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TITOLO

Prediction of lactate kinetics by tracking cardiovascular autonomic changes during vasopressor administration

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Contents:

Estratto

Intelligenza artificiale, tecnologia e medicina, oggi più che mai, agiscono in maniera interconnessa e lavorano a stretto contatto tra loro. Il progresso nei dispositivi di monitoraggio e l'utilizzo di cartelle cliniche elettroniche hanno permesso la raccolta e la successiva analisi di grandi quantità di dati, per fornire nuove informazioni e migliorare la cura del paziente. Questo è possibile in particolare nelle terapie intensive, ambienti molto critici e complessi, nei quali i pazienti sono costantemente monitorati.

Lo scopo di questo studio è quello di provare a prevedere un cambiamento nel livello di lattato a 12 ore dalla somministrazione vasopressoria. In primo luogo, si è tentato di caratterizzare le variazioni autonomiche rispettivamente prima e dopo la somministrazione ed utilizzarle in seguito per predire, a 12 ore, se il livello di lattato sarà sopra o sotto soglia. Lo studio è stato svolto considerando: (i) normale un livello di lattato nel sangue maggiore o uguale a 2mmol/L e (ii) considerando come anormale un valore superiore a 2mmol/L. Il lattato è un marker fisiologico di disfunzione metabolica e costituisce un adeguato indice del livello di ossigenazione dei tessuti. I vasopressori invece sono farmaci ampiamente utilizzati in terapia intensiva che hanno come principale compito quello di alzare la pressione sanguigna. L'utilizzo di vasopressori provoca sia effetti su parametri emodinamici sia sull' attività del Sistema Nervoso Autonomo.

I dati utilizzati in questo studio provengono dal MIMIC-III, database dal quale sono state estratte registrazioni elettrocardiografiche e di pressione arteriosa per 123 distinte degenze in terapia intensiva. Nello studio di predizione non sono state considerate soltanto le misure estratte dalle registrazioni delle forme d'onda, ma anche misure provenienti da esami di laboratorio, nonché da specifiche patologie e relativi trattamenti. Inoltre, grazie alla modellazione secondo processo puntuale, è stato possibile calcolare per ogni paziente diverse misure del baroriflesso e spettri tempo varianti.

Nella prima analisi, sono stati considerati soltanto i pazienti non sottoposti a ventilazione meccanica invasiva e/o sedati. È infatti noto come questi trattamenti influenzino fortemente il sistema nervoso autonomo. I risultati ottenuti mostrano un significativo aumento della pressione sistolica e diastolica media, una diminuzione del battito cardiaco ed un aumento degli indici temporali di

variabilità cardiaca. Inoltre, un'analisi in frequenza degli spettri ottenuti dalla serie RR mostra uno spostamento della bilancia simpato-vagale determinato da una maggiore prevalenza di attività simpatica rispetto a quella parasimpatica a seguito dalla somministrazione vasopressoria. Per quanto riguarda il baroriflesso, il meccanismo che contribuisce alla regolazione della pressione tramite il battito cardiaco, esso mostra una diminuzione dell'attività dopo la somministrazione vasopressoria.

Le stesse analisi sono state poi condotte includendo nello studio anche pazienti con ventilazione meccanica e/o sedati. I trend generali relativi a pressione, battito cardiaco e baroriflesso sono stati mantenuti mentre si sono perse tutte le informazioni riguardanti la bilancia simpato-vagale.

Si è notato un comportamento anomalo per alcuni pazienti, i quali manifestano una diminuzione della pressione sanguigna invece che un aumento, in seguito alla somministrazione vasopressoria. Classificando questi soggetti come "*non-responding*" e il resto della popolazione come "*responding*" è stata condotta analisi evidenziando molteplici differenze tra le due popolazioni.

Una seconda tipologia di divisione è stata in seguito effettuata stratificando la popolazione in base al valore di lattato. Definendo come "*low level*" i soggetti che, partendo da un lattato sotto soglia, lo mantenevano anche a dodici ore dalla somministrazione vasopressoria oppure quando subivano un abbassamento del valore di lattato, passando da sopra soglia a sotto soglia.

Sono stati classificati come "*high level*" i pazienti con lattato sempre anormale o per i quali si è verificato un consistente aumento del livello di lattato. Anche in questo caso le due popolazioni hanno mostrato comportamenti tra loro differenti sia prima che dopo la somministrazione vasopressoria. Un'ultima analisi multivariata è stata effettuata stratificando la popolazione per le diverse patologie e trattamenti.

È stato inoltre condotto uno studio di correlazione per verificare se effettivamente esiste un legame tra gli indici estratti dalle forme d'onda e il valore di lattato nel sangue.

Una correlazione maggiore è stata trovata tra le variabili estratte prima e dopo la somministrazione e il lattato nelle dodici ore precedenti. La correlazione aumenta considerando solamente la popolazione di soggetti che non rispondoo al farmaco o che mostrano livelli di lattato fuori norma.

In fine, tutte queste informazioni sono state utilizzate per lo studio di predizione. Si evidenza che i risultati migliori sono stati ottenuti utilizzando la regressione logistica per la selezione delle variabili e un modello di classificazione a foresta casuale (AUROC=0.84). Nonostante non sia stato possibile trovare studi svolti in precedenza, con un set up simile a quello utilizzato, i risultati ottenuti sono migliori di modelli precedenti in cui è stato utilizzato solamente il lattato o solamente informazioni

relative alla somministrazione vasopressoria. Ad esempio, il miglior risultato ottenuto da Liu et al [61] presenta un AUROC di 0.664, mentre quello di Vallabhajosyula et al di 0.73 [62].

In conclusione, questa tesi mostra che l'effetto dei vasopressori si rivela non solo nell' aumento della pressione ma anche nell'aumento della bilancia simpato-vagale del sistema autonomico periferico. Inoltre, i parametri relativi a variazioni di attività autonomica indotti da vasopressore sono correlati con il livello di lattato nel sangue e possono essere in grado di fornire indicazioni sul futuro livello di lattato e di conseguenza sullo stato di ossigenazione dei tessuti.

Abstract

In the intensive care unit of a hospital, healthcare professionals carefully monitor patients with serious injuries, post-operative trauma or unstable health conditions using bed monitoring systems that continuously record waveforms such as electrocardiogram (ECG) and blood pressure (ABP). The large amount of data collected in the intensive care units can be also used to develop algorithms that can support clinicians in their decision-making process, optimizing the amount of treatments, evaluating the state of risk of patients.

The aim of this study is to try to predict a change in lactate level 12 hours after vasopressor administration. First, an attempt was made to characterize the autonomous changes before and after vasopressor administration and use them to predict, at 12 hours, whether the lactate level will be above or below threshold. Considering (i) normal a blood lactate level less or equal than 2mmol/L (ii) while greater than 2mmol/L. as abnormal. Lactate is a physiological marker of metabolic dysfunction, providing an index of tissue oxygenation. Vasopressors, on the other hand, are medications widely used in intensive care, with the aim to raise blood pressure. They affect both hemodynamic parameters and the activity of the autonomic nervous system.

The data used in this study come from MIMIC-III, a database from which electrocardiographic and blood pressure records have been extracted for 123 different stays in intensive care. In the prediction study are used not only the measurements extracted from the waveform recordings but also measurements from laboratory tests, pathologies and treatments were extracted. In addition, thanks to the use of point process modelling, was possible to calculate different baroreflex measurements and varying time spectra for each patient.

In the first analysis, only patients who were not subjected to invasive mechanical ventilation and/or sedation were considered. It is known that these treatments strongly influence the autonomic nervous system. The results obtained show a significant increase in mean systolic and diastolic pressure, a decrease in heart rate and an increase in cardiac variability time indices. In addition, a frequency analysis of the spectra obtained from the RR shows a shift in the sympato-vagal balance determined by a greater prevalence of sympathetic activity compared to vagal activity following

vasopressor administration. With regard to baroreflex, homeostatic mechanism that regulates pressure and heartbeat, a decrease in activity after vasopressor administration was noticed.

The same analysis was then conducted including patients with mechanical ventilation and/or sedatives in the study. The general trend related to pressure, heart rate and baroreflex was maintained, whereas all information regarding the sympato-vagal balance was lost. Some patients showed a decrease in blood pressure instead of an increase following vasopressor administration. These subjects were classified as "non-responding" and the rest of the population as "responding", other analyses were conducted showing multiple differences between the two groups.
A second type of division was then carried out by stratifying the population according to the lactate value. Defining as "low level" the subjects who, starting from a lactate below the threshold, kept it even hours after vasopressor administration or when they suffered a lowering of the lactate value, going from above threshold to below threshold. Patients with always abnormal lactate or for whom there was a significant increase in lactate level were classified as "high level". Again, the two populations showed different behaviors both before and after vasopressor administration. A final multivariate analysis was carried out by stratifying the population for the different pathologies and treatments.

A correlation study was also carried out to verify if there is actually a link between the indices extracted from the waveforms and blood lactate level. A stronger correlation was found between the features extracted before and after administration and lactate in the previous 12 hours. These correlations increase considering only the population of non-responding subjects or considering only subjects with abnormal lactate.

All this information was used for the prediction study. Best results were obtained using logistic regression for the selection of variables and random forest (ROC area= 0.84, PRC area = 0.57) or support vector machines (ROC area= 0.81 and PRC area= 0.56) classification model. Similar performances were also obtained with XGBoost classifier without feature selection (ROC area= 0.81 and PRC area= 0.69). Our best results were obtained using logistic regression for the selection of variables, and a random forest classification model (AUROC= 0.84). Although it we could not find previous studies with a similar set up, the results obtained far outperform those from other models found in literature, in which either lactate or vasopressor administration were selectively used for

mortality prediction. For example, the best result obtained by Liu et al [61] reports an AUROC of 0.664, while those reported by Vallabhajosyula et al show an AUROC of 0.73 [62].

In conclusion, this thesis shows that vasopressors may be responsible for an increase in pressure, as well as a parallel increase in the sympathetic-vagal balance. In addition, parameters related to changes in autonomic activity induced by vasopressors are correlated with the level of lactate in the blood and may be able to provide indications on future lactate level and consequently on the oxygenation status of tissues.

Summary

In the intensive care unit of a hospital, healthcare professionals carefully monitor patients with unstable health conditions using bed monitoring systems that continuously record waveforms such as electrocardiogram (ECG) and blood pressure (ABP). The large amount of data collected in the intensive care units can be used to develop algorithms that can support clinicians in their decision-making process, optimizing the amount of treatments and evaluating the state of risk of patients.

The aim of this study is to try to predict a change in lactate level 12 hours after vasopressor administration. First, an attempt was made to characterize the autonomous changes before and after vasopressor administration and use them to predict, at 12 hours, whether the lactate level will be above or below threshold. Blood lactate level less or equal than 2mmol/L is considered to be in a physiological range, whereas, blood lactate greater than 2mmol/L is considered abnormal. Blood lactate concentration reflects the level of anaerobic cellular metabolism and is most commonly used as an indicator of tissue hypoperfusion. Although the use of blood lactate monitoring for risk assessment in the critically ill patient has remained controversial, it is possible to find of large variety of clinical studies demonstrating that lactate is a predictor of clinical outcomes. Vasopressors, on the other hand, are medications widely used in intensive care; a powerful class of drugs that induce vasoconstriction and thereby elevate mean arterial pressure, affecting both hemodynamic parameters and the activity of the autonomic nervous system.

Some studies previously examined the relationship between the responses of the cardiac autonomic nervous system and blood lactate during exercises but still no one has tried to investigate this link in ICU patients during vasopressor administration.

The data used in this study come from MIMIC-III, a database from which electrocardiographic and blood pressure records have been extracted for 123 different stays in intensive care. In the prediction study are used, not only the measurements extracted from the waveform recordings, but also measurements from laboratory tests, pathologies and treatments were extracted. In addition, thanks to the use of point process modelling, was possible to calculate different baroreflex

measurements and varying time spectra for each patient. More specifically, for each patient were extracted generic information, severity indexes, laboratory value, particularly lactate, medications and treatments administered, in particular vasopressors, sedatives and mechanical ventilation modes and recordings of waveforms temporally placed around the first administration of vasopressor.

Due to the fuzziness of the theoretical vasopressor administration onset, features from the waveforms were computed in two 15-minute windows leaving a 30 left in between to be sure to analyze the signals only before and after administration. With regard to lactate measurements, due to the very low number of available data, two 12-hour windows were considered before and after administration. To get the lactate measure nearest to the vasopressor onset, the first available measure before the administration was considered for each subject. As “initial lactate” was considered the last available measure before the vasopressor onset while, as “final lactate” the first available lactate measure for each subject after vasopressor administration.

First of all, at the beginning of the characterization analysis, using the Lilliefors test, the normality of the population was verified. Wilcoxon Rank Sum Test was performed intra groups while Wilcoxon Signed Rank Test was used to compare the pre and post segment into groups. In the cohort used in the first part of the characterization study were included only patients without mechanical ventilation and/or sedation. It is known that these treatments strongly influence the autonomic nervous system. The results obtained show a significant increase in mean systolic and diastolic pressure, a decrease in heart rate and an increase in cardiac variability time indices. In addition, a frequency analysis of the spectra obtained from the RR shows a shift in the sympato-vagal balance determined by a greater prevalence of sympathetic activity compared to vagal activity following vasopressor administration. With regard to baroreflex, homeostatic mechanism that regulates pressure and heartbeat, a decrease in activity after vasopressor administration was noticed.

The same analysis was then conducted including patients with mechanical ventilation and/or sedatives in the study. The general trend related to pressure, heart rate and baroreflex was maintained, while, all information regarding the sympato-vagal balance were lost. Some patients showed a decrease in blood pressure instead of an increase following vasopressor administration. These subjects were classified as "non-responding" and the rest of the population as "responding", other analyses were conducted showing multiple differences between the two groups.

A second type of division was then carried out by stratifying the population according to the lactate value. Defining as "low level" the subjects who, starting from a lactate below the threshold, kept it even hours after vasopressor administration or when they suffered a lowering of the lactate value, going from above threshold to below threshold. Patients with always abnormal lactate or for whom there was a significant increase in lactate level were classified as "high level". Again, the two populations showed different behaviors both before and after vasopressor administration. A final multivariate analysis was carried out by stratifying the population for the different pathologies and treatments and the. Fisher's exact test was computed looking if there is a nonrandom association between the subdivision in responding and non-responding subjects with relative subgroups.

A correlation study was also carried out to verify if there is a link between the indices extracted from the waveforms and blood lactate level. The method used is the Spearman's correlation coefficient. A stronger correlation was found between the features extracted before and after administration and lactate in the previous 12 hours. These correlations increase considering only the population of non-responding subjects or considering only subjects with abnormal lactate.

Finally, all this information was used for the prediction study. To accomplish the prediction task, due to the high number of features with respect to the number of patients available, feature selection was performed before training the models. Data were divided into training set and testing set through a cross validation procedure and then a feature selection process was exploited. Different approaches were adopted for feature selection and after it, the chosen sets of features were employed to train classification algorithms such as Logistic Regression, Random Forest, XGBoost, k-Nearest Neighbors and Support Vector Machine.

Our best results were obtained using logistic regression for the selection of variables, and a random forest classification model (AUROC= 0.84). Although it we could not find previous studies with a similar set up, the results obtained far outperform those from other models found in literature, in which either lactate or vasopressor administration were selectively used for mortality prediction. For example, the best result obtained by Liu et al [61] reports an AUROC of 0.664, while those reported by Vallabhajosyula et al show an AUROC of 0.73 [62].

In conclusion, this thesis shows that vasopressors may be responsible not only for an increase in pressure but also for an increase in the sympathetic-vagal balance. In addition, parameters related to changes in autonomic activity induced by vasopressors are correlated with the level of lactate in the blood and may be able to provide indications on future lactate level and consequently on the

oxygenation status of tissues. The obtained results need to be improved by increasing the number of patients, increase the number of lactate measure and by trying to build a more general and flexible model that can account for time-varying dynamics following lactate kinetics. Finally, the results need a validation on a larger cohort possibly using a multicenter database.

List of Figure:

Chapter 1

Introduction

Intensive care units (ICU), also called critical care units, are sections within a hospital that look after critically ill patients that are in a constant need of care, close monitoring and support. Laboratory measure and vital signs of the patient (Electrocardiogram, Arterial Blood Pressure and, in some cases, Respiration signal) are continuously extracted using bedside monitoring systems. This allow to get information instantaneously about any change of the patient's physiological parameters in order to guide the administered therapy. Nevertheless, this big amount of information is not analyzed in a statistical framework or using complex method. Only recently Artificial intelligence and Machine Learning techniques [7] are used to analyze, interpret and extract information from the large amount of data available, in order to support decision-making processes and find optimal solutions for very high-complexity problems.

Patient admitted to the ICU are characterized by a wide spectrum of diseases and conditions and hence subjected to a variety of interventions and therapies. Vasopressors drugs are given to hypotensive patients, in order to rise blood pressure and restore blood flow to vital organs, generating effects on the cardiovascular system and on the autonomic nervous system. [8] These effects can be characterized extracting parameters from the vital signs of the patients.

The range of available laboratory parameters, for every patient, is huge. Among these laboratory measure, blood lactate level is particularly interesting. Lactate is a marker of tissue hypoperfusion and thus of oxygen debt, in fact, an increase of lactate level (hyperlactatemia) is associate with septic shock. According to some studies it can be considered an independent predictor of sepsis prognosis and an independent factor for mortality prediction.

Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. [9]
All patients receiving a vasopressor are hypotensive, thus, lactate level can be used as a biomarker to assess how well their organs are perfused.
It's well known that, after a vasopressor administration, if there is an increase in blood pressure, the patient is responding well to therapy. Likewise, a patient with a decrease in lactate level is experiencing an improvement of his medical condition. Thus, after the vasopressor administration is interesting to investigate the relationship between lactate level and vasopressor response.

The goal of this study is to characterize the effect induced by the administration of vasopressor on the autonomic nervous system and use them to develop a prognostic tool; using the extracted autonomic indexes to try to predict an abnormal lactate level 12 hours after the vasopressor administration.

The main questions this study is trying to answer are: Is it possible to determine a difference between patients who have responded positively or not to the vasopressor therapy, in relation to lactate level changes, by looking at the autonomic indexes extracted from the vital signals during their ICU stay? Can those autonomic indexes and initial lactate level, be used as prognostic indication of lactate level within pressure response a few hours later?

After this brief introduction, the thesis will be organized as follows: second chapter contains a description of the autonomic nervous system, control mechanisms on cardiovascular system and heart rate variability; some basics of the vasopressors pharmacology and classification, an overview on blood lactate levels and the state of art regarding the characterization of the effects induced by the vasopressors and other machine learning studies. The third chapter contains the description of the database from which the data were extracted (both waveforms and clinical data), the methods used to clean the raw data and the tool used for signal annotations; also a detailed description of the study design, feature engineering, feature selection, machine learning techniques and point process modeling. The fourth chapter shows the results for both characterization and prediction studies, while the last chapter discusses the results illustrated in previous chapter, together with conclusions, limitations and future developments to focus on.

Chapter 2

Background

2.1 Autonomic Nervous System

Nervous System is subdivided in Central Nervous System (CNS), constituted by brain and spinal cord, and Peripheral Nervous System (PNS), composed by nerves and ganglia placed outside the CNS. The PNS is to connect the CNS to the limbs and organs, making a connection between the brain and the spinal cord and the rest of the body. The peripheral nervous system is itself divided into somatic nervous system and autonomic nervous system. The autonomic nervous system exerts involuntary control over smooth muscles and glands, regulating and controlling certain body processes, such as blood pressure and the rate of breathing. This system works automatically (autonomously), without a person's conscious effort, constituting the connections between CNS and organs allowing the system to function in two different functional states.

Autonomic nervous system is in turn divided in sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Anatomically the sympathetic pathway starts mainly from the thoracic section of the spinal cord; conversely, the parasympathetic pathway starts from the Medulla Oblungata precisely from the nerve X (Vagus nerve). The PNS contain both afferent and efferent fibers that provide sensory input and motor output, respectively, to the central nervous system.

A schematic representation of the organization of the ANS is visible in figure 2.1 1

The sympathetic nervous system is responsible for long-term variations (order of minutes) through the production of chemical messengers releasing neurotransmitters (such as norepinephrine, epinephrine) that, once in the bloodstream, reach the target cells. It is activated during situation of stress or danger and it's associate to "fight, flight, fright" response, causing pupil dilatation, increasing of heart rate, increasing of blood pressure etc..

The parasympathetic nervous system is characterized by faster responses (order of milliseconds or seconds), generating electrical signals. It is associate with “rest and digest” response and the primarily neurotransmitter, which is acetylcholine, is released as a mediator allowing the body to increase salivation and activity in digestion, decreasing heart rate and of blood pressure.

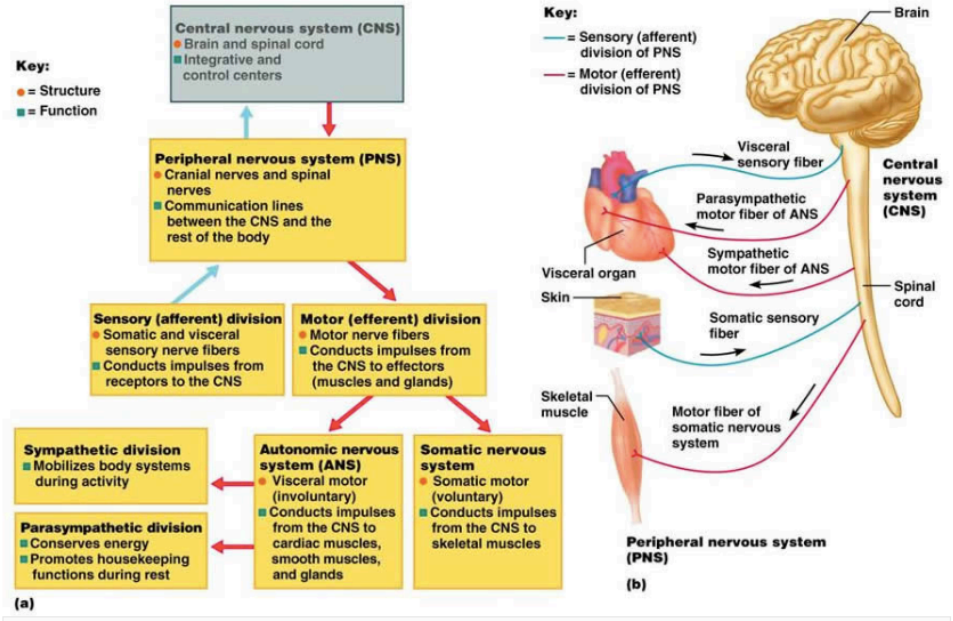


Figure2.1 1 Left (a): schematic representation of the divisions and functions of the autonomic nervous system. Right (b): simple representation of the sensory and motor divisions and connections between the different organs involved in the peripheral nervous system

2.2 Link between Heart Rate Variability, Blood Pressure Variability and mechanisms of the cardiovascular control system

Parasympathetic and sympathetic systems, work in a complementary way interacting with each other. The concept of “sympatho-vagal balance” reflects the autonomic state resulting from the sympathetic and parasympathetic influences that is fundamental for the modulation of the cardiovascular activity and in particular in the variation of the heart rate. Such physiological variation is called heart rate variability (HRV). Both branches of the ANS have connections with the Sino-Atrial Node of the heart, determining an increase or a decrease of the heart rate. Only in the Sympathetic Nervous System efferent nerve fibers have connections also with the blood vessels and

the modulation of their activity contribute in determining the value of blood pressure (Blood Pressure Variability, BPV).

Cardiac cycle is calculated as the time interval between one ventricular depolarization and the following one, detected in the electrocardiographic signal (ECG) as the RR interval. ECG, ABP, cardiac output and peripheral resistance are signals strongly related to the heart rate (HR) so characterized by the cardiac cycle. The studies of such control mechanism are mainly on the HRV. Using the power spectral density (PSD) of discrete beat-to-beat series is possible to extract parameters that are able to quantify the effect on the control mechanism and, hence, to obtain significant indicators of physiological conditions in a non-invasive way. [3]

From the electrocardiogram (ECG) and the arterial blood pressure (ABP), we can derive three time series from which measures of HRV and BPV can be extracted (fig2.1 2).

- The Tachogram is a signal obtained from the ECG by measuring the time distance between two successive R peaks (RR) and so it is sampled in correspondence of each beat.
- The Systogram is a signal whose amplitude is represented by the value of systolic arterial pressure (SAP).
- The Diastogram is a signal whose amplitude is represented by the value of diastolic arterial pressure (DAP).

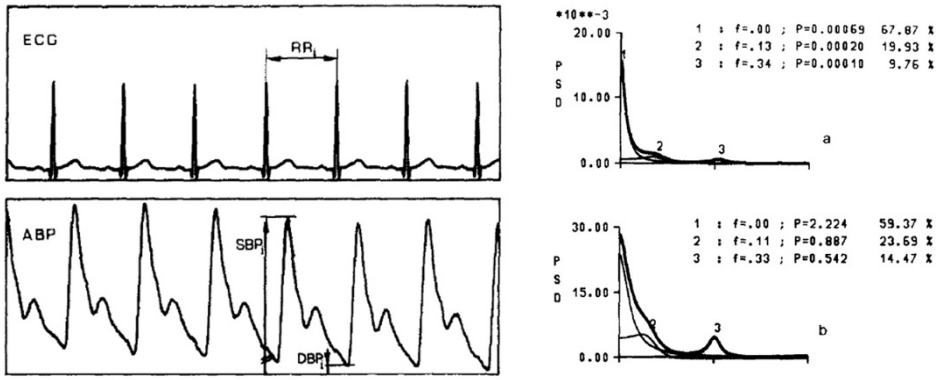


Figure2.1 2 Left: ECG signal and definition of the RR interval (top), ABP signal and definition of the systolic blood pressure (SBP) and diastolic blood pressure (DBP) (bottom); Right: Power Spectral Density of the two signals rispectively

The power spectral density of the tachogram has been used to quantify how the HRV signal variance (power) is distributed in the various frequency bands and so the autonomic influences on Sino-Atrial

Node and blood pressure. The PSD is characterized by three main frequency bands: the VLF band (0.003-0.04 Hz), which represents the very slow variations and may contain information about hormonal changes; the LF band (0.04-0.15 Hz), influenced by both the sympathetic and parasympathetic (or vagal) activity, accounts for vasomotion regulatory mechanism; the HF band (0.15-0.45 Hz), which is mainly related to parasympathetic control and respiratory rate.

By integrating the PSD (ms^2/Hz) in these three bands we obtain the VLF, LF and HF indices in absolute values (ms^2), from which other indices can be derived. The normalization of the LF and HF indices by the total power minus VLF yields the LF n.u. (normalized units) and HF n.u. indices, which respectively represent indicators of sympathetic and vagal activity. The ration LF/HF is therefore a simple tool to quantify the sympatho-vagal balance effect elicited on the control of heart rate, under normal conditions the value of this pameter is between 2 and 3. (example in Fig 2.1 3)

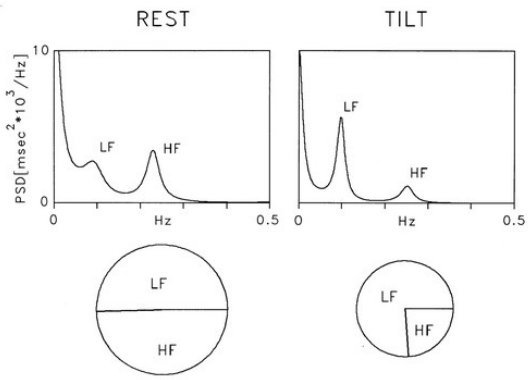


Figure2.1 3.PSD in normalized frequency and pie chart. Left: During the standard condition the sympathetic and the vagal activity are balanced. Right: PSD during tilt condition the LF component is dominant due to the sympathetic stimulation

Many different mechanisms contribute to the control of circulation, different models have been developed over the years to try to establish a mathematical model which may contribute to the explanation of qualitative properties of circulation dynamics.

The first representation of the vascular mechanical system was probably the Windkessel model that described the hemodynamics of the arterial system in terms of resistance and compliance. Taking as input ventricular pressure and aortic inflow from the heart, models the peripheral resistance and aortic compliance to obtain the total impedance of the circulatory system taking inspiration from

an RC electric analogue and of simple resolution. The representation of the three elements Windkessel model in Figure 2.1 4,5.

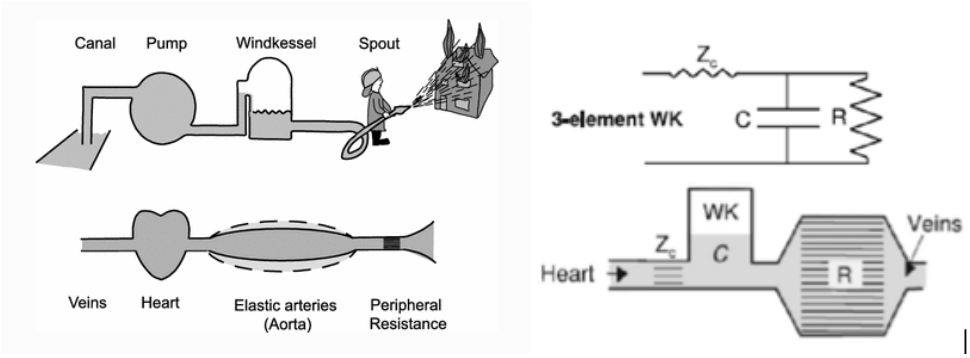


Figure2.1 4 Left: Heart as a pump, Windkessel model. Right: Three-element Windkessel model in both hydraulic (bottom) and electrical (upper) representation.

The Windkessel model does not take into account ANS influence. Both ABP and HR variabilities are synchronous with respiration. The auto-spectra, as simple superimposition of HF and LF bands, is related to the complex action of the vasomotor and respiratory centers. Coupling the two cycles, respiratory cycle and heart-beat oscillation causes oscillations of the heart rate with a frequency of approximately 0.25 Hz (4 s), referred to as respiratory sinus arrhythmia (RSA), responsible for the increase of the heart rate during the inspiration and a decrease during the expiration. This effect is due to the interaction of many mechanisms in the cardiac center in the medulla, in addition to mechanical control. The continuous interaction of the center with the periphery forms an interconnected regulation loop. To represent this complex system, the estimations of closed-loop gains such as the baroreflex response is required. The negative feedback loop, in which an elevated blood pressure reflexively causes the heart rate to decrease and blood pressure to increase decrease, is due to the baroreflex mechanism, an homeostatic mechanism of the body that helps to maintain blood pressure at a nearly constant level. Baroreflex sensitivity (BRS) assessment provides a valuable measure of cardiovascular autonomic regulation in normal or diseased states. [4]

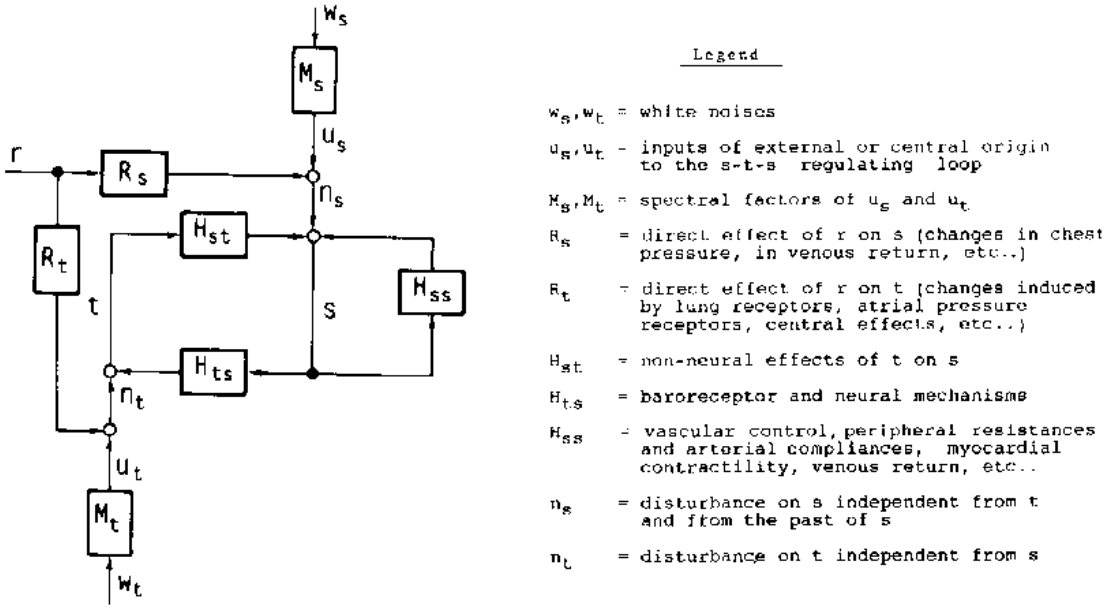


Figure2.1 5 Baselli. Close-loop model

The first step in the identification of a closed loop model was given by the work of Baselli et al. [6], considering the interactions between respiration, arterial pressure and heart period through the estimation of the relative transfer functions (Figure 2.1 5). It describes few aspects of the interactions among the signals themselves, by identifying the transfer functions of the model, providing causal relation-ships between the different variability signals.

A more complex model was identified by Berger, Saul & Cohen [11], describing the relationship between respiration, heart rate and blood pressure with an autoregressive moving-average equation with linear constant-coefficient. They proposed a block diagram in which the respiration enters the closed-loop through centrally induced heart rate variations (RSA) and by mechanical coupling to arterial vasculature within the thorax. Not only arterial baroreflex contributes to modulate the heart rate but also chemoreflex. Chemoreflexes are chemical control mechanism important for the modulations of the sympathetic activation. Both baroreflex and chemoreflex are able to perceive the amplitude of the pressure level and send the information to the brain. At the central level, the brain controls breathings that, in turn, affects the peripheral levels. In response to changes in arterial pressure blood pressure, homeostasis is maintained by modulating sympathetic activity in response to changes in arterial pressure.

A schematic representation of the model is shown in Figure2.1.6.

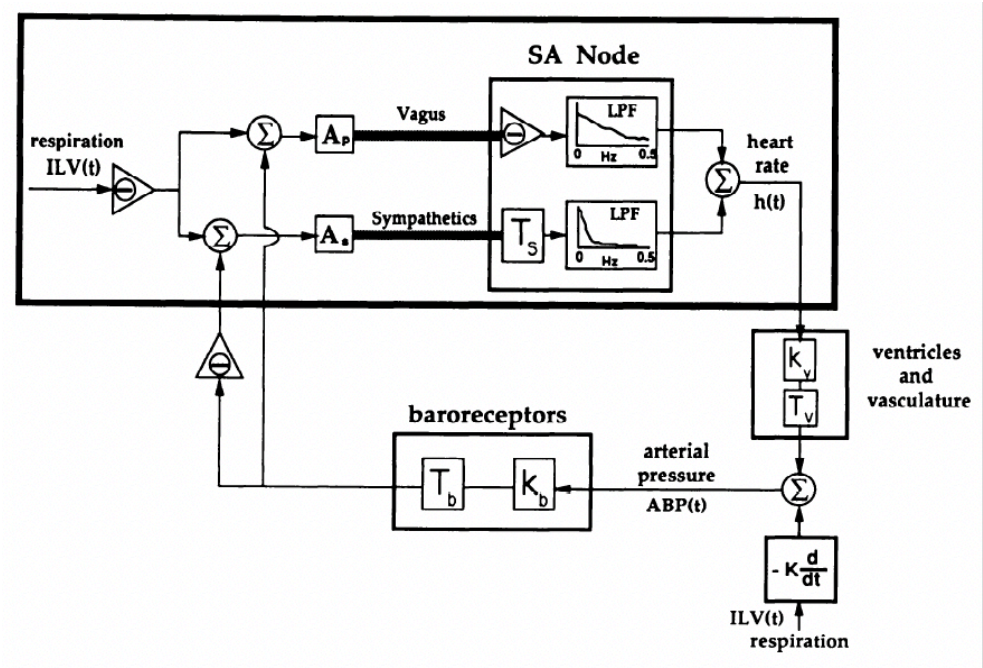


Figure2.1 6 Block diagram of the Saul et al. cardiovascular control model

2.3 Vasopressors

ICU patients receive a large number of drugs and, among these, vasoactive agents are medications which have an impact on blood pressure through the action on blood vessels; acting to increase (vasoconstrictors) or decrease (vasodilators) blood pressure and to increase (positive inotropes) or decrease (negative inotropes) the contractility of the heart and so the cardiac output.

The cardiac output (CO) is controlled by heart rate (primary determined by the CNS) and stroke volume (SV). The latter is directly influenced by the preload, the contractility and afterload, Fig.

- Preload = amount of blood present in the heart chamber, the end-diastolic stretch of the heart muscle fiber
- Contractility = the strength of the cardiac contraction that is related to the systemic vascular resistance (SRV).
- Afterload = the pressure against which the heart must work, the forces that impede the flow of blood out of the heart

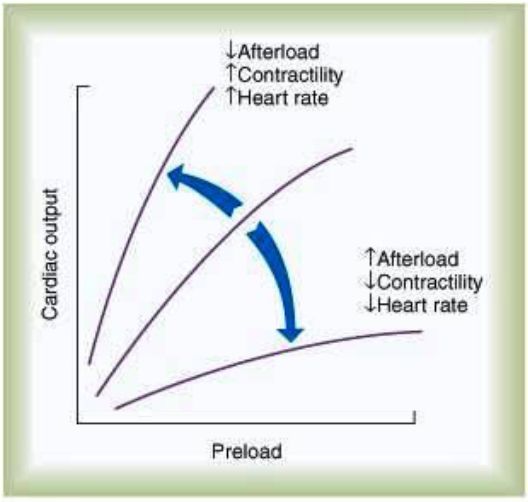


Figure2.1 7 Relationship between Cardiac output, Preload, Contractility, Afterload and Heart rate

The main role of vasopressor is to activate the adrenergic receptor in order to increase blood pressure, acting as vasoconstrictors, to increase the peripheral resistance and so the SVR. Despite that, since a lot of vasopressors are acting on adrenergic receptors, they might induce several effects as increasing or not CO, effecting the contractility or heart rate or the preload.

The vasopressors belong to the class of anti-hypotensive agents, together with colloid solutions, glucocorticoids and inotropic agents. The first one increase volemia (i.e. blood volume), Glucocorticoids are a class of steroid hormones that are part of the feedback mechanism in the immune system and inotropes increase myocardial contractility to increase the cardiac output sensitizing adrenoreceptors to catecholamines and glucocorticoids.
The widest class of vasopressors are the synthetic catecholamines or sympathomimetics, whose name is derived from the type of action they exert, which is, indeed, mimicking the action of the sympathetic nervous system. Catecholamines mediate their cardiovascular actions predominantly through mainly two groups of adrenergic receptors called α and β. The amount of vasoconstructive and inotropic power is determined by the affinity of the specific drug with the target receptors. Adrenergic drugs will bind directly to one or more of these receptors to induce various physiologic effects and some indirectly act to induce certain other effects. [17] It is possible to have two opposite type of binding. Agonist fully activate the receptors to which is biding to, while antagonist binding does not activate the receptor, instead block the effect of the agonist.

Major agonist binding at adrenergic receptor are:

- α_1 receptors, located on arterial vascular smooth muscle cells, are responsible for smooth muscle contraction increasing the blood pressure.
- β_1 receptors, located in the heart, are responsible for positive chronotropic effects. They increase the heart rate and they have a positive inotropic effect (increase contractility).
- β_2 receptors are located in the lungs and are responsible for smooth muscle relaxation, that could cause a drop in blood pressure.

There are other activated receptors:

- D1, present in the renal smooth muscle, that cause smooth muscle contraction
- V1, also located in the smooth muscle, responsible for vasoconstriction.

A summary of the main vasopressors (also the one considered in this thesis), together with their clinical indications, dose ranges, degree of receptor binding and major side effects are shown in Fig.2.1.8

Medication	Receptors	Actions	Usual dose range	Titration
Dopamine Low dose:	D_1 & D_2	Vasodilation of renal and mesenteric blood vessels	0.5–2 micrograms per kilogram per minute (mcg/kg/min)	Low dose not usually titrated
Moderate dose:	Beta-1	↑ Myocardial contractility and heart rate	2–10 mcg/kg/min	1–3 mcg/kg/min. every 10 min
High dose:	Alpha-1	Vasoconstriction	10–20 mcg/kg/min	
Phenylephrine	Alpha-1	Vasoconstriction	Bolus: 100 mcg over 1 min Infusion: 20–200 mcg/min. Max: 300 mcg/min	20 mcg/min. every 10 min
Norepinephrine	Strong Alpha-1 Weak Beta-1	Strong vasoconstriction Weak ↑ myocardial contractility	2–12 mcg/min Max: 30 mcg/min	0.5 mcg/min. every 10 min
Epinephrine	Beta-1 Beta-2 Alpha-1	Strong ↑ myocardial contractility and heart rate, bronchodilation, and vasoconstriction	2–10 mcg/min. Max: 30 mcg/min	0.5 mcg/min. every 10 min
Vasopressin	V1 & V2	Vasoconstriction	0.01–0.04 units/min (commonly fixed dose of 0.03 units/min) Max: 0.1 units/min	

Figure2.1 8 Vasopressor Drug Names, Receptors, Major effects, Standard Dose Range, Titration (adjusted dose for the maximum benefit without side effects)

- Norepinephrine is a major endogenous neurotransmitter liberated by postganglionic adrenergic nerves. Is a potent α1-adrenergic receptor agonist with modest β agonist activity. For these reasons has a great effect of increasing SVR, potent vasoconstrictor, but a small effect on heart rate and contractility. Prolonged Norepinephrine infusion can have a direct toxic effect on cardiac myocytes by inducing apoptosis via protein kinase A activation and increased cytosolic Ca^{2+} influx [18]. It is a direct acting vasopressor agent, so directly activate the receptors. The recommended starting dose is from 0.01 mg/kg/min to 0.03 mg/kg/min; maximum suggested dose is 0.1 mg/kg/min [14]. Norepinephrine is considered a first-line drug in the management of hypotension related to sepsis.

- Phenylephrine is a pure α-adrenergic antagonist with no affinity for β-adrenergic or other receptors; it increases peripheral vascular resistance and blood pressure. The rise in blood pressure stimulates baroreceptors by vagal reflex, leading to bradycardia and having an effect on patient cardiac output. It has a strong effect on the systemic vascular resistance but no effect on contractility, increasing oxygen consumption. For this reason, is not used for acute heart failure. The recommended starting dose is 0.01 mg/kg/min to 0.03 mg/kg/min; maximum suggested doses are 0.1 mg/kg/min to 0.3 mg/kg/min.

- Vasopressin s a neurohypophysis hormone with various actions. It exerts his effect through v1 and v2 receptors. V1 agonist primary effect is to cause smooth vessel contraction while

mediate water reabsorption by enhancing renal collecting duct permeability increasing SVR, having no effect in contractility and heart rate. The onset is not as quick as the other vasopressors and it's really used for septic shock. The recommended dose is from 0.01 mg/kg/min to 1 mg/kg/min; fixed suggested doses is usually 0.04 mg/kg/min.

- Epinephrine is a nonspecific α and β adrenergic agonist. β-Adrenergic effects are more pronounced at low doses and α1-adrenergic effects at higher doses. It mainly increases SVR and contractility causing peripheral vasoconstriction and increasing cardiac output. It's usually used only when the other are non-functioning because of its non-selective agonist action. The recommended dose is .01 mg/kg/min to 0.10 mg/kg/min.

- Dopamine is an endogenous central neurotransmitter; the effect is totally dependent on the dose and acts on both dopaminergic and adrenergic receptors. At low doses, <3 µg/kg/min, stimulate dopaminergic D1 receptor that promotes vasodilation, increasing blood flow to these tissues. As the dose is increased the main effect change, at intermediate doses, 3 µg/kg/min to 5 µg/kg/min, dopamine predominantly stimulates β1 and β2 receptors causing positive chronotropic and inotropic effects. At higher doses, 5 mg/kg/min to 15 mg/kg/min, α-adrenergic stimulation occurs, causing peripheral arterial and venous constriction.

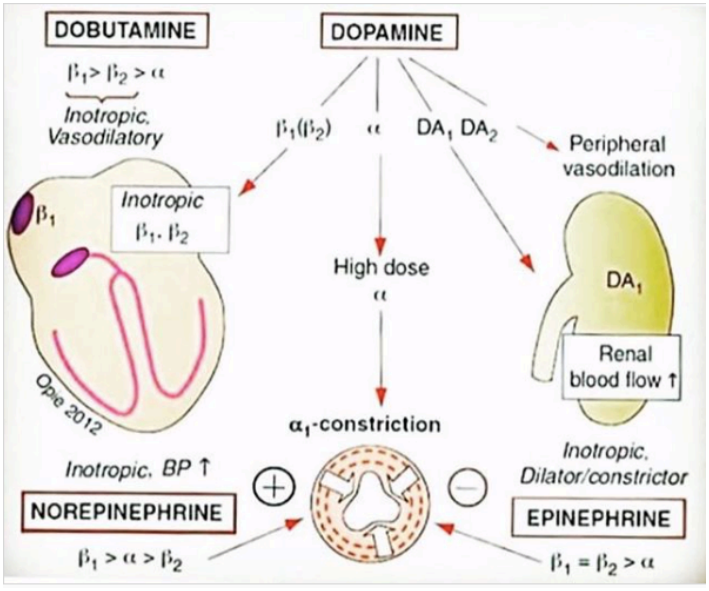


Figure2.1 9 Schematic representation of effects, main receptors and localization

2.4 Clinical use of Lactate

Lactate is a crucial metabolite in the two main energy (ATP)-producing processes that power life: glycolysis and oxidative phosphorylation (OxPhos). Glycolysis is an oxygen-independent metabolic pathway that converts glucose into two molecules of pyruvate with the concomitant generation of 2 ATP. While oxidative phosphorylation is the process in which ATP.

Although all oxygen-consuming tissues possess the ability to consume lactate, liver and kidneys also possess the ability to convert this lactate back into glucose (gluconeogenesis) and export this glucose into the circulation. In most (patho)physiological conditions, acute energy requirements are key drivers of local or systemic lactate levels, irrespective of local oxygen tension. In non-stressed steady-state conditions glucose is converted to pyruvate, which is subsequently fully oxidized to Co2, generating approximately 36 ATP (adenosine tri-phosphate) per glucose molecule. In stressed situation, where tissue immediately requires more ATP, glycolysis generates only 2 ATP but can very rapidly increase by two or three orders of magnitude. Even with optimal mitochondrial oxygenation and function, this rate of pyruvate production will saturate the much more complex but much less flexible process of oxidative phosphorylation. Thus, for glycolysis to continue, pyruvate must be converted to lactate. In post stress situation, lactate is converted back to pyruvate and fully oxidized. Since lactate can be transported both at micro and at macro scales, lactate shuttles exist that allow the simultaneous production and consumption of lactate by different cells or tissues. [24] Three Metabolic states with Respect to Lactate Production and Consumption are shown in figure2.1.10

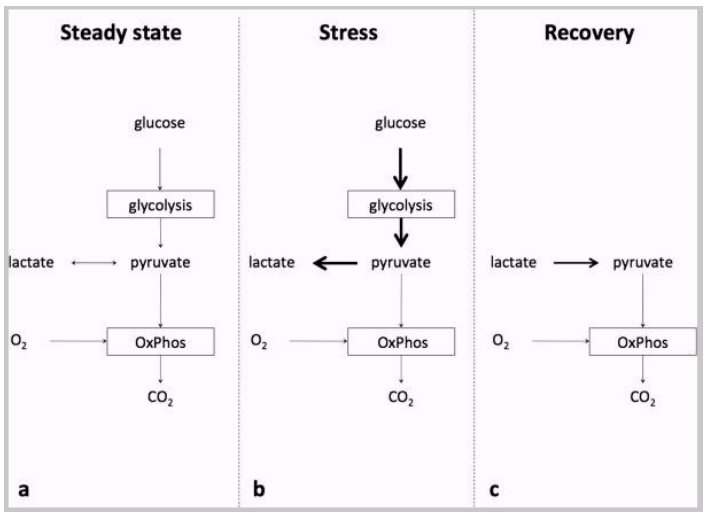


Figure2.1 10Lactate at the cellular level. Usually not oxygen shortage per se, but acute energy requirements is a key determinant of lactate levels.

Serum lactate levels are traditionally low in normal individuals. The reference range is around 1 ± 0.5 mmol/L, less than 2 mmol/L. In critically ill patients, lactate value varies from 2 mmol/L to 5 mmol/L in hyperlactatemia and above 5 mmol/L in lactic acidosis [20]. Lactate is a product of anaerobic metabolism, in fact, high levels of lactate in tissue is direct indication of tissue hypoxia. Organ failure, associated with tissue hypoxia, is common feature seen in septic or septic shock patients. Tissue hypoxia for long time can cause irreversible damage to the tissue resulting in its death. Hyperlactatemia in fact is associated with long periods of tissue hypoxia and subsequent organ failure [21]. Thus, serum lactate levels serve as diagnostic maker in critically ill patients.

2.5 State of Art

2.5.1 Characterization of Vasopressors-induced Autonomic changes and prediction studies

In literature, it is possible to find of large variety of clinical studies based on testing autonomic functions by administrating vasopressors.

Ahmed MW et al. evaluated and compared the effects of physiologic and pharmacologic sympathetic stimulation on time and frequency domain indexes of heart rate variability. Five-minute electrocardiographic recordings were obtained in triplicate after physiologic and pharmacologic sympathetic stimulation: during upright tilt, after maximal exercise, during epinephrine and isoproterenol infusions at 50 ng/kg body weight per min, during beta-adrenergic blockade and during combined beta-adrenergic and parasympathetic blockade [30]. From this experiment it was seen that beta-adrenergic stimulation resulted in a significant decrease in time domain measures of heart rate variability.

Goldberger et al. conducted a study in order to evaluate the effects of parasympathetic stimulation on time and frequency domain in normal (healthy) subjects. Ten normal subjects were evaluated, with five-minute electrocardiographic recordings were obtained at baseline and during 1) combined alpha-adrenergic stimulation with baroreflex-increased cardiac parasympathetic activity produced by phenylephrine infusion; 2) parasympathetic blockade (atropine 0.04 mg/kg); and 3) isolated alpha-adrenergic stimulation produced by phenylephrine infusion after parasympathetic blockade. Phenylephrine infusion resulted in a decrease in the time domain measures and in the high-frequency power, increasing systolic blood pressure.[29]

A. Belletti et al. performed a meta-analysis of randomized trials published in the last 20 year to investigate the effect of vasopressor drugs on mortality. In a total of 28 280 patients from 177 trials, reduction in mortality was associated with inotrope/ vasopressor therapy use in settings of vasoplegic syndromes, sepsis and cardiac surgery. Subgroup analysis did not identify any groups with increased mortality associated with inotrope/vasopressor therapy. It was found that inotrope/vasopressor therapy is not associated with differences in mortality in the overall population and in the majority of sub settings. [14]

Many severity scores related to ICU patients have been developed, some to predict the outcome, for example the Charlson comorbidity index, and some to describe the degree of organ dysfunction, the most famous are the Acute Physiology And Chronic Health Evaluation-III (APACHE-III) and Sequential Organ Failure Assessment (SOFA) scores.

Vasoactive medications are essential in septic shock but are not fully incorporated into current mortality prediction risk scores. Vallabhajosyula et al. developed a novel mortality prediction model for septic shock incorporating quantitative vasoactive medication usage. Quantitative vasopressor use was calculated in a cohort of 5352 septic shock patients and compared using norepinephrine equivalents (NEE), cumulative vasopressor index and the vasoactive inotrope score models. Having best discrimination prediction, $\log_{10}$NEE was selected for further development of a novel prediction model for 28-day and 1-year mortality via backward stepwise logistic regression. This model termed 'MAVIC' (Mechanical ventilation, Acute Physiology and Chronic Health Evaluation-III, Vasopressors, Inotropes, Charlson comorbidity index) was then compared to APACHE-III and SOFA scores in an independent validation cohort for its accuracy in predicting 28-day and 1-year mortality. The MAVIC model was superior to the APACHE-III and SOFA scores in its ability to predict 28-day mortality (area under receiver operating characteristic curve [AUROC] 0.73 vs. 0.66 and 0.60) and 1-year mortality (AUROC 0.74 vs. 0.66 and 0.60), respectively. The incorporation of quantitative vasopressor usage into a novel 'MAVIC' model results in superior 28-day and 1-year mortality risk prediction in a large cohort of patients with septic shock. [15]

As mentioned above the dose of vasopressor used, but also the titration and the duration of the administration, are crucial to be able to get the maximum benefit from the dose of the medication without adverse effects. The Xiaowu Bai et al investigated the incidence of delayed norepinephrine administration, following the onset of septic shock, and its effect on 28-day hospital mortality. A strong relationship between delayed initial norepinephrine administration and 28-day mortality was noticed. The average time to initial norepinephrine (NE) administration was 3.1 ± 2.5 hours. Every 1-hour delay in norepinephrine initiation during the first 6 hours after septic shock onset was associated with a 5.3% increase in mortality. Twenty-eight-day mortality rates were significantly higher when norepinephrine administration was started more than or equal to 2 hours after septic shock onset. Their results show that early administration of norepinephrine in septic shock patients is associated with an increased survival rate. Mean arterial pressures at 1, 2, 4, and 6 hours after septic shock onset were significantly higher and serum lactate levels at 2, 4, 6, and 8 hours were

significantly lower in the Early-NE than the Late-NE group. The duration of hypotension and norepinephrine administration was significantly shorter, and the quantity of norepinephrine administered in a 24-hour period was significantly less for the Early-NE group compared to the Late-NE group.[31]

J. Goldberger, in 1999, evaluated for the effects of sympathetic and parasympathetic stimulation and blockade on HR and HR variability HR variability. A new parameter, termed the vagal-sympathetic effect (VSE), was defined as the ratio of the R-R interval to the intrinsic R-R interval (R-R_0) representing an index of sympathovagal balance. VSE > 1 reflects vagal predominance and a VSE < 1 reflects sympathetic predominance. Thus, the aim of this study was to assess the utility of the VSE, R-R interval, and heart rate variability measures, as indexes of sympathovagal balance using a broad range of autonomic maneuvers. R-R interval consistently changed in the expected directions with parasympathetic and sympathetic stimulation and blockade. Sympathetic stimulation with upright tilt, epinephrine infusion, and isoproterenol infusion resulted in significant decreases in the VSE.[33]

2.5.2 Blood lactate and Heart rate variability interaction

The delay with which oxygen consumption is brought to a steady state, depends on the relative slowness with which oxidative reactions adapt to an increased energy demand. As long as oxygen consumption remains below the steady-state value, energy is supplied by an anerobic system. Oxygen consumption huminites monotonically increase with the intensity of the work. The lactate threshold is a useful measure for exercise intensity. Lactate inflection point (LIP), is the exercise intensity at which the blood concentration of lactate and/or lactic acid begins to increase exponentially. The first method to measure lactate threshold is the direct invasive measurement of blood lactate. Alternatively, a noninvasive measurement, with indirect definition of lactate threshold, can be obtained investigating the ventilatory and gas exchange response.

In literature, it is possible to find of large variety of clinical studies that examine the relationship between the responses of the cardiac autonomic nervous system and blood lactate during physical exercise. Physical activity brings a significant PNS activation with oxygen consumption, increasing blood lactate concentration. Recent studies have suggested that HRV analysis may be a potential

tool to look for first and second physiological thresholds (i.e. lactate or ventilatory threshold LT_1, LT_2 and VT_1, VT_2 respectively) to estimate the intensity of the exercise.

The aim of the study presented by Nascimento et al. was to verify the validity and reproducibility of the heart rate variability (HRV) method to determine first and second lactate thresholds during a maximal running test. Nineteen male runners (30.4±4.1 years; body mass of 74.3±8.5 kg; height of 176±6.4 cm and body fat of 13.8±4.6 %) performed two progressive maximal tests on a treadmill, with initial speed at 5 $km.h^{-1}$ and 1 $km.h^{-1}$ increments every 3 minutes, until exhaustion. Measures of HRV and blood lactate concentrations were obtained during the tests and physiological thresholds were identified as lactate thresholds by using fixed concentrations (2.0 and 3.5 mmol/ L^{-1}) and Dmax method, as well as HRV thresholds. They found no differences between the first physiological thresholds identified as lactate (2.0 mmol/ L^{-1} = 11.9 ± 2.9 $km.h^{-1}$ and Dmax = 12.3±1.5 $km.h^{-1}$) or HRV threshold (11.6±1.6 km.h-1).[19]

Similarly, using a cycling exercise mode, Cottin et al. [28] found that nonlinear increases in HRV data, assessed by high frequency (HF) and peak frequency spectrum (ƒHF) of the beat-to-beat RR intervals, identified VT_1 and VT_2. They also showed that instantaneous HF multiplied by ƒHF (HF.ƒHF) provided a reliable and accurate index to identify these threshold.

Another study examined the relationship between the responses of the cardiac autonomic nervous system and blood lactate during incremental resistance exercises of the lower limbs in older men, showing that HRV indexes were associated with blood-lactate levels during RE. Ten healthy men participated in a progressive leg-press protocol to maximal exertion. The measurement of instantaneous R-R interval variability from Poincare plots (SD1 and SD2) and time domain indexes (RMSSD and RMSM), blood pressure, and blood lactate were obtained at rest and all leg-press loads. Significant alterations of HRV and blood lactate were observed from 30% of 1RM leg press ($p < 0.05$). Additionally, significant correlations were found between the lactate threshold (LT) and the RMSSD threshold ($r = 0.78$; $p < 0.01$), and between the LT and SD1 threshold ($r = 0.81$, $p < 0.01$), showing that metabolic and cardiovascular alterations are apparent during relatively low resistance exercise (RE) loads in apparently healthy subjects. In addition, HRV indexes were associated with blood-lactate levels during exercises.[25]

2.5.3 Lactate as independent predictor for mortality

In literature, it is possible to find of large variety of clinical studies demonstrating that lactate is a predictor of clinical outcomes, although the use of blood lactate monitoring for risk assessment in the critically ill patient has remained controversial. Several studies have shown how lactate value can be used as a valuable predictor of sepsis or mortality. Breakthrough studies done on human lactate levels showed that an increase in lactate levels from 2.1 to 8 mmol/L decreased the survival from 90% to 10% [22]

A retrospective cohort study was done by Ralphe Bou Chebl & al., showing that serum lactate is associated with increased ICU and hospital mortality, independent of comorbidities, organ dysfunction, or hemodynamic status. Patients were stratified into 3 groups according to normal (<2 mmol/L), intermediate (2 to 4 mmol/L) and high (>4 mmol/L) lactate level. The primary outcome was in-hospital mortality, secondary outcomes included ICU and hospital lengths of stay and mechanical ventilation duration. Hospital mortality was the highest in high lactate level, followed by the intermediate and the normal level group (47.4% vs 26.5% vs 19.6%; $P < .0001$). Intermediate and high lactate levels were independent predictors of hospital mortality as well as ICU mortality.[26]

Lactate predicts risk of death in all patients, although patients with sepsis have a higher mortality for any given lactate level. Villar J et al used lactate level to measure the relationship between lactate and mortality in hospital with outcomes of interest (3-day, 30-day, and 1-year all-cause mortality) for septic and non-septic patients. Statistical analysis of peak lactate level (mmol/L) was performed during the most recent admission for patients who died and peak lactate level during an admission for surviving patients; showing that higher levels of lactate had the greatest mortality risk in the short term, while lower elevations of lactate were still associated with mortality at 30 days and 1 year. [27]

Lactate level has been used as a prognostic indicator for mortality, in particular, patients with an initial lactate level > 4.0 mmol/L had higher mortality risks, and the probability of death was substantially increased with a high initial lactate level [34]

The concept of repeating blood lactate concentrations over time, using it as a marker of altered tissue perfusion and as indicator of response to therapy, was first proposed in 1983[37]. Over time many any studies have emphasized that changes in lactate over the first hours of treatment may represent a valuable monitoring tool.

The lactate kinetics is related to dynamics of blood lactate, that is, the "behavior" of lactate during and/or after an exercise. If the decrease in lactate concentration in the blood as a result of intense physical effort is measured, lactate kinetics can be measured with a bi exponential function. The blood lactate is triggered by rate of production and removal.

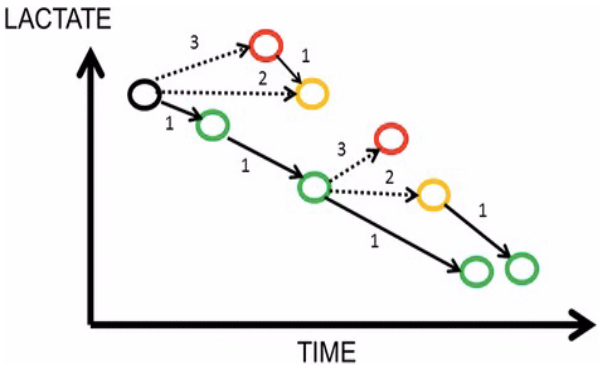


Figure2.1 11Schematic showing some of the possible evolutions of blood lactate levels over time: decreasing (1), remaining stable (2), or increasing (3)

Predicting the kinetics of lactate is therefore very complex. Changes are relatively slow and is difficult to give an indication of the rate of decrease in lactate concentration. It turns out that repeating measurements every 12 hours can generally separate those who will do well from those who are likely to die. A decrease in lactate concentrations as better prognosis is consistent throughout the literature. It has been demonstrated that these concepts are applicable not only to septic patients but in a general homogeneous population of patients.[36]

As was pointed out in the recent study conducted by Mamandipoor, predicting blood lactate concentration is a particularly challenging problem that hardly anyone has tried to solve yet. The distribution of lactate measurements follows a long-tailed distribution, resulting in a highly imbalanced dataset, almost 80% of lactate readings are concentrated within normal and mild levels. In fact, a missing value indicator is informational and increases predictive power. LSTM-based method performed by them, can predict lactate level with a Mean Absolute Error of 0.665 across 13,464 patients from different hospitals and ICU units. [40]

2.6 Lactate and Vasopressors

Shock and infections can cause dilatation of the vessels thus vasopressors are used to constrict those areas, in order to increase blood pressure that can reduce blood flow to the organs. Cardiac patients are vulnerable to impaired cardiac output (CO) and peripheral tissue hypoperfusion. Theoretically, as mentioned earlier, vasopressors can improve hemodynamic parameters by increasing CO, and reducing left and right ventricular filling pressures. Therefore, inotropes are indicated for the treatment of all cardiac patients with clinical conditions characterized by peripheral hypoperfusion resulting from impaired cardiac contractility. Although these agents benefit cardiac patients by improving CO, they have been also associated with arrhythmogenesis, increased myocardial oxygen demands, myocardial ischemia and damage [13]. Hemodynamic instability is a common cause of morbidity and mortality in cardiac patients. In clinical practice, hemodynamic instability is routinely defined as a systolic blood pressure <90 mm Hg. However, when considering hemodynamic instability, clinicians should be more concerned with organ hypoperfusion rather than a fixed blood pressure. In most patients with hemodynamic instability, administration of intravenous fluids is initially used as an attempt to improve hemodynamics. Patients with hemodynamic instability, resulting from distributive shock, typically present decreased systemic vascular resistance (SVR), leading to a decrease in blood pressure. [41]

According to the third international consensus definitions, patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[32] Already from this definition, can be seen that the average blood pressure value and the lactate value in the blood are important indicators of the patient's health status. Hemodynamic instability and organ hypoperfusion are strongly related to lactate level, lactate is a marker of tissue hypoperfusion and thus of oxygen debt, in fact, an increase of blood lactate level (hyperlactatemia) is associate with septic shock.

Therefore, blood lactate level could be a helpful indicator to assess a patient’s response to therapy. In literature not many studies investigate the relationship between lactate and vasopressors.

A study in 2015[38] found that. lactate level tends to increase, or at least not decrease, with time, among non-survivors, but lactate levels significantly decrease over time in survivors after 48 hours. In addition, lactate clearance of at least 10% at 6, 24, and 48 hours and the use of vasopressors are independent factors related to mortality, even after adjusting for critically ill status or sepsis

severity. Further, vasopressors should be avoided in lactic acidosis, if possible, because they may worsen tissue perfusion and increase lactate production. Over sixty percent of survival patients have used vasopressors, but significantly fewer used them compared to the non-survival patients assessed in this study. It is notable that the percentages of survival patients still using vasopressors at 24 and 48 hours were significantly lower compared to those of non-survival patients.

M. N. Cocchi et al. Developed a model to predict outcomes in cardiac arrest survivors, dividing patients into groups according to the vasopressor status (receipt of vasopressors vs. no vasopressors); and according to the initial blood lactate (lactate <5 mmol/L, lactate 5 to 10 mmol/L, lactate ≥10 mmol/L). They discovered that the combination of two clinical parameters, vasopressor need and lactic acid levels, is an accurate severity of illness classification system and can predict mortality in patients following out-of-hospital cardiac arrest. Patients who received vasopressors had significantly higher mortality rates compared to patients who did not receive vasopressors (80% vs. 52%; P=0.002). A stepwise increase in mortality is associated with increasing lactate levels. [39].

Chapter 3

Methods and Materials

3.1 MIMIC-III Database

The data used in this work are public, freely available and stored on the PhysioNet platform, one of the largest *freely accessible critical care databases* in the world, containing recorded physiologic signals and clinical ICU-data. The archive was created by the Laboratory for Computational Physiology (LCP), at Massachusetts Institute of Technology (MIT).

MIMIC-III integrates deidentified, comprehensive clinical data of patients admitted to the Beth Israel Deaconess Medical Center in Boston, Massachusetts, and makes it widely accessible to researchers internationally under a data use agreement Fig.3.1 It includes demographics, vital signs, laboratory tests, medications, and more. The open nature of the data allows clinical studies to be reproduced and improved in ways that would not otherwise be possible [34].

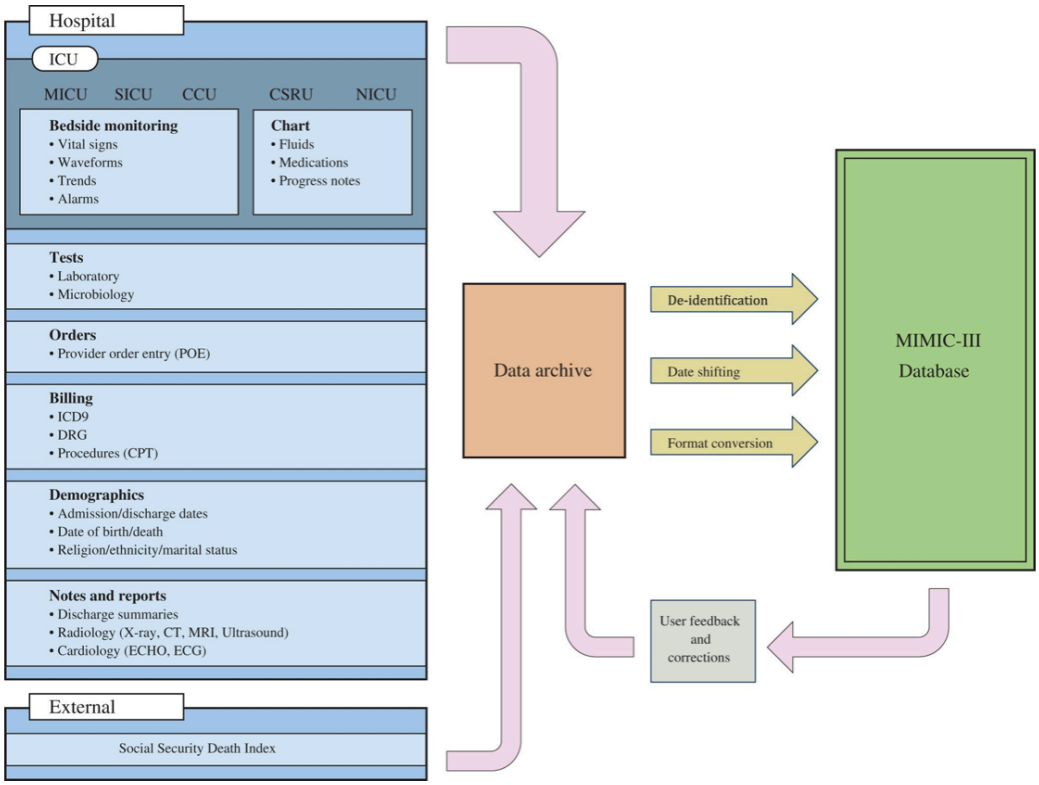


Figure 3.1 MIMICIII critical care database general overview.

3.1.1 Clinical Database

MIMIC-III is a relational database which contains comprising de-identified health-related data from electronic health records associated with 53423 distinct hospital admissions for adult patients (aged 16 years or above) admitted to critical care units between 2001 and 2012. In addition, it contains data for 7870 neonates admitted between 2001 and 2008. The database includes information such as demographics, vital sign measurements made at the bedside, laboratory test results, procedures, medications, nurse and physician notes, imaging reports, and out-of-hospital mortality. It encompasses a diverse and very large population of ICU patients and contains high temporal resolution data including lab results, electronic documentation, and bedside monitor trends and waveforms. Data are organized in 40 tables, a data storage structure which is similar to a spreadsheet: each column contains consistent information and each row contains an instantiation of that information. Data were collected with two different systems, having data archived a different format, depending on the year of the patient's admission. The oldest is CareVue (CV) system (2001-

2008) and the newest is MetaVision (MV) system (2008-2012), which contains a more detailed nomenclature, with a more precise time indication for the various fluid and drug administrations.

3.1.2 Waveforms Database

Waveform Database contains thousands of recordings of multiple physiological signals and time series of vital signs, collected from bedside patient monitors in adult and neonatal intensive care units (ICUs). Waveforms almost always include one or more ECG signals and often include continuous arterial blood pressure (ABP) waveforms. Additional waveforms (up to 8 simultaneously) are available, usually fingertip photoplethysmogram (PPG) and sometimes respiration rates, SpO2. Recording lengths also vary; most durations are of a few days, some are very short (hours), and others are several weeks long [34].

The MIMIC-III Waveform Database Matched Subset (mimic3wdb/matched) contains all MIMIC-III Waveform Database records that have been matched and time-aligned with the MIMIC-III Clinical Database records. The record matching process is still ongoing, for now the matched subset contains 22,317 waveform records, matched and time aligned with 10,282 patients. This reduce the number of available subjects available for this study. All data associated with a particular patient have been placed into a single subdirectory, named according to the patient's MIMIC-III Subject_ID. These subdirectories are further divided into ten intermediate-level directories (p00 to p09).

3.2 Study design

First of all, there is the need to understand how to turn a clinical question into a research, carefully defining the study sample (or patient cohort), the exposure of interest and the outcome of interest. As mentioned above, this study aims to characterize the autonomic changes induced by the administration of vasopressors extracted from waveforms and use them, together with information about blood lactate level, to see if it is possible to predict an increase or decrease in lactate level and if this value is in line with the positive outcome or not of vasopressor therapy. To get the most accurate information possible about the recording of administration and timing of laboratory measurements, data are taken only from the Metavsion database, considering only the data that

comes from the integration between the clinical and the matched waveform database, reaching an amount of correctly linked 17721 waveform and relative clinical data.

Unfortunately, one of the biggest limitations of this study is having to consider only the subjects with an ECG signal and blood pressure signal around the vasopressor administration, in order to be able to extract the autonomic indexes.

The fundamental requirements about waveforms are reported as follow:

- At least 1 electrocardiogram (ECG) signal, recorded according to I, II, or V lead;
- At least 1 Arterial Blood Pressure (ABP) signal;
- At least 1 hour of recording around the vasopressor onset, defined as the time instant of administration of the vasopressor;

Less than 50% of non-usable part of the signal, comprehending missing values, gaps, saturation, motion trigger and various types of noises.

3.2.1 Signal annotations and processing

The annotation and synchronization of ECG and blood pressure signals is a very complex problem, especially if we are talking about signals coming from intensive care patients. The annotation problem ì is based on the detection of fiducial points, respectively the onset, offset, and peak of each waveform. Respectively the QRS complex for the ECG signal, systole, diastole, and onset for blood pressure. A correct R peak detection is critical to obtain useful clinical information such as RR intervals, allowing heart rate variability analysis and the extraction of some features, such as the baroreflex gain. The great multitude of noise, due to physiological and non-physiological artifacts such as muscle activity or skin movements, electrical devices or incorrect use of the equipment, makes this task very complex. It is possible to find much literature on the recognition of the QRS complex and several algorithms have a been used previously, the most famous is Pan Tomkins. The problem is that does not work very well with very noisy or irregular signals. The toolbox used in this thesis for signal annotation was developed in the SpinLab of Politecnico of Milan using Matlab. First of all, consists on identification of fiducial points, on both physiological signals, using customized algorithms, then on the synchronization on the obtained annotations and in the creation of a data structure that could be directly fed into monovariate and multivariate models for features extraction, after a filtering stage based on pan Tompkins algorithm

The QRS complexes, so the R peaks, are identified performing a digital analysis of the ECG waveform, sampled with a sampling frequency of 125 Hz. For the ABP three points are defined, maximum pressure value, minimum pressure value and the point of maximum positive derivative of the pulse pressure.

Once both signals are processed, relative annotations must be synchronized. The synchronization process consists in associating each detected R peak, and so each heartbeat, to the respective values of the ABP pulse. Sometimes some holes are left due to the lack of signal quality that might have introduced a wrong variability.
The output of the algorithm is a data struct. The field “annotations” (6xN matrix), contains information about the detected R peak, the sample of pressure onset, pressure systole and its absolute value, pressure diastole and its absolute value. The field “PAT” is a 1XN array, containing the PAT value for each synchronized peak.

The graphical interface is structured in such a way to be easily understood by the users, allowing them to perform navigation, manual checking and eventually some corrections. Tools for data navigation allow for zooming in and out, suppression of part of signal, manual identification of fiducial points and signal flipping, in figure 3.2.1 it's possible to see how signals are displayed. Data can be edited and processed through five side buttons, to load the files, synchronize the signals, annotate them, identifying ectopic beats and save them.

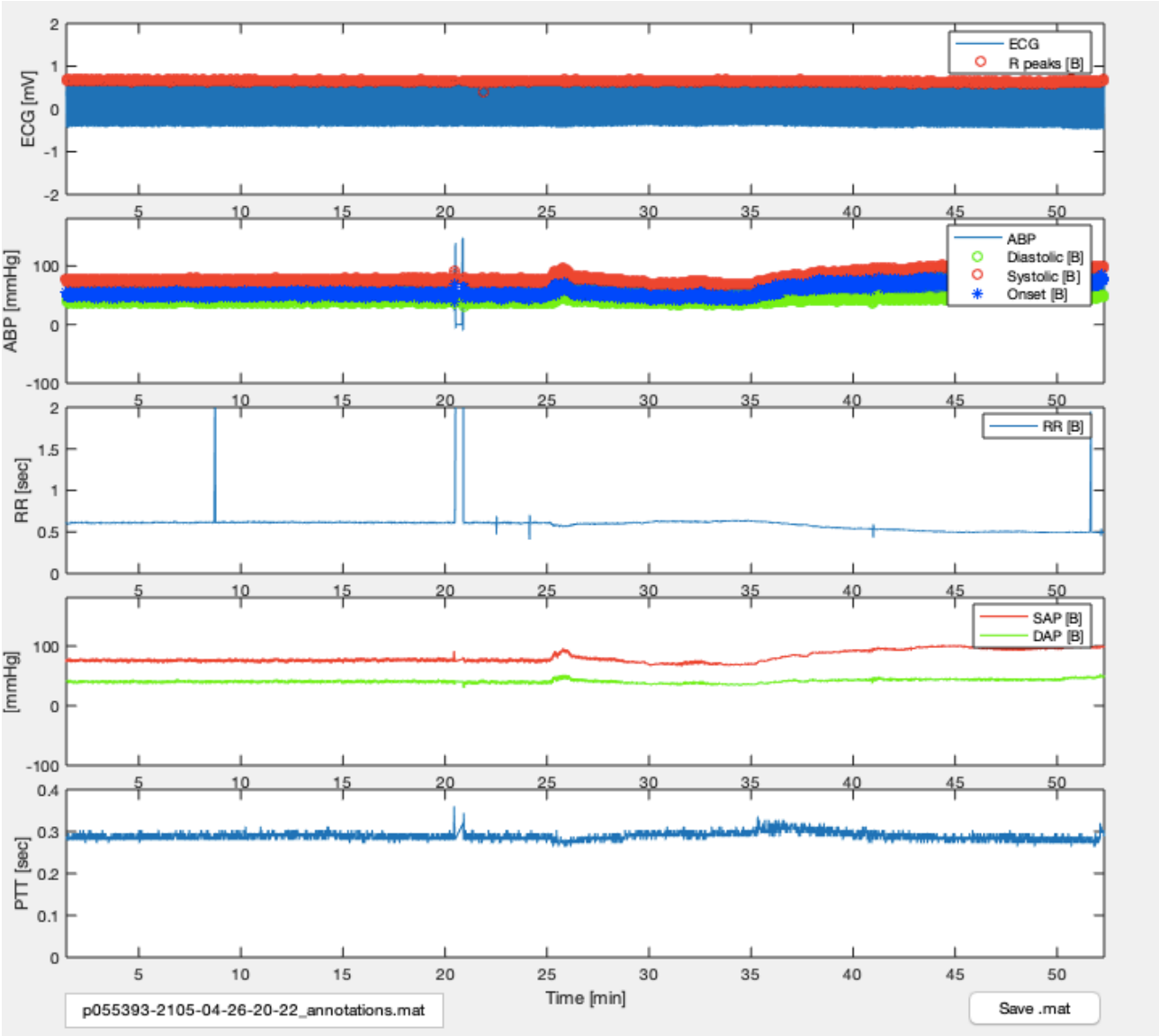


Figure 3.2.1 ECG and ABP signals with relative annotations of fiducial point form which are derived diastogram, systogram and PAT

3.2.2 Cohort selection

The subjects considered in this study are all receiving vasopressors, thus should all be hypertensive subjects. ICU patients receive a large number of different types of vasoactive agents; therefore, the first choice was to consider which vasopressors take into account, in this study are consider only the most common vasopressors used in intensive care: Epinephrine, Phenylephrine, Vasopressin, Dopamine and Norepinephrine. In figure 3.2.2 we can notice that a lot of patients received Phenylephrine (82 patients) while nearly no one received Epinephrine (only4) or Dopamine (only 6).

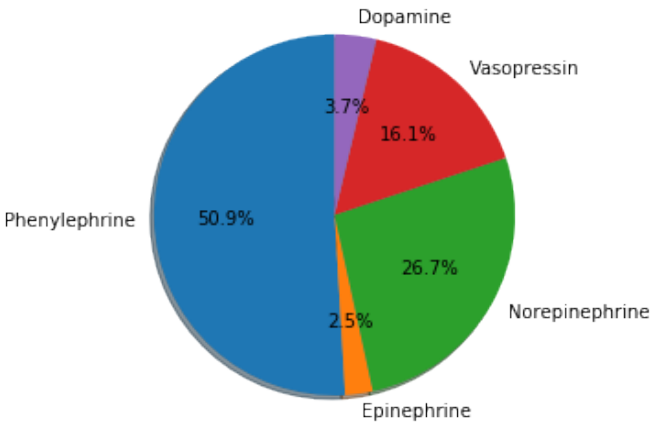


Figure 3.2.1 Pie chart, percentage of subjects receiving that vasopressor

ICU patients often receive more than one vasopressor simultaneously or at very close intervals so, for each patient, was considered as administration onset, the first vasopressor administration since entering the ICU while the duration of therapy was calculated considering the combination of all consecutive vasopressor administrations. Therefore, considering the end of the therapy as the moment when the subject is no longer receiving any vasopressor. For those reasons, vasopressor doses were converted to Norepinephrine equivalent, according to the table in the figure 3.2.3.

Drug equivalent	Dose	Norepinephrine
Epinephrine†	0.1 μg/kg/min	0.1 μg/kg/min
Norepinephrine†	0.1 μg/kg/min	0.1 μg/kg/min
Dopamine†	15 μg/kg/min	0.1 μg/kg/min
Phenylephrine‡	1.0 μg/kg/min	0.1 μg/kg/min
Vasopressin§	0.04 U/min	0.1 μg/kg/min

* Conversion scale developed by the authors (L C, J R and G T).
† Conversion based on the cardiovascular Sequential Organ Failure Assessment score. ‡ Conversion based on medical literature.
§ Conversion developed (by J R) using Vasopressin and Septic Shock Trial data set.[11]

Figure 3.2.3 Norepinephrine equivalents conersion table

In figure 3.2.4 is possible to see the mean duration of the therapy for each vasopressor considered, Norepinephrine administration are usually very long (duration of days) while Epinephrine durations usually last just a couple of hours, the mean vasopressor therapy duration is around 10 hours.

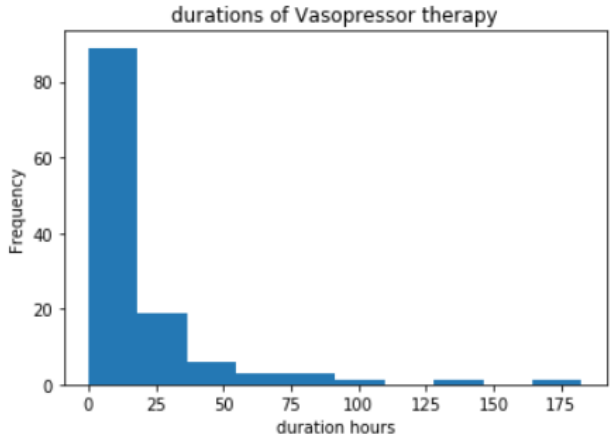


Figure 3.2.4 Histogram of vasopressors duration in hours

Starting from ~60,000 subjects in the MIMICIII database, the choice to consider only data from Metavision reduced the number to 17680 patients, of which only 10282 are present in the MIMICIII Waveforms Matched database (only 5406 with both available ECG and ABP signal).

Based on these data the cohort was selected including all adults with administration of one of the 5 vasopressors mentioned previously, taking into account only the first vasopressor administration since the entrance in ICU. Only adult patients were considered and only the first ICU stays for each patient. After verifying and synchronizing the clinical information related to the first vasopressor administration, 60 minutes waveforms were extracted for each subject around the onset of the administration. The autonomic indexes were computed from the pre and post-administration

segments, consisting of two 15-minute windows respectively, leaving a 30-minute hole around the onset, as it's shown in figure 3.2.5.

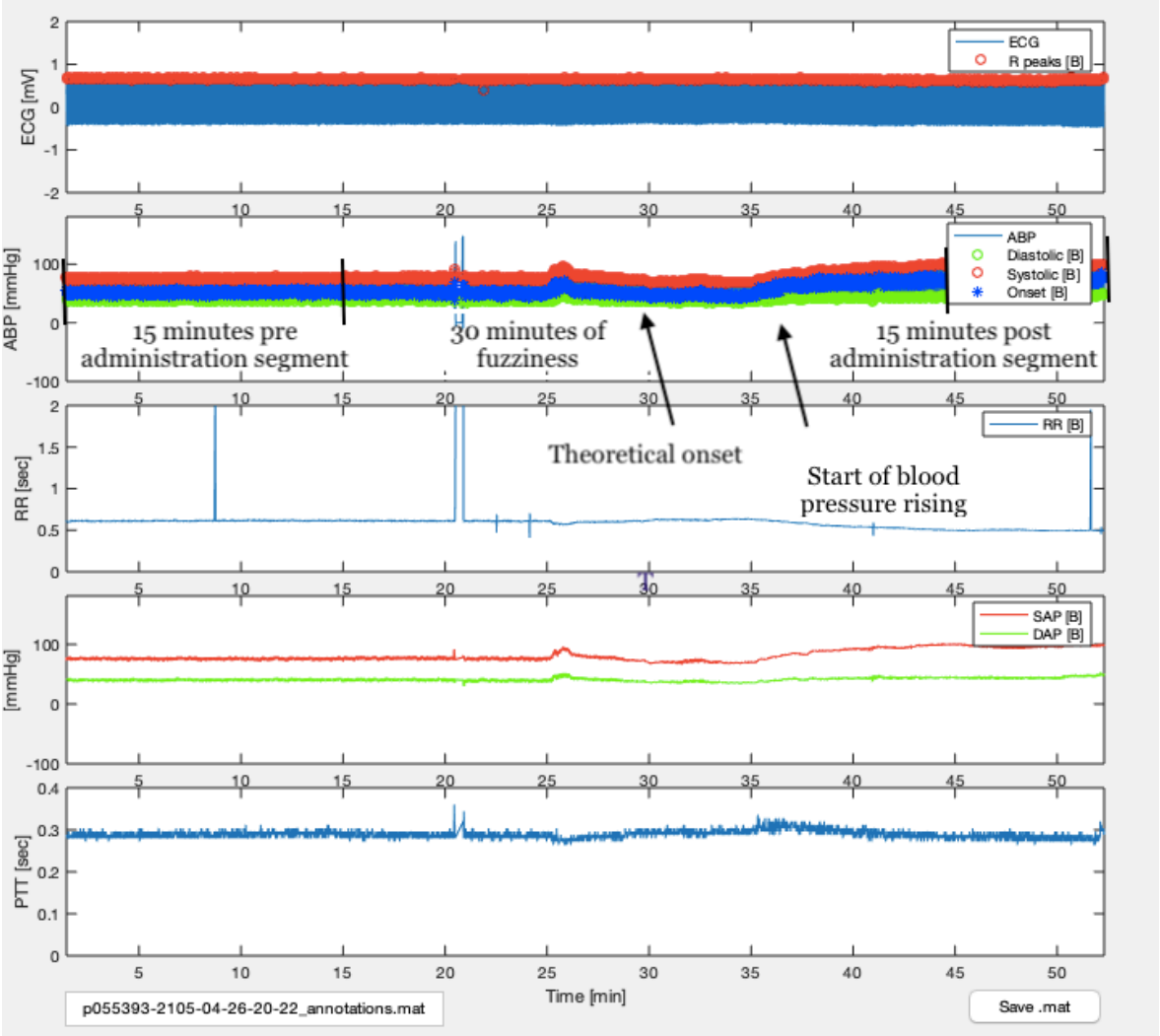


Figure 3.2.5 GUI of the waveforms annotation toolbox

The onset for the vasopressor administration indicated in the database is often inaccurate, since it is entered manually by the nurses. In addition, vasoactive drugs need a few minutes before enters in the bloodstream and so before the effects can be seen. Due to the fuzziness of the theoretical administration onset, a 30 minutes window was left in between. Two 15-minute windows have been chosen to make sure to analyze the signals before and after administration. Obtaining an indication of the condition the patient was in before administration and after, to be sure that the vasopressor drug has already entered the bloodstream, in order to analyze the effects and compare the difference of the two segments. The computation of the autonomic indexes was possible only after the synchronization and annotation of the signals, using the special tool developed at spinLabs. All

signals required also a manual checked to verify the quality of the signal and consequently its usability.

After this severe selection process, the flowchart of cohort selection is shown in figure 3.2.6.

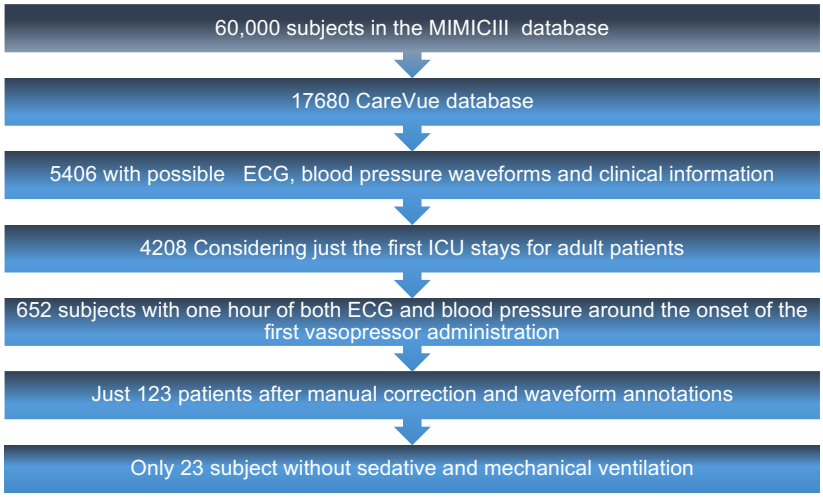


Figure 3.2.6 Flowchart of cohort selection

The remaining cohort was composed by 123 subjects, those represent the cohort for the lactate prediction study, instead, for the characterization study were initially removed all the patients whose signals were affected by the effects induced by sedation and mechanical ventilation. Only getting 23 subjects. This was done because it is very well-known that sedatives and mechanical ventilation highly influence the autonomic activity. The first part of the characterization analysis aims to characterize as much as possible the changes only induced by a single class of drugs, i.e. vasopressors. In fact, the same analysis was repeated considering the whole cohort, composed by 123 patients, to see if the obtain results still preserve themselves. We can assume that, knowing that mechanical ventilation and sedatives are present both in the pre and post segments, the changes induced by the vasopressor are still visible. For the correlation part all 77 subjects were considered, since in 46 out of 123, were not found any lactate measures available in the two 12-hour windows around the administration. With regard to the search for lactate value around vasopressor administration, several problems were found. One of the major concerns encountered, was finding homogeneous lactate measures for the entire population. On average, the number of lactate measures per subject varies a lot, from one measure every two days to six measures per day. To get the lactate measure nearest to the vasopressor onset, the first available measure before the administration was considered for each subject.

As lactate output was at first considered the first available measure after the vasopressor therapy. Considering the end of the therapy as the point at which the subject is no longer under vasopressor administration. The measure at the end of the therapy for each subject is considered, as before, as the first lactate measure closest to that point.

In both cases the big problem is the great variability of lactate measure available for each subject and the different duration of vasopressor therapy, increasing the difficulty of achieving a prediction problem and finding a correlation between lactate level and features extracted. For those reasons instead of using lactate at the end of therapy, it was decided to consider the first available lactate measure 12 hours after vasopressor administration and the last measure 12 hours before the administration for each subject, as shown in Figure 3.2.7. We further investigate the correlation with the waveform features considering both 12- and 3-hours windows. However, a 12 hours window seems to be the optimal choice to avoid a too drastic reduction in the number of patients due to the limited lactate measures available.

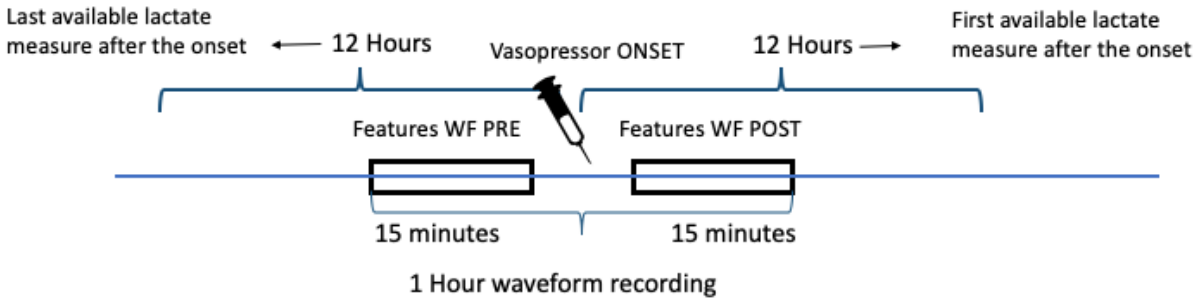


Figure 3.2.7 Lactate measure selection

For the machine learning part, we tried to vary the time window considered trying to make a prediction of lactate level changes at 12 hours. In order to not decrease further the already reduced number of patients and lose statistical significance, working with Boolean variables, a different method was chosen. Knowing that, for some subject, there are no lactate measures for a long period of time, missing values were replaced with a Boolean variable. In fact, for this part of the study, instead of considering lactate measure, a Boolean variable was introduced: 1 if the lactate is abnormal (>2 mmol/L), 0 if the lactate level is in a normal range (<= 2 mmol/L). Doing so, a missing value is substituted with a 0, assuming that lactate level is in a physiological range. It was possible to do this knowing that subject that are in a not excessively severe pathological condition that not excessively severe serum lactate will be relatively (< = 2 mmol/L). It is important to specify that the sickest patients are the higher is lactate level and, on average, many more measures are available.

3.2.3 Clinical data

For each patient included in the cohort, a set of clinical and demographic information such as age, gender and mortality, has been extracted from the database; then other information about therapies and interventions like diagnosis, laboratory measures and severity scores were taken into account.

For each patient considered in the study, the first available laboratory measurement available around vasopressor administration was considered. Laboratory data are measures taken from blood sample, frequently collected throughout care of critically ill patients, the one considered in this study are listed in this table 3.2.7:

Laboratory measures
Albumin [g/dL]
Bilirubin [mg/dL]
Creatinine [mg/dL]
Glucose [mg/dL]
Hematocrit [g/dL]
Hemoglobin (Hb) [g/dL]
Platelets [counts per mcL of blood]
Potassium (K) [mEq/L]

Albumin is a globular protein present in blood plasma, it constitutes about half of serum protein. It is produced in the liver and transports hormones, fatty acids, and other compounds, buffers pH, and maintains oncotic pressure, among other functions. Normal range in adult is 3.5–5.0 g/dL (35–50 g/L).

Bilirubin is a compound excreted in bile and urine, elevated levels may indicate certain diseases and its physiological values is about 0.5 mg/dL.

Creatinine is an important indicator of kidney health because it is an easily measured byproduct of muscle metabolism, 0.5 mg/dL to 1.0 mg/dL (about 45 µmol/L to 90 µmol/L) for women and 0.7 mg/dL to 1.2 mg/dL (60 µmol/L to 110 µmol/L) for men.

Glucose is the most abundant monosaccharide and the most important source of energy in all organism, with physiological range of values between 70 and 130 mg/dL is one of the most important medications needed in a basic health system.
Hematocrit is the result of a blood test that measures volume percentage of red blood cells in blood, with normal values between 40% and 50% for men and between 36% and 44% for women. Hemoglobin, expressed in g/dL, is the protein contained in red blood cells responsible for delivery of oxygen to tissues, with normal values between 14 and 18 g/dL for male and between 12 and 16 g/dL for female.
Platelets, with the function to react to bleeding, are another solid component of blood, a normal platelet count is between 150,000 and 400,000 per microliter of blood.
Potassium, which has physiological values around 4 mEq/L, and also Sodium concentration, which has normal values around 140 mEq/L.

In the ICU the most common medications and interventions in ICU are:

- Administrations of fluids.
- Administration of vasoactive agents
- Administration of sedative
- Mechanical ventilation

In particular, many treatments are delivered through intravenous administration, with a certain rate of administration and an infusion prolonged in time. It's important to take into account not only the type of drugs or treatments to which patients are subjected but also their modalities and durations.

The types of vasopressor administered to each subject have also been reported.

Main duration and type of sedatives, mechanical ventilation and fluids administered to the considered populations are represented in figure 3.2.8, 3.2.9 and 3.2.19.

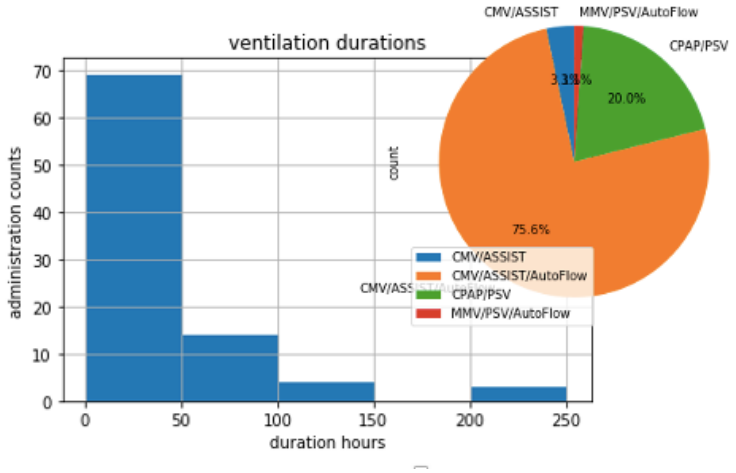


Figure 3.2.8 below: Histogram representing the number of mechanical ventilation with the relative duration (in hour). Above: The pie chart representing the proportion of the type of ventilation administered

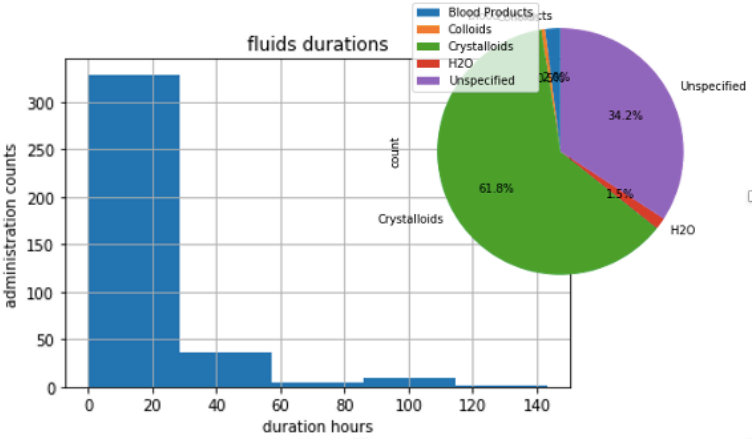


Figure 3.2.9 below: Histogram representing the number of fluid administration with the relative duration (in hour). Above: The pie chart representing the proportion of the type of fluid administered

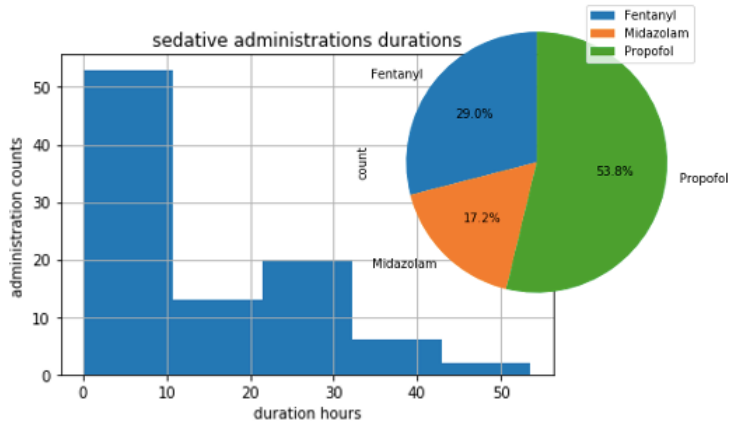


Figure 3.2.10 Below: Histogram representing the number of fluid administration with the relative duration (in hour). Above: The pie chart representing the proportion of the type of fluid administered

3.2.4 Comorbidities and severity score

Severity scales and scores are important adjuncts of treatment in the intensive care unit (ICU) in order to predict patient outcome, comparing quality-of-care and stratification for clinical trials and represents an essential part of improvement in clinical decisions and in identifying patients with unexpected outcomes [42]

In most of the scoring systems, scores are calculated from data collected on the first ICU day, the most famous are:

- Acute physiology and chronic health evaluation (APACHE)
- Sequential organ failure assessment (SOFA)

APACHEII is a severity of disease classification based upon initial values of 12 routine physiologic measurements, age, and previous health status to measure the severity of disease for adult patients in the first 24h from the admission in the ICU. This index can be used to evaluate the use of hospital resources and compare the efficacy of intensive care in different hospitals or over time.[43]

SOFA score assesses the acute morbidity of critical illness and was developed following a consensus meeting in 1994, recently has become extensively used in a range of other applications. SOFA was based on six different scores, one for each of the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems in order to determine the rate of failure of the organ function, an increase in score reflect the worsening of the organ dysfunction. [44]

Two other different scoring system, one the evolution of the other, that are becoming popular are:

- Deyo-Charlson Comorbidity Index (DCCI)
- Elixhauser-van Walraven Comorbidity Index (EVCI)

In the scoring system proposed by Elixhauser each comorbidity was considered separately, so the measure was composed by 30 different binary variables (comorbidities measures), making it quite complex to use and interpret [46]. Therefore, it had been rearranged by van Wal- raven et al. into a single numeric score [47]. The score was computed through a process of backward stepwise multivariate logistic regression, to determine independent association of each comorbidity group with death in hospital, then, modified into a scoring system that reflected the strength of each comorbidity group's independent association with hospital death. One of the most innovative part of the DCCI and EVCI indexes is that both can be calculated at the time of intensive care unit (ICU)

admission and do not require the interpretation of laboratory and bedside clinical data. It is necessary underline that all scores are computed by using data from the first day of stay in ICU, and they are no more updated with the progress of the stay. This is for sure a limitation, but at the same time reflects what it is actually done in clinical practice, with the use of those measures as scores to quantify risk level of patient at admission in ICU, and not with the purpose of monitoring the evolution of patient during the stay itself. [45]

These scoring systems have been useful to identify and divide patients into groups stratifying for confounders and comorbidities during the characterization study, in order to Characterize differences between subjects., dividing them into different groups. Having the opportunity to highlight whether particular pathologies or treatments may be indicative of a different response of the subject to the therapy.

3.2 Point Process Modeling

Heart rate variability and baroreflex, are an important quantitative measure of cardiovascular regulation by the autonomic nervous system. From a mathematical point of view, baroreflex can be seen as a coefficient that quantify the influence of the blood pressure on the heart rate, physiologically is the homeostatic mechanism that helps to regulate blood pressure A simple method to estimate this gain, is an evaluation of it is assuming that the amplitude of the systoles has an effect on heart rate, with no feedback from the variation the heart period ΔRR to a variation of blood pressure ΔP. In this open loop system, the gain ca be measure doing the ratio between the spectral power of the heart rate variability and the spectral power of the systogram in the Low Frequency band (LF = 0.04 - 0.15 Hz):

$$\alpha = \sqrt{\frac{\mathrm{P_{LF}}(RR)}{\mathrm{P_{LF}}(S)}}\,[\mathrm{ms/mmHg}]$$

Exists also more sophisticated models that allows the computation of the baroreflex gain α, taking into account the feedbacks so using a closed loop. For example, baroreflex can be computed as the absolute value of the transfer function that describe the transfer of information from systole to heart period (H_{ts}).

$$\alpha = \left|\frac{\mathrm{A12}}{1-\mathrm{A11}}\right|$$

This requires building a mathematical model that describe the dynamics between the two systems and the Point Process model is the perfect one.

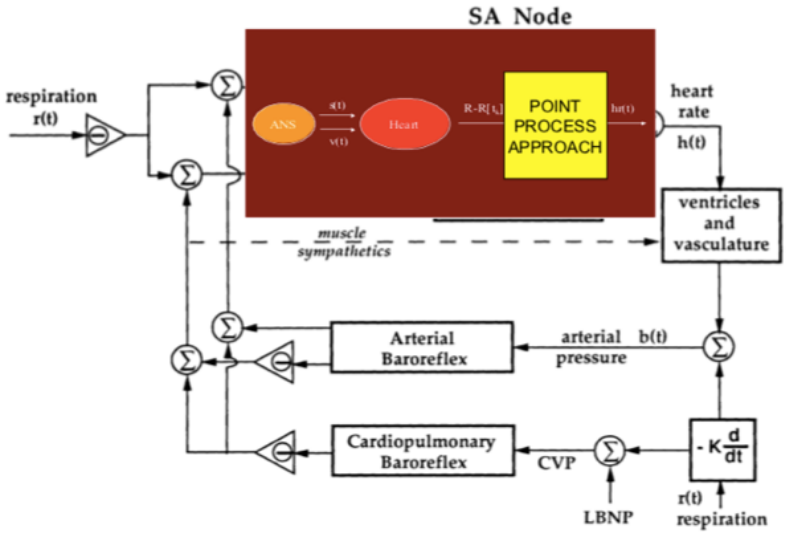


Figure 3.3.1 Same simplified model of HR and ABP control for systems identification presented above speaking about baroreflex but with the introduction of the point process model.

The point process model was developed in order to estimate the R-R interval and the baroreflex gain, in a time-varying way. Considering the natural point-process structure of human heartbeats, whereas all previous models treated the R-R interval as a continuous-valued signal. The generation of normal heartbeats (R-wave events) is assumed to be related to previous and future heartbeat, so the probability of having an event is given by the history of past events. In fact, the duration of the increase or decrease in the R-R intervals depends on the cause of the change in parasympathetic and/or sympathetic input, as well as the response of the other components of the cardiovascular control circuit and everything is regulated at the higher level (CNS). [50]. The point process model allows us to analyze the RR series as punctual series of events, estimating the probability of having a beat (1) or not (0), the representation of a point process in time domain is shown in figure 3.3.2.

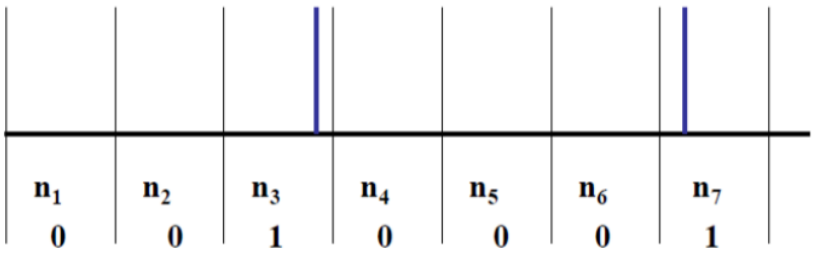


Figure 3.3.2 Point process a binary stochastic process (0-1) that occurs in time or space.

It's possible to get a continuous estimation over time of the R-R interval, interpolating the data, keeping update the function and so the probability. In this way, the stochastic structure of heartbeat

intervals can be modelled as a history-dependent inverse Gaussian process. From it ,an explicit probability density can be derived, giving a new definitions of heart rate and heart rate variability. From a point process approach a precise probabilistic estimation of HR and HRV can be derived each moment in time: instantaneous R-R interval and heart rate standard deviations.

Assuming that, given any R-wave the event u_k and the length of the next R-R interval (times between threshold crossing), the process obeys an HDIG probability density $f(t|H_{uk}, \theta)$, where *t* is any time satisfying $t > u_k$, H_{uk} is the history of the R-R intervals up to u_k and θ is a vector of model parameters (estimated with local maximum likelihood). The model is defined as

$$f(t|H_{uk}, \theta) = \left[\frac{\theta_p + 1}{2\pi(t - u_k)^3}\right]^{\frac{1}{2}} exp\left\{-\frac{1}{2} - \frac{\theta_p + 1 - [t - u_k - \mu(H_{uk}, \theta)]^2}{\mu(H_{uk}, \theta)^2(t - u_k)}\right\}$$

- μ RR(t) represents the instantaneous mean R-R parameter
- $u_k = K^{th}R - beat$
- $wk = uk - uk_{-1}$ is the *kth* R-R interval
- H_{uk} is the History of the R-R intervals up to uk
- $\theta_p + 1$ Is the scale parameter
- $\mu(H_{uk}, \theta) = mean = \theta + \sum_{j=1}^{p} (\theta_j wk - j + 1)$

It represents the dependence of the R-R interval length on the recent history of parasympathetic and sympathetic inputs to the SA node, by modeling the mean as a linear function of the last *p* R-R intervals. If we assume that the series of elapsed times between beats (the R-R intervals) is modeled as independent, the equations simplifies to a renewal inverse Gaussian (RIG) model. The times between threshold crossings (R-R intervals), is well known to be an inverse Gaussian. The R-R interval probability model, together with the local maximum-likelihood method, provides an approach for estimating instantaneous mean R-R interval, heart rate, R-R interval standard deviation and heart rate standard deviation, from a time series of R-R intervals. The assessment of model goodness of fit is done by Kolmogorov-Smirnov (KS) tests based upon the time-rescaling theorem.

Time rescaled R-R intervals are defined by:

$\tau_k = \int_{u_{k-1}}^{u_k} \lambda\,(H_t, \hat{\theta}t)$

Where $(H_t, \hat{\theta}t)$ is the probability Conditional Intensity Function (CIF), use to evaluate the goodness-of-fit of the probabilistic heartbeat interval model. Given a point process specified by k discrete events, thanks to the rescaling theorem, is possible to define τ_k random variables with unit mean and exponentially distributed. [52] Using the further transformation z_k = 1- exp $(-\tau_k)$, z_k values are independent uniform random variables on the interval (0,1]. The KS test was constructed to assess agreement between the z_k values, and the uniform probability density. The one to one transformation allows the comparison of the empirical quantiles of z_k against the theoretical quantiles of a random variable distributed in the region [0,1]. The KS distance, measures the largest distance between the cumulative distribution function of the R-R intervals, transformed to the interval (0,1], and the cumulative distribution function of a uniform distribution on (0,1]. The smaller the KS distance, the closer is the agreement between the original heartbeat interval time series and the proposed model. Approximate independence of these transformed intervals suggest that the proposed model is highly consistent with the heartbeat interval series. Another method to evaluate model fitting properties is to look at the autocorrelation function of the rescaled times τ_k. Small values of the series of the autocorrelation function at all lags, would suggest that the τ_k values are uncorrelated and this would be consistent with their being independent.

The simplest model that can be realized is the Monovariate Point Process model, where the history dependence of point process can be taken into account with an univariate p-order autoregressive model on $\mu_{RR}(t)$ so :

$$\mu_{RR}(t) = a_0(t) + \sum_{i=1}^{p} (a_i(t) RR_{t-1})$$

The mean RR interval is assumed to be dependent on the last p RR interval values. The measure of $\mu_{RR}(t)$ is time-varying and is determined by the time-varying AR coefficients of the AR model $a_i(t)$. From the previous formula the instantaneous variance of the inverse Gaussian can be derived. The frequency response, f_s is not the sampling frequency of the signal, but is the beat rate of R-R, sampled at the same frequency as the beat.

$$\sigma_{RR}^2(t) = \frac{\mu(t)_{RR}^3}{\theta(t)}$$

$$H_{RR}(w,t) = \frac{1}{|\sum_{i=1}^{p} a(t)_i z^{-i}|^2_{z=e^{j\omega 2\pi fs}}}$$

Combining the described above formulas is possible to compute also the dynamic power spectrum:

$$P(w,t) = \sigma(t)_{RR}^2 H(w,t)_{RR}$$

The model can be extended using more complex probability structures, including non-linearities and taking into consideration other cardiovascular mechanisms that increases the complexity of the model. In fact, in order to describe the interactions between R-R interval (RR[t]) and systolic blood pressure (SBP[t]) series, its necessary to consider a bivariate system. The Bivariate point process model, so the autoregressive model will be transform as follow:

$$\mu_{RR}(\mathrm{t}) = a_0(t) + \sum_{i=1}^{p}(a_i(t)RR_{t-1}) + \sum_{i=1}^{p}(b_i(t)SAP_{t-1})$$

SAP is the series of systolic values synchronized with the series of the R events (same things can be done with the diastolic pressure instead), the transfer function is :

$$H_{RR-SAP}(f,t) = \frac{\sum_{j=1}^{q} bj(t)z^{-j}|_{e^{j2\pi fs}}}{|1 - \sum_{i=1}^{p} a_i(t)z^{-i}|^2_{e^{j\omega 2\pi fs}}}$$

Power spectra of the SAP:

$$P_{SAP}(f,t) = \frac{\sigma_{SAP}^2(t)}{|1 - \sum_{j=1}^{q} b_j(t)z^{-j}|^2_{e^{j\omega 2\pi fs}}}$$

Having the power spectra of R-R and SAP we can estimate the cross spectrum in the closed-loop system, assuming that, noise variance and the non-linear interactions in the feedforward and

feedback loops are sufficiently small. Given the baroreflex gain $|H_{RR-SAP}(f,t)|$, we can estimate the cross spectrum (between BP and RR) in the feedback loop $C_{RR-SAP}(f,t)$:

$$C_{RR-SAP}(f,t) = H_{RR-SAP}(f,t)P_{SAP}(f,t)$$

The coherence:

$$\mathrm{Coh}(f,t) = \frac{|\,\mathrm{C}\mathrm{RR}-\mathrm{SAP}(f,t)|}{\sqrt{\mathrm{P}\mathrm{RR}(f,t)\;\mathrm{P}\mathrm{SAP}(f,t)}}$$

The frequency-dependent baroreflex gain, characterized by $|\mathrm{H}_{\mathrm{RR\text{-}SAP}}(f,t)|$, represents the effect of BP on heartbeat, mediated by the neural autonomic reflexes. The effect of the interaction is graphically explained in figure 3.3.3 [50] :

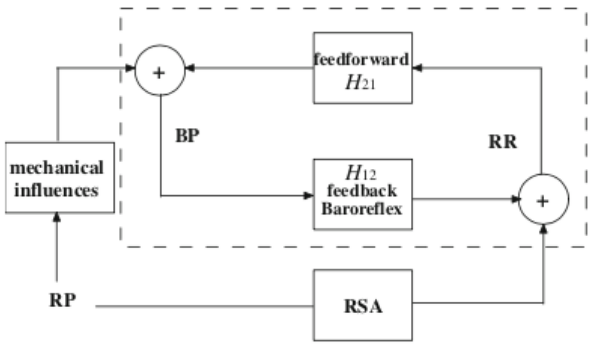


Figure 3.3.3 Simplified diagram of the close loop model of the cardiovascular system where the R-R is modulated by the BP (so SAP) trough baroreflex feedback loop (H12 is $H_{RR-SAP}(f,t)$). In a more complex model is also possible to introduce the modulation of the R-R trough RSA. And BP with mechanical influences.

The order of the AR model also determines the number of poles, or oscillations, in the frequency range. Modifying the AR coefficients is equivalent to changing the positions of the poles and reshaping the frequency response curve. With the time-varying AR coefficients estimated from the point-process filter, we may evaluate the dynamic frequency response of at different ranges (we are particularly interested in the LF and HF frequencies). In order to choose the right order of the AR model many experimental tests were performed, varying the order of the model for both the Monovariate and Bivariate model. Evaluating KS distance, number of points outside the 5% confidence intervals of KS distance and number of points outside the 5% confidence intervals of autocorrelation function (ACF). Results respectively in figures.

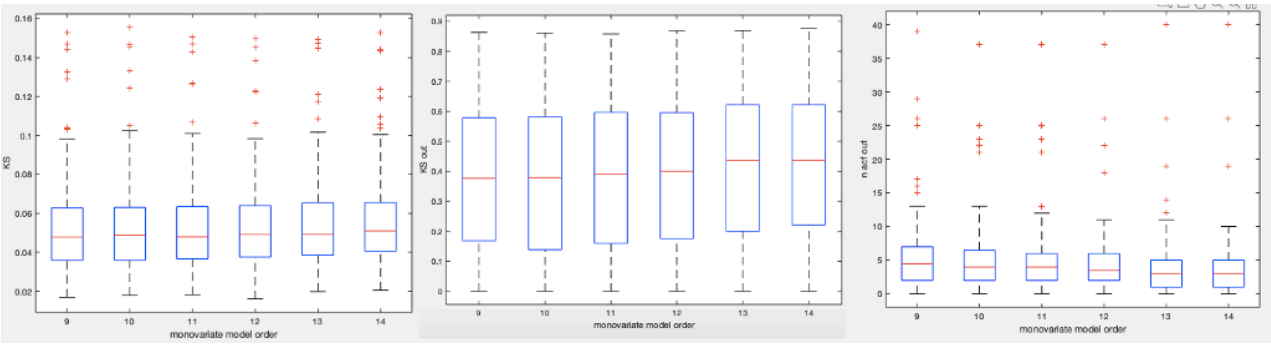


Figure 3.3.4 Boxplot of different orders (9,10,11,12,13,14) for the bivariate model. Right: point outside the 5% confidence intervals of ACF. Middle: point outside the 5% confidence intervals of ACF. Middle: point outside the 5% confidence intervals of KS distance. Left: Ks distance

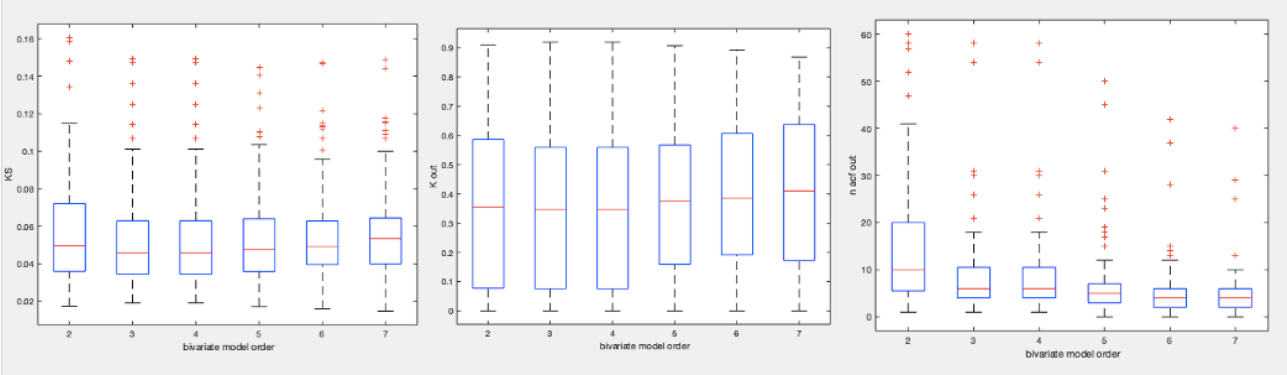


Figure 3.3.5 Boxplot f different orders (2,3,4,5,6,7) for the bivariate model. Right: point outside the 5% confidence intervals of ACF. Middle: point outside the 5% confidence intervals of KS distance. Left: KS distance

The final choice was a model order equal to 13 (6*2+1 for the Bivariate), it's s trade-off between KS distance (increasing with the order of the model) and ACF (decreasing with the order of the model). Increasing the order over 13, the ACF is not decreasing anymore while KS start increasing. Moreover, a higher order of the model allows to obtain a time varying spectral content with a better resolution, this represents a key improvement, especially with evaluation of Power of Spectrum in Low Frequency band.

3.5 Feature Engineering

During the cohort selection process, the biggest problem regarding missing data was due to the very small number of subjects with waveform available in the required time window, the subjects with missing one were removed. Relatively to the laboratory measure, the problem of dealing with missing data is not dramatic thanks to the choice made to consider only the closest available value of the laboratory measure for each subject, next to the vasopressor administration. If some measures miss in some patients, the criteria imposed were the following:

- If a feature has more than 5% of missing values, the feature was removed;
- If a feature has less than 5% of missing values, the missing observation is substituted with men value obtained from the whole population

3.5.1 Time domain features

The time domain features extracted from the estimated from the time series extracted from vital sign:

- AVNN: average of the NN intervals
- SDNN: standard deviation of all NN intervals.
- SDNNIDX: mean of the 5-min standard deviation of the NN intervals
- SDANN: standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.
- SDSD: standard deviation of differences between adjacent NN intervals.
- NN20: number of pairs of adjacent NN intervals differing by more than 20 ms in the entire recording (defined as the mean number of times an hour in which the change in successive normal sinus (NN) intervals exceeds 20 ms)
- pNN20: NN20 count divided by the total number of all NN intervals.
- NN50: number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (defined as the mean number of times an hour in which the change in successive normal sinus (NN) intervals exceeds 50 ms)
- pNN50: NN50 count divided by the total number of all NN intervals.
- RMSSD: square root of the mean squared differences of successive NN intervals.

- TRI: integral of the density distribution (i.e. the number of all NN intervals) divided by the maximum of the density distribution.
- TINN: baseline width of the distribution measured as a base of a triangle, approximating the NN interval distribution.

Time domain features are extracted not only from the tachogram but also from the time series, corresponding to values of systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, pulse pressure and pulse transit time.

3.5.2 Spectral domain features

The frequency domain features were extracted from the Power Spectral Density (PSD) of a time series in 5 minutes non-overlapping stationary windows. Estimated with the Yule-Walker method and after averaging in order to obtain a single value for each measure. The indices computed in this way were:

- Very Low Frequency (VLF) power: spectral power in very low frequency range (from 0.0033 Hz to 0.04 Hz).
- Low Frequency (LF) power: spectral power in low frequency range (from 0.04 Hz to 0.15 Hz).
- High Frequency (HF) power: spectral power in high frequency range (from 0.15 Hz to 0.45 Hz).

- Total power (TOTPWR): spectral power in the entire range of frequencies.
- Normalized Low Frequency (LFn) power: LF normalized by (TOT- PWR - VLF), which is equivalent to (LF + HF).
- Normalized High Frequency (HFn) power: HF normalized by (TOT- PWR - VLF), which is equivalent to (LF + HF).
- Sympatho-vagal balance (LF/HF) power: ratio between LF and HF.
- Spectral slope (α_{spect}): slope of the linear interpolation of the spectrum in a log-log scale.

3.5.3 Non-linear domain features

- SD1: standard deviation of the second principal component of the RR values distribution in the Poincaré plot (RR_i vs RR_{i+1} space), representing the short-term variability.
- SD2: standard deviation of the first principal component of the RR values distribution in the Poincaré plot (RR_i vs RR_{i+1} space), representing the long-term variability.
- SD1/SD2: ratio between SD1 and SD2 measures the unpredictability of the RR time series.
- Correlation Dimension (CD): measure of chaoticity and non-linear dynamics of RR time series.
- Hurst exponent (H): It is a is a dimensionless estimator for the self-similarity of a time series that measure the long-term memory of a time series. It quantifies the relative tendency of a time series either to regress strongly to the mean or to cluster in a direction.[53]. The value describes the nature of the process:

  0< H < 0.5 antipersistence (negative correlation)

  0.5 < H < 1 persistence (positive correlation)

  H = 0.5 random walk

- Detrended fluctuation analysis (DFA):

  DFA is a simple but very efficient mathematical method used to investigate the power law of long-term correlation of nonstationary time series.

$$Fn = \sqrt[2]{\frac{1}{N}\sum_{K=1}^{N}[y(k) - y(k)_n]^2}$$

  $y(k)_n$ is the regression line of a time series X_t depolarized from its mean values and N is the number of elements in the selected time window. The process is then repeated over a range of different sizes and the resulting fluctuation can be approximated as

  $F(n) \approx n^{\alpha DF\ A}$ Where α_{DFA} is the key scaling exponent that can be extracted as the slope of the regression line in a log-log scale of F(n). [54] Depending on the values that this measure assumes, the following characteristics about series self-correlation can be highlighted:

– $\alpha_{DFA} \approx \frac{1}{2}$: White noise behavior;

– $\alpha_{DF\ A} \approx 1$: 1/f noise behavior;

– $\alpha_{DFA} \approx \frac{3}{2}$: Brownian noise behavior;

– $\alpha_{DFA} < \frac{1}{2}$: Anti-correlated;

– $\alpha_{DFA} > \frac{1}{2}$: Correlated.

- Approximate and Sample Entropy (ApEn, SampEn): Are methods for entropy measures. ApEn quantifies the similarity probability of patterns of length m and m + 1 . With robustness against noise and its capability to detect complexity changes, using finite size datasets using similarity threshold r, is defined as a fraction of the standard deviation of the input data. ApEn is also scale-independent. SampEn is a similar statistic, it also measures the probability of subsequences, being close at two lengths m and m + 1 within tolerance r. However, SampEn does not include self–comparisons and exhibits greater consistency than ApEn.[55]
- First Lyapunov exponent: it is a measure of chaoticity of the signal, a positive value indicates that the system has a highly sensitive dependence on initial conditions and is a common signature of chaos [55]

3.5.4 Other features

Thanks to the point process model approach, dynamic baroreflex gain, maximum and average coherence were extracted in LF and HF bands. All the first four statistical moments, first, second and third quartile and the angular coefficient of the linear regression in time were also computed.

3.6 Characterization methods

The first part of the study focuses on characterization analysis, performed to identify differences before and after vasopressor administration. To perform the characterization, distinct types of analysis were applied:

- First of all, using the Lilliefors test, the normality of the population was verified. Lilliefors test is a two-sided goodness-of-fit test based on that of Kolmogorov-Smirnov. It is used to test the null hypothesis that come from a normally distributed population. It does not specify the mean and the standard deviation of the distribution but if the null hypothesis H0 is rejected you can conclude that the data distribution is not normal [59]
- The characterization was performed using the Wilcoxon Signed Rank Test a non-parametric statistical paired hypothesis test, used to compare two related samples, or repeated measurements on a single sample, to assess whether their population mean ranks differ. Generally, it is used as an alternative to the paired Student's t-test, when the distribution of the difference between two samples' when the distribution of differences is not normal.
- A primary analysis was performed in order to assess if the values of the extracted features significantly changed, after the administration of vasopressor, with respect to the values of the before segment. Considering a cohort composed by 23 subjects, with no mechanical ventilation or sedation, due to the non-normality of the population, the Wilcoxon Signed Rank test was applied.
- A secondary analysis was performed extending the cohort to 123 subjects, considering also mechanically ventilated and sedated patients. The purpose is to verify whether the changes, before and after vasopressor administration, are maintained despite the action of treatments that heavily affect the autonomic system. Afterwards, since an abnormal systolic pressure behavior was noted for 35 out of 123 subjects, a further division was then made dividing between responding and non-responding subjects. The main role of a vasopressor drug id to rise blood pressure. According to this definition, the division was made looking at the difference between the mean systolic value before and after the administration. A subject was classified as responding if : AVSS post – AVSS pre >0 (rise in blood pressure after vasopressor injection) while if AVSS post – AVSS pre <0 (decrease in blood pressure) classified as non-responding subject. A stratified analysis was then carried out using again Wilcoxon Signed Rank Test comparing the features of the post and pre segment inside the

same population while the Wilcoxon Rank Sum Test was used to compare the two population.

- Dealing with lactate, another stratification was performed. Starting from123 patients, a subjects was considered a “low level” subject if it undergoes a decrease in lactate level passing from an abnormal value (> 2 mmol/L) to a normal one(< 2 mmol/L) or if belongs to those who kept lactate below the threshold both before and after administration. Instead “High level” population is composed by the subjects who maintain an abnormal lactate or those who switch from normal to abnormal lactate after administration.
- Since the considered subjects are affected by different kind of pathologies, a stratified analysis was performed, starting from the 123 cohort, to verify if a particular condition to which the patient is subjected significantly influences the response to vasopressor therapy. This stratification was not done to provide some kind of characterization of certain pathologies but, to make sure whether a specific result, obtained on the whole population, was due to a certain morbidity or due to the action of the vasopressor drug. The pathologies or administrations considered are as follows:

1. Ventilation
2. Sedation (Propofol)
3. Sepsis
4. Liver disease
5. Hypotension
6. Diabetes

All the administration where considered looking around the vasopressor administration while the pathologies are taken from the diagnosis at the admission in the ICU.

- To look if there is a nonrandom association between the subdivision in responding and non-responding subjects with relative subgroups and again with high and low lactate level and relative subgroups. Fisher’s exact test was computed. Fisher’s exact test is another non-parametric method for small sample size used to determine if there are non-random associations between the variables. H=0 for all. H = 0 indicate that fisher’s test does not reject the null hypothesis of no nonrandom association between the categorical variables.

- Initially the Wilcoxon Rank Sum Test for non-doubled pair was performed to detect the differences intra groups and with respect to the control ones, while afterwards the Wilcoxon Signed Rank was used to find the difference into groups.
- The last stratification was then made using the same pathologies and treatments considering first the population of subjects classified as non-responding and then the population of responding.

3.7 Correlation study

A correlation study was carried out to analyze whether there is a relationship between the features extracted from waveforms and the lactate value, in order to verify how and how much these variables vary together.

The method used is the Spearman's correlation coefficient. A non-parametric method that measures the degree of relationship between two variables. Unlike Pearson's linear correlation coefficient (used for normally distributed data), Spearman's coefficient does not measure a linear relationship. A generalization of Spearman's coefficient is useful in situations where you want to verify that the observations take place in a particular order, for example when you want to verify that if a variable A grows, variable B grows too, i.e. that the trend of the values of two different variables (A and B) is somehow associated. If this relationship is significant, it may be useful to represent the link between A and B with an interpolating function.

At first, was analyzed the correlation between the indices extracted from waveforms and lactate measurements prior to vasopressor administration. As initial lactate level was considered for each subject the last lactate measure in a window of 12 hours before the administration, then, the same thing, was performed using the first available measure in a 12 hours window after the administration (final lactate). The number of subjects with both measurements available are 77. Same procedure was applied using the features extracted from the post segment. Was also analyzed the correlation between changes both in lactate and features of waveforms. The same test was repeated again dividing the population, as we did in the characterization part, between responding and non-responding subjects (looking at blood pressure changes) and between subjects with normal or abnormal lactate.

3.8 Classification

Predictive models can be subdivided into two main categories: regression models and classification models. The purpose of explanatory models is to functionally identify a possible relationship between a dependent variable and a set of independent attributes. The last part of this study aims to predict if the lactate value will be normal or abnormal 12 hour after the vasopressor administration. Machine learning algorithms adopted to perform this task belongs to the class of supervised classification problem. Particularly this is a binary classification problem because exists only two classes in the target variable. Abnormal lactate (>2 mmol/L) is represented with 1 and normal lactate (<= 2 mmol/L) with a 0. Whereas this is a classification framework, some important concepts should be introduced before going forward with description of the algorithms. Several combinations have been tested, trying to classify with a different combination of features trying to predict lactate level 12 hours after the administration. The difficulty of the prediction is not only due to the time distance between the moment of features extraction were extracted and the lactate measure but also the difference in the time instant in which the lactate value was measured, due to the amplitude of the considered time window. Moreover, trace the lactate kinetics it's a very complex problem in itself because changes in lactate level are very quickly.

3.8.1 Features selection algorithms

A feature selection pre-process, also called feature reduction, in necessary to eliminate from the dataset a subset of variables which are not deemed relevant for the purpose of the data mining activities. One of the most critical aspects in a learning process is the choice of the combination of predictive variables more suited to accurately explain the investigated phenomenon.
Moreover, feature reduction has several potential advantages, the models generated after the elimination from the dataset of uninfluential attributes are often more accurate and easier to understand, it reduces overfitting and also, speed up the training process.

Feature selection methods can be classified into three main categories: filter methods, wrapper methods and embedded methods.

- Logistic Regression

Logistic regression is a statistical standard statistical technique addressing binary classification problems. By means of a proper transformation converting binary classification problems can be converted into linear regression ones. We are using logistic regression as a classifier, with the purpose of obtaining a decision hyperplane that separates different classes. The logistic regression model postulates that the posterior probability P(y|**x**) of the response variable conditioned on the vector **x** follows a logistic function so:

$$P(y=0|x) = \frac{1}{1+e^{\omega' x}}$$

$$P(y=1|x) = \frac{e^{\omega' x}}{1+e^{\omega' x}}$$

The standard logistic function is a sigmoid function, the ratio between the conditional probabilities of the two classes depends linearly on the predictive variables. The binary classification problem is traced back to the identification of a linear regression model between the dependent variable z and the original explanatory attributes, the w coefficients are computed using iterative methods, usually by minimizing the sum of logarithms of predicted probabilities to maximize the likelihood:

$$z = \frac{P(y=0|x)}{P(y=1|x)}$$

When we use logistic regression for feature selection each feature is feed to a logistic regression model and if the weight of that feature was significantly different from zero, the variable was included. This process was repeated for all available features.

- Principal Component Analysis (PCA)

Principal Component Analysis (PCA) is a classical technique in statistical data analysis used for feature extraction and data reduction, aiming at explaining observed signals as a linear combination of orthogonal principal components. Given a set of multivariate measurements, the purpose is to find a smaller set of variables with less redundancy, that would give as good representation as possible. The redundancy is measured by correlations between data elements. Generally speaking,

the purpose of this method is to obtain a projective transformation that replaces a subset of the original numerical attributes with a lower number of new attributes obtained as their linear combination, without this change causing a loss of information. Before applying the principal component method, it is necessary to standardize the data, so as to obtain, for all the attributes, the same range of values, usually represented by the interval [−1,1]. The mean of each attribute is made to zero, the applied transformation is:

$$X_{ij}^{\sim} = x_{ij} - \frac{1}{m}\sum_{i=1}^{m} X_{ij}$$

Let **X** denote the matrix resulting from applying the transformation to the original data, and **V** = **X**′**X** is the covariance matrix of the attribute Starting from the n attributes in the original dataset, represented by the matrix **X**, the principal component method derives n orthogonal vectors, namely the principal components, which constitute a new basis of the space R^n. Principal components are better suited than the original attributes to explain fluctuations in the data, in the sense that usually a subset consisting of q principal components, with q < n, with almost the same information of the original dataset. As a consequence, the original data are projected into a lower-dimensional space of dimension q having the same explanatory capability. Principal components are generated by an iterative algorithm. The interpretation of the principal components may be obtained from the coefficients of the vector $\mathbf{w}_j = \mathbf{u}_j$ which express their relationship with the original attributes. To this end, notice that the principal component $\mathbf{p}_h$ assumes the form

$\mathbf{p}_h = u_{h1}\mathbf{a}_1 + u_{h2}\mathbf{a}_2 + \cdots + u_{hn}\mathbf{a}_n$.

The coefficient u_{hj} can be therefore interpreted as the weight of the attribute $\mathbf{a}_j$ in determining the component $\mathbf{p}_h$. The greater the absolute value of u_{hj} is, the more the component $\mathbf{p}_h$ is characterized by the attribute $\mathbf{a}_j$. At the same time, $\mathrm{var}(\mathbf{p}_h) = \lambda_h$ represents a measure of the proportion of total variance explained by the principal component $\mathbf{p}_h$. For this reason, the index

$$I_q = \frac{\lambda_1 + \lambda_2 + \cdots + \lambda_q}{\lambda_1 + \lambda_2 + \cdots + \lambda_n}$$

expresses the percentage of total variance explained by the first q principal components and provides an indication of the amount of information preserved by the first q components. In order

to determine the number of principal components to be appropriately used, it is possible to go on until the level of overall importance I_q of the considered components exceeds a threshold I_{min} deemed reasonable, in relation to the properties of the dataset. The number of principal component is therefore determine by $I_q > I_{min}$ [VERCELLIS].

- Forward selection

Forward selection algorithm starts with a null model and then iteratively adds one feature at time and after the evaluation of a criterion function, for any extracted feature, includes the one that obtain the best results. This process is repeated until no further improvements in the chosen criterion happen

- LASSO

LASSO Least Absolute Shrinkage and Selection Operator is a solution to prevent over-fitting using a logistic regression model, considering a norm penalty l1 on the regression weight values. LASSO is an algorithm that can be used both for feature selection and classification, was originally introduced in the context of least squares, and it can be instructive to consider this case first, since it illustrates many of lasso's properties in a straightforward setting. Consider a sample consisting of N cases, each of which consists of p covariates and a single outcome. Let y_i be the outcome and $X_i = (x_1, x_2, \ldots . x_p)^T$ be the covariate vector for the i^{th} case. Then the objective of lasso is to solve

$$min_{\beta_0 \beta} = \{\sum_{i=1}^{N} (y_i - \beta_0 - x_i^T \beta)^2\} \text{ subject to } \sum_{j=1}^{p} |\beta| \leq t$$

where t > 0 is a tuning parameter and $||\beta||_p$ is the p-norm of the coefficients.[57]

3.8.2 Cross validation

Cross-validation is a statistical method used to estimate the skill of machine learning models. Learning the parameters of a prediction function and testing it on the same data is a methodological mistake that lead to overfitting. Splitting the data set into a training set and validation set can be an easy solution to solve this overfitting problem. If desired, another split obtaining a test set can be done to estimate the true error of the selected hypothesis. To do cross-validation, we partition our data into a number of disjoint folds. In general, k fold cross validation can be done with any number

starting from two to the number of data points (called leave-one-out-cross-validation). Starting form n samples, doing k-fold cross validation, n/k samples are placed into k disjoint folds. We train our model with all folds but one, validate on the fold that was left out, and repeat for all folds. In the end we average the validation error, and this gives us an estimate of the true error. Cross validation can also be used to find parameter to optimize the regularization parameters.

3.8.3 Classification algorithms

Classification is one of the main tasks of machine learning problems, requires the use of machine learning algorithms that learn how to assign a predefined class label based on training examples. In this specific case, using mainly the features extracted from the waveforms before and after the vasopressor administration, to be able to predict if the lactate level will be abnormal after 12 hours or not.

Exits many types of classification problems, we talk about binary classification problem for those tasks that have two class labels, in this case 1 for abnormal lactate level (>2 mmol/L) and 0 for normal lactate level (<= 2 mmol/L).

It is common to model a binary classification task with a model that predicts a Bernoulli probability distribution for each example.

The Bernoulli distribution is a discrete probability distribution that covers a case where an event will have a binary outcome as either a 0 or 1. For classification, this means that the model predicts a probability of an example belonging to class 1, or the abnormal state.

Popular algorithms that can be used for binary classification include all the algorithms used in this study:

- Logistic Regression
- k-Nearest Neighbors
- Decision Trees
- Support Vector Machine
- Naive Bayes

- Logistic Regression

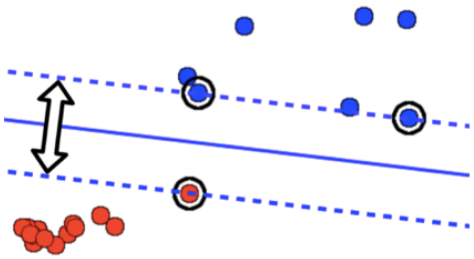
As explained before other than feature selection process, the logistic regression might be also used as classification algorithm, by inserting all the features of the set and fitting a multivariate logistic regression with the purpose of obtaining a decision hyperplane that separates different classes.

- K-Nearest Neighbors

A k-nearest neighbors' classifier is an example of a lazy learning method due to the fact that generalization of the training data is, in theory, delayed until a query is made to the system. More specifically, an instance learning method, because the algorithm involves comparing new instances with instances in the training set. Keeping the labelled training set, the k-NN classifier will label a new point with the label of the majority of the k points in the training set that are closer to the new point. To implement a k-NN classifier, we need to start by defining a distance function, Minkowski distance for continuous numerical features and Hamming distance for categorical features. When data increases k-NN classifier is an impractical choice in environments where predictions need to be made rapidly. Moreover, there are faster algorithms that can produce more accurate classification and regression results.

- Support Vector Machines

Support vector machines (SVM) are a family of separation methods for classification and regression developed in the context of statistical learning theory. A margin classifier is a classifier that provides a measure of the distance between the frontier and the points closest to it. This is the margin of the classifier. A maximum margin classifier is a classifier that maximizes this distance. With logistic regression, we can approximate this using regularization, but this requires modifying the loss function to include the regularization term. A better option is to make margin maximization an explicit goal for our loss function. Figure.3.8.3.1 shows the margin, which is the distance between the frontier and the examples closest to it. These vectors are called the support vectors. To explicitly maximize the margin, we can consider the signed distance between a vector and the decision hyperplane:



$$r = \frac{\overrightarrow{w}^{t} x + w_0}{\left|\left|\overrightarrow{w}\right|\right|}$$

Figure 3.8.3.1Margin, is the distance to the point that is closest to the frontier

The goal is to find the hyperplane that maximizes the minimum distance to points being classified. The value of r is positive on one side of the decision hyperplane and negative on the other, the value. Normalize distance is invariant to scaling: the problem of maximizing the margin is equivalent to the problem of minimizing the norm of w increasing the distance between the discriminant and the closest points. This is thus a constraint optimization problem. Usually the dataset is linearly non separable, it is necessary to relax the constraints by replacing them with weaker conditions which allow for the presence of possible misclassification errors, and to modify the objective function of the optimization problem. This can be done by introducing a new set of slack variables d_i , i ∈ M, which measure the positive differences between the values of the misclassified examples on the vertical axis and the ordinate values along the canonical hyperplane that defines the region associated with the class value y_i.

$$min_{\boldsymbol{w},b,d} = \frac{1}{2}\left|\left|w^2\right|\right| + \lambda \sum_{i=1}^{m} d_i$$

$$\begin{cases} y_i(\boldsymbol{w}'\boldsymbol{x}_i - b) \geq 1 - d_i & i \in M \\ d_i \geq 0 & i \in M \end{cases}$$

One method for solving constraint optimization problems is to use Lagrange multipliers. Often dealing with non-linearly separable dataset we have to move away from a 2d view of the data to a higher dimension. In such cases, one may resort to mappings of the attributes which allow one to obtain linearly separable datasets in the transformed space, which is called the feature space. m points in a general position in the n-dimensional space can be linearly separated if m ≤ n + 1, the VC dimension of the class of hyperplanes is n + 1, so that the number of possible linear separations is 2^m. Fortunately, there exists a wide class of mappings which can be evaluated in a very efficient

way, consisting of kernel functions, for which the mapping of the original observations into the feature space is not explicitly computed.

- Naïve Bayes Classifier

Naïve Bayes classifier are a family of probabilistic classifier based on Bayes' theorem:

$$P(C = c|X = x) = \frac{P(C = c)P(X = x|C = c)}{P(X = x)}$$

P(C=c|X=x) is the probability that a given observation c belongs to a specific target class x, called posterior probability, while the opposite, P(X=x|C=c), is called conditional probability. P(X=x) and P(C=c) are prior probabilities, sowing the likelihood of an outcome in a given dataset.
The Bayes classifier is ideal in the sense that it minimizes the probability of misclassifying. This Naïve Bayes classifier is so called because of the assumption that all features are conditionally independent on the the target class. This hypothesis allows us to write

$$P(X = x \mid C = c) = \prod_{j=1}^{N} P(x_i|c)$$

In general, this is not true. However, since we are not concerned with the absolute probability values but merely with finding the class that maximizes these values, the Naïve Bayes classifier tends to work rather well. In addition, it is very easy to apply. For a Naïve Bayes classifier we would only need to find the probability distribution of each feature given the class. We would only need to compute the proportions of features belonging to the different classes. The Naïve Bayes classifier can be written as:

$$C^{\text{Naïve Bayes}} = \text{argmax}_{K\in\{0,1,\dots,K\}} \ln P(C_k) + \sum_{j=1}^{N} \ln P(X_i|C_x)$$

- Decision Trees

Classification trees are a wide used method for both classification and regression, due to their simplicity, easy interpretability and robustness to outliers. The development of a classification tree

corresponds to the training phase of the model and is regulated by a recursive procedure of heuristic nature, based on a divide-and-conquer partitioning scheme referred to as top-down induction of decision trees, creating a model that is able to predict the value of a target variable by learning simple decision rules inferred from the data features. It is also necessary to set a metrics that evaluates the impudicity of split data and minimize this metric at each node. For each node of the tree it is necessary to specify the criteria used to identify the optimal rule for splitting the observations and for creating the descendant nodes. Usually, both choices are performed by calculating an evaluation function, for each attribute and for each possible partition, which provides a heterogeneity measure in the values of the target class between the examples belonging to the parent node and those belonging to the descendants. It is necessary to maximize the evaluation function, which provides a heterogeneity measure in the values of the target class between the examples belonging to the parent node and those belonging to the descendants. Heterogeneity indices satisfy these properties, also referred to as impurity or inhomogeneity measures. The most popular are the misclassification index, the entropy index and the Gini index. At the end of the procedure, when no tree node can be further subdivided, each leaf node is labeled with the value of the class to which the majority of the observations in the node belong, according to a criterion called majority voting. It is necessary to decide a stopping criterion to establish at each node whether the development should be continued recursively, or stopped, considering the current node as a leaf. Finally, it is appropriate to apply a few pruning criteria, first to avoid excessive growth of the tree during the development phase (pre-pruning), and then to reduce the number of nodes after the tree has been generated (post-pruning). Starting from a training dataset it is possible to construct an exponential number of distinct classification trees. The main problems of decision trees are that, building it, requires algorithms capable of determining an optimal choice at each node and also are prone to overfitting, especially when the tree is particularly deep.

Ideally, we would like to minimize both error due to bias and error due to variance, random forests mitigate this problem well. A random forest is simply a collection of decision trees whose results are aggregated into one final result. Their ability to limit overfitting without substantially increasing error due to bias is why they are such powerful models. Random forest or random decision forest are an ensemble learning method for classification, regression and other tasks that operate by constructing a multitude of decision trees at training time and outputting the class that is the mode of the classes (classification) or mean prediction (regression) of the individual trees. Those algorithms correct for

decision trees' habit of overfitting to their training set. Is difficult to interpret but is able to cellulate some feature importance.

Another technique really popular derived from decision trees, that have been used a lot in this thesis project is gradient boosting. Boosting is a sequential technique which works on the principle of an ensemble. It combines a set of weak learners and delivers improved prediction accuracy. At any instant t, the model outcomes are weighed based on the outcomes of previous instant t-1. The outcomes predicted correctly are given a lower weight and the ones miss-classified are weighted higher. With the ensemble strategy, a “strong” predictive model is constructed by combining simple (“weak”) trees. This is known to lower the risk of overfitting that would arise when having a single (highly complex) tree. With respect to other tree-based ensemble algorithms, XGBOOST can handle missing values by defining, for each node, a default direction to be followed in case a missing value is present in that node.

- Confusion matrices and ROC curves

After the construction and selection of a specific model using the greed search for parameter optimization, in order to test the performance of the considered binary classifier the used statistical measures of performance. The confusion matrix is one of the accuracy measurement methods that not only consider the number of accurate predictions, but also the type of error committed. should be accounted for, rows correspond to the observed values and whose columns are associated with the values predicted using a classification model, as shown in figure.3.8.3.2.

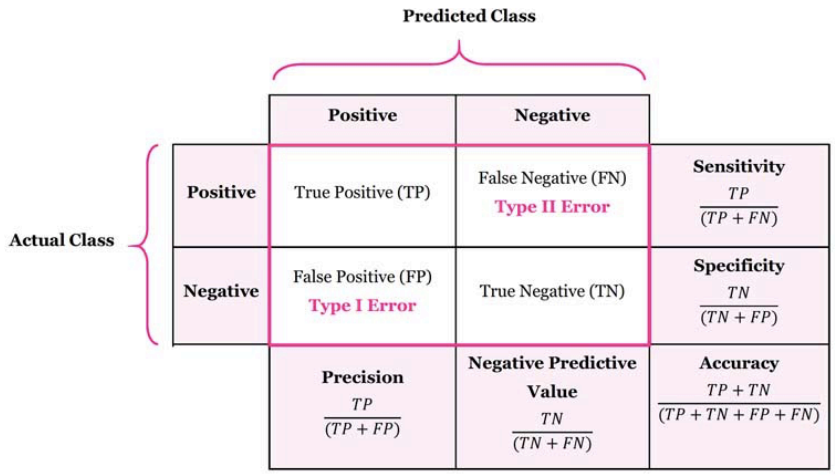


Figure 3.8.3.2 Confusion matrix

The elements of the confusion matrix have the following meanings:

1. *True positive*: the example belongs to class 1 and was predicted to belong to class 1.

2. *False positive*: the example belongs to class 0 and was predicted to belong to class 1.

3. *True negative*: the example belongs to class 0 and was predicted to belong to class 0.

4. *False negative*: the example belongs to class 1 and was predicted to belong to class 0.

The different possible error measures are:

• Accuracy (Ac)of the classifier is the proportion of correctly classified observations with respect to the total.

• Sensitivity (Se), also called recall or true positive rate. Measures the proportion of correctly classified positive observations with respect to the total number of positive observations defined as:

Se = TP (3.41) TP +FN

• Specificity (Spe), also called true negative rate, is the proportion of correctly classified negative observations with respect to the total number of negative observations defined as:

Spe = TN (3.42) TN +FP

Those gives us another useful measure of the performance of a classifier, the *F1* score, which is the harmonic mean of *precision* and *recall*:

$$F1 = \frac{2 \times \text{true positives}}{2 \times \text{true positives} + \text{false positives} + \text{false negatives}}$$

$$F1 = \frac{2\,\text{precision} \times \text{recall}}{\text{precision} + \text{recall}}$$

Sensitivity, therefore, quantifies the avoidance of false negative and specificity does the same for false positives. For any test, there is usually a trade-off between the measures, this trade-off can be represented graphically using a receiver operating characteristic curve (ROC) plotted by computing the fraction of true positives and false positives at different score thresholds. The ROC chart visually expresses the information content of a sequence of con- fusion matrices and allow the ideal trade-off between the number of correctly classified positive observations and the number of incorrectly classified negative observations to be assessed. The point (0,1) represents the ideal classifier, which makes no prediction error since its proportion of false positives is null (fp = 0) and its proportion of true positives is maximum (tp = 1). The point (0,0) corresponds to a classifier that predicts the class {−1} for all the observations, while the point (1,1) corresponds to a classifier predicting the class {1} for all the observations. [60]A classifier performs all the better the greater the fraction of true positives relative to the false positives for different threshold levels. In other words, the larger the area below the *ROC* curve the better the classifier's performance

Chapter 4

Results

4.1 Characterization Study

As mentioned earlier, according to literature, the main role of vasopressor is to activate adrenergic receptor in order to increase blood pressure, acting as vasoconstrictors. Despite that, they might induce several effects as increasing or not CO, effecting the contractility or heart rate or the preload. Many experiments were made previously to evaluate and compare the effects of physiologic and pharmacologic sympathetic stimulation with vasopressor infusion. As mentioned above, the dose of vasopressor used, but also the titration and the duration of the administration, are able to generate different effects on the autonomic system.

First of all, the cohort used in this study, after performing Lilliefors's statistical test, resulted to be non-normally distributed.

Afterwards the Wilcoxon Signed Rank Test was performed to analyze the differences between the features computed respectively on the segment extracted before and after the vasopressor administration in a cohort composed by 23 non-ventilated and non-sedated subjects. This choice has been made in order to obtain, in the first place, results not influenced by other administrations and treatments. In order to describe only the changes induced only by the vasopressor to the cardiovascular system. As expected, blood pressure is significant high after vasopressor administration, with a median increase of the Systolic Arterial Pressure of $\Delta\mathrm{AVSS} = 14{,}91310725$ mmHg (pValue 0,002603199). A significantly increase is observed also in Diastolic Pressure $\Delta\mathrm{AVDD} = 3{,}778764871$ (pValue 0,000915678). Even if is not significant, it's interesting to notice that AVNN is increasing too ($\Delta\mathrm{AVNN} = 27{,}19368858$, pValue 0,059331739) so the heart rate is decreasing. Several temporal indexes accounting for variability were found to be higher (SDNN, SDNNIDX, NN20, pNN20, RMSSD, logRMSSD, SD, SD1, SD2) after the administration even if not significant.

Investigating the features obtained from the RR spectrum, there is a significant increase in VLF and LF. Median $\Delta\mathrm{VLF} = 0{,}033250395$ pValue0,033250395, $\Delta\mathrm{LF} = 0{,}084449547$ pValue0,038619639.

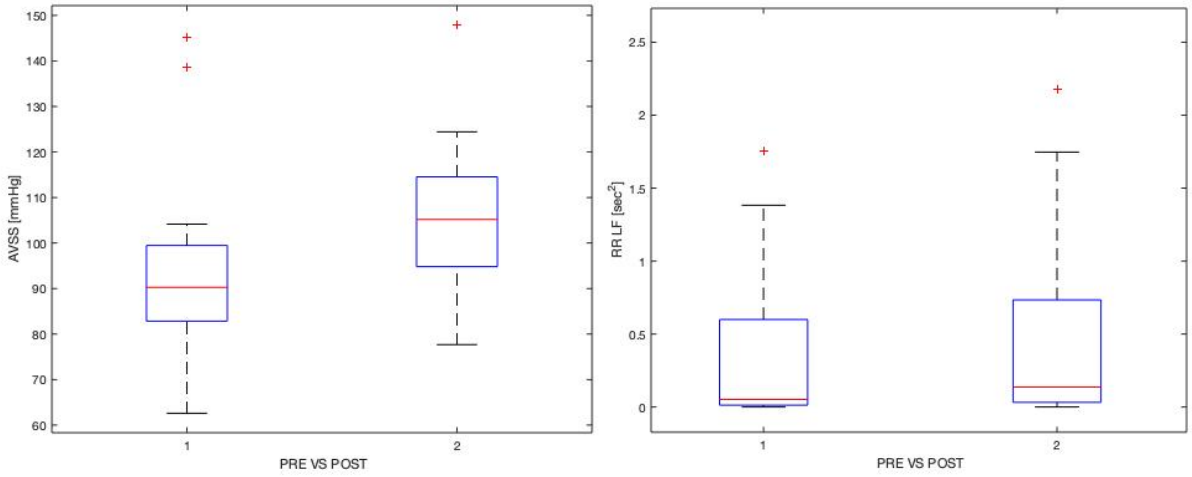


Figure 4.1.2 Left: boxplot of the median Gain12 (feedback) between the before and after administration. Right: boxplot of the median Gain21(feedforward) between the before and after administration in non-sedated, non-ventilated patients

Investigating the features extracted from the BP spectrum, no significant differences were found between the pre and post administration segment, in general SS LF are increasing while SS HF decreasing, especially, DD LF and DD HF behave the opposite way.

Looking the feature computed using Point process model, Gain12 represents the feedback mechanism of the baroreflex and is decreasing $\Delta GAIN12$ =-30,079963 p value 0,135356. Hence the feedforward gain G21, is significantly increasing $\Delta GAIN21$ =0,000373366 pValue= 0,204330247.

Total Cross spectrum and coherence were found to increase even if not significantly increase in median and average but with a significant increase standard deviation of both of them: $\Delta BivaCRTOT$ std =1952,69445 pValue(0,02080324) $\Delta ChoTOT$ std =0,01132959 pValue 0,03861964) .

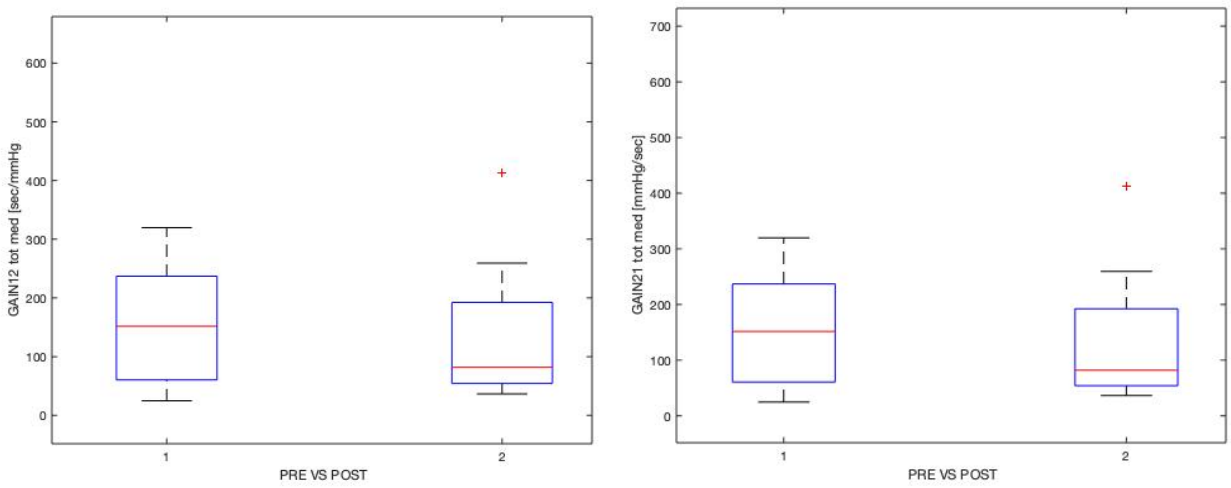


Figure 41.2 Left: boxplot of the median Gain12 (feedback) between the before and after administration. Right: boxplot of the median Gain21(feedforward) between the before and after administration in non-sedated, non-ventilated patients

Regarding non-linear features sample, entropy is increasing while the Hurst exponent significantly decrease (pValue = -0,000202), this might indicate an improvement in the subject's condition even if, as it is possible to see in Figure 4.3, H value is still >0.5 for most of the subjects before and after the administration.

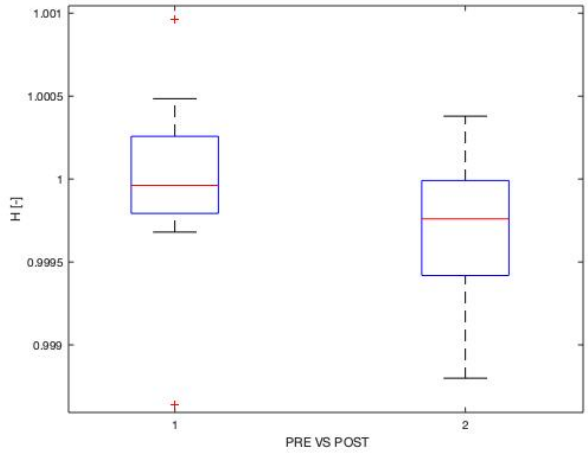


Figure 4.1.3 Left: boxplot of the Hurst exponent between the before and after administration in non- sedated, non-ventilated patients

The same test was repeated on the entire population of 123 subjects, thus including those who were sedated and ventilated. As specified above, the purpose is to verify whether the changes found, before and after vasopressor administration, are maintained in the whole population despite the action of treatments that heavily affect the autonomic system. The patients considered are sedated and ventilated for the whole-time window considered. In addition, being in intensive care, they are subjected to many treatments and affected by different pathologies. We can consider all the different pathologies, treatments, administrations as included in the baseline and see if the action of the vasopressor drug is still trackable using the features extracted from the waveforms.

The difference in the pressure value before and after administration remains significant, in addition the AVNN also becomes significant (pValue 0,001955035) with a mean increase of 18,63541569, while VLFs and LFs lose their significance and temporal indexes that account for variability are now decreasing.

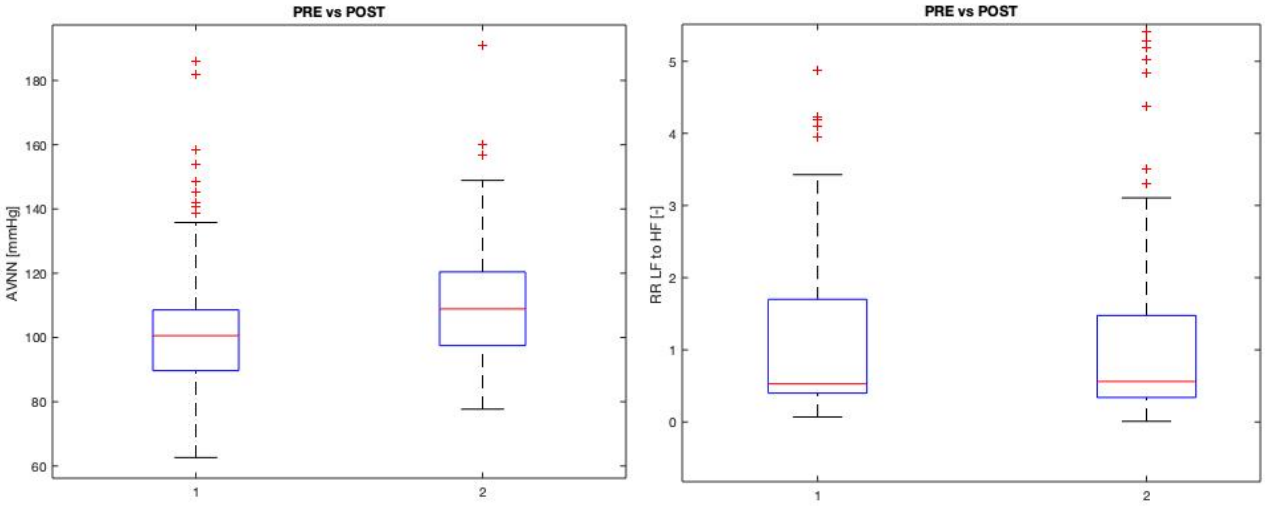


Figure 4.1.4 Left: boxplot of the SAP between the before and after administration. Right: boxplot of RR LF to HF between the before and after administration in the hole cohort

No significant change can be seen in this case looking at the simpatho-vagal balance.

Computing the Wilcoxon Rank Sum Test, comparing non ventilated and ventilated patients respectively before and after the vasopressor administration, the behavior in the LF and HF band results to be opposite.

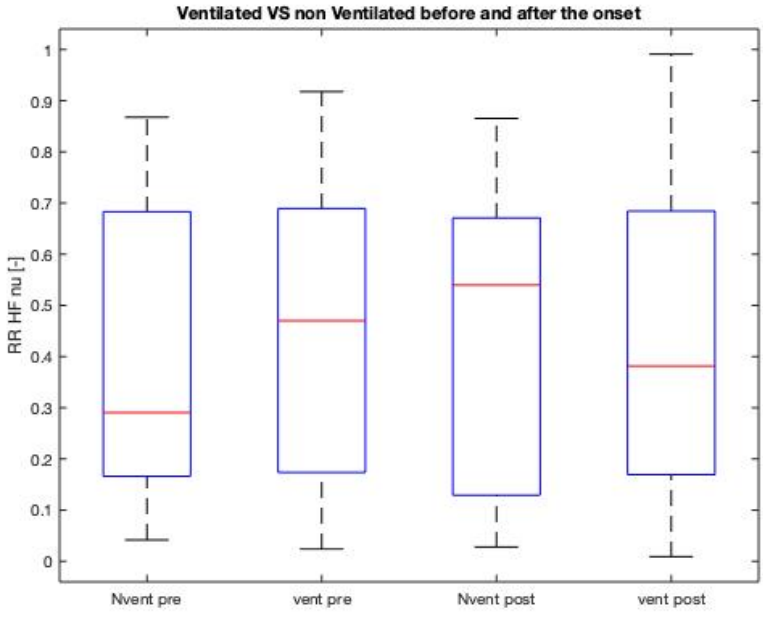


Figure 4.1.5 Starting from the left boxplot of the RR HF nu before administration for non-ventilated subjects then for ventilated again RR HF nu for non-ventilated subjects after administration and again for ventilated

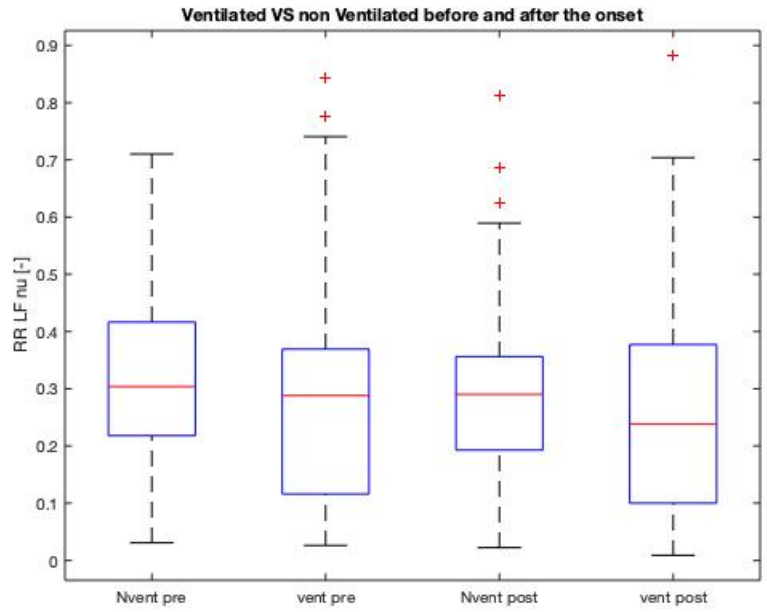


Figure4.1.6 Starting from the left boxplot of the RR LF nu before administration for non-ventilated subjects then for ventilated, again RR LF nu for non-ventilated subjects after administration and again for ventilated

Looking at time varying frequency components, other significant results are found, Gain12 is still decreasing with significant slope both in low frequency, high frequency band and the total ($\Delta\text{Gain12TOT}_{\text{Slope}} = -0{,}0044094, \text{pValue} = 0{,}00967801$). Looking at the G21 gain, not only the slopes are significant, but also the mean and median value ($\Delta\text{Gain21TOT}_{\text{median}}$ =0,00026204, pValue = 0,00205729), showing a significant increase. Cross spectrum is also significant (average, slope and standard deviation) while coherence is now significative only in LF band ($\Delta\text{bivaCRTOT}_{\text{Avg}} =$ 113,100548 pValue 0,01718712, $\Delta\ \text{CohLF}_{\text{Slope}}$ =-6,159E-06 0,02828014)

It was noticed that, about 35 patients out of 123, instead of a decrease in the heart rate are experiencing a significative increase. Therefore, the Wilcoxon Signed Rank Test was performed on the whole cohort dividing the population in two groups: non-responding subjects (35) and responding subjects (88).

Many significant differences were noticed between those two groups.

The Wilcoxon Signed Rank Test was performed again inter groups while the Wilcoxon Rank sum intra groups. In responding subjects, as they were defined, AVSS significantly increase (ΔAVSS=16,6517317 pValue 8,85746E-05),but also AVDD (ΔAVDD= 6,103157939, pValue 2,27714E-13) and AVNN (ΔAVNN= 10,15173416, pValue 0,014421754) while G12 is still decreasing (ΔG12 tot median = -30,079963 pValue 0,1353569).

In non-responding subjects ΔAVSS=-8,853826525 (pValue 2,47703E-07), AVDD decreases too, (ΔAVNN= -4,19173743, pValue=0,000937681), AVNN (ΔAVNN=12,24638888, pValue 0,055319323) still increasing non significantly, the baroreflex gain G12 remains pretty much the same. Regarding RR and ABP spectra are still hard to interpret since different subjects show contrasting trends, in general responding subjects has a higher HF and LF activation also before the vasopressor administration, after it LF remains almost equal while HF decrease. For non - responding subjects LF are always very low while HF seems to increase a little after the administration, figure 4.1.11, 4.1.12.

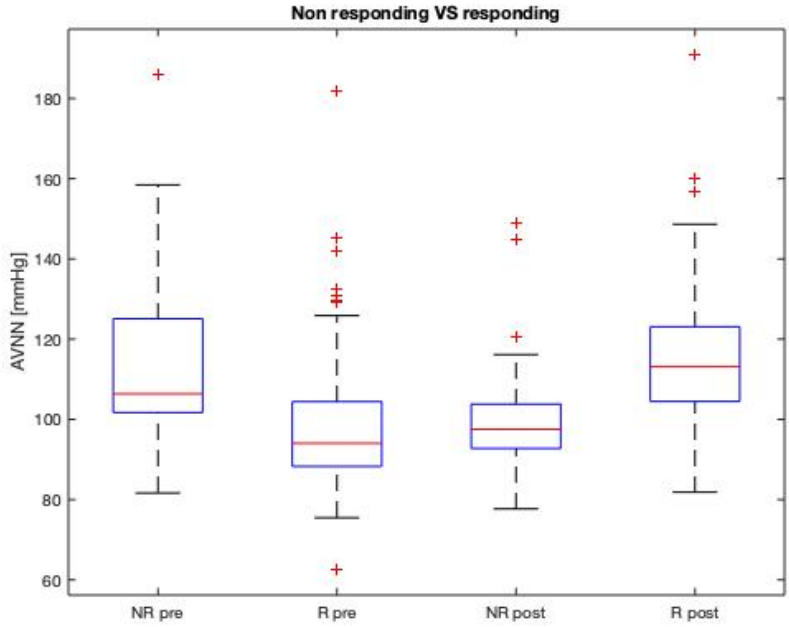


Figure 4.1.9 Starting from the left boxplot of the mean SAP nu before administration for non-responding subjects then for responding, again the mean SAP for non-responding subjects after administration and again for responding

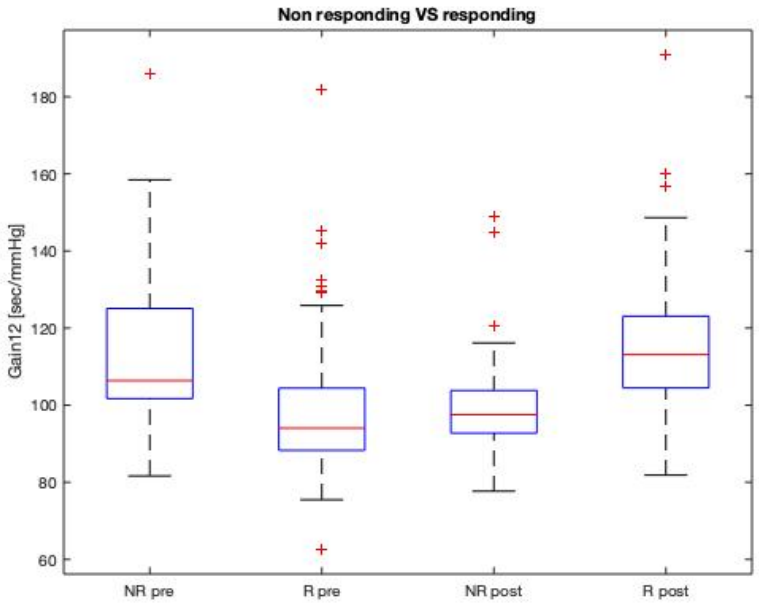


Figure 4.1.10 Starting from the left boxplot of the median Gain12(feedback) before administration for non-responding subjects then for responding, again median G12 gain (feedforward) for non-responding subjects after administration and again for responding

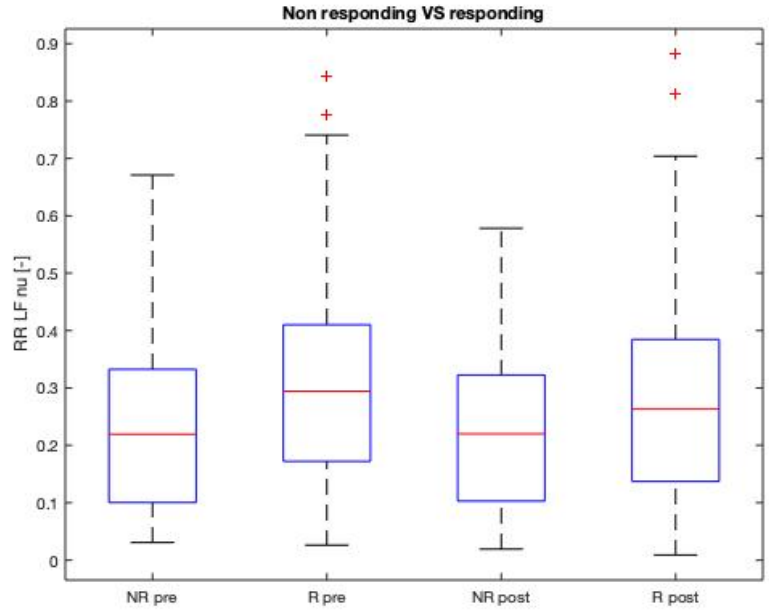


Figure 4.1.11 Starting from the left boxplot of the RR LF nu before administration for non-responding subjects then for responding, again RR LF nu for non-responding subjects after administration and again for responding

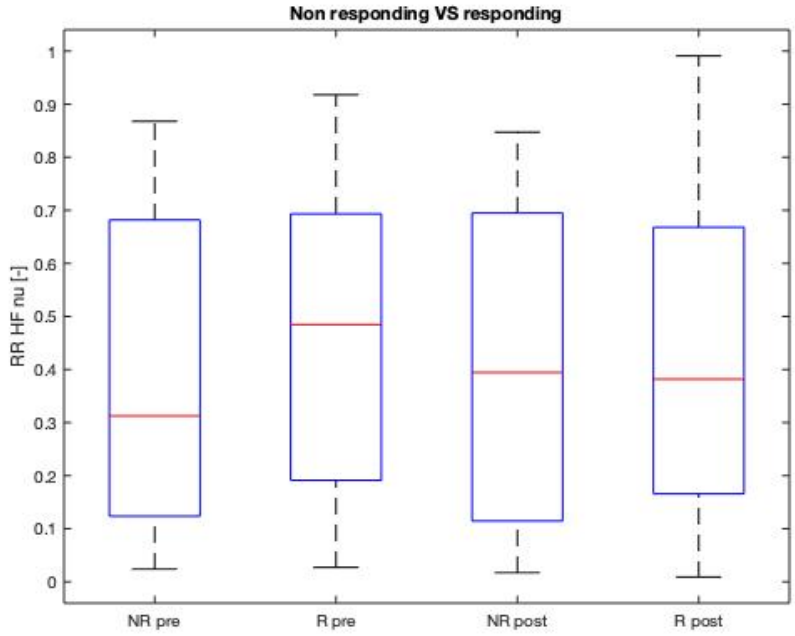


Figure 4.1.12 Starting from the left boxplot of the RR HF nu before administration for non-responding subjects then for responding, again RR HF nu for non-responding subjects after administration and again for responding

As was mentioned previously the cohort was divided according to changes in lactate level between "Low level" and "high-level" population. The former, experience a significant increase in systolic blood pressure ($\Delta AVSS$ =5,62124798) while the latter expressed a significant rise in diastolic blood pressure ($\Delta AVDD$ =6,299010869).

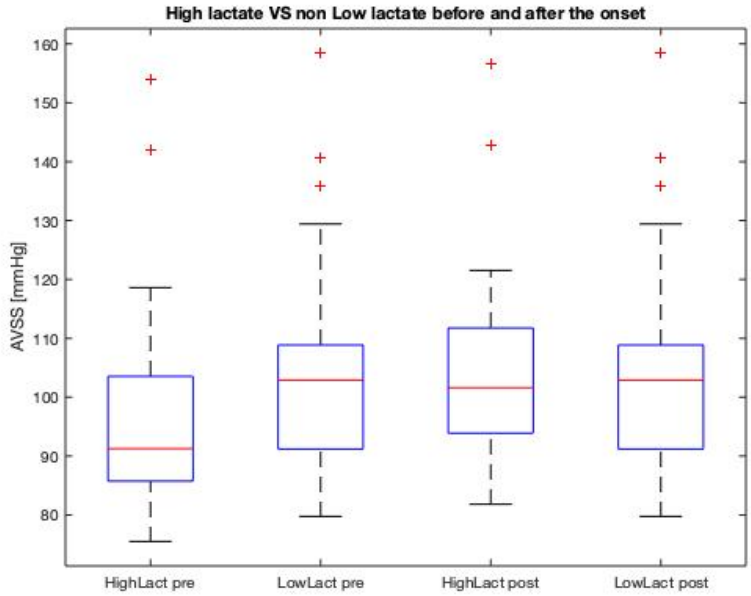


Figure 4.1.13 Starting from the left boxplot of the SAP before administration for high lactate subjects then for low lactate, again SAP for high lactate subjects after administration and again low lactate

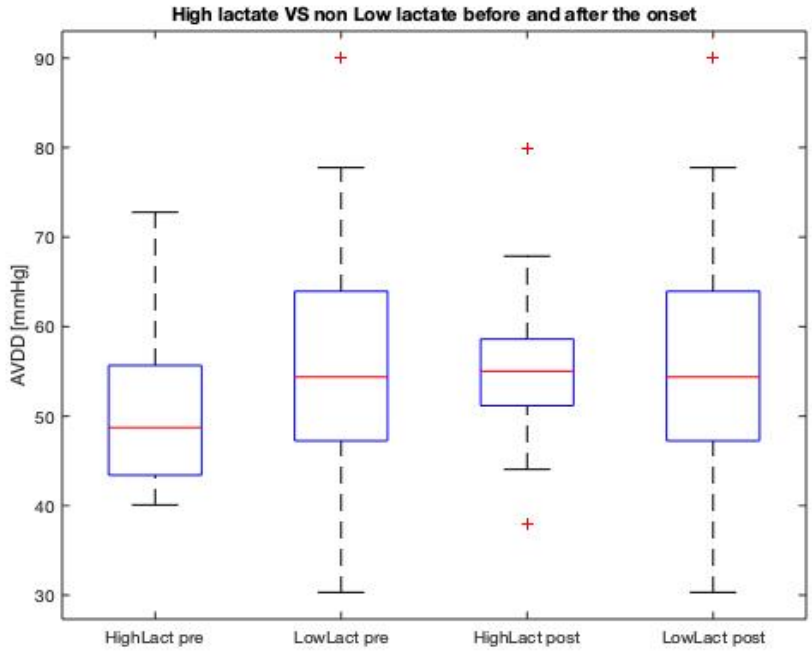


Figure 4.1.14 Starting from the left boxplot of the DAP before administration for high lactate subjects then for low lactate, again DAP for high lactate subjects after administration and again low lactate

In low level subjects also SS_HF becomes significative. It is interesting to notice that, looking at the RR spectra, even it is not significant, subjects with lower lactate has a higher LF component while subjects with higher lactate show a predominance of HF component after the administration. In fact, the sympathovagal balance is shifted downwards for low level patients and upwards for the others.

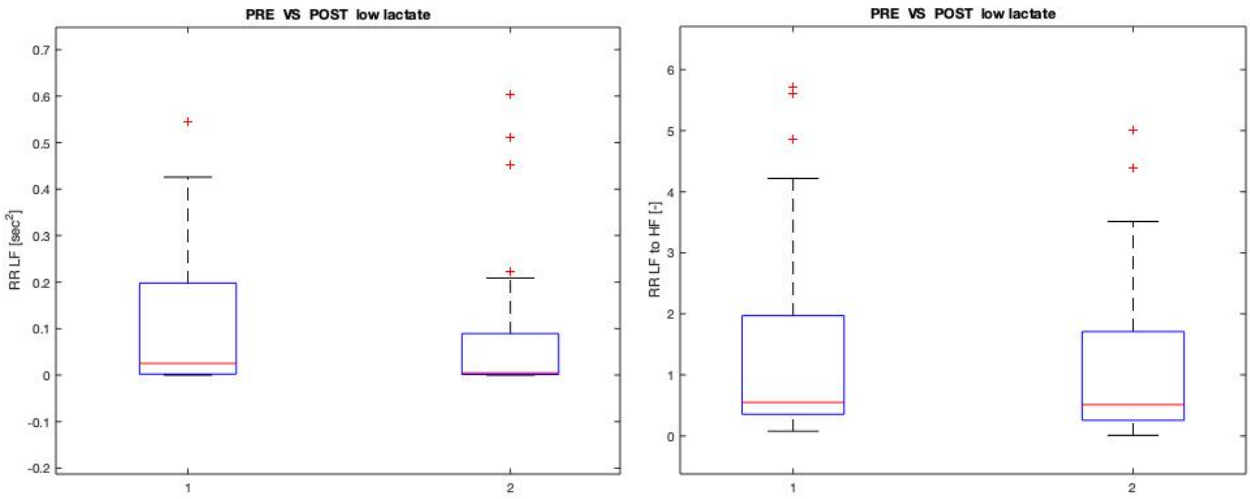


Figure 4.1.15 Left: boxplot of the RR LF between the before and after administration. Right: boxplot of the mean RF LF to HF between the before and after administration in low lactate population

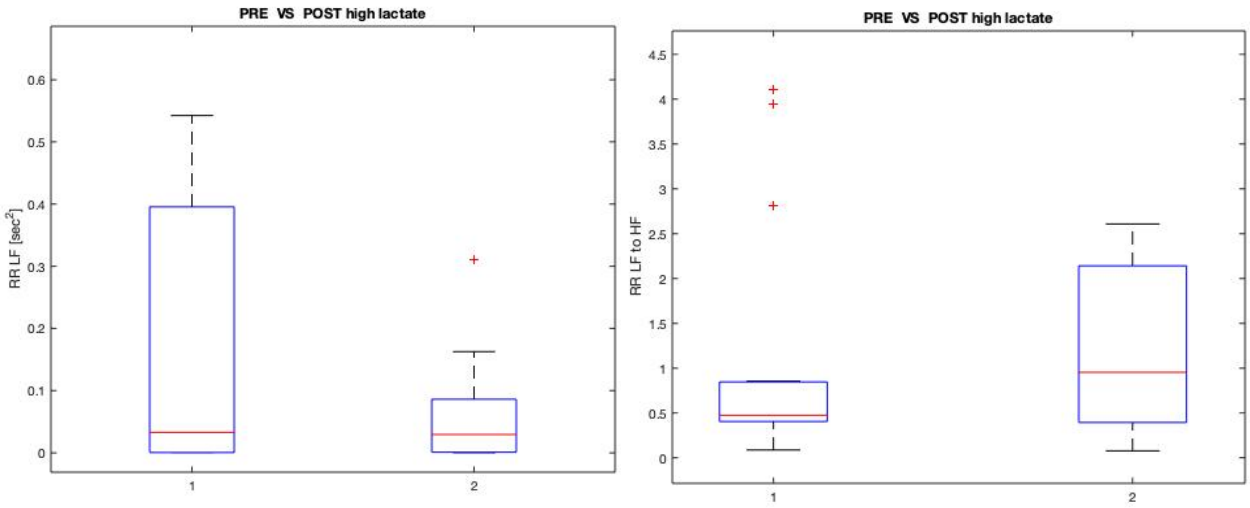


Figure 4.1.16 Left: boxplot of the RR LF between the before and after administration. Right: boxplot of the mean RF LF to HF between the before and after administration in high lactate population

Feedback and feedforward gains also seem to have conflicting behaviors in the two populations as can be seen in figures 4.1.17, 4.1.18:

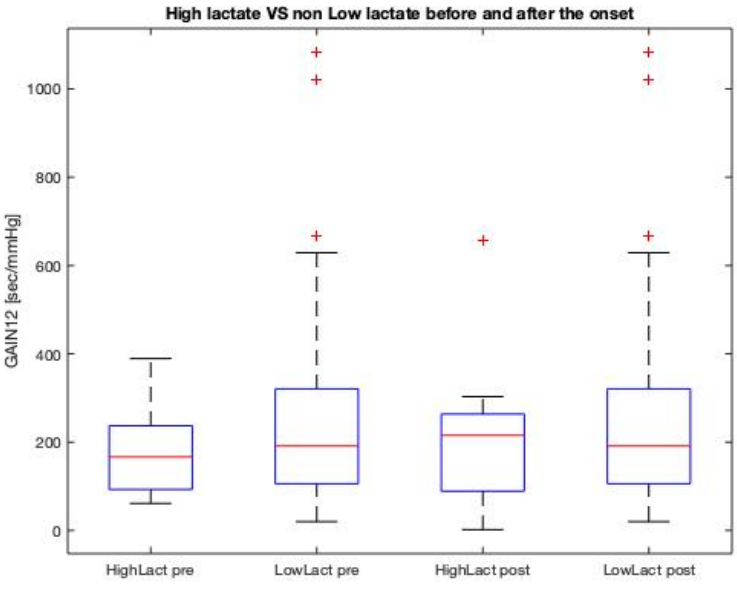


Figure 4.1.17 Left: boxplot of median G12 between high lactate and low lactate before and after administration.

Stratifying for other comorbidities: sepsis, diabetes, hypertension and liver disease no clear differences were found with respect to the total population of 123 subjects. Fisher's exact test confirms that there is no association between the non-responding/responding population and the

considered comorbidities. Initially the Wilcoxon Rank Sum Test for non-doubled pair was performed to detect the differences intra groups and with respect to the control ones, while afterwards the Wilcoxon Signed Rank was used to find the difference into groups. No significant differences were found between the starting population and the different groups. In general, however, the less a subject is affected by serious diseases or powerful administration, the more visible are the autonomic changes induced by vasopressor therapy.

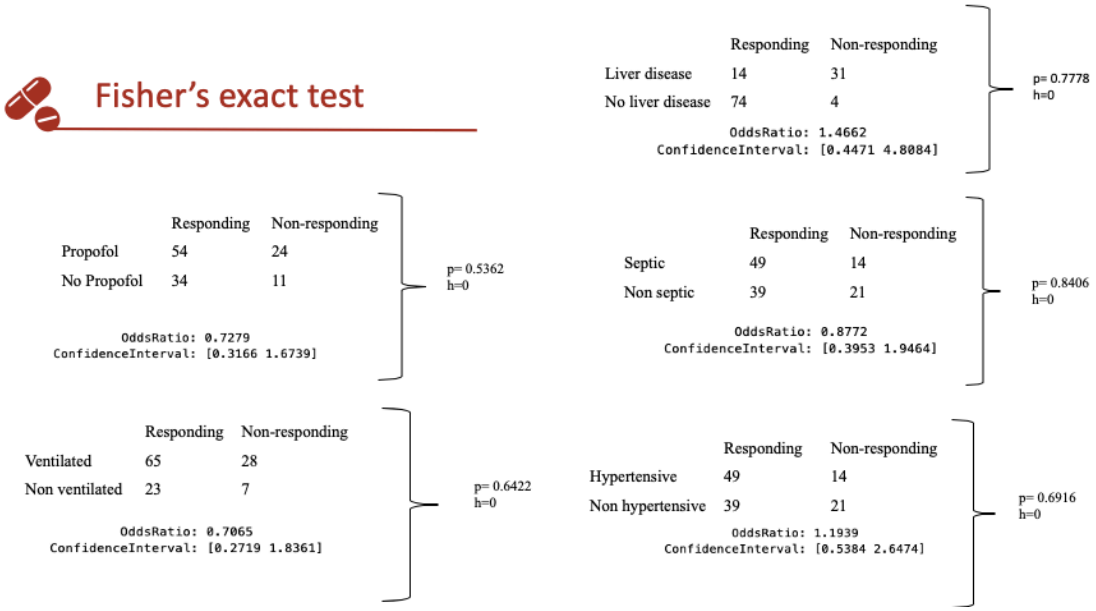


Figure 4.1.19 Fisher's exact test

4.2 Correlation

The correlation study was carried out using the Spearman's correlation coefficient to analyze whether there is a relationship between the features extracted from waveforms and the lactate value, in order to verify how and how much these variables vary together.

Association does not mean necessarily a causal relation between both variables; the correlation coefficient rho shows how strong is the relationship between the two variables. If it's positive they are moving in the same direction while, if is negative implies that when one is increasing the other is decreasing. A strong correlation is+/-0.8 and above while a weak correlation is below +/-0.5, for values in between there is a sufficient correlation.

First of all, was tested the correlation of the features extracted from the pre and post segments with the lactate level collected in the 12 hours before (initial lactate level) and after (final lactate level) the administration. Features from both segments result more correlated with the lactate level before the onset as we can see in Figure 4.2.1, 4.2.2. Spearman's Rho highest value is 0.6 for features of the waveform and initial lactate, while for final lactate the highest Rho value is 0.3, stating a low correlation.

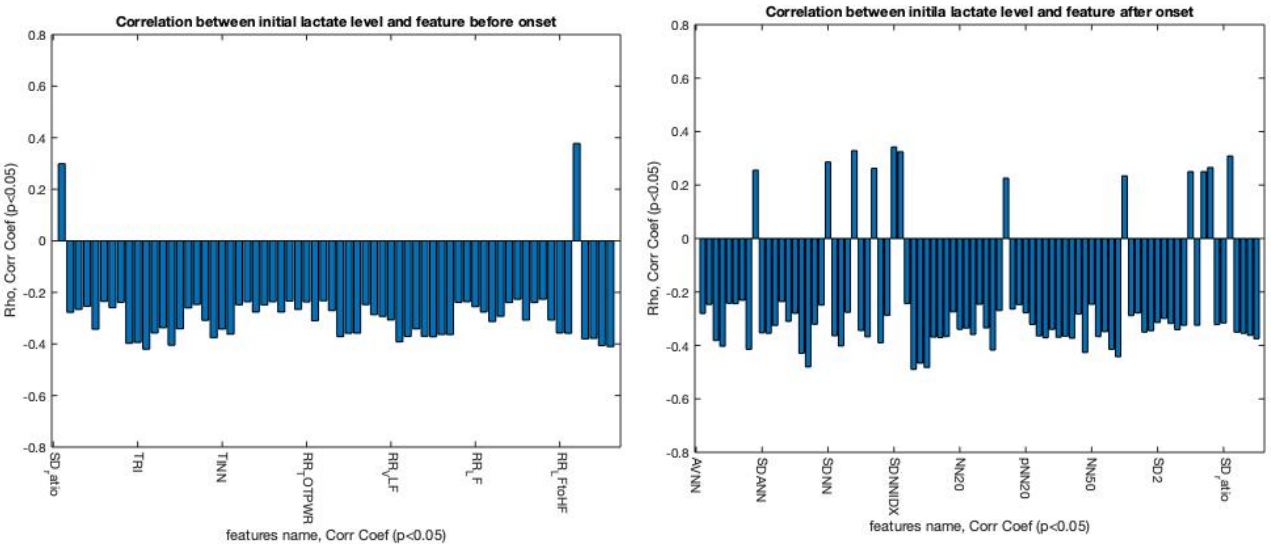


Figure 4.2.1 Left: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features before the onset. Right: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features after the onset and initial lactate level

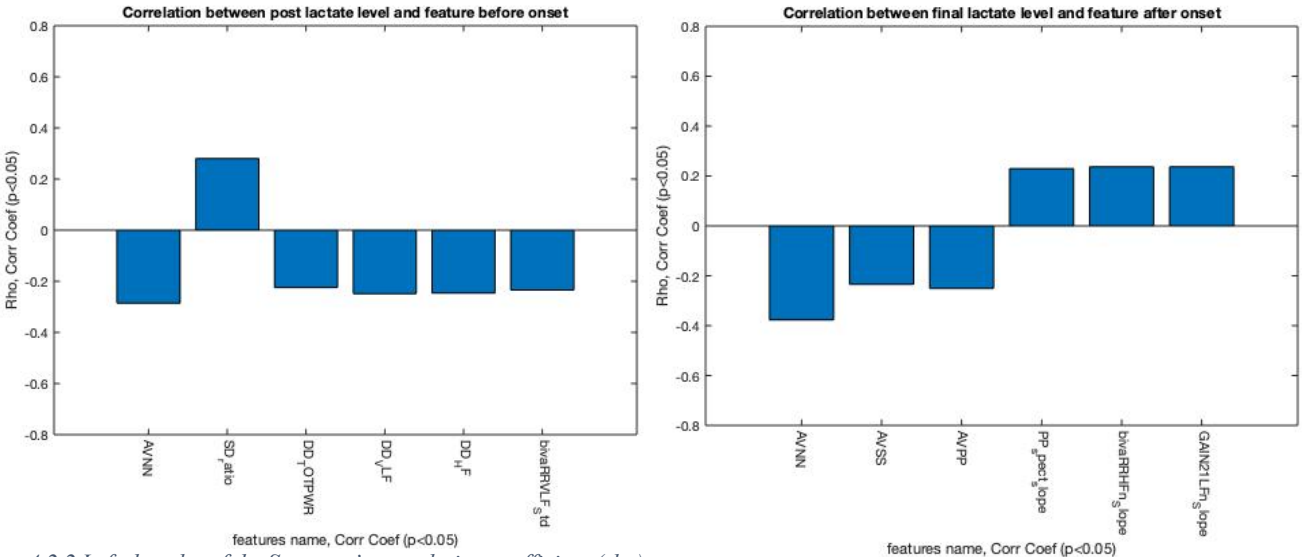


Figure 4.2.2 Left: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between final lactate level and features before the onset. Right: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features after the onset and final lactate level

Stratifying the population according to normal (<2 mmol/L) and abnormal (>2 mmol/L) lactate. Testing all possible combinations subjects with abnormal lactate level seems to have higher correlation with indexes as shown in Figure. 4.2.3, 4.2.4.

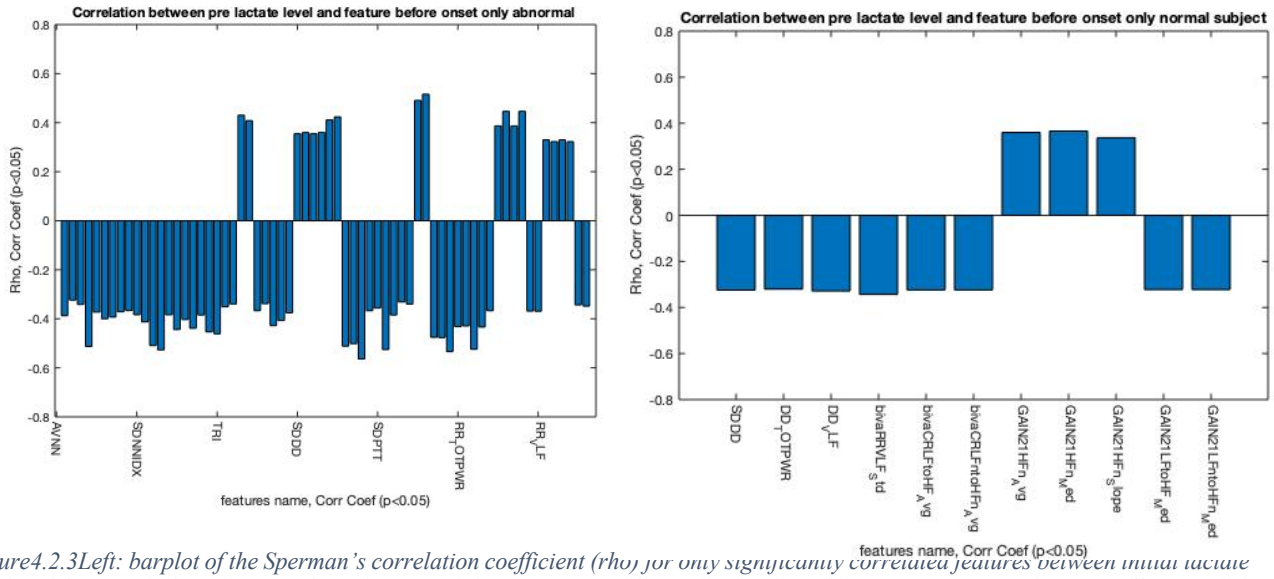


Figure4.2.3Left: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features before the onset for subjects with lactate >2 mmol/L. Right: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features before the onset and initial lactate level for subjects with lactate <= 2 mmol/L

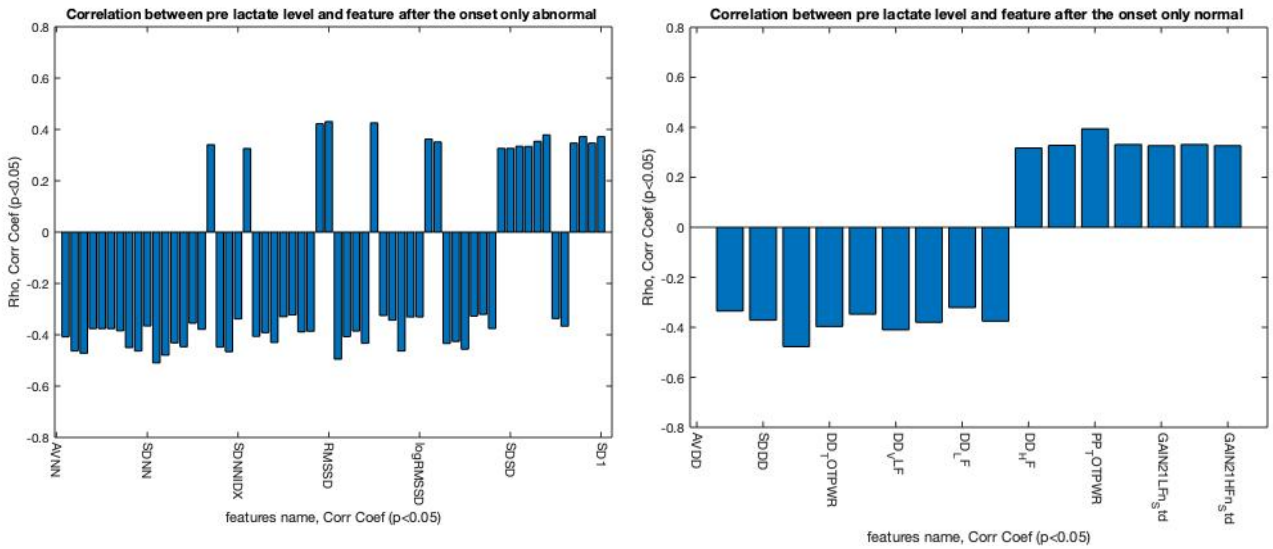


Figure 4.2.4Left: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features after the onset for subjects with lactate >2 mmol/L. Right: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features after the onset and initial lactate level for subjects with lactate <= 2 mmol/L

The features the features that gave the highest correlation values are:

From the scatterplot in Figure 4.2.5 we can see that subjects with normal lactate seems to follow a different dynamic compared to subjects with abnormal lactate.

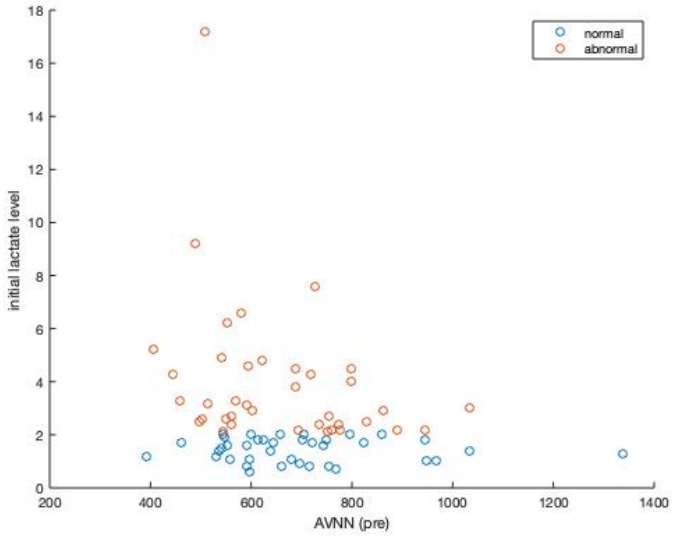


Figure 4.2.5 Scatterplot of mean SAP of the before segment and initial lactate level dividing normal and abnormal subjects

Considering lactate division in tree range instead of two: below 2 mmol/L, between 2 and 4 mmol/L and higher than 4 mmol/L, the division between groups is still visible.

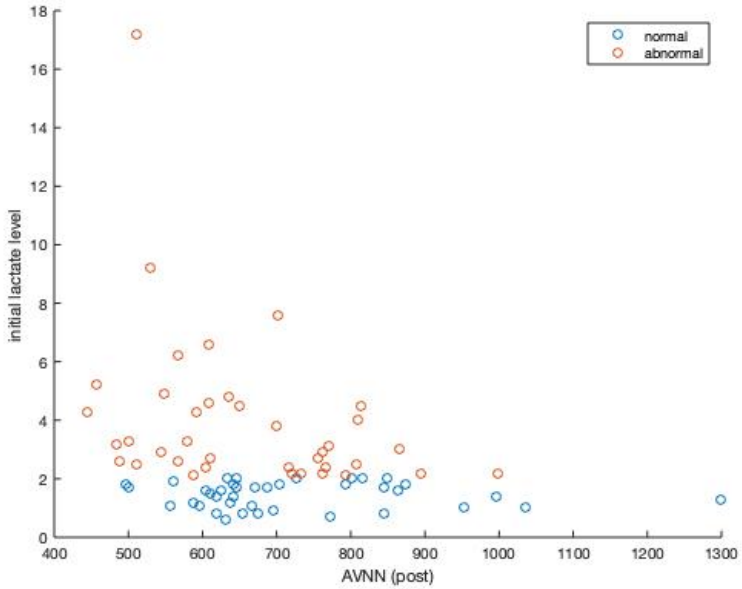


Figure 4.2.6 Scatterplot of mean SAP of the after segment and initial lactate level dividing normal and abnormal subjects

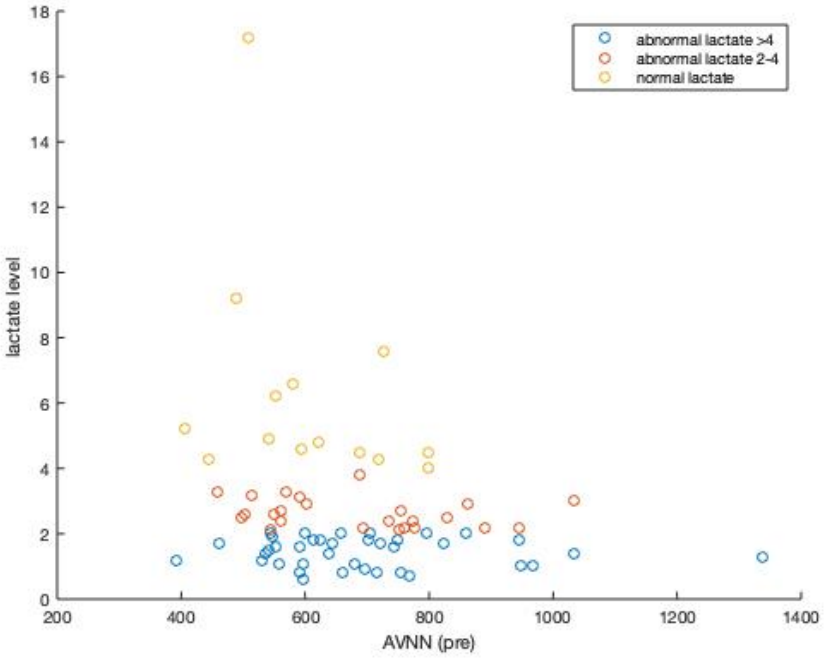


Figure 4.2.7 Scatterplot of mean SAP of the before segment and initial lactate level dividing normal lactate level (<=2 mmol/L), mid-level (2-4 mmol/L) and abnormal level (>= 4 mmol/L).

Last correlation analysis was made dividing between responding and non-responding subjects according to blood pressure as in the characterization part. Responding subject seems to be more correlated, especially with the features extracted from the waveform after the vasopressor administration.

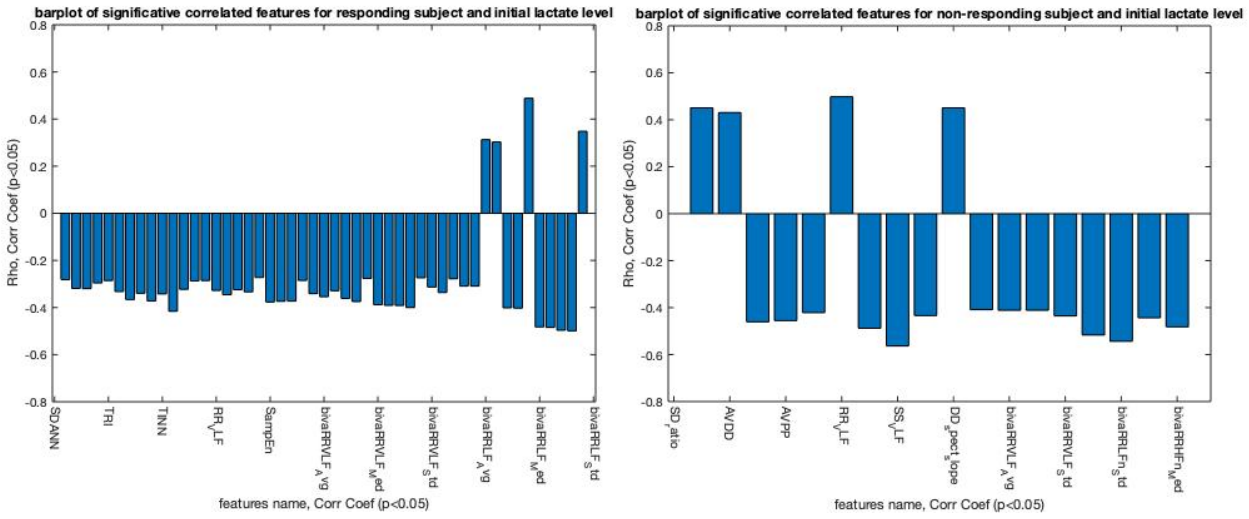


Figure 4.2.8 Left: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features after the onset for responding subjects (according to pressure). Right: barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features before the onset for non-responding subjects (according to pressure

In this case, looking at the scatterplot using the same feature, there is no clear division between responding and non-responding population.

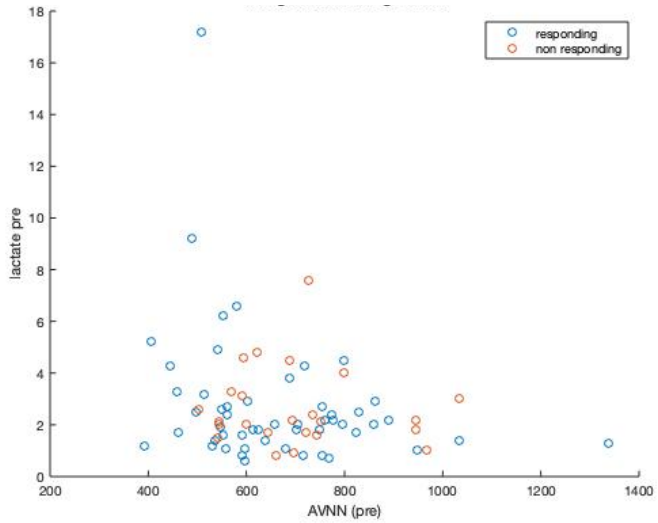


Figure 4.2.9 Scatterplot of mean SAP of the before segment and initial lactate level dividing responding and non-responding subjects

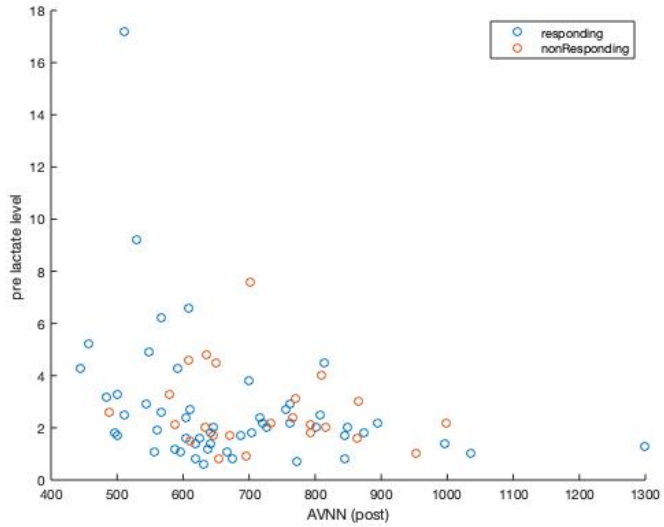


Figure 4.2.10 Scatterplot of mean SAP of the after segment and initial lactate level dividing responding and non-responding subjects

Trying to fit the data of the previous graphs the line of the linear regression model seems to have different slopes.

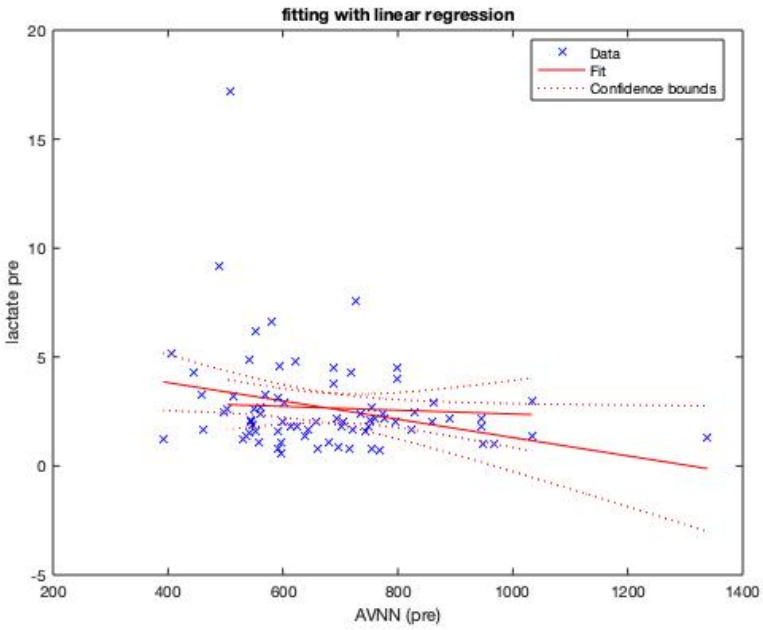


Figure 4.2.11 Scatterplot of mean SAP of the before segment and initial lactate level dividing responding and non-responding subjects and fittimg the data with a linear regression model

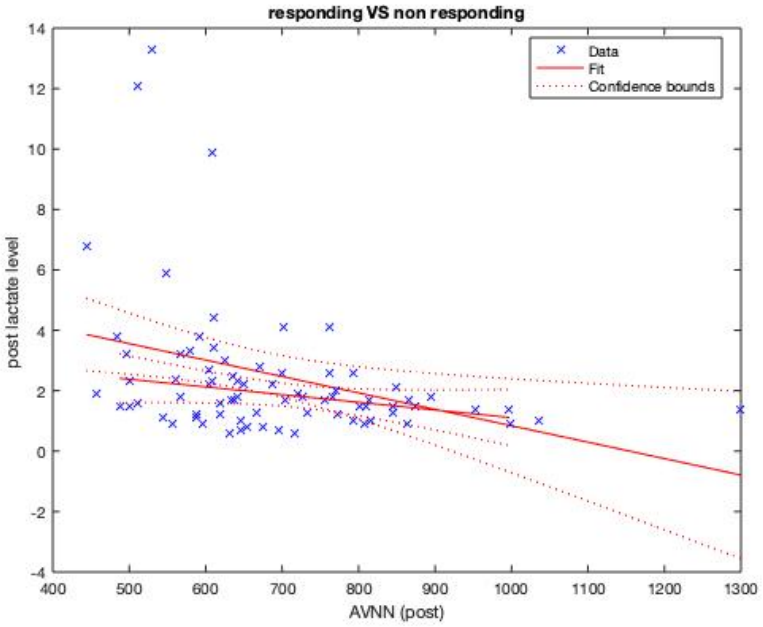


Figure 4.2.12 Scatterplot of mean SAP of the after segment and final lactate level dividing responding and non-responding subjects and fittimg the data with a linear regression model

At the end looking at the correlation between the differences, unexpectedly, the correlation was very low and almost not significant.

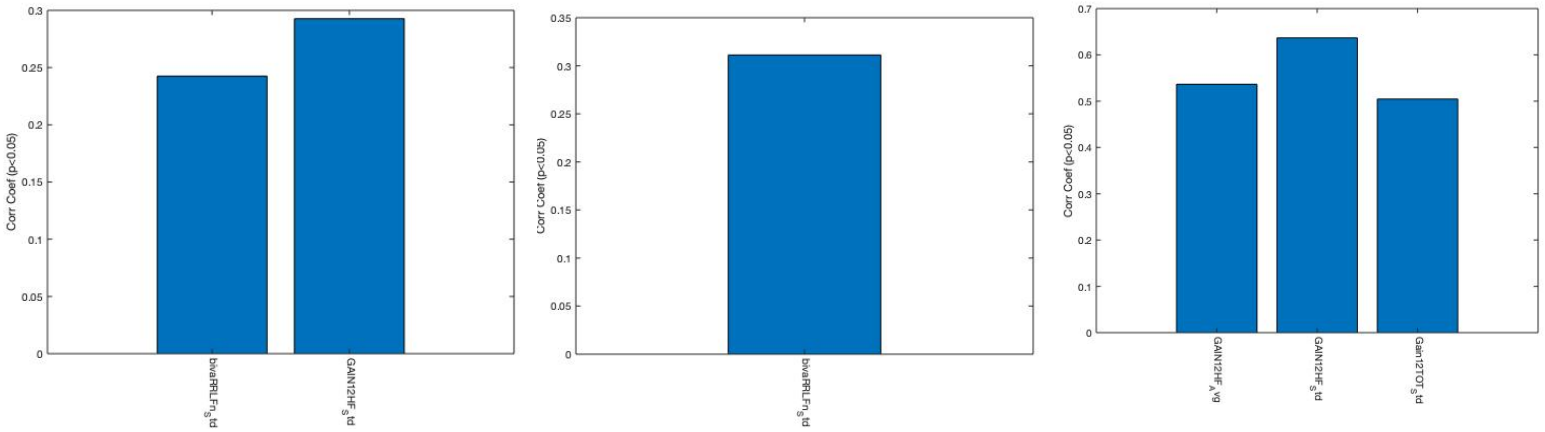


Figure 4.1.14 Left: Correlation of the difference in features value and in lactate value (12h). Middle: Correlation of the difference in features value and in lactate value (12h) only in responding (pressure subjects). Right: Correlation of the difference in features value and in lactate value (12h) only in non-responding (pressure subjects).

The correlation study was repeated narrowing the width of the time windows considered to three hours around the administration. Considering therefore the reduced number of subjects, a small increase in the rho value can be noticed arriving at -0.6 for some features while considering the whole population and the 12-hour window the maximum rho value was 0.4

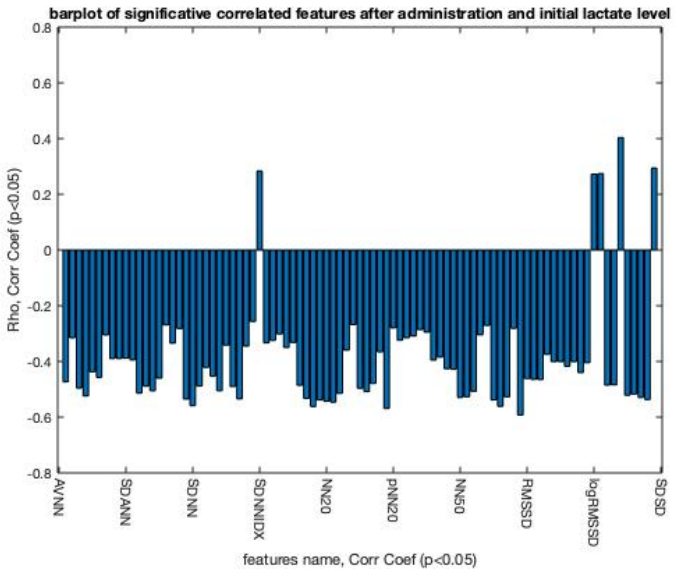


Figure 4.1.15 Barplot of the Sperman's correlation coefficient (rho) for only significantly correlated features between initial lactate level and features after the onset.

4.3 Lactate prediction

Lactate is a product of anaerobic metabolism, in fact, high levels of lactate in tissue is direct indication of tissue hypoxia and organ failure. Thus, serum lactate levels serve as diagnostic maker in critically ill patients. Predicting the kinetics of lactate is therefore very complex. Changes are relatively slow and is difficult to give an indication of the rate in lactate concentration. In addition, very few lactate sizes are available per patient. However, a decrease in lactate concentrations, as better prognosis, is consistent throughout the literature. In the extracted cohort is composed 123 patients, as mentioned above. For whom no lactate measurements were found, was considered to have normal lactate level, in order to not decrease further the cohort.

The method that gave best results for feature selection was logistic regression.

The flag of initial lactate level (at the time of administration) was often chosen by features selection algorithm. It was verified that the results of the algorithm were not dictated solely by this information. Selected features are in line with the features found to be significant in the correlation and characterization studies.

Some models performed better using only the features extracted from waveforms and lactate level others used also clinical information.

Best results were given by:

- Support vector machines, PRC curve area=0.56, ROC curve area =0.80. Optimizing parameter with grid search after features selection logistic regression. To build this model were used only the differences between the features in the pre and post segment, the features before the administration and the flag regarding lactate level in the 12 hours before the onset. SVM were trained using only the selected features: Flag lactate pre administration, pNN20_diff, DD spect slope_diff, bivaBP HF slope_diff, Gain12Lf_Med_diff, Gain12HFn_slope_diff, Coherence LF std_diff, SD ratio_pre, AVPP_pre, AVPTT_pre.

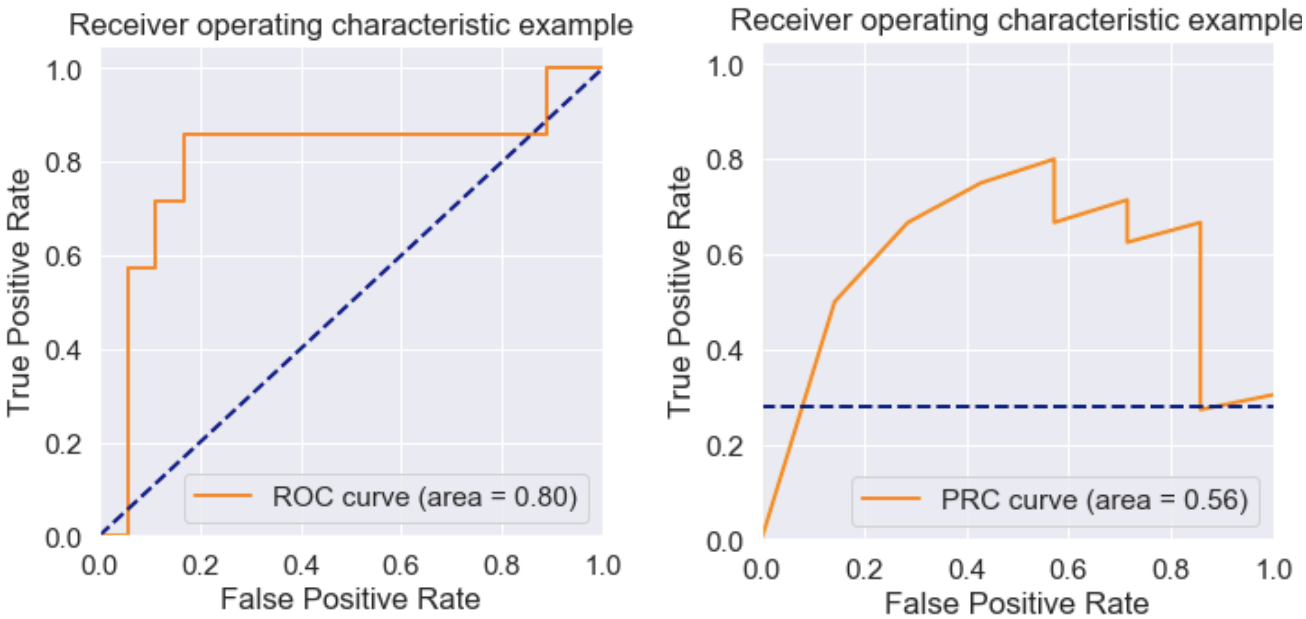


Figure 4.2.1 Left: ROC curve SVM classifier. Right: PRC curve for SVM classifier

- Random forest PRC curve area=0.57, ROC curve area =0.80. Optimizing parameter again with greed search after features selection logistic regression. To build this model were used the differences between the features in the pre and post segment, the features before the administration, the flag regarding lactate level in the 12 hours before the onset and also demographic information and laboratory value. Random forest was trained using only the selected features: Flag lactate pre, SD_ratio_pre, AVNN_post, AVPP_post, AVPTT_post, 'PTT_spect_slope_post, Gain12TOT_Avg_post, DD_spect_slope_diff, 'bivaRRLFn_Std_diff, GAIN12LFn_Med_diff, CohLF_Std_diff, gender, sedflag, propoflag, bilirubin, hemoglobin, lactate, platelet, potassium.

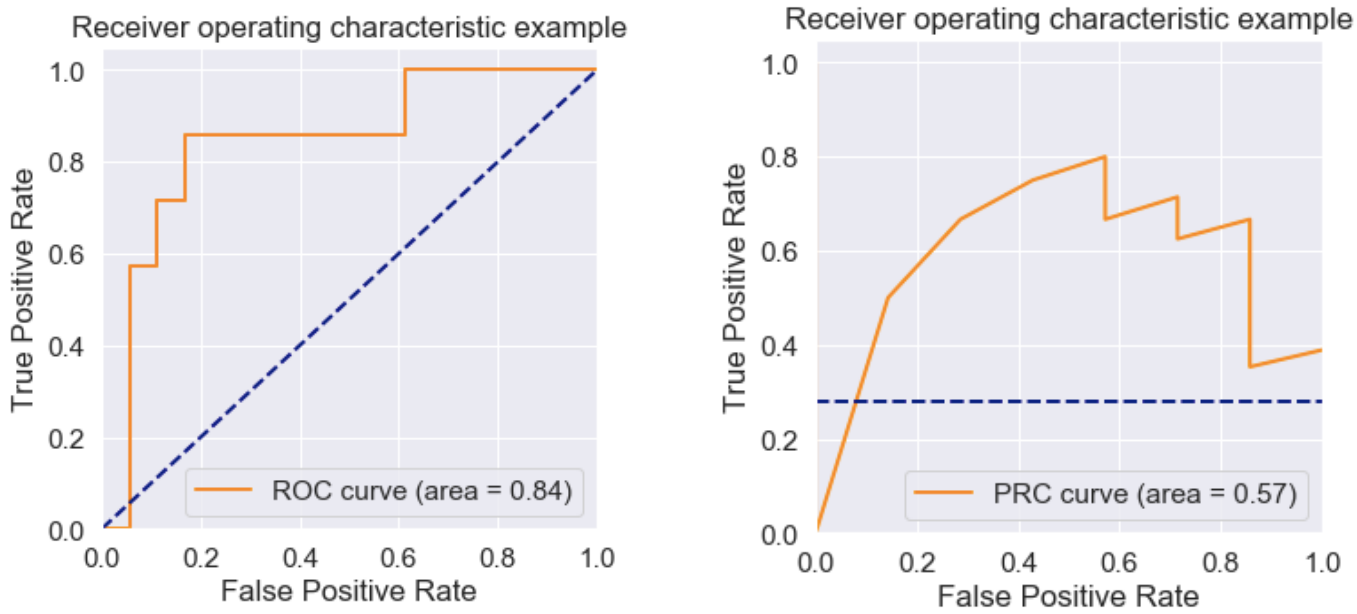


Figure 4.3.2 Left: ROC curve Random Forest classifier. Right: PRC curve for Random Forest classifier

- XGBoost: PRC curve area=0.69, ROC curve area =0.81. To build this model were used again differences between the features in the pre and post segment, and the flag regarding lactate level in the 12 hours before the onset and also demographic information and laboratory value.

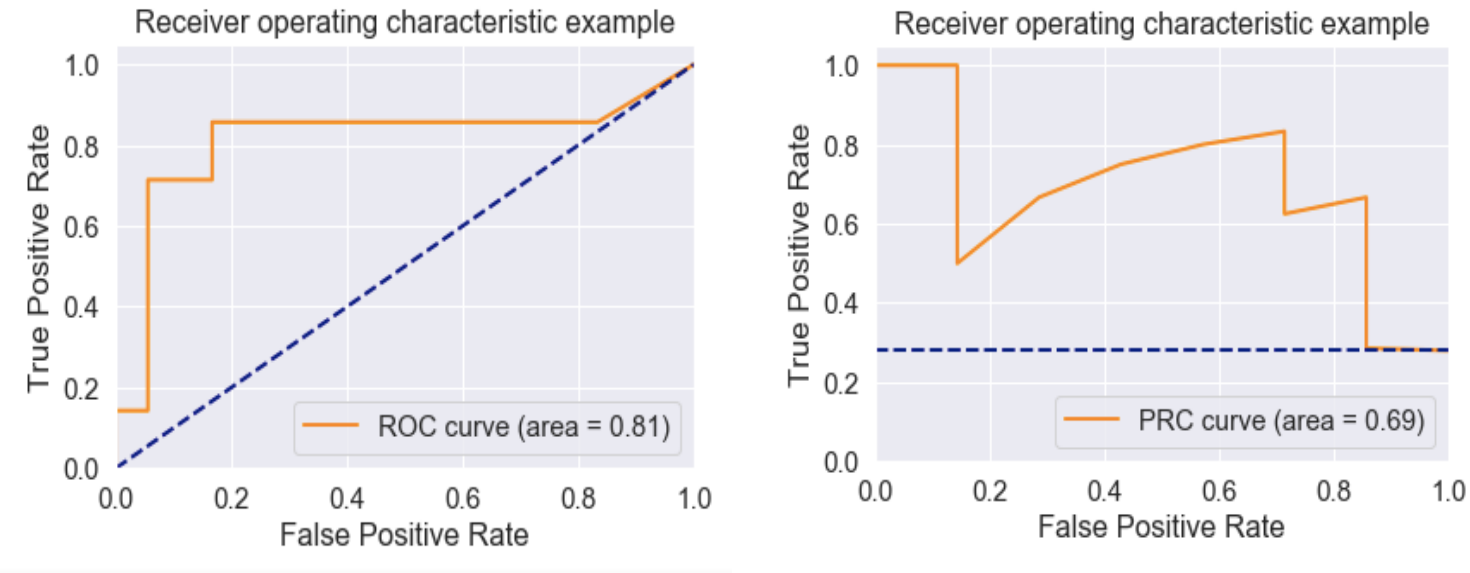


Figure 4.3.3 Left: ROC curve XGBoost classifier. Right: PRC curve for XGBoost classifier

More relevant features according to the xgboost algorithm are:

Figure 4.3.4 Most relevant features according to the XGBoost classifier

All features used indicates the difference between pre and post segment.

4.4 Example of time varying dynamic

As mentioned previously, point process modelling approach allows to obtain time-varying estimations of the power spectra in both LF and HF bands of RR, SAP and DAP, of coherence, cross spectrum and the two Gains, feedback (baroreflex sensitivity) and feedforward. Is therefore interesting to show the dynamics happening in these time-varying measures for some subjects.

The following figures report, in order, the ECG and ABP signal for the whole hour extracted and then for the two 15 minutes window considered, with relative Tachogram, the systolic and diastolic blood pressure time series (blue and red respectively, in the same plot). Then the indexes extracted using the point process modelling, LF range and in HF range are color-coded, with blue representing LF range while red representing HF range.

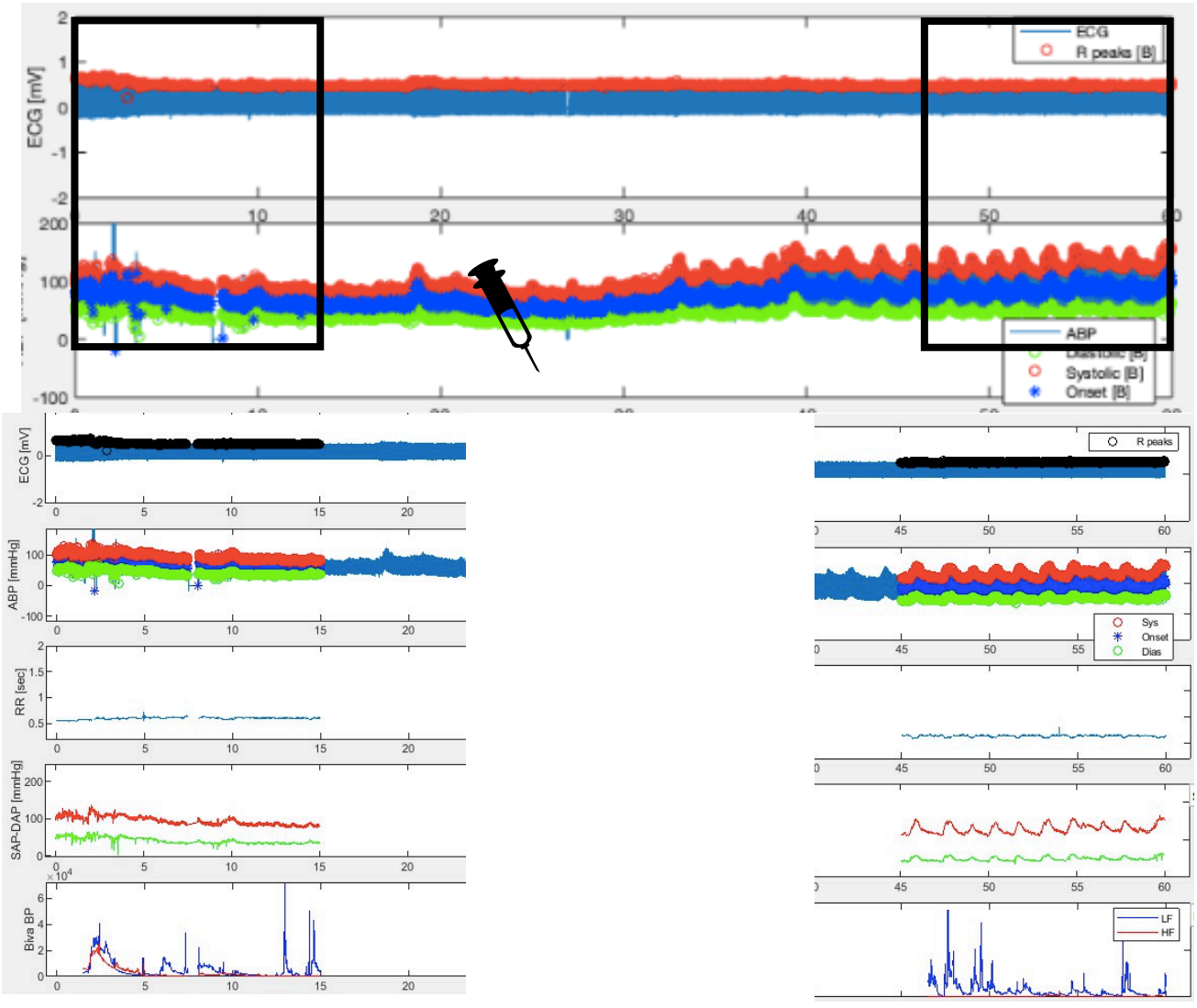


Figure 4.5.4 Top: original ABP and ECG waveforms. Left: First 15 minutes before the vasopressor administration. Respectively from the top: ECG; ABP, RR series, SAP, DAP and ABP power spectra in LF and HF band. Right: Last 15 minutes before the vasopressor administration. Respectively from the top: ECG; ABP, RR series, SAP, DAP and ABP power spectra in LF and HF band.

The shown waveforms come from a subject with no mechanical ventilation and sedative. The administration of vasopressor occurs around minute 25, the two black boxes represent respectively the first and the last 15 minutes of signal analyzed around it. After the vasopressor administration we clearly see a rise in blood pressure and a higher heart rate variability. There is an increase of sympatho-vagal balance due to the increase in the LF power after the vasopressor administration. All those aspects, very straightforward cached by visual inspection are consistent with what was discovered during the characterization analysis.

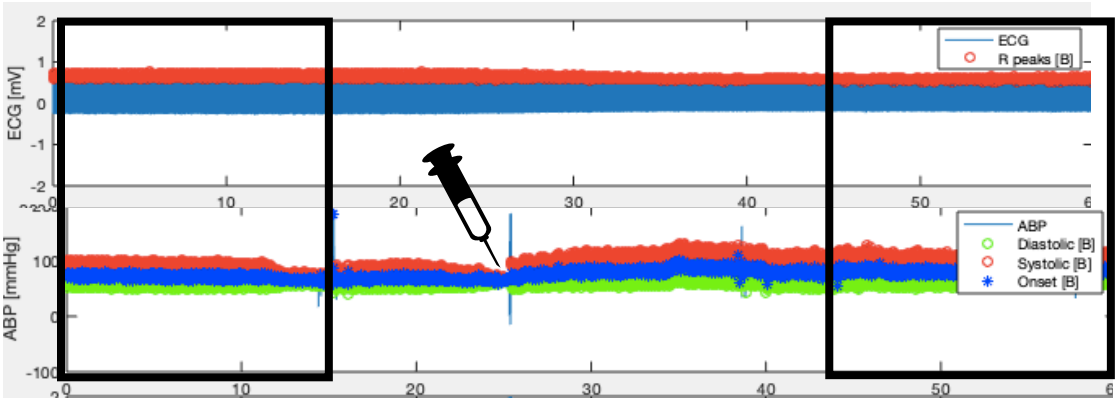


Figure4.5.1 ECG and ABP waveforms. Annotate and analyzed using PP model only the first and last 15 minutes highlighted in black boxes. 30 minutes around the administration are not considered.

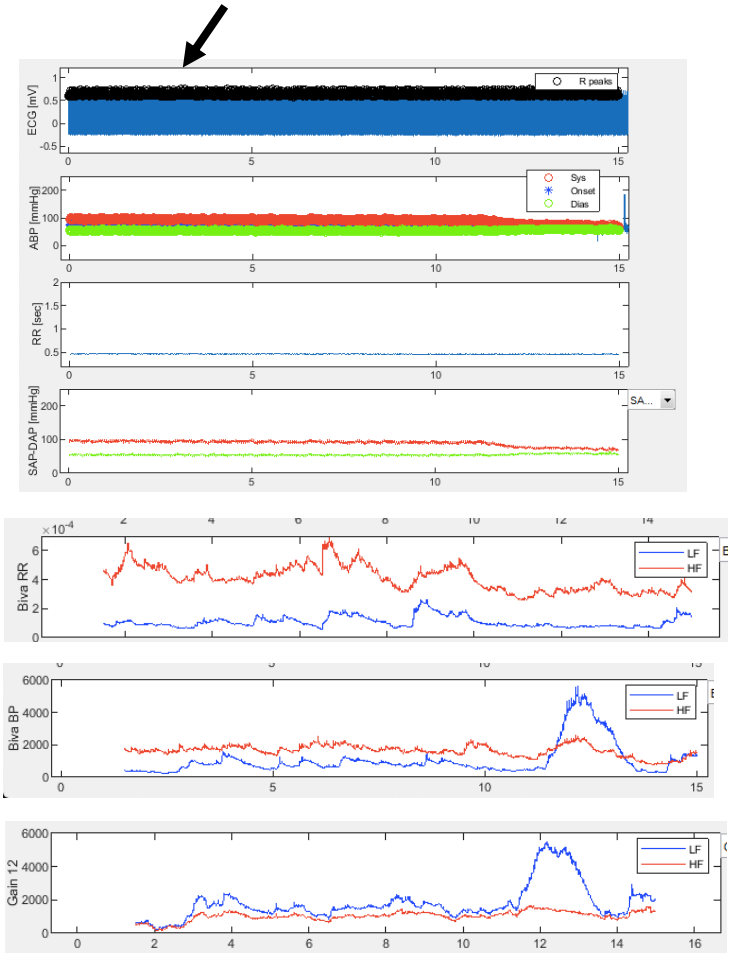


Figure 4.5.2 First 15 minutes before the vasopressor administration. Respectively from the top: ECG; ABP, RR series, SAP, DAP, RR and SAP power spectra in HF and LF band, Gain 12 (baroreflex sensitivity)

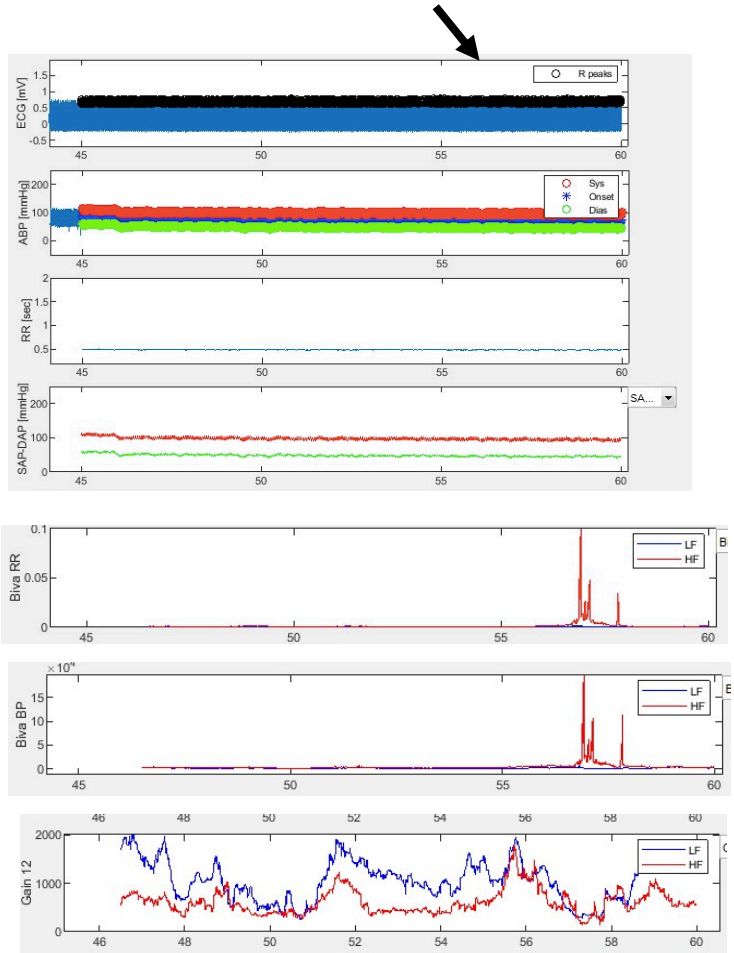


Figure 4.5.3 Last 15 minutes before the vasopressor administration. Respectively from the top: ECG; ABP, RR series, SAP, DAP, RR and SAP power spectra in HF and LF band, Gain 12 (baroreflex sensitivity)

From Figure 4.5.1 we can see the whole ECG and ABP waveforms. 30 minutes around the vasopressor onset are not considered due to the fuzziness of the measure. In figure 4.5.1 and 4.5.2 it's possible to look at the changes respectively before and after the administration. The considered subject was classified as non-responding subject, no rise in blood pressure is experienced, instead it decreases. Low lactate level subject, lactate is 1.4 mmol/L before the administration and 1.2 mmol/L after. This is one of the subjects for whom an abnormal behavior occurs. RR power spectra in the LF band are almost after administration. The G12 rises leading to an increase in the work done by the baroreflexes. The autonomic nervous system is certainly influenced by the administration of sedatives and mechanical ventilation. This example is important to underline the complexity of an environment like the intensive care unit. In fact, analyzed signals are often noisy, irregular and influenced by different things.

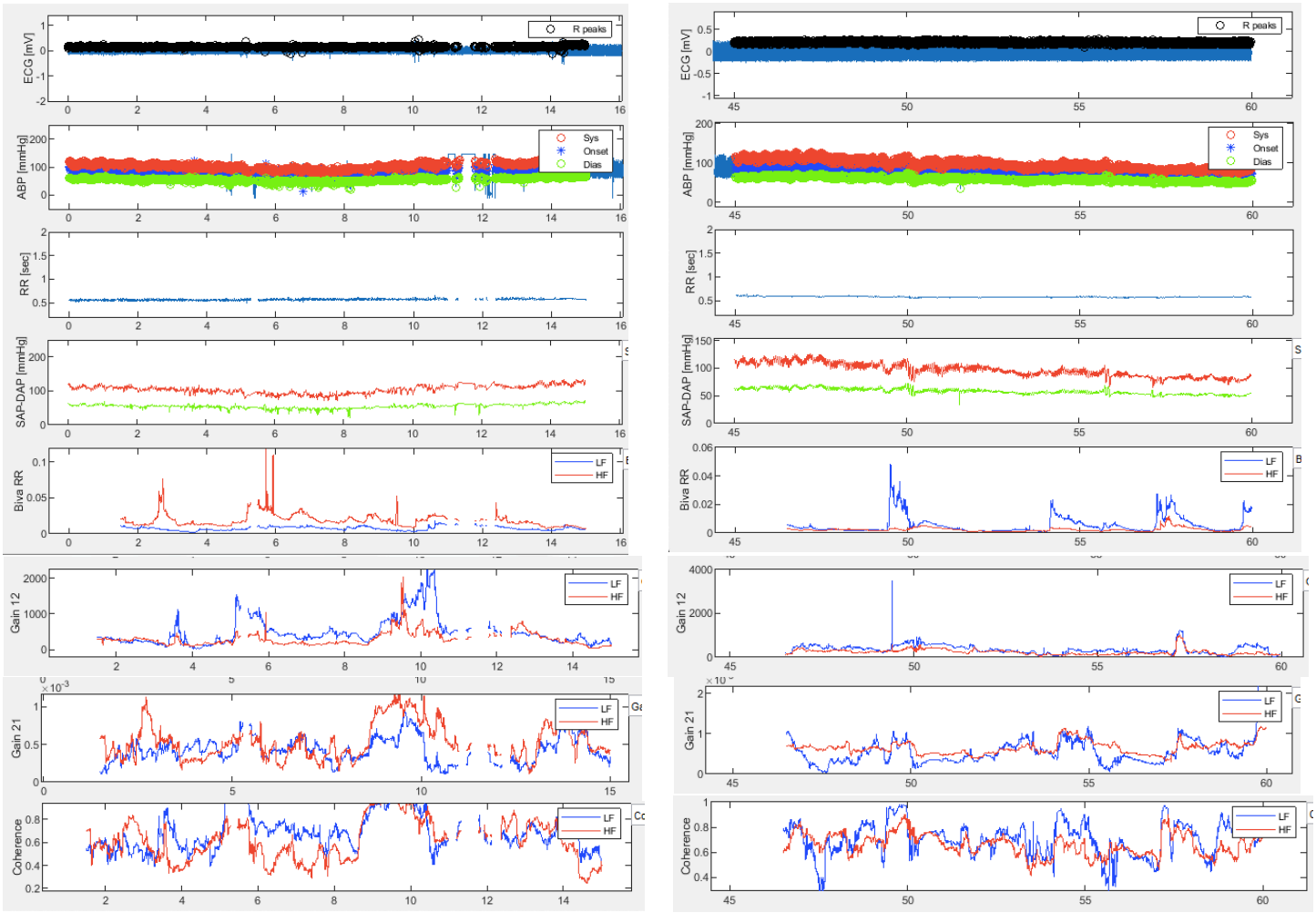


Figure4.5.4Left: ECG,ABP,SAP(red),DAP(green).Then Bivariate. RR spectra, Gain12, Gain21,coherence in blue in the low frequency band, in red high frequency band.For the first 15 minutes beforef administration. Right: ECG,ABP,SAP(red),DAP(green).Then Bivariate. RR spectra, Gain12, Gain21,coherence in blue in the low frequency band, in red high frequency band.For the first 15 minutes after administration.

In this example the two considered windows show respectively 15 minutes before and after the vasopressor administration. Using the toolbox developed at spinLab it is possible to calculate and see the different dynamics in the RR spectra, baroreflex sensitivity, feedforward gain and coherence in both LF and HF range. During the 15 minutes after the vasopressor administration blood pressure, LF power of RR spectrum present higher values while HF decrease. The baroreflex sensitivity is also decreasing while the coherence which already had high values before administration increases still further. Lactate value is high 3 mmol/L before the administration and 3.2 mmol/L 12 hours later.

Chapter 5

Discussions and Conclusions

5.1 Discussions

5.1.1 Characterization Study

Considering the results obtained for non-sedated and non-ventilated subjects, as expected, all the average measures related to the Arterial Blood Pressure (SAP, MAP, DAP, Pulse Pressure) significantly increase after the vasopressor administration and heart rate is decreasing. Thus, we can say that, after the drug starts to be infused, blood pressure tends to be restored. Several temporal indexes accounting for variability were found to be higher after the administration, even if not significantly, higher heart rate variability is a sign of health conditions improvement. Before the administration, the heart was working hard to try to raise blood pressure, so heart rate was high. After the administration, Vasopressor drugs act as vasoconstrictors and blood pressure rises, consequently the heart muscles can relax. It's interesting to notice that, not for all patient heart rates is decreasing, for a few subject heart rates is increasing. In fact, could be one of the reasons for AVNN loss of significance. To the subjects were administered 5 different types of vasopressor which have different effects on the cardiovascular system depending on type and titration. It's worth mentioning that, more than 50% of the patients considered in this study received phenylephrine, a pure α-adrenergic antagonist that cause rise in blood pressure, stimulates baroreceptors by vagal reflex and might lead to bradycardia. Instead Epinephrine infusion for example, tends to increase heart rate.

Significant increase in RRVLF, RRLF, clearly shows a shift upwards in the sympatho-vagal balance after vasopressor administration. A possible interpretation is an increase in the predominance of the sympathetic tone with respect to the vagal tone. In fact, despite the decrease in heart rate, temporal indexes accounting for variability tends to stay high consistent with the imbalance of the system towards the sympathetic.

Looking at the ABP spectra, SS LF are associated to vasomotor tone and systemic vascular resistance, even if not significantly tends to slightly increase after the administration, probably due to the action of the drugs to the vascular resistance. SS HF are associated to mechanical effects of respiration and

vagally mediated changes and is decreasing in the post segment, according to the decrease of the vagal activity.

Moreover, some interesting findings can be appreciated also in time-varying frequency features, generally low values of baroreflex sensitivity, both in low and in high frequency bands. In support to the assumptions made previously, we can hypothesize that G12 is decreasing because the working point of the baroreflex mechanism is repositioned in a lower point. In fact, the rise in blood pressure is due to the action of the vasopressor drug not to the baroreflex mechanism. All these trends confirm that autonomic control of the heart is already compromised right before the administration, baroreflex was not working well, in fact, the cardiovascular system was working too much without results, needing for pharmacological intervention. After it, blood pressure starts to increase, the sympatho-vagal balance moved towards the sympathetic. It is also evident an increase in coherence, for many patients, both in low frequency and high frequency band. Suggesting a loss of linear relationship in the system, which can be attribute to the pathology.

In the end, the analysis of complexity of the heart rate variability shows no significant difference in the measure of Sample Entropy. Anyway, the slight increase in most of the subjects expresses an increase in the information content of the heart rate variability.

Considering the study extended to the entire population of 123 subjects, result related to blood pressure, have maintained almost the same. All the subjects receiving sedatives and/or under mechanical ventilation are very often associated with precautionary vasopressor administrations aimed to avoid or reduce hypotensive side-effects. After the drug infusion, blood pressure tends to rise, the same can't be said for autonomic indices. These interventions strongly influence the autonomic system by not making any more visible the changes in the sympatho-vagal balance. Looking at the spectra obtained from the RR series, subjects behave differently before and after administration. From these results we can affirm that looking at the power spectra, the effect of mechanical ventilation and sedatives is predominant. The time variance indices obtained from the point process model remains significant, Gain12 increases while G21 decreases, confirming what was been obtained in the previous characterization analysis excluding sedated and ventilated patients.

Considering separately responding and non-responding subjects many differences has been found.

It is also noticeable that subjects who experience a decrease in blood pressure already start from a hypertensive condition. In particular, non-responding group shows significantly higher values in SDANN and TRI before the administration, this difference is not significative anymore. These findings do not surprise, because of the general hypotensive condition, which is well known to affect septic shock patient, even if this condition is not always present, as already discussed in the first part of this section.

The quite opposite stands and unexpected behavior of non-responding subjects would suggest the administration of some vasodilator or other vasoactive agents but looking at the different administration in the databases only two subjects have been observed, among 123, to which a vasodilator was administered around the vasopressor onset but one of the two experiences a pressure rise being classified among the responding. Table of subjects receiving other vasoactive agents. By varying the dosage of the administered vasopressor its effect changes, this could therefore be an explanation for the administration of a vasopressor drug in the presence of an already high-pressure value and a consequent decrease. Administered on purpose to hypertensive subjects with the intent to return the pressure to a normal level.

filename	starttime	vasonum	starttime	lbl	lbl2	NR_subjects
p026502-2118-09-25-17-32	25/09/18 22:11	5	25/09/18 22:01	Milrinone	Inotrope	0
p052641-2121-09-08-17-17	10/09/21 16:35	3	10/09/21 12:40	Milrinone	Inotrope	0
p059147-2138-07-18-21-14	18/07/38 21:45	1	18/07/38 21:15	Nitroglycerin	Vasodilator	0
p066654-2118-12-29-04-26	29/12/18 15:00	2	29/12/18 10:16	Nicardipine	Vasodilator	1
p069693-2195-06-25-18-00	25/06/95 19:58	1	25/06/95 19:58	Milrinone	Inotrope	0
p076372-2129-12-26-16-09	26/12/29 16:55	1	26/12/29 16:15	Nitroglycerin	Vasodilator	0
p076410-2181-08-17-17-06	18/08/81 01:00	1	17/08/81 17:16	Milrinone	Inotrope	0
p076410-2181-08-17-17-06	18/08/81 01:00	1	17/08/81 18:41	Nitroglycerin	Vasodilator	0
p080410-2187-04-17-18-42	18/04/87 00:18	2	17/04/87 19:42	Milrinone	Inotrope	0
p085892-2181-08-17-15-55	17/08/81 21:00	1	17/08/81 19:33	Dobutamine	Inotrope	0

Figure 4.1.13 Table representing other vasoactive agents administered to the subjects. only two vasodilators

Looking again at the differences in the pre segment, the population classified as non-responsive starts from a much lower G12, increasing in the post segment, showing again an opposite behavior with respect to the responding subjects that undergoes to a decrease in G12. RR and ABP spectra are still hard to interpret since different subjects shows contrasting trends. In general, responding subjects has a higher HF and LF activation before the vasopressor administration. In the post segment LF remains almost equal for both populations, always lower in non-responding that in responding subjects, while HF decrease much more in responding subjects.

Regarding lactate level subdivision, it is interesting to notice that low level patients experience a much more significative increase in SAP while high level patient in DAP. They showed also different behavior also in the sympatho-vagal balance. Although not significantly, subjects classified as high-level experience an increase in sympatovagal balance moving towards the sympathetic system. In subjects in with normal lactate value, 12 hours after administration, adecrease in the sympato-vagal balance shows a predominance of the vagal activity.

5.1.2 Correlation Study

Serum lactate is a frequently monitored physiological marker in patients with sepsis, however, its importance as a therapeutic target is still a matter of debate. Some studies previously conducted examine the relationship of vasopressin use on serum lactate levels in patients with sepsis. Vasopressin is used in conjunction with norepinephrine during treatment of patients with septic shock. It turns out that patients receiving vasopressin were more likely to have their serum lactate levels rise when compared to matched patients who did not receive vasopressin [58].

In general, Sperman's correlation coefficient indicates a significant slight correlation (pValue <0.05) for several features extracted from waveforms and lactate values considered. Considering the lactate 12 hours after administration rho remains around 0.3, indicating a weak correlation for both pre and post segments; while increase to 0.5, showing a higher correlation considering lactate level before the administration.

Dividing the population between normal and abnormal lactate level, for some features, correlation increase up to 0.6 on subjects with abnormal lactate. From the scatterplot it's possible to see a different behavior according to lactate level.

Temporal indexes accounting for variability that shows a significant sufficiently high correlation coefficient are AVNN, SDNNIX, TRI, SDDD. The correlation turns out to be negative, when the lactate drops time indexes of cardiac variability rises and vice versa. In fact, a decrease in lactate value and an increase in cardiac variability are both signs of an improvement in the patient's health condition.

Looking at the frequency component, power spectra derived from the RR series but also varying indexes extracted with the point process modelling (both cross spectra, gain and coherence) in both LF and HF band results to be slightly correlated.

Moreover, stratifying for responding and non-responding subjects, according to blood pressure response, non-responding population seems to have a higher correlation with lactate level. From

the scatterplot the two population seem to behave in the same way but, fitting the data with linear regression, the different seems to indicate a different trend. We can interpret those results saying that higher lactate level is more correlated with the features extracted from the waveforms around the vasopressor administration. This can be related to the fact that according to literature vasopressor administration tends to increase lactate level. Moreover, higher lactate is associated with worsening condition so there could be a link between some features of waveforms that represent a need for vasopressor and the lactate level, or it could be an explanation considering the major correlation found in non-responding subjects.

The studies cited above shows that no difference was found between the first physiological thresholds identified as lactate or HRV threshold during exercise. Physical activity brings a significant PNS activation with oxygen consumption, increasing blood lactate concentration. The results obtained in this study, confirm, as expected, the existence of a correlation between the features extracted from waveforms and the lactate value even if is not a strong correlation. Probably higher correlation values would probably have been obtained by measuring the lactate value at the time the autonomy indices were calculated, in fact, consider the three-hour window close to administration, all the correlation coefficients increase a little.

Moreover, Shock and infections can cause dilatation of the vessels thus vasopressors are used to constrict those areas, in order to increase blood pressure that can reduce blood flow to the organs, thus vasopressors should be avoided in lactic acidosis, if possible, because they may worsen tissue perfusion and increase lactate production. This could be an explanation for the fact that the extracted indexes are more correlated with the population that has an abnormal lactate or an abnormal response to vasopressor therapy.

5.1.2 Lactate level prediction Study

Logistic regression for feature selection achieved the best results through the Random Forest classifier, reaching AUROC = 084. Thus, showing that, the developed model, was capable of providing very valuable information regarding lactate changes using the features extracted before and after the vasopressor administration.

First, it is nice to see that, for both Random Forest, SVM and xgboost the best combination of features includes the differences between the pre and post segment.

It is interesting to notice that, all three models obtain better results by using the differences between pre and post-administration segments, although they were not significant in the correlation study. One of the most significant features in all three models is the difference in GAIN21LF. During the characterization study, in both cohorts, considering of only 23 patients and including ventilated and sedated patients, Gain21LF is always significant. Comparing the differences in the populations defined as responding and non-responding this variable lost its significance while comparing the differences between high level and low-level population it was significant again. A possible interpretation can be that, the increase in blood pressure brings a sympathetic activation and increase oxygen consumption, which in turn increase blood lactate concentration.

Because to our knowledge there are no other studies trying to predict lactate level by using vasopressor-induced autonomic changes related parameters so there was no possibility of directly comparing our results with studies with a similar set-up.

5.1.3 Summary of findings and innovations

The most innovative aspect that characterize this study is the use of clinical data with indexes extracted from waveforms dealing with a real ICU scenario and not with a prospective cohort.
In addition, there are very few studies in literature that combine the study of blood lactate level with vasopressor administration. Moreover, no one else investigates the link between these two elements using a time-varying model to extract autonomic indices from pressure and electrocardiogram signals. Main achievements obtained through this study can be summarized as follow:

- From the characterization analysis we found that vasopressors might be responsible, not only for an increase in pressure, but also for a parallel increase in the sympathetic-vagal balance.
- From the correlation study was discovered that parameters related to changes in autonomic activity induced by vasopressors are correlated with the level of lactate in the blood
- We can also say that parameters related to changes in autonomic activity induced by vasopressors may be able to provide indications on future lactate level and consequently on the oxygenation status of tissues.

- From the results obtained we observed that it might be a link between activation of the sympathetic system due to vasopressor administration and an increase in lactate value.
- With more precise and especially a higher number of data, it might be possible to develop a model for the prediction of lactate kinetics using the indexes extracted from waveforms.

5.1.4 Limitations

There are several limitations in this study. First, the number of subjects was very low, and the selected waveforms were very noisy. Even with a manual correction of the signals, some extracted indices, especially using the point process model, are affected by noise.

For all tree studies was the very small the number of available subjects. For the characterization part the number of subjects without ventilation and sedative was very low. Regarding the correlation part the number of lactate measures in the considered time windows has further reduced the population. In addition, carrying out a correlation study considering lactate measurements taken in different moments of time for each subject and very often at hours distance from the features considered greatly reduces the possibility of finding a high correlation. Regarding the prediction part the low number of subjects used for training and testing the models was also one of the biggest problems.

Another important limitation is that the timestamps related to the administration of the vasopressors were not quite precise, for this reason a 30-minute hole was left around it. Considering only the other 30 minutes, 15 before and 15 after may lead to a loss of information.

In conclusion, The ICU is for sure the most complex environment in hospital care, there are many sources of noise in the data, the procedure under study does not follow a specific experimental protocol for each patient.

Finally, since all the data considered came from a single-center database (Beth Israel Deaconess Medical Center), the developed models need to be validated on databases from other clinical centers.

5.2 Conclusions

The ICU is a very critical and complex environment in which patients are constantly monitored by continuous acquisition of physiological measures, in fact MIMIC-III furnishes a huge amount of data. In the last years, there has been higher and higher interest in using big data and applying powerful machine learning and artificial intelligence techniques in medicine. The goal of big data analytics is ss I did in this study, to use mathematical algorithms and statistical methods helping physicians and nurses to make more personalized clinical decisions, reducing waste and errors and possibly reducing the cost of care.
This work represents an attempt to apply algorithms and analysis to a real case scenario and not on a prospective cohort combining clinical data with indexes extracted from waveforms.
The main innovations introduced in this study were those of binding autonomy indexes extracted from waveforms, using time models variants to a physiological marker such as lactate.

We have used the acquired ECG and ABP waveform to characterize the physiological changes before, during, and after administration by assessing the variations in the autonomic nervous system action on the heartbeat and blood pressure. In addition, apart from having a confirmation on the drug's success in increasing blood pressure, it has been observed that vasopressor administration could be bring a sympathetic predominance with respect to their baseline autonomic state. However, this information is lost with the introduction of other invasive treatments so those changes should be further investigated. With regard to lactate, although it is still a debated element, it has been seen how, having more data and tools available, we can use lactate level as a marker for the patient's state of health and also try to predict its kinetics.

Although we were not able to find previous studies with a similar set up, the results obtained (AUROC=0.84) are better than other considering either only lactate or only vasopressor administration for mortality prediction. For example, Liu et al [61] compared the prognostic accuracy of the lactate level, the SOFA score and the qSOFA score for mortality prediction in septic patients using the MIMIC III database, obtaining an AUROC of 0.664, using lactate as independent predictor. On the other hand, Vallabhajosyula et al developed a novel mortality prediction model for septic shock incorporating quantitative vasoactive medication usage, and obtained an AUROC of 0.73 [62].

5.2.1 Future steps

The first future step is for certain to try to increase the number of subjects and of available lactate measures. Then reduce the width of the time windows considered and improve the signal quality of the waveforms.

Having more subjects, it would be possible to carry out a correlation study by stratifying for the various treatments and comorbidities obtaining clearer results, coming from cleaner samples, in which only the dynamics of response to vasopressor therapy is captured. Finally, modifications introduced by dose titrations could be interestingly analyzed. Has been seen in addition how, despite the low number of measures, the correlation between lactate and indexes extracted from waveforms increases as the time window considered decreases. So much better results could be obtained by having lactate measurements within the same 15 minutes considered for waveforms.

Having more patients and more lactate measures available would bring not only an improvement in the characterization and correlation study but also in the performance models. More data would not only increase statistical validity but would also solve one of the main problems regarding the prediction part the low number of subjects used for training and testing the models was also one of the biggest problems. Also, prediction study could be repeated using different time window trying to predict lactate level at different moment in time tracking its kinetics.

Also, due to the collinearity of the measures, before the actual feature section process, an iterative multi-collinearity reduction process should be done. Besides, more complex machine learning algorithms might be used to try to have better results entering in the field of Deep Learning and Neural Networks.

As a first future step towards multi-center validation, the models will be externally validated on other databases.

Appendix

Table 5 W.S.R. Test for non-ventilated and non-sedated patient pre Vs post administration (23 subjects)

Name	Delta(median)	h	Pvalue	n° increasing	n°decreasing
AVNN	27,19368858	FALSO	0,05933174	16	7
SDANN	1,38287833	FALSO	0,7842886	10	13
SDNN	31,8990453	FALSO	0,15285977	13	10
SDNNIDX	21,0990239	FALSO	0,12086272	12	11
NN20	109	FALSO	0,1710768	16	7
pNN20	9,6294824	FALSO	0,31552639	14	9
NN50	3	FALSO	0,21939719	12	11
RMSSD	76,518925	FALSO	0,22375715	13	10
logRMSSD	1,89710868	FALSO	0,08297979	13	10
SDSD	76,5518532	FALSO	0,22375715	13	10
SD1	50,2378152	FALSO	0,12832317	14	9
SD2	32,6037589	FALSO	0,15285977	13	10
SD_ratio	0,14238314	FALSO	0,42906726	12	11
SD_prod	4039,56687	FALSO	0,23554997	13	10
TRI	2,06004989	FALSO	0,20145117	14	9
TINN	23,4375	FALSO	0,61330497	10	13
AVSS	14,9131072	VERO	0,0026032	20	3
AVDD	3,77876487	VERO	0,00091568	19	4
AVPP	8,31235008	VERO	0,00890484	19	4
AVPTT	-0,0001474	VERO	0,0480448	7	16
RR_VLF	0,03474423	VERO	0,03325039	18	5
RR_LF	0,08444955	VERO	0,03861964	16	7
RR_HF	0,8586236	FALSO	0,56334236	11	12
RR_LFtoHF	0,07606433	FALSO	0,56334236	12	11
RR_HFnu	0,14774194	FALSO	0,60511832	9	14
RR_LFnu	0,01101809	FALSO	0,85519842	11	12
SS_VLF	-2962,3643	FALSO	0,54298914	9	14
SS_LF	-396,77265	FALSO	0,90316844	11	12
SS_HF	-804,37937	FALSO	0,54298914	8	15
SS_spect_slope	0,16430628	FALSO	0,41153023	13	10
DD_TOTPWR	1366,32972	FALSO	0,85519842	13	10
DD_VLF	-28,134732	FALSO	0,97573612	11	12
DD_LF	-132,95967	FALSO	0,64822869	10	13
DD_HF	210,051559	FALSO	0,97573612	12	11
Gain21TOT_Avg	0,00081481	VERO	0,03861964	14	9

Gain21TOT_Med	0,00076158	FALSO	0,08297979	13	10
Gain21TOT_Std	0,00033291	VERO	0,01375452	18	5
Gain12TOT_Med	-69,805122	FALSO	0,15285977	9	14
Gain12TOT_Std	-7,0883622	FALSO	0,13613678	10	13
Gain12TOT_Slope	-0,0052908	VERO	0,0480448	10	13
bivaCRTOT_Std	1952,69445	VERO	0,02080324	16	7
GAIN21LF_Std	0,00066921	VERO	0,00424971	18	5
GAIN21LFn_Slope	-5,174E-05	VERO	0,01767456	7	16
GAIN21HF_Avg	0,00058016	VERO	0,0480448	15	8
GAIN21HF_Std	0,0002397	VERO	0,01062317	17	6
GAIN21LFtoHF_Slope	-0,0002925	VERO	0,00424971	7	16
GAIN21LFntoHFn_Slope	-0,0002925	VERO	0,00424971	7	16
GAIN12HF_Slope	-0,0061975	VERO	0,0480448	8	15
CohLF_Slope	-1,225E-05	VERO	0,02254126	7	16
CohTOT_Std	0,01132959	VERO	0,03861964	14	9
CohTOT_Med	0,03621391	FALSO	0,39442576	13	10
bivaCRTOT_Med	22,9980189	FALSO	0,60511832	12	11
H	-0,000202	FALSO	0,07772065	8	15
SampEn	0,11198615	FALSO	0,76101397	12	11

Table 2 W.S.R Test for non-ventilated, non-sedated responding patient pre Vs post administration (20 subjects)

Name	Delta (median)	h	pValue	N increasing	N decreasing
AVNN	26,90343807	FALSO	0,15600358	13	7
SDANN	0,73885085	FALSO	0,39053287	10	10
SDNN	45,3559578	FALSO	0,10045796	11	9
SDNNIDX	39,9196122	FALSO	0,12585852	10	10
NN20	233	VERO	0,03332485	16	4
pNN20	29,442832	FALSO	0,06195279	14	6
NN50	151	FALSO	0,07848091	12	8
RMSSD	85,5330533	FALSO	0,39053287	11	9
logRMSSD	1,88115272	FALSO	0,14539978	11	9
SDSD	85,5749173	FALSO	0,39053287	11	9
SD1	54,1185627	FALSO	0,2471446	12	8
SD2	35,9243003	FALSO	0,10842674	11	9
TRI	2,75276044	FALSO	0,07313807	13	7
TINN	50,78125	FALSO	0,44268698	10	10
AVSS	16,6517317	VERO	8,8575E-05	20	0
AVDD	6,80479233	VERO	0,00021908	18	2
SDDD	0,56230021	FALSO	0,20433025	12	8
AVPP	15,5351039	VERO	0,00033845	18	2
SDPP	0,08597389	FALSO	0,37026127	11	9

AVPTT	0,00249795	FALSO	0,06195279	6	14
SDPTT	-0,0016145	FALSO	0,91082499	11	9
RR_TOTPWR	1,0707532	FALSO	0,1353569	13	7
RR_VLF	0,03591625	FALSO	0,08592386	15	5
RR_LF	0,27380722	VERO	0,0400438	14	6
RR_HF	0,83549222	FALSO	0,65415894	9	11
RR_LFtoHF	0,08054292	FALSO	0,57548623	11	9
RR_HFnu	0,11118427	FALSO	0,55029194	8	12
RR_LFnu	0,01224764	FALSO	0,91082499	10	10
SS_TOTPWR	-3407,683	FALSO	0,65415894	6	14
SS_VLF	2536,58717	FALSO	0,88129271	8	12
SS_LF	464,386151	FALSO	0,57548623	10	10
SS_HF	-476,64964	FALSO	0,97021976	8	12
DD_TOTPWR	2437,18483	FALSO	0,73687537	12	8
DD_VLF	433,90163	FALSO	0,60121271	10	10
DD_LF	30,4371581	FALSO	0,97021976	9	11
DD_HF	-42,612144	FALSO	0,76519844	11	9
H	-0,0003215	VERO	0,03656129	7	13
SampEn	0,20250315	FALSO	0,57548623	11	9
bivaRRVLF_Slope	-1,041E-05	VERO	0,0400438	6	14
bivaRRLF_Std	0,11318219	VERO	0,03334022	13	7
bivaCRLF_Std	-3,6616649	VERO	0,01237422	15	5
Gain12TOT_Med	-30,079963	FALSO	0,1353569	8	12
Gain21TOT_Med	0,00037337	FALSO	0,20433025	11	9
GAIN21LF_Std	0,00049257	VERO	0,01237422	15	5
GAIN21LFn_Slope	-0,0001306	VERO	0,01524006	6	14
GAIN21HF_Std	0,0002389	VERO	0,03334022	14	6
Gain21TOT_Std	0,00028611	VERO	0,04380372	15	5
GAIN21LFtoHF_Slope	-0,0007285	VERO	0,00171302	5	15
GAIN21LFntoHFn_Slope	-0,0007285	VERO	0,00171302	5	15
CohHF_Std	0,01289413	VERO	0,04785751	12	8
CohTOT_Std	0,01695785	VERO	0,01237422	14	6

Table 3 W.S.R Test including ventilated, sedated patient pre Vs post administration (123 subjects)

Name	Delta (median)	h	pValue	N increasing	N decreasing
AVNN	18,63541569	VERO	0,00195503	81	42
SDANN	-0,0395936	FALSO	0,34004231	64	59
SDNN	-4,50136	FALSO	0,99194461	62	61
SDNNIDX	-3,5344408	FALSO	0,9215853	65	58
NN20	-3	FALSO	0,45531623	57	66
pNN20	-0,4653022	FALSO	0,32953543	60	63

NN50	-2	FALSO	0,48760403	49	74
RMSSD	-1,6968883	FALSO	0,68447215	62	61
logRMSSD	-0,1508831	FALSO	0,6261613	62	61
SDSD	-1,6984054	FALSO	0,68447215	62	61
SD1	-1,2073871	FALSO	0,89557808	64	59
SD2	-7,3732443	FALSO	0,94566727	64	59
TRI	0,12489218	FALSO	0,09424289	68	55
TINN	0	FALSO	0,16101072	56	67
AVSS	8,35294959	VERO	1,053E-06	88	35
AVDD	4,74164749	VERO	3,1881E-05	87	36
SDDD	-0,2659668	FALSO	0,3648696	58	65
AVPP	4,83825729	VERO	2,2568E-05	89	34
SDPP	0,08056658	FALSO	0,49396827	58	65
AVPTT	-0,006376	VERO	0,00068675	43	80
SDPTT	-0,0007939	FALSO	0,13315001	56	67
RR_TOTPWR	-0,0991873	FALSO	0,69936639	66	57
RR_VLF	-0,0207381	FALSO	0,56156004	69	54
RR_LF	-0,0133136	FALSO	0,95571738	60	63
RR_HF	-0,0094955	FALSO	0,90756919	64	59
RR_LFtoHF	0,03239447	FALSO	0,85975835	59	64
RR_HFnu	-0,0781461	FALSO	0,73900493	60	63
RR_LFnu	-0,0378011	FALSO	0,36220411	55	68
SS_TOTPWR	-2075,937	FALSO	0,82226069	61	62
SS_VLF	-45,922534	FALSO	0,86174148	59	64
SS_LF	185,389165	FALSO	0,38801831	61	62
SS_HF	775,080353	FALSO	0,79099199	59	64
bivaRRHF_Slope	-1,562E-07	VERO	0,00769034	52	71
bivaRRTOT_Avg	0,74434823	VERO	0,00621828	79	44
bivaRRTOT_Std	3,9393081	VERO	0,02357098	76	47
bivaRRTOT_Slope	-9,587E-08	VERO	0,03731315	54	69
bivaBPHF_Slope	-0,2027072	VERO	0,00327694	43	80
bivaBPHFn_Std	0,00483112	VERO	0,00707835	73	50
bivaBPHFn_Slope	-9,051E-06	VERO	0,01571395	52	71
bivaCRLFn_Slope	3,1596E-07	VERO	0,04726876	56	67
bivaCRHF_Slope	-0,0001145	VERO	0,00059212	41	82
bivaCRHFn_Std	0,01296884	VERO	0,01376075	78	45
bivaCRTOT_Avg	113,100548	VERO	0,01718712	76	47
bivaCRTOT_Std	502,651853	VERO	0,04898296	73	50
bivaCRTOT_Slope	-0,003231	VERO	0,03420409	49	74
GAIN21LF_Std	0,00016119	VERO	0,00338533	79	44
GAIN21LF_Slope	-4,422E-08	VERO	0,00093631	49	74
GAIN21LFn_Slope	-3,127E-05	VERO	0,00147137	47	76

GAIN21HF_Avg	0,00042727	VERO	0,00016767	77	46
GAIN21HF_Med	0,00022395	VERO	0,00051942	77	46
GAIN21HF_Std	0,00024305	VERO	1,1912E-05	85	38
Gain21TOT_Avg	0,00038053	VERO	0,00160481	75	48
Gain21TOT_Med	0,00026204	VERO	0,00205729	75	48
Gain21TOT_Std	0,00012601	VERO	0,00102433	76	47
GAIN21LFtoHF_Slope	-3,449E-05	VERO	0,00088691	48	75
GAIN21LFntoHFn_Slope	-3,449E-05	VERO	0,00088691	48	75
GAIN12LF_Slope	-0,0038579	VERO	0,01033514	53	70
GAIN12HF_Slope	-0,0030581	VERO	0,01649278	54	69
Gain12TOT_Med	-6,800947	FALSO	0,1752896	54	69
Gain12TOT_Slope	-0,0044094	VERO	0,00967801	51	72
GAIN12LFtoHF_Slope	-1,048E-05	VERO	0,03191914	57	66
CohLF_Slope	-6,159E-06	VERO	0,02828014	49	74
CohTOT_Med	-0,0278279	FALSO	0,52638733	63	60
H	6,3113E-06	FALSO	0,3648696	58	65
SampEn	-0,0873504	FALSO	0,32617575	64	59

Table 4 W.S.R Test for responding (according to pressure) patient pre Vs post administration (88 subjects)

name	Delta(median)	h	pValue	N increasing	N decreasing
AVNN	10,15173416	VERO	0,01442175	57	31
SDANN	0,514495849	FALSO	0,05250636	52	36
SDNN	-5,795270672	FALSO	0,73923358	44	44
SDNNIDX	-3,458612349	FALSO	0,86781524	45	43
NN20	0	FALSO	0,2190925	41	47
pNN20	-0,275534517	FALSO	0,35908651	42	46
NN50	-2	FALSO	0,27388847	36	52
RMSSD	-5,531799345	FALSO	0,46652193	41	47
logRMSSD	-0,416576595	FALSO	0,3406732	41	47
SDSD	-5,538523317	FALSO	0,46652193	41	47
SD1	-3,916344537	FALSO	0,66521167	43	45
SD2	-6,661320978	FALSO	0,59720185	47	41
SD_ratio	-0,099627174	FALSO	0,26838577	38	50
SD_prod	-83,32267219	FALSO	0,96349404	43	45
TRI	0,572484884	VERO	0,02163062	50	38
TINN	11,71875	FALSO	0,05943509	44	44
AVSS	19,08642669	VERO	3,732E-16	88	0
AVDD	6,103157939	VERO	2,2771E-13	79	9
SDDD	-0,03515984	FALSO	0,96017796	46	42
AVPP	13,33610541	VERO	9,4815E-14	80	8
SDPP	0,009765439	FALSO	0,80607668	42	46

AVPTT	-0,009498904	VERO	9,5958E-08	19	69
SDPTT	-0,001333995	FALSO	0,10113474	39	49
RR_TOTPWR	-0,066843332	FALSO	0,68650468	46	42
RR_VLF	-0,017731821	FALSO	0,37997599	50	38
RR_LF	-0,025848227	FALSO	0,71114694	46	42
RR_HF	-0,020021006	FALSO	0,72046786	43	45
RR_LFtoHF	0,046625457	FALSO	0,74237671	46	42
RR_HFnu	-0,102761054	FALSO	0,46397902	40	48
RR_LFnu	-0,031211588	FALSO	0,3687886	41	47
RR_spect_slope	-0,21422929	FALSO	0,10643809	34	54
SS_TOTPWR	841,6620783	FALSO	0,23241321	49	39
SS_VLF	-551,7550086	FALSO	0,34490693	47	41
SS_LF	352,9850996	FALSO	0,19854625	46	42
SS_HF	720,9500356	FALSO	0,59720185	43	45
H	8,90278E-06	FALSO	0,40531236	45	43
SampEn	-0,078734642	FALSO	0,23898716	49	39
CohTOT_Med	-0,035290713	FALSO	0,95686256	46	42
Gain21TOT_Med	0,000461315	VERO	0,00573064	56	32
Gain12TOT_Med	-38,10034555	FALSO	0,10027167	39	49
bivaCRTOT_Med	-11,98354673	FALSO	0,67126882	47	41
bivaRRHF_Slope	-6,70208E-08	VERO	0,0356206	38	50
bivaRRTOT_Avg	0,418473117	VERO	0,02116019	59	29
bivaRRLFtoHF_Slope	-1,42213E-05	VERO	0,04230599	35	53
bivaRRLFntoHFn_Slope	-1,42213E-05	VERO	0,04230599	35	53
bivaBPHF_Slope	-0,25588843	VERO	0,00897467	30	58
bivaBPHFn_Std	0,007130784	VERO	0,0321259	52	36
bivaBPHFn_Slope	-1,04916E-05	VERO	0,02259886	36	52
bivaCRLFn_Slope	-3,37114E-06	VERO	0,02954573	36	52
bivaCRHF_Slope	-8,2435E-05	VERO	0,0014573	28	60
bivaCRHFn_Std	0,011538147	VERO	0,04625599	55	33
bivaCRTOT_Avg	110,0266365	VERO	0,0435897	55	33
GAIN21LF_Avg	0,000477833	VERO	0,04490616	53	35
GAIN21LF_Std	0,000181517	VERO	0,00210593	59	29
GAIN21LF_Slope	-4,77914E-08	VERO	0,00158807	34	54
GAIN21LFn_Slope	-2,02823E-05	VERO	0,00746334	35	53
GAIN21HF_Avg	0,000508547	VERO	0,00085963	58	30
GAIN21HF_Med	0,000268868	VERO	0,00241924	58	30
GAIN21HF_Std	0,000392639	VERO	0,00017759	60	28
Gain21TOT_Avg	0,000456103	VERO	0,00301024	56	32
Gain21TOT_Med	0,000461315	VERO	0,00573064	56	32
Gain21TOT_Std	6,16603E-05	VERO	0,00595361	53	35
GAIN21LFtoHF_Slope	-2,96517E-05	VERO	0,00113877	33	55

GAIN21LFntoHFn_Slope	-2,79521E-05	VERO	0,00113877	33	55
GAIN12HFn_Std	0,008768721	VERO	0,01510134	51	37
GAIN12HFn_Slope	-2,04269E-05	VERO	0,00683957	34	54

Table 5 W.S.R Test for non-responding (according to pressure) patient pre Vs post administration (35 subjects)

name	Delta(median)	H	pvalue	N increase	N decrease
VNN	12,2463889	FALSO	0,05531932	24	11
SDANN	-6,3561504	FALSO	0,27246545	12	23
SDNN	-5,8633733	FALSO	0,62316175	18	17
SDNNIDX	-0,8146543	FALSO	0,88280661	20	15
NN20	-5	FALSO	0,52694584	16	19
pNN20	-0,3562689	FALSO	0,55530478	18	17
NN50	0	FALSO	0,61106454	13	22
RMSSD	0,19876827	FALSO	0,54449597	21	14
logRMSSD	0,0205068	FALSO	0,54449597	21	14
SDSD	0,1988287	FALSO	0,54449597	21	14
SD1	-0,0574661	FALSO	0,54449597	21	14
SD2	-8,1680281	FALSO	0,51236106	17	18
SD_ratio	0,04748493	FALSO	0,88280661	16	19
SD_prod	-70,341835	FALSO	0,74322708	19	16
TRI	-1,2412046	FALSO	0,58884418	18	17
TINN	-15,625	FALSO	0,68032295	12	23
AVSS	-8,8538265	VERO	2,477E-07	0	35
AVDD	-4,1917374	VERO	0,00093768	8	27
SDDD	-0,7068833	FALSO	0,13184112	12	23
AVPP	-8,1285993	VERO	0,00013545	9	26
SDPP	0,73879482	FALSO	0,41281086	16	19
AVPTT	0,01081936	VERO	0,0248361	24	11
SDPTT	0,00060696	FALSO	0,79327034	17	18
RR_TOTPWR	-0,0564848	FALSO	0,74322708	20	15
RR_VLF	-0,0365231	FALSO	0,83138245	19	16
RR_LF	-0,0051965	FALSO	0,45118521	14	21
RR_HF	-0,0029059	FALSO	0,52296178	21	14
RR_LFtoHF	0,07436663	FALSO	0,29451646	13	22
RR_HFnu	0,08188392	FALSO	0,56646189	20	15
RR_LFnu	0,00073585	FALSO	0,85701866	14	21
RR_spect_slope	0,03045379	FALSO	0,76812789	17	18
SS_TOTPWR	-9174,795	FALSO	0,16886869	12	23
SS_VLF	-3350,5516	FALSO	0,10490292	12	23
SS_LF	-344,54013	FALSO	0,74322708	15	20

SS_HF	29,3874707	FALSO	0,68218849	16	19
bivaRRTOT_Slope	-1,786E-05	VERO	0,00088429	9	26
bivaBPTOT_Slope	-2,3468428	VERO	0,01466726	12	23
bivaCRLFn_Std	0,01385351	VERO	0,04568897	26	9
bivaCRTOT_Slope	-0,051955	VERO	0,00031407	8	27
GAIN21LFn_Avg	-0,0565089	VERO	0,04749309	13	22
Gain12TOT_Med	1,52577612	FALSO	0,97386734	15	20
Gain21TOT_Med	0,0002411	FALSO	0,16385362	19	16
GAIN21HF_Std	4,6563E-05	VERO	0,02002718	25	10
GAIN12LF_Slope	-0,0056097	VERO	0,04394295	12	23
Gain12TOT_Slope	-0,0071048	VERO	0,01278762	10	25
GAIN12LFtoHF_Slope	-8,703E-05	VERO	0,04935672	14	21
GAIN12LFntoHFn_Slope	-8,703E-05	VERO	0,04935672	14	21
CohLF_Slope	-1,357E-05	VERO	0,01916954	11	24
H	-7,486E-05	FALSO	0,63479043	13	22
SampEn	-0,1119978	FALSO	0,88280661	15	20
bivaCRTOT_Med	1,00163757	FALSO	0,53367399	17	18

Table 6 W.S.R Test Low lactate patients pre VS post administration (48 subjects)

Name	Delta(median)	H	PValue	N increase	N decrease
AVNN	33,76504459	FALSO	0,136962249	33	15
SDANN	3,159884834	VERO	0,024692264	24	24
SDNN	-5,351138269	FALSO	0,69672237	26	22
SDNNIDX	-6,318456495	FALSO	0,727297625	27	21
NN20	-18,5	FALSO	0,887769622	22	26
pNN20	-1,9416934	FALSO	0,960788456	23	25
NN50	-2	FALSO	0,77722711	20	28
RMSSD	-1,949368656	FALSO	0,674106827	25	23
logRMSSD	-0,202421284	FALSO	0,829465256	25	23
SDSD	-1,951052465	FALSO	0,674106827	25	23
SD1	-1,662946006	FALSO	0,622497267	26	22
SD2	-7,656882211	FALSO	0,572679285	28	20
SD_ratio	0,003389593	FALSO	0,674106827	21	27
SD_prod	-99,44906924	FALSO	0,821478322	26	22
TRI	0,192089602	VERO	0,026036274	26	22
TINN	0	FALSO	0,080321422	21	27
AVSS	5,621247982	VERO	0,01832399	33	15
AVDD	1,537090599	FALSO	0,259227035	30	18
SDDD	-0,185350542	FALSO	0,861581552	30	18
AVPP	5,019232628	VERO	0,020450452	32	16

SDPP	0,893500679	FALSO	0,89392838	27	21
AVPTT	-0,005205422	FALSO	0,126456628	17	31
SDPTT	-0,000931576	FALSO	0,491963936	23	25
RR_TOTPWR	-0,085914444	FALSO	1	27	21
RR_VLF	-0,028645242	FALSO	0,644407981	28	20
RR_LF	-0,020228615	FALSO	0,821478322	22	26
RR_HF	-0,01031704	FALSO	0,789723121	28	20
RR_LFtoHF	-0,038405848	FALSO	0,934605076	20	28
RR_HFnu	-0,042783965	FALSO	0,918307864	24	24
RR_LFnu	-0,041140149	FALSO	0,447861925	20	28
RR_spect_slope	-0,084279595	FALSO	0,447861925	22	26
SS_TOTPWR	2309,234118	FALSO	0,372221745	31	17
SS_VLF	326,2404035	FALSO	0,967275024	27	21
SS_LF	284,1822217	FALSO	0,355960795	28	20
SS_HF	1002,764122	FALSO	0,148128723	27	21
DD_TOTPWR	34,52801163	FALSO	0,98363407	29	19
DD_VLF	141,8418544	FALSO	0,704322418	28	20
DD_LF	-256,1019001	FALSO	0,441750324	26	22
DD_HF	43,70545681	FALSO	0,861581552	29	19
H	1,22668E-05	FALSO	0,98363407	25	23
SampEn	-0,051833402	FALSO	0,286116048	28	20
bivaCRLF_Med	-0,332612589	FALSO	0,166164535	26	22
bivaCRTOT_Med	-16,77381451	FALSO	0,674106827	25	23
Gain21TOT_Med	-0,000215679	FALSO	0,196244727	29	19
Gain12TOT_Med	1,258081894	FALSO	0,26798843	21	27
CohTOT_Med	0,034431842	FALSO	0,666632055	24	24
PP_spect_slope	-0,187111076	VERO	0,043327469	19	29
bivaRRLFtoHF_Slope	-2,11919E-05	VERO	0,013833008	20	28
bivaRRLFntoHFn_Slope	-2,11919E-05	VERO	0,013833008	20	28
bivaCRTOT_Avg	133,097108	VERO	0,045497424	34	14
GAIN21LF_Slope	-1,52202E-07	VERO	0,001325971	20	28
GAIN21LFn_Slope	-3,44846E-05	VERO	0,012690433	18	30
GAIN21LFtoHF_Slope	-4,69685E-05	VERO	0,015065478	19	29
GAIN21LFntoHFn_Slope	-4,69685E-05	VERO	0,015065478	19	29
CohLF_Slope	-1,02128E-05	VERO	0,012690433	16	32

Table 7 W.S.R Test High lactate patients pre VS post administration (48 subjects)

Name	Delta(median)	H	pValue	N increasing	N decreasing
VNN	35,4287101	FALSO	0,65800879	33	15
SDANN	1,59371638	FALSO	0,74750008	24	24
SDNN	-8,9013591	FALSO	0,74750008	26	22

SDNNIDX	-4,432873	FALSO	0,60087101	27	21
NN20	8	FALSO	0,71729044	22	26
pNN20	0,79545133	FALSO	0,71738089	23	25
NN50	3	FALSO	0,83618164	20	28
RMSSD	-5,8759285	FALSO	0,25983505	25	23
logRMSSD	-0,4250186	FALSO	0,33413808	25	23
SDSD	-5,8777963	FALSO	0,25983505	25	23
SD1	-4,9678023	FALSO	0,4445089	26	22
SD2	-7,7077097	FALSO	0,87211803	28	20
SD_ratio	-0,1378279	FALSO	0,18418075	21	27
SD_prod	-68,927559	FALSO	0,42090992	26	22
TRI	-0,182152	FALSO	0,49390123	26	22
TINN	0	FALSO	0,62445068	21	27
AVSS	10,3416646	FALSO	0,05340584	33	15
AVDD	6,29901087	VERO	0,02687559	30	18
SDDD	0,44136404	FALSO	0,24320097	30	18
AVPP	-3,5999239	FALSO	0,27724064	32	16
SDPP	-0,1269357	FALSO	0,84053366	27	21
AVPTT	-0,0125961	VERO	0,01575549	17	31
SDPTT	-0,0006286	FALSO	0,51965655	23	25
RR_TOTPWR	-0,0718538	FALSO	0,51965655	27	21
RR_VLF	-0,0977618	FALSO	0,65800879	28	20
RR_LF	-0,0034705	FALSO	0,29542406	22	26
RR_HF	0,00070897	FALSO	0,57316897	28	20
RR_LFtoHF	0,47754758	FALSO	0,74750008	20	28
RR_HFnu	-0,1359171	FALSO	0,39806293	24	24
RR_LFnu	0,02946865	FALSO	0,33413808	20	28
RR_spect_slope	0,18454634	FALSO	0,90390763	22	26
SS_TOTPWR	3171,80109	FALSO	0,25983505	31	17
SS_VLF	450,597835	FALSO	0,39806293	27	21
SS_LF	-3,3170878	FALSO	0,13649771	28	20
SS_HF	1385,4481	VERO	0,0486248	27	21
SS_spect_slope	0,0192372	FALSO	1	20	28
DD_VLF	1129,83398	FALSO	0,11654426	28	20
DD_LF	435,269274	FALSO	0,13649771	26	22
DD_HF	789,454886	FALSO	0,09895737	29	19
H	3,5822E-05	FALSO	0,96790005	25	23
SampEn	0,02829287	FALSO	0,80920397	28	20
bivaCRTOT_Med	0,48613041	FALSO	0,68737362	25	23
Gain21TOT_Med	0,00038171	FALSO	0,25983505	29	19
Gain12TOT_Med	48,9104012	FALSO	0,57316897	21	27
CohTOT_Med	-0,0419794	FALSO	0,49390123	24	24

bivaRRLFn_Std	0,02384344	VERO	0,01575549	25	23
GAIN21LF_Std	0,00016295	VERO	0,0175828	31	17
GAIN21HF_Std	0,0001954	VERO	0,01959328	36	12
GAIN12HF_Slope	-0,0134825	VERO	0,0486248	21	27
CohHF_Std	0,01439769	VERO	0,04420844	29	19
CohTOT_Std	0,00928294	VERO	0,04420844	26	22

Table 8 W.R.S. Test responding VS non-responding population before administration

Name	Delta(median)	H	P
AVNN	52,3693071	FALSO	0,29068844
SDANN	7,67568957	VERO	0,00485199
SDNN	-4,239808	FALSO	0,74721871
SDNNIDX	-4,4826386	FALSO	0,41153978
NN20	-11	FALSO	0,23760825
pNN20	-0,9726588	FALSO	0,27648807
NN50	-1	FALSO	0,16395333
RMSSD	-6,6423572	FALSO	0,21232593
logRMSSD	-0,5257563	FALSO	0,21232593
SDSD	-6,6492599	FALSO	0,21232593
SD1	-4,7017356	FALSO	0,29325528
AVSS	12,3179749	VERO	8,4494E-06
AVDD	10,3476768	VERO	0,00022823
SDDD	1,63411055	VERO	0,03293753
AVPP	6,92642063	VERO	0,010168
RR_HF	-0,0247191	FALSO	0,20622596
RR_LFtoHF	0,03940509	FALSO	0,91296078
RR_HFnu	-0,1720808	FALSO	0,21027829
RR_LFnu	-0,0747966	FALSO	0,08995693
RR_spect_slope	-0,5873173	VERO	0,00310816
SS_TOTPWR	8381,89798	FALSO	0,17762882
SS_VLF	5815,26378	FALSO	0,19248979
SS_LF	367,203887	FALSO	0,82041009
SS_HF	-175,38415	FALSO	0,84227002
SS_spect_slope	-0,1069792	FALSO	0,43754591
DD_TOTPWR	3766,35406	FALSO	0,08376307
DD_VLF	2150,58001	FALSO	0,10344847
DD_LF	305,689871	FALSO	0,37731945
DD_HF	105,041241	FALSO	0,5770257
H	2,7818E-05	FALSO	0,42442641
SampEn	-0,0723274	FALSO	0,25399764
bivaCRTOT_Med	-20,701293	FALSO	0,24478299

Gain21TOT_Med	-0,0006286	FALSO	0,26826759
Gain12TOT_Med	32,5303871	FALSO	0,28057254
CohTOT_Med	-0,0427024	FALSO	0,60020742
CohLF_Med	-0,0709198	FALSO	0,9307643

Table 9 W.R.S. Test responding VS non-responding population after administration

Name	Delta(median)	H	PValue
AVNN	54,4639618	FALSO	0,12945537
SDANN	0,805043327	FALSO	0,94414022
SDNN	-4,307910657	FALSO	0,43424433
SDNNIDX	-1,838680527	FALSO	0,40835477
AVSS	-15,62227831	VERO	2,266E-06
NN20	-16	FALSO	0,44026717
RR_VLF	-0,025610702	FALSO	0,692711
RR_LF	-0,01999558	FALSO	0,19440984
RR_HF	-0,007604007	FALSO	0,35066799
RR_LFtoHF	0,067146265	FALSO	0,692711
RR_HFnu	0,012564131	FALSO	0,7771222
RR_LFnu	-0,042849197	FALSO	0,17762882
RR_spect_slope	-0,342634175	VERO	0,0168167
SS_TOTPWR	-1634,559123	FALSO	0,87749326
SS_VLF	3016,467161	FALSO	0,96199864
SS_LF	-330,3213444	FALSO	0,79436259
SS_HF	-866,9467183	FALSO	0,692711
SS_spect_slope	-0,167104289	FALSO	0,84665721
DD_TOTPWR	3257,631289	FALSO	0,32800639
DD_VLF	822,2496494	FALSO	0,38647374
DD_LF	107,9210621	FALSO	0,70932914
DD_HF	272,6110236	FALSO	0,20824498
H	-5,59407E-05	FALSO	0,33078595
SampEn	-0,105590575	FALSO	0,31164823
bivaCRHF_Med	0,962749628	FALSO	0,5770257
Gain21TOT_Med	-0,000848792	FALSO	0,55052601
Gain12TOT_Med	72,15650876	FALSO	0,08177689
CohTOT_Med	0,080884883	FALSO	0,49229824
RR_spect_slope	-0,342634175	VERO	0,0168167
bivaBPTOT_Slope	-2,771096927	VERO	0,03293753
bivaCRTOT_Slope	-0,05019362	VERO	0,04945096
GAIN21LF_Slope	5,35707E-08	VERO	0,04816683
GAIN12LF_Med	104,6547978	VERO	0,03940101

GAIN12LF_Std	32,40266569	VERO	0,03293753

Table 10 W.R.S. Test of difference (post -pre) in responding VS non-responding population

Name	medianNR	medianR	h	pValue
AVNN	13,10527597	12,21454229	FALSO	0,759990882
SDANN	-2,19646844	1,621338044	VERO	0,048805353
SDNN	0,778164679	0,021080168	FALSO	0,619841213
SDNNIDX	1,206564283	0,14435256	FALSO	0,966466581
NN20	-1	0	FALSO	0,265738454
pNN20	0,162335116	0	FALSO	0,91517925
NN50	0	0	FALSO	0,452880232
RMSSD	0,633154816	-0,625822601	FALSO	0,481760306
logRMSSD	0,065005276	-0,013965154	FALSO	0,374297973
SDSD	0,631124197	-0,626040337	FALSO	0,481760306
SD1	0,446236416	-0,079279962	FALSO	0,588563844
SD2	-1,5138815	0,313140689	FALSO	0,440861876
SD_ratio	-0,010899333	-0,025222417	FALSO	0,655866663
SD_prod	5,997330411	-3,740050646	FALSO	0,713505752
TRI	0,026915114	0,341948252	FALSO	0,110773014
TINN	0	3,90625	FALSO	0,169981005
AVSS	-8,278198997	12,19591164	VERO	6,1637E-18
AVDD	-4,796321013	5,502361562	VERO	4,10257E-11
RR_VLF	0,001584067	0,001858175	FALSO	0,481760306
RR_LF	-0,000356351	3,78017E-05	FALSO	0,417953842
RR_HF	0,000708971	-1,89182E-05	FALSO	0,546789815
RR_LFtoHF	-0,03346958	0,00726011	FALSO	0,362362339
RR_HFnu	0,011569162	-0,005831086	FALSO	0,39265125
RR_LFnu	-0,031187343	-0,004584656	FALSO	0,899636252
RR_spect_slope	-0,036764029	-0,087428455	FALSO	0,6885791
SS_TOTPWR	-2184,30518	665,8390394	FALSO	0,067226931
SS_VLF	-1540,490458	117,0111844	FALSO	0,052105473
SS_LF	-14,39746525	70,52285494	FALSO	0,481760306
SS_HF	-85,48589627	-15,40571338	FALSO	0,584705968
SS_spect_slope	-0,000846464	-0,046456655	FALSO	0,655866663
DD_TOTPWR	-864,0558865	498,1580408	FALSO	0,144235295
DD_VLF	-367,2160018	58,25494308	FALSO	0,104641761
DD_LF	-99,07598213	-0,882678517	FALSO	0,308975081
DD_HF	-28,2472522	37,80487912	FALSO	0,953066483
DD_spect_slope	0,028164785	-0,036844201	FALSO	0,235805538
H	-4,6339E-05	4,11629E-06	FALSO	0,855445719
SampEn	-0,026131687	0,0169568	FALSO	0,47480377

Gain21TOT_Med	0,000176107	0,000182076	FALSO	0,608027208
Gain12TOT_Med	-8,05314913	-11,73332261	FALSO	0,306317137

Table 11 W.R.S. Test of difference (post -pre) in high lactate VS low lactate population

Name	delta(mean)	H	pValue
AVNN	35,42871011	FALSO	0,658008785
SDANN	1,593716382	FALSO	0,747500078
SDNN	-8,901359097	FALSO	0,747500078
SDNNIDX	-4,432872986	FALSO	0,600871012
NN20	8	FALSO	0,71729044
pNN20	0,79545133	FALSO	0,717380888
NN50	3	FALSO	0,836181641
RMSSD	-5,875928501	FALSO	0,259835047
logRMSSD	-0,42501865	FALSO	0,334138081
SDSD	-5,87779629	FALSO	0,259835047
SD1	-4,967802296	FALSO	0,444508903
SD2	-7,707709717	FALSO	0,872118031
AVDD	6,299010869	VERO	0,026875592
AVPTT	-0,012596131	VERO	0,015755486
AVSS	10,34166458	FALSO	0,053405841
RR_VLF	-0,097761827	FALSO	0,658008785
RR_LF	-0,003470544	FALSO	0,295424056
RR_HF	0,000708971	FALSO	0,573168974
RR_LFtoHF	0,477547582	FALSO	0,747500078
RR_HFnu	-0,135917052	FALSO	0,398062926
RR_LFnu	0,029468654	FALSO	0,334138081
RR_spect_slope	0,184546344	FALSO	0,903907633
SS_TOTPWR	3171,80109	FALSO	0,259835047
SS_VLF	450,5978352	FALSO	0,398062926
SS_LF	-3,317087776	FALSO	0,136497711
SS_HF	1385,448102	VERO	0,048624802
SS_spect_slope	0,019237201	FALSO	1
DD_TOTPWR	2422,933113	FALSO	0,147416199
DD_VLF	1129,833976	FALSO	0,116544264
DD_LF	435,269274	FALSO	0,136497711
DD_HF	789,4548857	FALSO	0,098957365
Gain21TOT_Med	0,000381711	FALSO	0,259835047
Gain12TOT_Med	48,91040118	FALSO	0,573168974
bivaRRLFn_Std	0,023843443	VERO	0,015755486
GAIN21LF_Std	0,000162955	VERO	0,017582795
GAIN21HF_Std	0,000195404	VERO	0,019593285

GAIN12HF_Slope	-0,013482464	VERO	0,048624802
CohHF_Std	0,014397686	VERO	0,044208439
CohTOT_Std	0,009282942	VERO	0,044208439

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