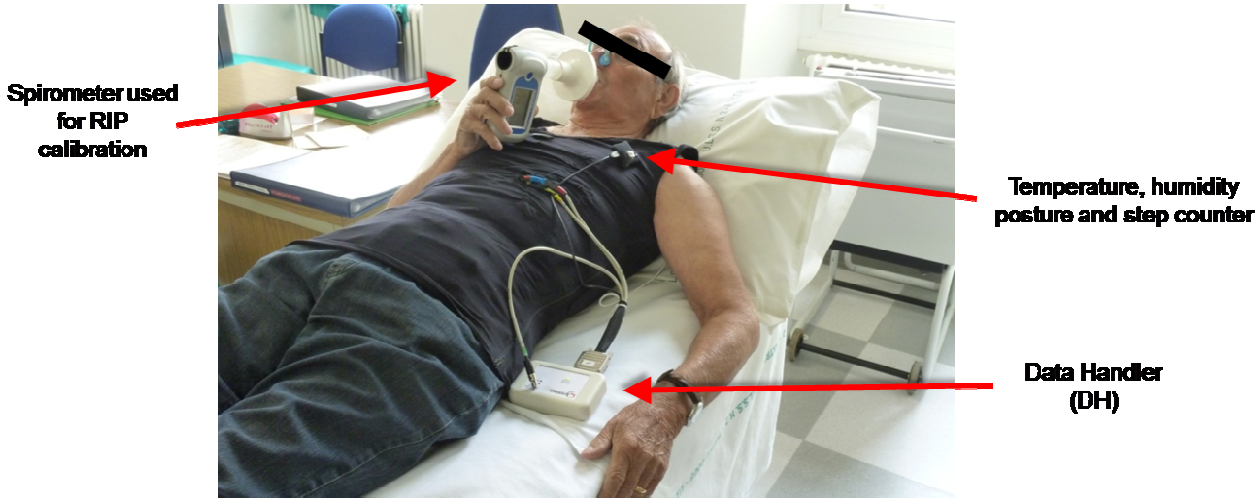

Figure 6.9: A patient during RIP calibration procedure in supine position

6.2.3 Results

	Age (yrs)	BMI (Kg/m²)	TLC (%pred)	RV (%pred)	FEV1 (%pred)	FVC (%pred)	FEV1/FVC (%pred)
mean ±sd	68,7 ±7,1	28,1 ±4,6	97,4 ±19,8	140,2 ±44,1	40,2 ±11,3	74,1 ±18,6	56,3 ±17

We studied 16 COPD patients (see Table above) using the wearable system. The evaluation of accuracy was focused on the following parameters: HR, SpO_2 and tidal volume

(VT). Linear regression analysis and Bland-Altman (1) analysis were performed on the data acquired, and resulted as follows:

- **Heart Rate**: r^2=0.99, m=0.99, q=-0.41, p<0.0001
  Absolute error: mean=0.73BPM, min=0.12BPM, max=3.61BPM

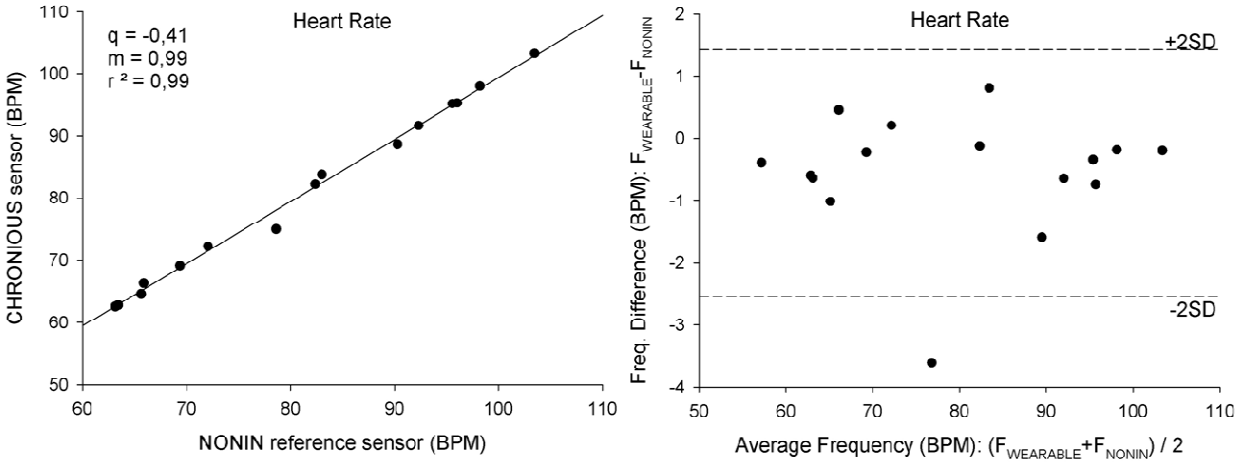

Figure 6.10: Regression analysis (on the left) and Bland-Altman analysis (on the right) of the sampled Heart Rate values, in both supine and seated positions.

- **Hemoglobin Oxigen Concentration SpO_2**: r^2=0.58, m=0.91, q=8.52, p=0.0024
  Absolute error: mean=1.19%, min=0.02, max=4.81

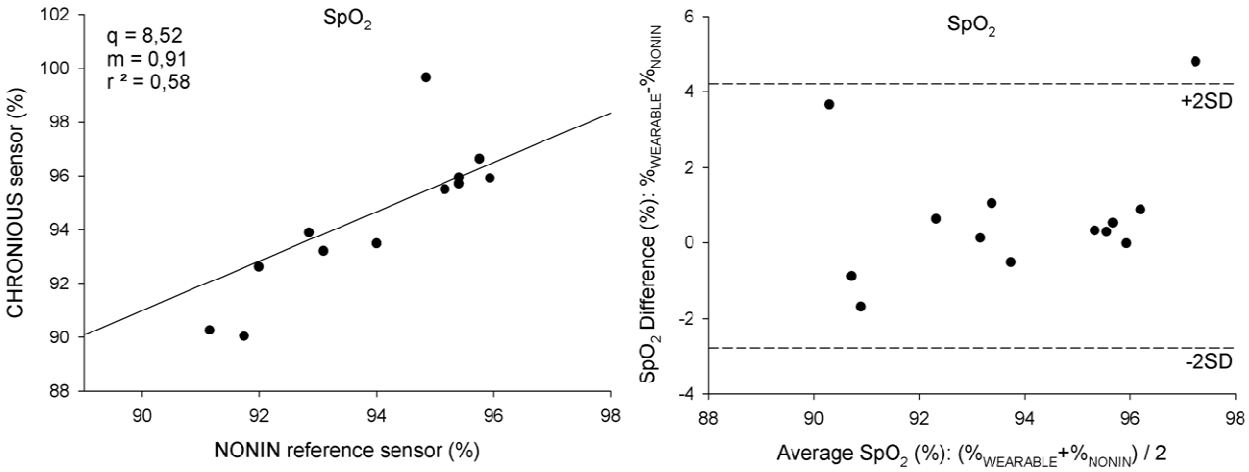

Figure 6.11: Regression analysis (on the left) and Bland-Altman analysis (on the right) of the sampled SpO_2 values, in both supine and seated positions.

- The calibration procedure chosen is the first one described in Chapter 3, and it has been used because it provided the more reliable set of data.

- **Tidal Volume:** r^2=0.79, m=0.9, q=-0.067, p<0.0001

Absolute error: mean=0.05L, min=0L, max=0.19L

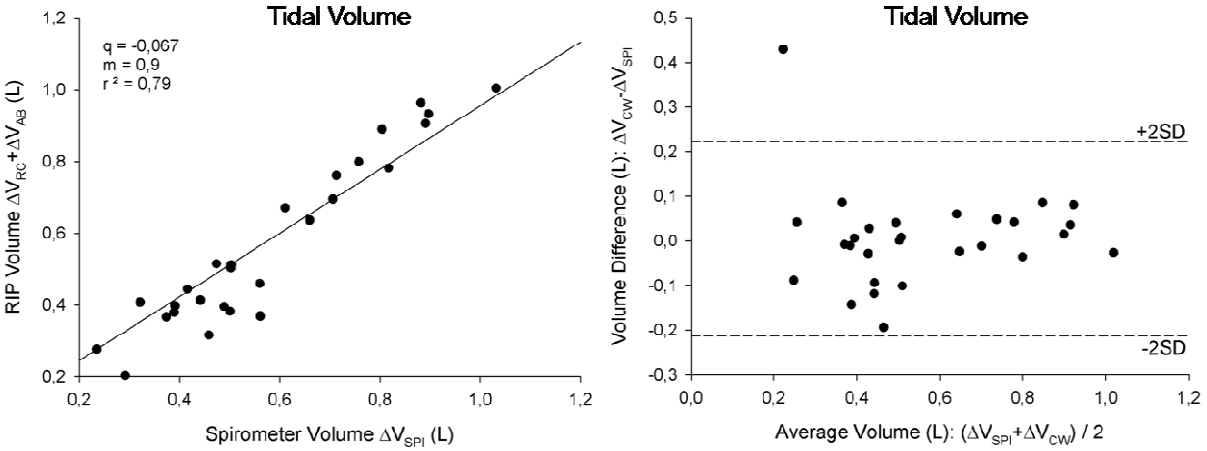

Figure 6.12: Regression analysis (on the left) and Bland-Altman analysis (on the right) of the sampled Tidal volume values, in both supine and seated positions.

Only a qualitative analysis on the electrocardiographic data has been made, in fact from the signals of the ECG electrodes it was possible to identify PQRST waves within the 3 derivations.

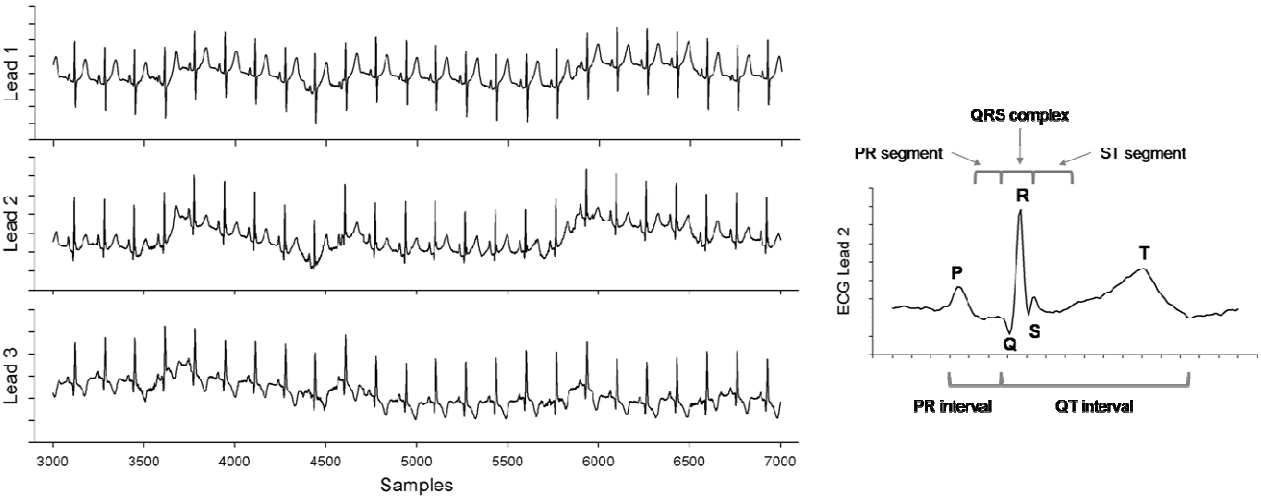

Figure 6.13: Electrocardiographic traces of the three leads (on the left). On the right a zoomed section of lead 2, with highlighted the typical characteristics of the ECG waveform, in both supine and seated positions.

6.2.4 Conclusions

The CHRONIOUS wearable monitoring system showed to be able provide reliable measurements of heart rate, tidal volume and electrocardiographic traces in both supine and

seated positions. SpO_2 measures showed less consistency with the gold standard and the origin of the problem has to be found in the sensor's holder used for these tests, which was the original Nonin adhesive holder. The newer and last developed holder, which was described in a previous paragraph, provides better measurements but has still to be tested on COPD patients.

The described procedure used to calibrate the respiratory inductive plethysmography in order to measure the tidal volume, showed its efficacy and effectiveness as the calibration was still consistent after one hour of use of the wearable system.

6.3 CHRONIOUS: The Central Decision Support System (CDSS)

The CHRONIOUS CDSS contains all the decision support functionalities needed to provide the continuous clinical evaluation of patient's current status with the aim of early detecting patients worsening according to the medical category of the patient and the patient specific data available. Furthermore, it will offer Decision Support Tools for Professionals involved in the Chronic Disease Monitoring and Management Process which will indicate and suggest the possible need of adjusting of the treatments.

In order to offer these services, the CHRONIOUS Core is constituted by the Central Clinical Decision Support System and is responsible for providing the continuous evaluation of patient's current conditions and the suggestions of possible adjustments in treatments accordingly to the medical category of the patient and the patient specific data available. The outcome of this process is based on the clinical guidelines that are formulated and stored in the CHRONIOUS clinical knowledge base, by the Clinical Guidelines and Template for Chronic Diseases.

6.3.1 General structure of CHRONIOUS clinical guidelines

The COPD clinical guidelines are defined by considering two different set of rules. The first will comprise all the rules which do not require a specific and comprehensive knowledge of the clinical phenotype and condition of the patient and that can be managed by the intelligence on the CHRONIOUS patient's framework, the second will comprise all other clinical rules.

Because of these criteria, the rules of the first set will be devoted to manage either emergency situations or to identify situation which may raise suspects of possible problems and

will require a quick further analysis which needs more information of the ones available at the patient side.

Clinical Guidelines for the Patients Sensing Framework

These rules must be defined by considering only simple logical functions (such as applying thresholds) on the variables acquired by the sensors. There are two different levels of actions, one is devoted to identify patient's critical conditions that must activate a request for an immediate reaction from the caregiver, the other is used to identify possible worsening conditions which have to be confirmed by more extensive analysis that has to be carried on by the CHRONIOUS core.

In this second case, the rules activate the immediate transmission of the data from the Patient Sensing Framework to the central system and request the activation of the CDSS for the proper and comprehensive evaluation of the patient's condition.

Clinical Guidelines for the CHRONIOUS core

These clinical guidelines represent the whole knowledge about the disease and its management which is coded into the Knowledge Base. These rules can refer to both data recorded by the patients sensing framework and the information acquired from clinical exams which comprises, for example, the results of laboratory exams. Moreover, the rules can be more complex if compared to the ones for the Patient Sensing Framework, in order to adequately model the knowledge needed to describe a very complex task such as the management of the disease.

6.3.2 COPD clinical guidelines

All available COPD clinical guidelines are not designed taking account the availability of continuous or frequent monitoring of several physiological variables and clinical parameters as it will happen in CHRONIOUS. For this reason they are not highly specific in the definition of the appropriate interventions and on how to optimize the therapies on a given patient, leaving most of this task to the experience of the physician in care of the patient.

After a further deep search in several scientific article databases and discussion and contacts with chest physicians highly experienced in the clinical management of COPD, we

identified and designed the CHRONIOUS COPD clinical guideline by considering the following aspects:

1) The most important aim of CHRONIOUS COPD clinical guidelines is the early detection of changes in the clinical condition of the patient.

This consideration results from the analysis of the scientific literature on clinical management of COPD. Published data offer several different follow-up models of home care in COPD patients. Reduction in hospitalization (2) and use of other acute healthcare services (3;4), reduction in mortality rate, improvement in the sickness impact profile scores and patient satisfaction (5) have all been reported with programs providing chronic home care interventions and patient education.

These programs were based on strict adherence to interventions enhancing symptoms self-monitored by patients and their caregivers and increasing their understanding of drug therapy, symptom and treatment monitoring, as well as acting as a liaison between primary care providers and hospital services.

Even if telemedicine resulted in a reduction in hospitalization and use of other acute health care services, there is still not enough evidence that this approach is cost-effective. Only recently it has been shown that, if the telemedicine approach is applied to COPD patients with the aim of early detecting patient worsening and of promptly beginning the treatment of exacerbations, the cost-effectiveness of teleassistance can be demonstrated.

To date, there are still very limited studies available, also because of the lack of availability of technological platforms able to continuously monitor the relevant physiological parameters at the patient's home. Nevertheless, it has been recently shown that in patients with severe chronic respiratory failure (CRF) needing home oxygen therapy and/or home mechanical ventilation, the integration of home monitoring and care with the aid of ICT can reduce the rate of hospitalizations by about 36%, General Practitioner (GP) urgent calls by 65%, home relapses by 71%, even in more severe patients. The results highlighted also that patients with COPD seem to take greater advantage of this kind of teleassistance compared to other pathologies (6).

Because of these considerations, CHRONIOUS COPD Clinical Guidelines have been designed with the specific aim of early detecting symptoms worsening, in order to promptly alert care providers and to allow the physician to identify and prescribe the appropriate treatment for a given patient.

2) The lack of availability of devices and ICT platform able to acquire a large variety of physiological parameters provided by wearable sensors and/or home monitoring systems prevented the scientific community to identify the best set of variables and rules to be used as clinical guidelines for tele-care of COPD. For this reason, the CHORONIOUS COPD clinical guidelines module has to be defined by combining established medical knowledge with the knowledge obtained from experienced physicians in order to define an initial set of rules to be used for the first validation study. Considering that CHRONIOUS platform will fill up the lack of data mentioned here above, it is very likely that the first set of clinical guidelines will be soon expanded and integrated while new knowledge will be derived from the data coming from the clinical trials. For this reason, the first set of rules of CHRONIOUS Clinical Guidelines should follow a simple structure in order to be easily expanded and tuned during the first clinical studies.

6.3.3 COPD clinical guidelines for the Patient Sensing Framework

These rules were defined on the basis of general clinical guidelines by considering physiologically acceptable parameters and by introducing some more restrictive parameters specific for COPD. Since COPD, like most of chronic diseases diffused in elderly patients, is often characterized by the presence of co-morbidities, at the Patient Sensing Framework level only general threshold values are suggested.

More specific reasoning is performed at the level of the CDSS, allowing different sensitivity to change in some of the parameters depending on patient's phenotype. The values suggested for the CHRONIOUS COPD Clinical Guidelines for the Patient Sensing Framework are reported in the table here below.

WEARABLE DEVICE RULES

	Alarm - immediate action	**Sending data to CDSS**
Body temperature (T)	T > 38°C	T > 37.5°C during 4 consecutive hours
Weight	>2Kg in 24h	(every 24h)
Heart Rate (HR)	HR > 120 BPM	HR > 100 BPM, with patient at rest
ECG	atrial fibrillation, atrial flutter, tachycardia supraventricular	
Arterial Pressure	Diastolic > 100 mmHg, systolic > 150 mmHg	Diastolic > 85 mmHg, systolic > 130 mmHg (hypertensive therapies?)
SpO2	SpO2 < 91% at rest; SpO2<88% during exercise or in supine position	91% < SpO2 < 94%
Respiratory Frequency (f)	f > 25 BPM	f > 18 BPM at rest
Inspiratory Time (Ti)	Ti < 0.8 sec maintained for more than 5 consecutives respiratory cycles	
Expiratory Time (Te)	Te < 1.6 sec maintained for more tha 5 consecutives respiratory cycles	
Respiration Asinchrony		(every 24h)
(Resp. Freq.)/(tidal volume) = f/Vt	f/Vt > 100 BPM/L	60 < f/Vt <100 BPM/L
Minute Ventilation (Ve)	<6L/m	>12L/m at rest
Patient Activity		(every 24h)
Coughs Counter	> 60-70 per hour	
Ambient Temperature and Humidity		(every 24h)
Mental Solicitation Indicator		
Home Pollution		(every 24h)
Patient Position		(every 24h)
Sleep Quality		Apnoeas (detected by using both respiratory bands and SPO2), Position
Syntomps self evaluation (questionnaires: bcss, respicard...)	Dyspnoea at rest (borg, vas scale + check on respiratory frequency)	(every 24h)
Social context, envinmonet (microphone for sounds)		

6.3.4 COPD clinical guidelines for the CHRONIOUS Core

COPD is a complex and heterogeneous disease whose definition comprises very different manifestations, or phenotypes. In order to define the appropriate rules to evaluate patient's conditions, it is mandatory to consider which phenotype he/she belongs to. Several studies have been addressed to this issue, but COPD phenotyping is still an open question and it is nowadays considered a hot topic by the scientific community. After an extensive review of the scientific literature and also thanks to the support and interaction with physicians and scientists internationally considered opinion leader in the field a CHRONIOUS COPD, a phenotyping schema was defined taking into account the field of application of CHRONIOUS.

In particular, CHRONIOUS COPD phenotypes are identified by considering the most valuable and predictive parameters for prognosis. One of the first effective attempts to better characterize patients' condition is a study (7) which introduced the BODE index, derived by a retro prospective analysis of a large cohort of COPD patients.

As CHRONIOUS COPD Clinical Guidelines are aimed at early detecting patient worsening, it has been decided to add some feature to the BODE index, in particular considering smoking habits, physical activity performed by the patient and the attitude of the patient to develop exacerbations. Here below the CHRONIOUS phenotyping schema is described with the references to the relevant scientific literature.

Definition of CHRONIOUS phenotypes:

- BODE Index:

  It has been used the classification of the COPD patients on the basis of the BODE index (7). In this article are described eleven categories of COPD patients on the basis of four indexes which score the patient from 0 to 10. The categories are analyzed divided into four bigger groups that take into account a range of categories: first group 0-2, second group 3-4, third group 5-6, and fourth group 7-10. These bigger categories are the ones used for the BODE Index classification, thus allowing us to classify the patients into four groups.

- Smoker:

It has been proved that smoking is a determining factor for the progress of the disease in COPD patients (8).

- Number of exacerbations per year:

For a COPD patient an exacerbation means a worsening of the disease, hospitalization, pharmacological therapy and, in some cases, death. Therefore it is very important how many exacerbations the patient has per year. It has been chosen a value of two exacerbations per year as a threshold to classify COPD patients. A higher number of exacerbations means a major risk for the patient (9-11).

- Activity, number of steps per day:

In COPD patients' daily activity is an indicator of the progress of the disease; in fact activity is strongly related to the amount of available oxygen brought by the respiratory system. The more the patient is at severe stages of the disease the less oxygen is provided by the respiratory system to the whole body, thus limiting patient's movements (12).

By considering all definitions indicated above, we identified the following criteria to characterize COPD phenotypes:

Criteria:		1	2	3	4	
1	BODE Index	0-2	3-4	5-6	7-10	Bode 0-2 / 3-4 / 5-6 / 7-10
2	Smoker	yes	no			smoker / not a smoker
3	exhacerbation per year	≥ 2	<2			<2 exhacerbations per year / ≥ 2 exhacerbations per year
4	number of steps per day	>500	<500			active / sedentary

It is important to underline that these phenotypes are defined with the specific aim of identifying different attitude in developing symptoms worsening and exacerbations, not with the aim of solving the still discussed issue of disease phenotyping.
These criteria defined 32 COPD phenotypes, which are summarized in the following table:

	BODE	Smoker	exhacerb.	steps	=	Cathegory name
1	0-2	no	<2	>500	=	Bode 0-2, not a smoker, <2 exhacerbations per year, active
2	0-2	no	<2	<500	=	Bode 0-2, not a smoker, <2 exhacerbations per year, sedentary
3	0-2	no	≥ 2	>500	=	Bode 0-2, not a smoker, ≥2 exhacerbations per year, active
4	0-2	no	≥ 2	<500	=	Bode 0-2, not a smoker, ≥2 exhacerbations per year, sedentary
5	0-2	yes	<2	>500	=	Bode 0-2, smoker, <2 exhacerbations per year, active
6	0-2	yes	<2	<500	=	Bode 0-2, smoker, <2 exhacerbations per year, sedentary
7	0-2	yes	≥ 2	>500	=	Bode 0-2, smoker, ≥2 exhacerbations per year, active
8	0-2	yes	≥ 2	<500	=	Bode 0-2, smoker, ≥2 exhacerbations per year, sedentary
9	3-4	no	<2	>500	=	Bode 3-4, not a smoker, <2 exhacerbations per year, active
10	3-4	no	<2	<500	=	Bode 3-4, not a smoker, <2 exhacerbations per year, sedentary
11	3-4	no	≥ 2	>500	=	Bode 3-4, not a smoker, ≥2 exhacerbations per year, active
12	3-4	no	≥ 2	<500	=	Bode 3-4, not a smoker, ≥2 exhacerbations per year, sedentary
13	3-4	yes	<2	>500	=	Bode 3-4, smoker, <2 exhacerbations per year, active
14	3-4	yes	<2	<500	=	Bode 3-4, smoker, <2 exhacerbations per year, sedentary
15	3-4	yes	≥ 2	>500	=	Bode 3-4, smoker, ≥2 exhacerbations per year, active
16	3-4	yes	≥ 2	<500	=	Bode 3-4, smoker, ≥2 exhacerbations per year, sedentary
17	5-6	no	<2	>500	=	Bode 5-6, not a smoker, <2 exhacerbations per year, active
18	5-6	no	<2	<500	=	Bode 5-6, not a smoker, <2 exhacerbations per year, sedentary
19	5-6	no	≥ 2	>500	=	Bode 5-6, not a smoker, ≥2 exhacerbations per year, active
20	5-6	no	≥ 2	<500	=	Bode 5-6, not a smoker, ≥2 exhacerbations per year, sedentary
21	5-6	yes	<2	>500	=	Bode 5-6, smoker, <2 exhacerbations per year, active
22	5-6	yes	<2	<500	=	Bode 5-6, smoker, <2 exhacerbations per year, sedentary
23	5-6	yes	≥ 2	>500	=	Bode 5-6, smoker, ≥2 exhacerbations per year, active
24	5-6	yes	≥ 2	<500	=	Bode 5-6, smoker, ≥2 exhacerbations per year, sedentary
25	7-10	no	<2	>500	=	Bode 7-10, not a smoker, <2 exhacerbations per year, active
26	7-10	no	<2	<500	=	Bode 7-10, not a smoker, <2 exhacerbations per year, sedentary
27	7-10	no	≥ 2	>500	=	Bode 7-10, not a smoker, ≥2 exhacerbations per year, active
28	7-10	no	≥ 2	<500	=	Bode 7-10, not a smoker, ≥2 exhacerbations per year, sedentary
29	7-10	yes	<2	>500	=	Bode 7-10, smoker, <2 exhacerbations per year, active
30	7-10	yes	<2	<500	=	Bode 7-10, smoker, <2 exhacerbations per year, sedentary
31	7-10	yes	≥ 2	>500	=	Bode 7-10, smoker, ≥2 exhacerbations per year, active
32	7-10	yes	≥ 2	<500	=	Bode 7-10, smoker, ≥2 exhacerbations per year, sedentary

Once phenotypes are defined, it is necessary to define an index of the condition of the patient aimed at early identifying changes in patient conditions potentially leading to the development of an exacerbation.

For the COPD clinical guidelines, it was decided to use, for the first set of clinical rules, an evolution of the scoring card used in the most relevant clinical trial of telemonitoring of COPD (the Telemaco Project) and proposed and validated in literature (6).

This approach is based on the evaluation of several physiological variables measured by the CHRONIOUS Patients Sensing Framework. In particular, the following parameters have

been considered on the basis of scientific literature and the experience of the collaborating physicians:

- Dyspnea, cough, sputum, sputum color, wheeze, neurological status, ventilation interaction, walk, body temperature, weight, heart rate and SpO_2 (6).
- ECG and arterial pressure (systolic and diastolic) (13).
- Respiratory frequency, inspiratory time, expiratory time, respiratory asynchrony, respiratory frequency/tidal volume and minute ventilation (14-16).
- Patient activity (17;18).
- Depressive phenotype (HAD) (19-21).

The following parameters are also included in the guidelines because of the judgment of our clinical consultant. As soon as new scientific evidence of their importance will be available (also thanks to the CHRONIOUS validation studies), CHRONIOUS guidelines will be updated.

- Coughs
- Ambient temperature
- Ambient humidity
- Mental solicitation indication
- Home pollution
- Patient position
- Sleep quality (number of position changes)
- Sleep quality (questionnaire)
- Asthenia
- Social context, environment
- Age

These parameters are considered by assigning a score to each one on the basis of its value, as suggested by the RESPIcard introduced by Vitacca el al, (6).
The values of the scores for the CHRONIOUS COPD card have been defined as follow:

CHRONIOUS COPD CARD SCORES	0	1	2	3	4
Dyspnoea	Under strong activity	Speed walk or climb	Moderate activity with stops	Light activity, stop after few steps	At rest during daily activities
Cough	Spontaneous and strong	Weak, not productive	Strong but extremely productive	Weak, productive, frequent	No spontaneuos cough; need for suctions
Sputum	No need for sputum	Moderate	Copious	Very copius	Unbearable
Sputum Colour	No sputum	white	Yellow	Yellow/green	Greeen/brown or with blood
Wheeze	Never	Occasional	Under strong efforts	Under moderate efforts	At rest
Neurological Status	Normal, wakeful	Slow but answering	Confused, diurnal drowsiness	Difficult posture and verbal answer	No answer to manual stimulus
Ventilator Interaction	No troubles or no ventilator	Occasional alarms on ventilator	Alarms and need for suction, or mask discomfort	Alarms, occasional contrasts and dyspnoea under ventilator	Ventilator break; alarms and fighting against ventilator
Walk	Autonomous	Walk with stops, no dispnoea	Walk with stick and dyspnoea	Assisted walk, few steps, armchair use	No deambulation, bedridden
Body temperature (T)	Normal	>37°C and <37.5°C without antipiretic	>37°C and <38°C with antipiretic	>38°C with antipiretic and antibiotic for 1 day	>38°C with atibiotic for 3 days
Weight	Stable weight, no ankle oedema	Increase of <2Kg in 2 days	2-4Kg in 2 days	2-4Kg in 1 day	>4Kg in 1 day
Heart Rate (HR)	<90 BPM	90-100 BPM	100-110 BPM	110-120 BPM	>120 BPM
ECG	regular	extrasystols	atrial fibrillations	atrial flutter	ventricular arrithimia
Arterial Pressure (systolic)	120	120-140	140-160	140-160	>190
Arterial Pressure (dyastolic)	70	70-90	90-100	100-110	>110
SpO_2	>92% with room air and O_2	91% with air and 90-92% with O_2	<90% with room air	<90% with O_2	<80% with O_2
Respiratory Frequency (f)	<14	14-16	16-20	20-25	>25
Inspiratory Time (Ti)	1.6-1.8	< 1.6 > 1.20	< 1.2 > 1.0	> 0.80 < 1.0	<0.80
Expiratory Time (Te)	3.0-3.4	< 3 > 2.5	< 2.5 > 2.0	< 2.0 > 1.60	<1.60
Respiration Asinchrony (LBI mean value in the last 30mins)	1,0	1,2	1,4	1,6	1,8
(Resp. Freq.)/(tidal volume) = f/Vt	<80	80-95	95-110	110-120	> 120
Minute Ventilation (Ve)	<12 > 10	< 10	< 8	< 7	< 6
Patient Activity (steps num. per day)	>2000	< 2000 > 1800	< 1800 > 1000	< 1000 > 500	<500
Coughs Counter (n/min)	0	<2	<10	<15	>15
Ambient Temperature	22°C	24-26°C	26-28°C	28-30°C	>30°C
Ambient Humidity	50%	40% or 60%	30% or 70%	20% or 80%	<20% or >80%
Mental Solicitation Indicator					
Home Pollution					
Patient Position (supine) h	< 8	> 8 < 10	> 10 <15	>15 <18	> 18
Sleep Quality (N° position changes/h)	<10	> 10 < 15	> 15 < 25	25-30	> 30
sleep quality (questionnaire)	optimal	good	sufficient	bad	very bad
Do you feel tired? (asthenia)	never	occasionally	after light activity	after heavy activity	for the most part of the day
Social context, envinmonet (microphone for sounds)					
Age	<55	>55 and <60	>60 and <70	>70 and <75	>75
Depressive Phenotype (HAD)	never	sometimes	frequent	very frequent	pathological

Once scores have been attributed to all the parameters, we decided to consider a subset of them with different weights depending of the patient's phenotype in order to compute a total score which can be used to detect possible changes in patients' conditions.

The values of the weights presented in this chapter were defined in collaboration with experienced physicians, However, the availability of new data provided by CHRONIOUS

validation studies as well as by the data recorded during the use of CHRONIOUS on COPD patients will provide the possibility to update the values of the weights by tuning them on the basis of appropriate statistical analysis.

In order to compute the total score for each patient continuously, a set of equations, defined for each phenotype, has been written, and they can be extrapolated from the table below.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Dyspnoea	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Cough	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Sputum	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Sputum Colour	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Wheeze	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Weight/Ankle Oedema	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Neurological Status	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Ventilator Interaction	0	0	0	0	0	0	0	0	0	0	10	10	10	10	10	10	20	20	20	20	20	20	20	20	50	50	50	50	100	100	100	100
Walk	0	10	0	10	0	10	0	10	0	20	10	20	10	20	10	20	30	40	30	40	30	40	30	40	40	50	40	50	60	70	60	70
Body temperature (T)	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Heart Rate (HR)	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
ECG	10	10	10	10	10	10	10	10	20	20	20	20	20	20	20	20	40	40	40	40	40	40	40	40	50	50	50	50	80	80	80	80
Arterial Pressure	10	10	10	10	10	10	10	10	20	20	20	20	20	20	20	20	40	40	40	40	40	40	40	40	50	50	50	50	80	80	80	80
SpO_2	0	0	0	0	0	0	10	10	10	10	20	20	20	20	30	30	30	30	40	40	40	40	50	60	50	60	80	80	80	80	100	100
Respiratory Frequency (f)	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Inspiratory Time (Ti)	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Expiratory Time (Te)	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Respiration Asinchrony	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
(Resp. Freq.)/(tidal volume) = f/Vt	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Minute Ventilation (Ve)	0	0	0	0	0	0	10	10	0	0	10	10	0	0	20	20	30	30	40	40	50	50	60	60	70	70	80	80	90	90	100	100
Patient Activity	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Coughs Counter	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Home Pollution	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Patient Position	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Sleep Quality	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
astenia	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100
Social context, envinmonet (microphone for sounds)	0	0	10	10	0	0	20	20	20	20	20	20	20	20	30	30	30	30	40	40	40	40	50	50	50	50	60	60	60	60	80	80
Age	0	0	0	0	0	0	0	0	10	10	10	10	10	10	20	20	20	20	30	30	30	30	40	40	40	40	50	50	50	50	80	80
Depressive Phenotype	0	0	10	10	0	0	20	20	0	0	30	30	0	0	40	40	40	40	50	50	50	50	60	60	60	60	80	80	80	80	100	100

Table 6-1: Table summarizing the weights are assigned per physiological parameter to each patient cathegory in order to classify the patient's severity.

The value inside every cell is a percentage weight, so some example is listed here below:

- Phenotype 1 = (ECG score)*0.1 + (arterial pressure score)*0.1

- Phenotype 2 = (walk score)*0.1 + (ECG score)*0.1 + (arterial pressure score)*0.1

- Phenotype 3 = (dyspnoea score)*0.1 + (cough score)*0.1 + (sputum score)*0.1 + (sputum color score)*0.1 + (wheeze score)*0.1 + (weight score)*0.1 + (neurological status score)*0.1 + (body temperature score)*0.1 + (heart rate score)*0.1 + (ECG

score)*0.1 + (arterial pressure score)*0.1 + (respiratory frequency score)*0.1 + (inspiratory time score)*0.1 + (expiratory time score)*0.1 + (respiration asynchrony score)*0.1 + (resp. freq. / tidal vol. score)*0.1 + (patient activity score)*0.1 + (coughs counter score)*0.1 + (home pollution score)*0.1 + (patient position score)*0.1 + (sleep quality score)*0.1 + (asthenia score)*0.1 + (social context , environment score)*0.1 + (depressive phenotype score)*0.1

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CONCLUSIONS

Over the last 50 years, the number of people age 60 years or over has tripled, and is expected to triple again to almost two billion by 2050 (1). The proportion of older people is projected to reach 21% in 2050 (2). Population ageing is profound, having major consequences and implications for all facets of human life, including health and health care. Indeed the incidence and prevalence of chronic diseases, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), and diabetes, continue to increase (3).

Chronic pathologies like COPD, which WHO (World Health Organization) has predicted to become the third leading cause of death throughout the world by 2030 (19), determine a serious burden on patients and health care systems because of low quality of life and frequent and expensive hospitalizations.

The need to reduce this burden brought health care providers to rely on telemedicine services, which on one hand can perform a better follow up of the patient at home, on the other it aims to provide health services at home and to be able to prevent acute events that can lead to the hospitalization of the patient, reducing the costs for the health care providers.

The main reason why the implementation of telemedicine is difficult in its practical application is that the conventional telemedicine approach consists of a complex technological architecture based on centralized server systems, usually requiring commercial agreements between the HMV provider and the company providing the telemedicine platform. Given the complexity of information technologies in health care, these approaches hinder the widespread application of instrumentation telemedicine services. A new approach for Telemedicine provision must be simpler, cheaper and feasible.

During the Doctorate program a new Telemedicine approach has been proposed, designed and realized. The proposal rely on simple considerations about the bases for a reliable Telemedicine system.

An effective Telemedicine service must rely on new specific measurements that can be provided automatically, or by means of minimal patient's cooperation, by new methods and sensors suitable for domestic usage.

Automatic tools must be implemented inside home therapy devices in order to automatically optimize the delivered therapy.

The physician must have simple and quick access to all patient's data and values, offline and in real-time, in order to intervene to optimize the therapy, if needed.

A central server must able to collect all the data coming from patient's home, from specialist visits and clinical exams and from all the clinical history of the patient. The central system is provided with a decisional core able to analyze and evaluate all the available data in order to provide the physician significant indexes and therapy modification suggestions.

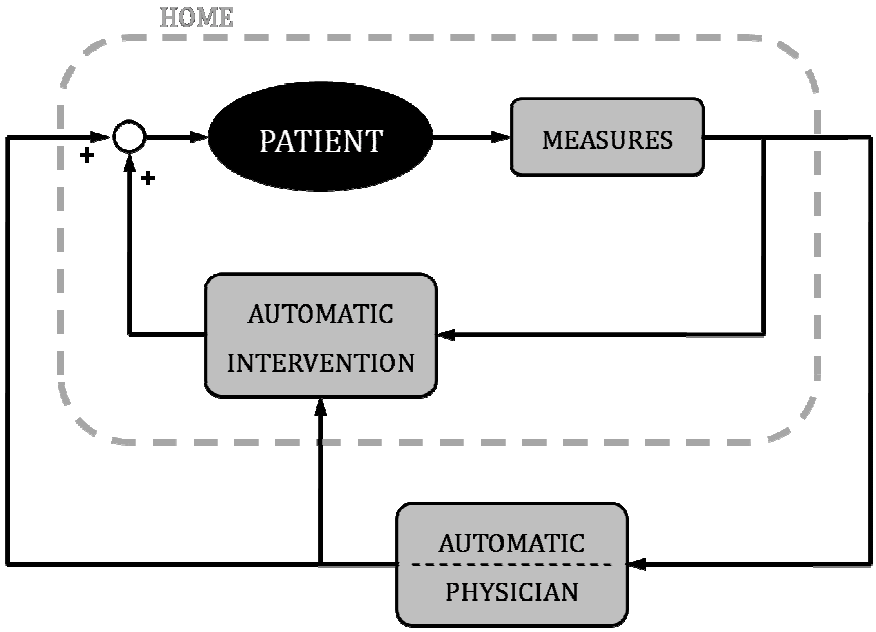

Figure1: The model of the new Telemedicine approach.

A new architecture is needed, a structure able to divide the fundamental tasks above described in order to lighten physician's load of work, that otherwise could not take care of an increasing number of chronic patients at home (see Figure 1).

The described system has been implemented during the Doctorate program. It provided very good, and encouraging results on preliminary clinical tests and showed its feasibility, reliability and value and all its potentialities. The system has been developed for chronic respiratory disorders, and it has been tested mainly on COPD and OSAS patients.

We introduced at patient's home the measurement of specific indexes about the conditions for the respiratory system of the patient thanks to the implementation of the FOT technique inside the home mechanical ventilator used for therapy provision. A wearable device designed inside the European project CHRONIOUS allowed the measurement of a set of vital parameters through a minimal collaboration of the patient.

Automatic tools have been implemented inside the mechanical ventilator in order to allow the automatic optimization of the ventilation delivered on the basis the FOT measurements.

The system has been provided with a central system both to allow easy access to all the data for the physician, and for an initial analysis of the data. The central system has been

developed with a decision system based on new clinical guidelines that allow it to fuse, compare and evaluate all the incoming data, and the previously stored data coming both from home data acquisition and from clinical exams, and visits. The central system produces some indexes and classification on patient's conditions.

The whole system is designed in order to firstly automatically intervene for therapy optimization and secondly to allow the physician to easily understand whether the patient needs therapy optimization, and guide him to this task, thus to allow the physician to be able to easily manage a great number of patients.

This system could be a solution for the problems encountered in Telemedicine development diffusion. Preliminary analysis show that the system can be really effective in the costs reduction for chronic patients, however a deeper costs analysis still need to be properly addressed.

Anyway the system has been designed in order to be scalable, to be possible simple upgrade interventions and adaptable to a number of chronic pathologies.

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SUMMARY

Telemedicine has been defined as the use of information and communications technologies (ICT), to deliver health services and transmit health information at distance for the purpose of improving patient's care and education. Telemedicine includes a growing variety of applications and services using two-way video, email, wireless phones and other forms of telecommunications technology. Starting out over forty years ago with demonstrations of hospitals extending care to patients in remote areas, the use of telemedicine has spread rapidly and became a standard medical practice and is in daily use across different countries. Thanks to the clinical effectiveness and cost savings of telemedicine, it has become a standard methodology for monitoring and treating patients directly at home, especially those with chronic pathologies.

Chronic diseases are the main cause of death in almost every developed country, and deaths from chronic respiratory diseases are second only to those from cardiovascular diseases. According to which structure of the respiratory system is injured, alteration or inflammation of lung parenchyma, disease of the pleura, chest wall, or neuromuscular apparatus, it is possible to distinguish different chronic pathologies like asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea syndrome (OSAS), neuromuscular pathologies, etc.

Chronic pathologies like COPD, which WHO (World Health Organization) has predicted to become the third leading cause of death throughout the world by 2030, determine a serious burden on patients and health care systems because of low quality of life and frequent and expensive hospitalizations. The need to reduce this burden brought health care providers to rely on telemedicine services, which on one hand can perform a better follow up of the patient at home, on the other it aims to provide health services at home and to be able to prevent acute events that can lead to the hospitalization of the patient.

In the last few years a number of studies and projects have been developed and tested which highlighted some problems and difficulties involving the use of telemedicine. The architecture of the conventional telemedicine systems is based on a complex informatics structure managed by external providers and centralized computer servers which operates through a call center. This structure requires complex and expensive agreements among the hospitals, the telemedicine service providers and the communication line providers and is the main obstacle to the wide application of the ICT in the medical routine. The existing telemedicine services are characterized by a rigid structure, not able to be configured and adapted to the necessities of different kinds of chronic pathologies. Telemedicine services must

implement automatic functions in order to assist autonomously the patient at home and must provide to the physician at the hospital updated data on significant physiological parameters. The present practice is to use the same technologies and devices used in the hospital to achieve significant measures of patient's conditions, limiting the quality and reliability of the acquired data because of the absence of the physician during the performing of the tests. The absence of specific devices and technologies designed to be used at patient's home without the presence of the physician is limiting the spread of telemedicine.

The purpose of the work here presented is to design, realize and test an easy to use new telemedicine system based on a simple and reliable architecture, able provide constant monitoring of patients affected by chronic diseases of the respiratory system, such as COPD and OSAS, using new technologies designed expressly for home care, and able to provide the physician a tool to optimize at distance the treatment at patient's home in real-time.

The work will be presented in five sections of which content is resumed below.

Chapter 1.

The first section describes the chronic pathologies of the respiratory system taken into consideration in this project and analyzes the current treatments and the telemedicine techniques used, focusing on two major chronic diseases, COPD and OSAS.

The pathologies of the respiratory system can be divided into two categories, restrictive and obstructive lung diseases. Restrictive diseases are characterized by the impairment of certain structures of the respiratory system that determine the reduction of lung expansion, thus resulting in a reduction of lung volumes, an increased work of breathing and inadequate ventilation and/or oxygenation. Among a great number of restrictive lung diseases there are some that are chronic and that can be treated at home, like neuromuscular diseases. So far there are no home telemedicine studies or concluded projects for the assistance of neuromuscular patients for the optimization of the ventilation therapy. Obstructive lung diseases are characterized by airways obstruction and/or inflammation of the pulmonary parenchyma, and among them are included COPD and OSAS.

COPD is a chronic pathology characterized by airflow limitation that is not fully reversible, it is a progressive, debilitating and life-threatening disease, with various stages of severity. Patients affected by COPD need to control the symptoms and reduce complications in order to avoid the so called exacerbations, acute conditions during which there is a considerable worsening of the disease that leads to hospitalization and even to death of the patient. COPD patients are treated at home, together with pharmacological treatments, through the use of

Non-Invasive Mechanical Ventilation (NIV) provided by home mechanical ventilators that are titrated by a physician in the hospital during a short visit. The settings provided will remain the same until the next visit that could be in the next six months, meaning that there is not an adaptation of the provided ventilation to the actual patient's needs. As continuous home monitoring of patient's conditions would be effective in prevention of exacerbations and cost saving for the health service providers, some projects and new approaches developed. It has been released a home mechanical ventilator that allows the physician to change from the hospital the settings during the inactivity of the device in order to better adapt to the patient. An recent project successfully showed that it is possible to prevent exacerbations and reduce hospitalization monitoring patients through a questionnaire on patient's conditions administered weekly by trained technicians.

Among COPD comorbidities and complications we find the obstructive sleep apnea syndrome which is a sleep disorder characterized by long apneas in breathing during sleep caused by the obstruction of the upper airways due to their collapse. These episodes, which occur repeatedly throughout sleep, are characterized by a duration of minimum 10 seconds, with either a neurological arousal and blood oxygen desaturation of 3-4% or greater. The main symptoms are apnoeas, snoring, sleep fragmentation, confusion and nocturnal restlessness, nocturnal gastro-oesophageal reflux, dry mouth, nocturnal sweating, morning cephalalgia and excessive daytime sleepiness. All these symptoms cause irritability, car driving danger, libido reduction, anxiety, depression, cardio-vascular problems etc. The preferred treatment is the use of home CPAP ventilators which maintain upper airways open and avoids apneas. The setting of the correct pressure value is done at the hospital during a whole night long exam called polysomnography, for which there are excessive waiting lists and elevated costs. Nowadays only few telemedicine projects have been developed in order to follow patient's conditions and satisfaction in the use of CPAP devices, mainly based on the administration of questionnaires.

Chapter 2.

The second section introduces and describes the new telemedicine approach, highlighting its structure and architecture. It also describes the home monitoring aspect of the whole system based on the experience gained in the context of the European project CHRONIOUS.

The purpose of the new telemedicine approach proposed with this work is to monitor and maintain the health conditions of the patient at home in stable state. This is achieved through the use of new technologies and procedures applied directly at patient's house. The first function is the home monitoring of patient's conditions and ventilation performances of the NIV device, and is achieved through the use of the CHRONIOUS platform for monitoring

patient's parameters (Pulse oximetry, ECG, respiration volumes, physical activity, temperature…), and a new telemonitoring device, the Data Transmission Server (DTS), to monitor sleep breathing parameters (pressures, flows, volumes…). The second function allows the physician to change the ventilator parameters from the hospital in order to optimize the ventilation therapy provided by CPAP or BIPAP devices during patient's sleep. Finally the use of automatic algorithms inserted into the NIV device able to optimize the ventilation therapy allows the patient to receive always the optimal ventilation that can by itself follow variations in conditions. Moreover the implementation of rules and a decision algorithm into the CHRONIOUS platform, allows the system to report to the physician patient's critical conditions or just their suspicious variations.

CHRONIOUS is a FP7 European Community project that aims to create a platform that evolves in monitoring patient's health status which also includes a new wearable platform for home monitoring of people suffering from chronic diseases. CHRONIOUS suggests the implementation of a generic system architecture to be easily adapted to any chronic disease management program. For testing purposes, it focuses on two major chronic conditions COPD and CKD (chronic kidney disease). The CHRONIOUS platform is composed of a wearable system that is a shirt made of washable stretch-material into which are sewn 4 ECG electrodes, two bands for respiratory inductive plethismography (RIP), a reflectance pulse oximeter, an activity sensor and a skin temperature sensor and an ambient humidity and temperature sensor. The data coming from the sensors are collected by the Data Handler, a microcontroller-based acquisition system and transmitted via wireless connection to the central database which is accessible by the physician in every moment, who can select and view all the parameters previously recorded, in order to perform an offline home monitoring of patient's conditions.

The DTS device can be adapted to acquire data both from the NIV device and from the CHRONIOUS wearable system in order to provide the physician a real-time monitoring system of both the NIV device traces and patient's parameters, acquired during the home mechanical ventilation sessions of the patient. Thanks to the numerousness of the parameters viewable, the physician can better situate patient's conditions and pathology development at distance.

Chapter 3.

The third section takes into consideration the aspect of real-time home monitoring and change of the ventilation therapy administered at patient's home, performed by a physician directly from the hospital. In particular it is described the implemented devices and functions

that allows the setting at distance of the CPAP (continuous positive airway pressure) and BIPAP (bilevel positive airway pressure) home mechanical ventilator's parameters.

Home CPAP titration with automatic devices is not possible in a non-negligible percentage of patients with sleep apnea-hypopnea syndrome (SAHS). The feasibility of a novel telemetric system for home CPAP titration has been tested. One-night home CPAP titration was carried out on 20 SAHS patients. A telemetric unit (DTS), based on the conventional GPRS mobile phone network and connected to a commercial CPAP device, allowed the hospital technician to monitor flow, pressure and airleaks by remote control and titrate CPAP (elimination of apneas, hypopneas, flow limitation and snoring) in real time. After one week, a full hospital polysomnography was performed while the patient was subjected to the value of CPAP that was previously titrated at home via telemetry. The home-titrated CPAP systematically improved patient's breathing: the apnea-hypopnea index and percentage of sleep time with arterial oxygen saturation below 90% were reduced from 58.1±5.1 to 3.8±0.6 events/h and from 19.8±1.1% to 4.4±0.7%, respectively. This CPAP value was virtually the same as the pressure that optimized breathing during hospital polysomnography. This pilot study shows that a simple telemetric system, requiring neither a special telemedicine network nor any infrastructure in the patient's home, made it possible to perform effective remote CPAP titration on SAHS patients.

The DTS system has been modified and upgraded in order to perform the titration of home mechanical ventilation which is applied to patients with different chronic respiratory diseases and, in order to be effective, it requires accurate individual titration, as for COPD patients. Nowadays this can be obtained only in the hospital during day or night visits, and this is associated with long waiting lists and high costs. The aim of this work was to realize and test a simple system that allows a remote titration of the ventilator at the patient's home by a physician at the hospital. The previous DTS system has been upgraded in order to get additional patient's parameters, it has been added a short-range wireless module, used to provide wireless connection with a pulse oximeter and is also connected to an infrared webcam through an USB port. When the ventilator is in operation, the system acquires and stores data from the ventilator and from the pulse oxymeter. It also connects to Internet and waits for remote connections. The physician can connect and look at the patient's ventilator tracings, oxygen saturation and heart rate and, if needed, he can also ask for snapshots of the patient through the webcam. Based on these information, the physician can change ventilator settings to titrate the ventilator parameters depending on the patient conditions. The system was tested during a titration procedure performed at the hospital with the ventilator controlled remotely

by a physician. The results of this pilot trial showed that with this system it was possible to titrate accurately patient ventilation. Given its simplicity and low-cost, this system could provide an effective way to remotely titrate home mechanical ventilation and to periodically verify its appropriateness for the actual conditions of the patients.

Chapter 4.

The fourth section describes the implementation and application of intelligent systems able to evaluate the clinical conditions of the patient at home and if necessary to intervene changing the delivered therapy or to inform the physician of significant variations of patient's conditions. In particular are described the technological aspects that have been developed in order to realize a system able to change automatically the settings of a BIPAP home mechanical ventilator and its testing phase. Moreover in this section is exposed the contribution to the realization of the decisional tree for the central decision support system (CDSS) of the CHRONIOUS European project able to identify patient's conditions variations.

The new telemedicine system has been developed to be able to perform the automatic adaptation of the home mechanical ventilation therapy to the conditions of the patient. Home mechanical ventilation consists on the ventilation of the patients using positive end expiratory pressure (PEEP) and inspiratory pressure (Pinsp) triggered by patient's effort. Expiratory flow limitation (EFL) is a common condition that occurs in COPD patients and it promotes dynamic hyperinflation (DH), leading to respiratory muscle inefficiency, patient discomfort and reduced exercise tolerance. The effects of DH can be reduced by applying the minimum level of PEEP or expiratory positive airway pressure (EPAP) able to abolish EFL during NIV. It has been shown that EFL can be detected by measuring the difference between inspiratory and expiratory respiratory reactance (ΔXrs), measured by both sinusoidal forcing (S) at 5Hz, and impulse oscillometry (IO). In order to select whether S or IO is the best technology solution to be used, the two methods have been tested in a clinical study.

We studied 21 patients, by S and IO in a randomized order, while patients were breathing normally for 2 min. The measurements were repeated in the same order after the administration of Albuterol (BD) delivered by a metered-dose inhaler. A commercial IO system was modified in order to switch to IO or S signals at 5Hz, while patients were connected to the same transducers and circuit. A difference between expiratory and inspiratory mean Xrs (DX5) >2.8cmH2O*s/l was taken as a marker of EFL. Pre-BD 9 patients were classified as EFL by S, and 8 post-BD. The same patients but one (only post-BD) were classified as EFL by IO. Linear regression analysis on DX5 was statistically significant in both EFL. In conclusion, both forcing signals identified similarly EFL in COPD. However, DX5 values computed by the two

techniques were much more correlated in non-EFL, suggesting that EFL is a source of non-linearities which affects Zin measurements when different forcing signals are used.

Therefore the sinusoidal forcing at 5Hz, which furthermore has already been shown to be effective during quiet breathing and CPAP, has been used to implement FOT in a commercial bilevel mechanical ventilator and has been evaluated its capability to detect of EFL in sitting and supine COPD patients submitted to NIV, without external additional equipments. We measured ΔXrs in 13 COPD patients subjected to nasal BiPAP. We started with the settings of EPAP=3cmH2O and IPAP=9cmH2O (Inspiratory Positive Airway Pressure) and we increased both pressures by 1cmH2O every 6mins of normal breathing up to 3 steps above the pressure able to abolish EFL. FOT at 5Hz was provided by a commercial ventilator (Synchrony, Respironics, USA) while flow and pressure were measured both at the inlet of the nasal mask by external sensors and at the outlet of the ventilator by the ventilator's sensors. We considered the data coming from the sensors at the outlet of the ventilator, compensated for the presence of the tube and the whisper swivel. We also measured esophageal pressure to use the Mead and Wittenberger (M-W) method as a reference technique to score each breath as flow-limited (FL), non-flow-limited (NFL) or indeterminate (I). Of the 13 COPD patients, 9 were studied supine and 4 seated. Eight patients were FL and 5 NFL. According to M-W scoring we found 534 FL, 567 NFL, 1396 I breaths. Considering flow and pressure signals measured at the outlet of the ventilator, the computed ΔXrs showed a sensitivity and specificity in detecting EFL in respect to M-W method of 98.5% for a value of ΔXrs=2.26cmH2O*s/L. These data suggest that it is possible to implement the FOT into commercial ventilators to automatically detect EFL. This information can help to set the EPAP during NIV to the minimum pressure able to abolish EFL in COPD patients receiving nasal BiPAP.

The automatic core of the CHRONIOUS platform is represented by the Central Clinical Decision Support System (CDSS) which supplies all the advanced decision functionalities of the platform. This is the brain of the CHRONIOUS platform and its intelligence is devoted to aid clinical professionals in managing chronic patients on a daily basis, by assessing their current status, facing worsening conditions and preventing exacerbation events. CHRONIOUS core functionalities rely on a sensing infrastructure which is fundamental for evaluating disease signs, patients' behavior and activity. Such information combined with patients' clinical data is exploited for monitoring disease course and adapting therapeutic plans according to any changed condition. However, although clinical guidelines pertinent to clinical practice are well established and provide clinicians with general instructions for disease diagnosis and treatment, the interpretation of continuously acquired patients' data and the correlation of specific signs

and conditions to acute disease events are still at an early stage of investigation, with only few medical studies carried out in home settings that have obtained assessed results. Moreover, the presentation of all the collected data, without any type of pre-processing, might overwhelm clinicians and have a counter effect on their activity, by making their decisions even more difficult. In this context, a system able to interpret acquired data, combine them with patients' clinical information, issue possible alarms and supply motivated suggestions can ease clinicians' activity in a really effective way. To this end, the CHRONIOUS platform includes intelligent services devoted to the analysis and understanding of patients' monitoring data, which are able to provide clinicians with filtered information and advices for their decision making. The Central CDSS represents the core of CHRONIOUS intelligence services and is aimed at supporting the medical personnel in their newly defined activity of telemonitoring chronic patients', by exploiting patients' data and formalized medical knowledge. The work described in this section presents the set of rules, categories and classification application of the conditions of the patient, performed on the basis of the data coming from the wearable system, in order to identify significant variations of patient's conditions and to notify it to the physician.

Chapter 5.

Conclusion.

The purpose of the presented work was to design and realize a new telemedicine approach characterized by easiness in configuration and use, based on a simple and reliable architecture, and able to provide constant monitoring of patients affected by chronic diseases of the respiratory system, such as COPD and OSAS, using new technologies designed expressly for home care, and able to provide the physician a tool to optimize at distance the treatment at patient's home in real-time.

The proposed approach is able to provide telemonitoring services to the physician in order to periodically monitor patient's conditions to be able to recognize critical variations on patient's conditions. The system provides the tools to allow the physician to perform real-time telemonitoring and telecontrol of a home mechanical ventilation device in order to perform the titration of the ventilator at home both for COPD and OSAS patients. Finally the system is provided with self decision systems able to continuously adjust PEEP value in home mechanical ventilators depending on patient's conditions, and is also provided with a central decision support system able to identify significant variations in patient's conditions starting from data acquired during the continuous monitoring of various physiological parameters.

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