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AUTOMATIC RISK EVALUATION IN ELDERLY PATIENTS BASED ON AUTONOMIC NERVOUS SYSTEM ASSESSMENT

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La conoscenza

è orgogliosa

per aver

imparato tanto,

la saggezza

è umile

per non saperne

abbastanza

(William Cooper)

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(Newton, Philosophiae Naturalis Principia Mathematica)

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Paolo

Summary

Keywords

Data-mining

Heart Rate Variability

Autonomic Nervous System

Hypertension

Congestive Heart Failure

Vascular event

Fall identification

Cardiovascular risk

Thesis Abstract

Background

Dysfunction of Autonomic Nervous System is a typical feature of chronic heart failure and other cardiovascular disease and is associated with severity of the disease and prognosis of cardiac patients. As a simple non-invasive technology, heart rate variability analysis provides reliable information on autonomic modulation of heart rate, and it has been a valuable tool to understand psychopathological mechanisms. A small number of studies focused on automatic discrimination between healthy subject and patients suffering from congestive heart failure using data-mining methods. However, to the best of author' knowledge no study investigated the assessment of disease severity by using Heart Rate Variability analysis and data-mining. Moreover, autonomic nervous system disturbance and cardiovascular disorders including carotid sinus hypersensitivity, serious arrhythmias, severe valvular heart disease, and coronary heart disease may be underestimated causes of falls. To best of author' knowledge, only one study investigate Heart Rate Variability in fallers and non-fallers among a geriatric population.

The aim of this thesis was to research and develop automatic methods based on Autonomous Nervous System assessment for evaluation of risk in cardiac patients. Heart Rate Variability analysis has been performed and several data-mining methods have been combined to achieve the following goals: automatic assessment of disease severity in Congestive Heart Failure patients; automatic identification of hypertensive patients at higher risk of developing vascular events, and automatic identification of hypertensive patients with a history of falls.

Materials and methods

Heart Rate Variability analysis was performed according to the international guidelines recommendation and the most recent scientific evidences, particularly for frequency domain and non-linear measures. Several features selection and machine learning algorithms have been combined to achieve the goals. In particular, in any application, methods which provide an intelligible output have been adopted and preferred in order to extract relevant information. Finally, cross-validation methods have been adopted and improved in order to provide a rigorous model selection and evaluation. When available, public datasets are preferred. Otherwise, ad hoc datasets have been developed and they are planned to be publicly available so that other investigators could replicate the results.

Results

Automatic assessment of disease severity in Congestive Heart Failure patients: For the first time, a completely automatic method, based on long-term Heart Rate Variability measures, that is extracted from nominal 24-h electrocardiographic recordings, was proposed in order to automatically assess the severity of Congestive Heart Failure (mild versus severe disease). It has been developed by using public databases, freely available from the physionet.org website. Since the dataset is unbalanced, an approach based on feature selection and tree-based classifier was proposed and compared to standard methods to handle the imbalance problem. The proposed methods outperformed the standard methods selected as benchmark achieving a sensitivity rate of 93% and a specificity rate of 64% in discriminating severe versus mild patients.

Automatic identification of hypertensive patients at high risk of vascular events: For the first time, a completely automatic system was proposed in order to identify hypertensive patients at higher risk to develop vascular events (e.g. stroke, myocardial infarction, syncope) in the 12 months following the electrocardiographic recordings. It was based on linear and nonlinear Heart Rate Variability analysis of a 5-minute ECG segment. A rigorous validation method, based on a crossvalidation loop nested in an hold-out splitting, was proposed to compare the performance of several data-mining algorithms, based on different approaches. The algorithms were trained on a database developed *ad hoc*, which is already available in Physionet.org website (PhysioNetWorks, i.e. area for registered users) and is planned to be published in the public area of the website. The proposed methods achieved a sensitivity rate of 71% and a specificity rate of 86% in identifying high risk subjects among hypertensive patients and outperformed the conventional echographic risk factors for vascular events.

Automatic identification of hypertensive patients with history of fall: For the first time, it was explored whether an automatic identification of fallers among hypertensive patients based on Heart Rate Variability was feasible. The proposed method outperformed several functional tests which were proposed in literature for faller identification. Moreover, it does not require the use of other technologies as wearable accelerometers or pressure matrices, which are not used in everyday clinical practices, not having direct benefits for cardiovascular outpatients.

Discussions and conclusions

The results obtained in this thesis could have implications both in clinical practice and in clinical research. The system has been designed and developed in order to be clinically feasible. In particular, Heart Rate Variability analysis and the automatic system for identification of high-risk patients are integrated in a web-based platform, developed in the framework of the Smart Health and Artificial Intelligence for Risk estimation (SHARE) project. The platform, now integrated in an open and interoperable cloud

computing platform for health and eGovernement (PRISMA), included a standalone software (for Windows operative system) and an Android application to acquire signals from wearable devices. This integration enable to test the clinical feasibility and uptake of the developed tool in a prospective study in subjects aged 55 and over recruited by the Center of Hypertension of the University Hospital of Naples Federico II. Moreover, since 5-minute ECG recording is inexpensive, easy to assess, and non-invasive, future research will focus on the clinical applicability of the system as a screening tool in non-specialized ambulatories (e.g. at General Practitioners'), in order to identify high-risk patients to be shortlisted for more complex (and costly) investigations. Improved identification of individuals at risk for the development of vascular events may result in more targeted and adequate prevention strategies. For example, adopting the model for vascular risk assessment in a cohort of 1000 hypertensive patients, about 200 high risk subjects should be identified, and among them, 80 will develop a vascular event in the following 12 months. Since, as reported by the European Guidelines on cardiovascular disease prevention in clinical practice, most of cardiovascular events could be avoided by changes in life styles and appropriate use of therapeutic treatments, it can be hypotized that the adoption of targeted strategies on the high-risk subjects could halve the number of vascular events.

The findings obtained by the data-mining methods (which did not use any a priori knowledge) reinforce the previous clinical observation that depressed HRV is a marker of cardiovascular risk and, for the first time, showed that it could be also an interesting parameter to be investigated in fall identification and prevention research. In particular, the proposed method does not require the use of other technologies as wearable accelerometers or pressure matrices, which are not used in everyday clinical practices, not having direct benefits for cardiovascular outpatients. For that reason, the method proposed could be used widely in outpatient settings to identify high-risk patients who need further assessment and could benefit from fall prevention programs or fall detection systems.

The main limitation of the achieved findings is the relatively small sample size of the datasets. This issue could be addressed in the next future by increasing the number of enrolled subjects by Center of Hypertension of the University Hospital of Naples Federico II. This would make the present findings clinically more relevant. Moreover, the dataset used in the fall identification issue was not specifically designed to study falls. Therefore, important information, such as the exposure to other independent intrinsic risk factors for falls could not be accessed or used to verify independently the results. Moreover, the fall recordings were based on patient self-reports, which are considered not every time reliable as some non-harmful falls can be forgotten and not reported. Therefore, the number of falls could have been underestimated.

Further developments of the current thesis could be the adoption of new Heart Rate Variability measures (e.g. point process time-frequency analysis), strong risk markers extracted from ECG (e.g. Heart Rate Turbulence or T wave alterations), and other non-invasive measures obtained by wearable sensors (e.g accelerometric signals, breath rate).

Outline

The thesis is organized as follows:

- in the chapter 1, the main topics which are addressed in the thesis, such as Autonomous Nervous System, Heart Rate Variability, cardiovascular diseases, are briefly introduced;
- the adopted databases are described in the Chapter 2;
- the adopted methods, including features computation and selection, machine learning algorithms, are reported in Chapter 3;
- in the Chapter 4, the main results are presented and discussed in relation with the state of art;
- the Chapter 5 provides the conclusions of the works.

1 Introduction

1.1 Autonomic Nervous System

The Autonomic Nervous System (ANS) innervates primarily the smooth musculature of all organs, the heart and the glands in order to mediate the neuronal regulation of the internal milieu. (Jänig, 1989) The functions of the ANS are to keep the internal milieu of the body constant or adjust it as required by changing circumstances (e.g. mechanical work, stressful situation, food intake). The actions of ANS are in general not under direct voluntary control. The ANS consists of two subdivisions: the sympathetic and the parasympathetic nervous system.

The nerves of the sympathetic system originate from the intermediate zone of the thoracic and lumbar spinal cord. The axons of these neurons are thin, but many are myelinated; their conduction velocities range from 1 to 20 m/s. They leave the spinal cord in the ventral roots and the white rami communicants, and terminate in the paired paravertebral ganglia or the unpaired paravertebral abdominal ganglia. The paravertebral ganglia are connected by nerve strands to form a chain on either side of the vertebral column. From these sympathetic trunks, the thinner, unmyelinated postganglionic axons either pass in the grey rami to the effectors in the periphery of the body, or form special nerves that supply organs in the head region or in the thorax, abdomen and pelvis.

The cell bodies of the preganglionic parasympathetic neurons are in the sacral cord and the brainstem. All the axons are very long as compared with those of the sympathetic preganglionic neurons. They form special nerves to the parasympathetic postganglionic neurons, which are near or in the effector organs.

The efficacy of the heart as pump is controlled by sympathetic and parasympathetic nerves, which supplied the heart. The parasympathetic nerves (the vagi) are distributed mainly to the sinoatrial and atrioventricular nodes, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. The sympathetic nerves, conversely, are distributed to all parts of the heart, with strong representation to the ventricular muscle as well as to all the other areas.

Stimulation of the parasympathetic nerves to the heart causes the hormone Acetylcholine to be released at the vagal endings. This hormone has two major effects on the heart. First, it decreases the rate of rhythm of the sinus node, and second, it decreases the excitability of the atrioventricular junctional fibers between the atrial musculature and the atrioventricular node, thereby slowing transmission of the cardiac impulse into the ventricles. Weak to moderate vagal stimulation slows the rate of heart pumping, often to as little as one half normal, and strong stimulation of the vagi can stop completely the rhythmical excitation by the sinus node or block completely transmission of the cardiac impulse from the atria into the ventricles through the atrioventricular mode. In either case,

rhythmical excitatory signals are no longer transmitted into the ventricles. The ventricles stop beating for 5 to 20 seconds, but then some point in the Purkinje fibers, usually in the ventricular septal portion of the atrioventricular bundle, develops a rhythm of its own and causes ventricular contraction at a rate of 15 to 40 beats per minute. This phenomenon is called ventricular escape.

The acetylcholine released at the vagal nerve endings greatly increases the permeability of the fiber membranes to potassium ions, which allows rapid leakage of potassium out of the conductive fibers. This causes increased negativity inside the fibers, an effect called hyperpolarization, which makes this excitable tissue much less excitable. In the sinus node, the state of hyperpolarization decreases the "resting" membrane potential of the sinus nodal fibers to a level considerably more negative than usual, to -65 to -75 millivolts rather than the normal level of -55 to -60 millivolts. Therefore, the initial rise of the sinus nodal membrane potential caused by inward sodium and calcium leakage requires much longer to reach the threshold potential for excitation. This greatly slows the rate of rhythmicity of these nodal fibers. If the vagal stimulation is strong enough, it is possible to stop entirely the rhythmical self-excitation of this node. In the atrioventricular node, a state of hyperpolarization caused by vagal stimulation makes it difficult for the small atrial fibers entering the node to generate enough electricity to excite the nodal fibers. Therefore, the safety factor for transmission of the cardiac impulse through the transitional fibers into the atrio-ventricular nodal fibers decreases. A moderate decrease simply delays conduction of the impulse, but a large decrease blocks conduction entirely.

Sympathetic stimulation causes essentially the opposite effects on the heart to those caused by vagal stimulation, as follows. First, it increases the rate of sinus nodal discharge. Second, it increases the rate of conduction as well as the level of excitability in all portions of the heart. Third, it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular. In short, sympathetic stimulation increases the overall activity of the heart. Maximal stimulation can almost triple the frequency of heartbeat and can increase the strength of heart contraction as much as twofold.

Stimulation of the sympathetic nerves releases the hormone norepinephrine at the sympathetic nerve endings. The precise mechanism by which this hormone acts on cardiac muscle fibers is somewhat unclear, but the belief is that it increases the permeability of the fiber membrane to sodium and calcium ions. In the sinus node, an increase of sodium-calcium permeability causes a more positive resting potential and also causes increased rate of upward drift of the diastolic membrane potential toward the threshold level for self-excitation, thus accelerating self-excitation and, therefore, increasing the heart rate.

In the atrioventricular node and bundles, increased sodium-calcium permeability makes it easier for the action potential to excite each succeeding portion of the conducting fiber

bundles, thereby decreasing the conduction time from the atria to the ventricles. The increase in permeability to calcium ions is at least partially responsible for the increase in contractile strength of the cardiac muscle under the influence of sympathetic stimulation, because calcium ions play a powerful role in exciting the contractile process of the myofibrils. (Guyton and Hall, 2006)

1.2 Heart Rate Variability

Heart Rate Variability (HRV) is the variation over time of the period between consecutive heartbeats (*RR* intervals) (Malik et al., 1996) and is usually extracted from electrocardiographic signal recorded through a non-invasive technique. HRV is commonly used to assess the influence of the ANS on the heart (Malik et al., 1996). HRV is usually extracted by electrocardiographic signals (ECG).

Many measures for assessing HRV have been described in literature, particularly with reference to their discrimination ability between different pathophysiological clinical conditions. In general, HRV measurement could be distinguished in: time-domain, frequency-domain and nonlinear measures.

1.2.1 Time-domain HRV measures

A number of standard statistical time-domain HRV measures have been proposed in literature:

- the Standard Deviation of all NN intervals, which is the most simplest variable to calculate, but it is dependent from the length of recording period(Malik et al., 1996);
- the standard deviation of the average NN interval calculated over short periods, usually 5 min, which is an estimate of the changes in heart rate due to cycles longer than 5 min(Malik et al., 1996);
- the mean of the 5-min standard deviation of the NN interval calculated over 24 h, which measures the variability due to cycles shorter than 5 min(Malik et al., 1996);
- the square root of the mean squared differences of successive NN intervals(Malik et al., 1996);
- the number of times in which the change in successive normal sinus (NN) intervals exceeds 50 ms (Ewing et al., 1984);
- percentage of differences between adjacent NN intervals that are longer than 50 ms (pNN50) (Bigger et al., 1988);
- the other measures of the pNNx familiy, where the threshold measure x is set to value different from 50 ms (Mietus et al., 2002).

Other time-domain measures are based on geometric methods, which can follow one of the following approaches:

- a basic measurement of the geometric pattern (e.g. the width of the distribution histogram at the specified level) is converted into the measure of HRV;
- the geometric pattern is interpolated by a mathematically defined shape (e.g. approximation of the distribution histogram by a triangle, or approximation of the differential histogram by an exponential curve) and then the parameters of this mathematical shape are used,
- the geometric shape is classified into several pattern-based categories which represent different classes of HRV (e.g. elliptic, linear and triangular shapes of Lorenz plots) (Malik et al., 1996).

The most common geometric measures are the following ones:

- the HRV triangular index, i.e. the integral of the density distribution (computed as the number of all NN intervals) divided by the maximum of the density distribution of NN intervals(Malik et al., 1996).
- the baseline width of the distribution measured as a base of a triangle, approximating the NN interval distribution (the minimum square difference is used to find such a triangle) (Malik et al., 1996).

1.2.2 Frequency-domain HRV measures

The frequency-domain HRV measures rely on the estimation of power spectral density (PSD). Several spectral methods have been applied for the PSD estimation and are usually distinguished in non-parametric and parametric. (Malik et al., 1996) The non-parametric method are based in most of the cases on the Fast Fourier Transform FFT and their advantages are: the simplicity of the algorithm employed and the high processing speed, but they suffer from spectral leakage effects due to windowing. The spectral leakage leads to masking of weak signal that are present in the data. The parametric methods (i.e. model based) avoid the problem of leakage and provide smoother spectral components which can be distinguished independently of preselected frequency bands, easy post-processing of the spectrum with an automatic calculation of low and high frequency power components and easy identification of the central frequency of each component, and an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationarity. (Malik et al., 1996) The widely used parametric methods is the Autoregressive (AR) model. In AR method, the estimation of AR parameters can be done easily by solving linear equations. In AR method, data can be modeled as output of a causal, all pole, discrete filter whose input is white noise(Acharya et al., 2006) Formally, AR model is expressed by the following equation:

$$x(k) = -\sum_{n=1}^{N} a(n)x(k-n) + w(k)$$

where a(n) is AR coefficient and w(k) is white noise of σ^2 variance and N is the order of the model. The parameters of the model are the AR coefficient and the variance σ^2. The most relevant issue related to PSD estimation by AR model is the selection of the order N. Different studies investigated this issue, particularly, by using the Akaike information criteria, enabling to conclude that the model order could be set to 16. (Boardman et al., 2002).

Three main spectral components are distinguished in a spectrum calculated from short-term recordings (2 – 5 minutes): very low frequency (VLF), low frequency (LF), and high frequency (HF) components(Akselrod et al., 1981). Spectral analysis may also be used to analyse the sequence in the entire 24-h period. The result then includes an ultra-low frequency component (ULF), in addition to VLF, LF and HF components. (Malik et al., 1996)

Moreover, the use of techniques such as the FFT require an evenly sampled time series. Since HRV is calculated from the variations in the RR interval series which are inherently irregularly spaced in time, in order to produce an evenly sampled time series prior to FFT-based spectral estimation, linear or cubic spline resampling is usually employed.(Laguna et al., 1998). Ectopic beats, arrhythmic events, missing data and noise effects may alter the estimation of the PSD of HRV. Proper interpolation (or linear regression or similar algorithms) on preceding/successive beats on the HRV signals or on its autocorrelation function may reduce this error(Malik et al., 1996). A recent study(Clifford and Tarassenko, 2005) showed that Lomb-Scamble periodgram, a more appropriate spectral estimation technique for unevenly sampled time series that uses only the original data,(Lomb, 1976) provides a superior PSD estimate of RR series compared to FFT techniques, with reference to ectopic beat removal or replacement.

1.2.3 Nonlinear HRV measures

Recent developments in the theory of nonlinear dynamics have paved the way for analysing signals generated from nonlinear living systems(Acharya et al., 2006). It is now generally recognized that these nonlinear techniques are able to describe the processes generated by biological systems in a more effective way. The most common nonlinear techniques applied to HRV analysis are: Poincaré Plot(Brennan et al., 2001), Approximate Entropy(Richman and Moorman, 2000), Sample Entropy(Richman and Moorman, 2000), Correlation Dimension(Carvajal et al., 2005), Detrended Fluctuation Analysis(Peng et al., 1995a, Penzel et al., 2003), and Recurrence Plot (Trulla et al., 1996, Webber and Zbilut, 1994, Zbilut et al., 2002).

1.2.3.1 Poincaré Plot

The Poincaré Plot, also known as return map, is a common graphical representation in which each point is represented as a function of the previous one. In HRV analysis, Poincaré Plot is the scatterplot of the successive *RR* versus previous one. A widely used approach to analyse the Poincaré plot of *RR* series consists in fitting an ellipse oriented according to the line-of-identity and computing the standard deviation of the points perpendicular to and along the line-of-identity referred as *SD1* and *SD2*, respectively(Brennan et al., 2001).

It has been shown that SD_1 and SD_2 are related to linear measures of HRV(Brennan et al., 2001). Moreover, the two Poincaré Plot measures are related to the autocovariance function and, for that reason, these two Poincaré Plot measures could not provide independent nonlinear information and in recent review on HRV(Rajendra Acharya et al., 2006) they are discussed in the standard time domain analysis instead of nonlinear methods. Two kind of generalization of the Poincaré Plot are proposed in the literature(Brennan et al., 2001): the lagged Poincaré Plot and the higher order Poincaré Plot.

The lagged Poincaré Plot is the plot of RR_{n+m} against RR_n where m is chosen from 2 to some small positive value (not higher than 8). SD_1 and SD_2 are computed similarly as lag m set to 1 and are also related to the autocovariance function. For that reason, the set of lagged Poincaré Plot is a description of the autocovariance function.

Poincaré Plot of order m is a m-dimensional scatter-plot of the m-ples (RR_n, RR_{n+1},…, RR_{n+m}). This plot resulted in 2-dimensional projection into each of the coordinate planes (RR_n, RR_{n+1}), (RR_{n+1}, RR_{n+2}),…,(RR_n, RR_{n+m}). The first two projections are equivalent to standard Poincaré Plot, the last one is equivalent to a Poincaré Plot with lag m, and the other projections are equivalent to Poincaré Plot with lag up to m. In other words, an order m Poincaré Plot is geometrically described by a set of Poincaré Plot with lag up to $m+1$.

Geometrically, SD_1 measures the width of the Poincaré cloud and, therefore, indicates the level of short-term HRV, while SD_2 measures the length of the cloud along the line-of-identity, reflecting the long-term HRV. Mathematically, the findings by Brennan et al. (Brennan et al., 2001) proposed the interpretation of *SD1* as a measure of short-term (over each beat) variability, and of *SD2* as a measure of the difference between total variability and short-term variability. This could be explained by considering a time series which shows variability only over a single beat, such as a sequence alternating between two value (RR_I, RR_{II}, RR_I, RR_{II},…,RR_I, RR_{II}). The Poincaré Plot of this series shows a zero length and zero value of SD_2, which are coherent with the absence of long-term variability, while the SD_1 has a non-zero value, reflecting the short-term variability of the time series.

Others techniques, such as central tendency measure(Hnatkova et al., 1995), density based approach(Cohen et al., 1996), have been applied in order to extract independent nonlinear information from Poincaré Plot, but they are not as widely used as *SD1* and *SD2*.

1.2.3.2 Approximate entropy

Approximate entropy (*AppEn*) is widely used method to measure the complexity of signal(Pincus, 1991). It shows the probability that similar observation patterns do not repeat. If a time series demonstrates complex, irregular behaviour, than it will have a high *AppEn* values. For instance, sinusoids give approximately zero value of *AppEn*. *AppEn* showed several advantages: it can be applied for both short-term and long-term recordings, it is scale invariant, model independent, easy to use and it is able to discriminate time series for which clear future recognition is difficult(Rajendra Acharya et al., 2006, Chon et al., 2009). For that reason, it has been applied in different fields, particularly in cardiovascular signal analysis to assess the irregularity of the *RR* series(Richman and Moorman, 2000).

The AppEn computation rely on the values of two parameters: *m*, the embedding dimension, and *r,* the tolerance threshold, which are required to be specified a priori. Several clinical studies(Pincus, 1991, Niskanen et al., 2004, Ho et al., 1997) have shown that either *m*=1 or 2 and *r* between 0.1 and 0.2 times the *SDNN* are suitable to provide valid value of *AppEn*. However, a recent study(Chon et al., 2009) recommended the use of the *r* value (r_{max}) which maximizes the *AppEn* ($AppEn_{max}$). This conclusion was derived by the observation that the *AppEn* computed with value of *r* within the recommended range 0.1 - 0.2 provided misleading results in simulated signals. The *AppEn* determines the conditional probability of similarity between a chosen data segment of a given duration and the next segment set of the same duration; the higher the probability the smaller the *AppEn* value, reflecting less complexity. Applying *AppEn* to the following three time series with decreasing complexity: white noise, cross chirp, and sinusoidal signals, $AppEn_{max}$ provides higher values for white noise, then for cross chirp and lower value for sinusoidal signals, according to their decreasing complexity. If other values of *r* threshold are adopted, misleading results can arise, such as higher values for cross chirp than for white noise. Moreover, a previous study on human HRV data (Castiglioni and Di Rienzo, 2008) showed that a selection of *r*=0.25 resulted in a 12% decrease of *AppEn* values, whereas r=0.1 results in 9% increase as subjects changed their body position from supine to upright. The $AppEn_{max}$ denotes the largest information difference between data length *m* and *m+1* for any given *r*, reflecting the maximum complexity. However, the choice of $AppEn_{max}$ is a computation burden and in order to avoid the computation of *AppEn* for each possible *r* value to find the maximum value, nonlinear models were proposed and validated to estimate r_{max} value from variability of the signals. In particular, for *m*=2, Chon et al.(Chon et al., 2009) proposed an empirical formula. However, a recent study by Liu(Liu et al., 2011) aimed to verify whether Chon's method was appropriate

for HRV by comparing *AppEn* in two groups: healthy subject and patients suffering from cardiac disease. *AppEn* value were computed with three different value of the threshold r :

$r = 0.2 * SDNN$ ($AppEn_{0.2}$);

$r = r_{max}$;

$r = r_{chon}$ ($AppEn_{Chon}$).

Surprisingly, only $AppEn_{Chon}$ (not $AppEn_{0.2}$ nor $AppEn_{max}$) was statistically different between the two groups. Another recent study analysed the three different type of *AppEn* in healthy subjects under stress compared to controlled resting condition(Melillo et al., 2011a). Also in this study, $AppEn_{max}$ was not statistically different between the two groups, while statistically significant differences were observed in $AppEn_{0.2}$ e $AppEn_{Chon}$. The findings of these studies could be explained according to the analysis of the Chon's empirical formula, particularly, its relationship with the ratio between short-term and long-term variability. Further studies should focus on development of methods which can reduce the influence from the different threshold values *r* in *AppEn* computation.

1.2.3.3 Sample entropy

Sample Entropy (*SampEn*) is a relatively new feature introduced by Richman et al.(Richman and Moorman, 2000) to measure the complexity and the regularity of clinical time series. It is very similar to *AppEn*, with some important differences in its calculation. *SampEn*, in theory, does not depend on the length of the time series, but it also relies on the choice of the parameters *m* and *r*, such as *AppEn*. However, the dependence on the parameter *r* is different: *SampEn* decreases monotonically when *r* increases. With high value of *N* and *r*, *SampEn* and *AppEn* provide comparable results(Rajendra Acharya et al., 2006), for that reason, the applications of the two measures are very similar.

1.2.3.4 Fractal Dimension, Correlation Dimension and Detrended Fluctuation Analysis

The term "fractal" was first defined as a geometric concept(Mandelbrot, 1982), referring to an object satisfying two properties: self-similarity and fractional dimensionality. The former property means that an object is composed of subunits (and sub-subunits on multiple levels) that statically resemble the structure of the whole object. The latter property means that the object has a fractional dimension. For example, in bidimensional curve, to verify self-similarity, a subset of the object is rescaled to the same size of the original object, using the same magnification factor for both its width and height, and its statistical properties are compared with those of the original object. Mathematically, this property should hold on all scales, however, in the real world, there are necessarily lower and upper bounds over which such self-similar behaviour applies. Moreover, the strict criterion requires that all the statistical properties (including all higher moments) are identical. Therefore, in practice, a weaker criterion is adopted by examining only the

means and variances (first and second moments) of the distribution. The second criteria distinguishes fractal from Euclidean objects, which have integer dimension. For example, a square satisfies self-similarity as it can be divided into smaller subunits that resemble the large square, but it is not a fractal since it has an integer (2) dimension. Fractal-like appearance was observed in several cardiovascular structures, such as the arterial and venous tree and His-Purkinje network.

The concept of fractal has been extended to the analysis of time series. For instance, in order to verify self-similarity in time series, a subset of the time series is selected and rescaled, but with two different magnification factors (since the two axes have independent physical units). Mathematically, a time series is self-similar if

$$x(t) \equiv a^{a} x\left(\frac{t}{a}\right)$$

where a is the self-similarity parameter or scaling exponent and the operator ≡ indicate that the statistical properties of both side of the equation are identical; however, as already stated, in practice, only the first and second moment statistical properties are compared. The scaling exponent could be estimated by Detrended Fluctuation Analysis, while the Higuchi's algorithm could be adopted for estimation of the fractal dimension (*FD*)(Higuchi, 1988). The correlation dimension *CD* is one of the most widely used measures of the fractal dimension and has been adopted to measure the complexity for the HRV time series(Carvajal et al., 2005).

Detrended Fluctuation Analysis is used to quantify the fractal scaling properties of short *RR* time series, by measuring the correlation within the signal(Penzel et al., 2003, Peng et al., 1995a). It is a modified version of root-mean-square analysis of random walks(Huikuri et al., 2000) and consists into: integration of the root-mean-square fluctuation, computation of detrended time series at observation window of different size and plot against the windows sizes on a log-log scale and the scaling exponent α is computed the slope of the regression line. The value of α for white noise, for fractal-like signal and Brownian noise (integral of Gaussian noise) are 0.5, 1 and 1.5, respectively(Huikuri et al., 2000, Ho et al., 1997). In HRV analysis, other two additional indexes are usually computed(Schulz et al., 2010, Peng et al., 1995b): short-term fluctuations ($Alpha_1$) and long-term fluctuations ($Alpha_2$).

1.2.3.5 Recurrence Plot

Recurrence Plot was introduced by Eckmann et al.(Eckmann et al., 1987) as a graphical tool to discover hidden periodicities, difficult to be detected otherwise, and can be used to reveal non-stationarity in the time series. The recurrence plot is an array of dots in an N x N square, where a dot is placed at (i,j) whenever RR_j is sufficiently close to RR_i. The plots will be symmetric along the diagonal $i = j$, because if RR_i is close to RR_j, then RR_j is close to RR_i. For normal cases, the Recurrence Plot has diagonal line and less squares

indicating more variation indicating high variation in the heart rate. Abnormalities like ischemic/dilated cardiomyopathy cases, show more squares in the plot indicating the inherent periodicity and the lower heart rate variation(Acharya et al., 2006).

1.3 Congestive Heart Failure

Congestive Heart Failure (CHF) is a patho-physiological condition due to an abnormal cardiac function, which is responsible for the failure of the heart to pump blood as required by the body. It is a common end-stage of heart disease, greatly shortening survival. CHF is associated with profound derangements of the ANS, which worsen disease progression(Cohn, 1990). Sympathetic tone is markedly increased while parasympathetic modulation of heart rate is markedly decreased(Floras, 1993). Hemodynamic and metabolic abnormalities probably serve as the afferent stimulus for this response. This chronic activation is accompanied by an attenuation of reflex responsiveness to unloading of the central baroreceptors and mechanoreceptors. Loss of the buffering capacity of these afferent receptors may contribute to the sustained sympathetic stimulation. The renin-angiotensin system is uncoupled from the sympathetic nerves, probably because the intrarenal mechanisms subserving renin release are preserved. Chronic activation of the sympathetic nerves may contribute to disturbed hemodynamics as well as to long-term structural changes that may influence the natural history of the disease. (Cohn, 1990)

CHF severity can be measured with the symptomatic classification scale of the New York Heart Association (NYHA) (Fleg et al., 2000). Classification via NYHA scale has been proved to be a risk factor for mortality (Redfield et al., 1998, Gheorghiade et al., 2005). NYHA functional classification identifies patients in one of four categories based on physical symptoms and activity restriction:

- Class I – No symptoms with ordinary activity. No limitations on activity
- Class II – Slight to moderate symptoms with normal activity. Slight limitation of activity.
- Class III – Moderate symptoms with less than normal activity. Marked limitation of activity.
- Class IV – Inability to carry out any physical activity without discomfort. Symptoms may occur at rest(Carels, 2004).

1.4 Hypertension and risk assessment

Hypertension is the most common cardiovascular disease. Hypertension is defined as values higher than 140mmHg for systolic blood pressure and/or higher than 90mmHg for diastolic blood pressure. Limited comparable data are available on the prevalence of hypertension and the temporal trends of blood pressure values in different European

countries(Pereira et al., 2009). Overall, the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing.

1.4.1 Cardiovascular risk estimation

Estimation of total cardiovascular risk is easy in particular subgroups of patients, such as those with antecedents of established cardiovascular disease, diabetes, or with severely elevated single risk factors. In all of these conditions, the total cardiovascular risk is high or very high, calling for intensive cardiovascular risk-reducing measures. However, a large number of patients with hypertension do not belong to any of the above categories and the identification of those at low, moderate, high or very high risk requires the use of models to estimate total cardiovascular risk, so as to be able to adjust the therapeutic approach accordingly.

Several risk estimation system have been developed(Pyorala et al., 1994, D'Agostino et al., 2008, Conroy et al., 2003, Woodward et al., 2007, Hippisley-Cox et al., 2008, Assmann et al., 2002, Ridker et al., 2008, Ridker et al., 2007) and their values and limitations have been reviewed recently(Cooney et al., 2009). Most of the current risk estimation systems include the conventional risk factors: age, sex, smoking, blood pressure, and lipid levels. Recently, there has also been increasing interest in the inclusion of family history of chronic heart disease (Woodward et al., 2007, Hippisley-Cox et al., 2008, Ridker et al., 2008, Ridker et al., 2007), social deprivation measures (Woodward et al., 2007, Hippisley-Cox et al., 2008), ethnicity(Hippisley-Cox et al., 2008), and interaction variables that adjust for the use of antihypertensive medication (Woodward et al., 2007, Hippisley-Cox et al., 2008, Wilson et al., 1998).

Most of the current risk estimation systems are based on proportional hazards models, such as Cox (semiparametric) or Weibull (parametric). The Cox method has the advantage of not making any assumptions regarding the shape of the underlying survival, in contrast to the Weibull method, which imposes a parametric function on the baseline survival. One limitation of all risk estimation systems is that they assume constant effects of the risk factors at differing ages and levels of the other risk factors. One system (QRISK2) has attempted to overcome the problem of differing effects of the risk factors with increasing age by including interaction variables between age and several of the other risk factors(Hippisley-Cox et al., 2008). However, this method still assumes that the interaction effect with age remains constant at all ages. Certain combinations of risk factors may act synergistically to increase risk in a manner that is more than additive. Some data-mining methods, such as cluster analysis, neural networks and tree-based algorithm, attempt to account for this. These methods are particularly useful for selecting the most appropriate variables when a large number of potential predictors of risk are available. Neural networks do not assume that risk factors function in a constant and continuous fashion and can account for complex nonlinear relationships and interactions between risk factors. Cluster analysis focuses on the identification of groups of persons

with similar risk factor characteristics who have similar levels of risk. Tree-based algorithms attempt to progressively split the population into smaller subgroups, through sequential introduction of the risk factors, starting with the simplest. The advantage is that some persons can be classified as high or low risk based on very few risk factors, reducing unnecessary laboratory testing for them. However, these methods introduce other problems. The main problem with all of these methods is model shrinkage, that is, their predictive ability declines sharply once the model is applied to an external dataset, which limits their utility in clinical practice. Moreover, there is difficulty in obtaining large epidemiological datasets with extensive numbers of predictor variables available. Additionally, the necessity for measurement of multiple factors in clinical practice adds to complexity and is, therefore, likely to limit clinical usage of these systems.

1.4.2 Fall risk

Falls represent one of the most common causes of injury-related morbidity and mortality in later life. The consequences of falls range from psychological harm, through serious physical injuries (Lord et al., 2006) and hospitalization, to death (Rubenstein, 2006), often causing a reduction of independence in the faller. Falls reduce overall well-being, mobility and quality of life, of individuals and families (Katz and Shah, 2010). The mean and median costs of a fall is about 9,000 and 11,000 euro (Siracuse et al., 2012).

Over 400 risk factors for falls have been identified and classified as either extrinsic, such as environment and circumstances, or intrinsic, which include deterioration of neurological functioning and sensory and/or cardiovascular impairments. The prioritization of those risk factors remains unclear and the sensitivity, specificity and applicability of subject-specific assessment of fall risk remains imprecise (Pecchia et al., 2011, Gates et al., 2008).

Only 31% of falls appear to be due to accidents (Rubenstein, 2006) and also those accidental falls may be due to complex and dynamic unrevealed interactions between intrinsic and extrinsic risk factors (guidelines, 2013). According to Rubens(Rubenstein, 2006), 42% of falls are due to transient problems, including: gait/balance disorders or weakness (17%), dizziness/vertigo (13%), drop attacks (9%), postural hypotension (3%). For that reason, ANS disturbance and cardiovascular disorders including carotid sinus hypersensitivity, serious arrhythmias, severe valvular heart disease, and coronary heart disease may be underestimated causes of falls(Isik et al., 2012).

Several test have been developed for assessing mobility, some of which have also been suggested as predictor of falls(Tiedemann et al., 2008):

- Sit-to-stand test: this test is used as a measure of lower limb strength (Csuka and McCarty, 1985) and is included in fall risk assessment scales(Tinetti, 1986, Berg et al., 1992, Smith, 1994). For the sit-to-stand test with five repetitions (STS-5),

subjects were asked to rise from a standard height (43 cm) chair without armrests, five times, as fast as possible with their arms folded. Subjects undertook the test barefoot and performance was measured in seconds, as the time from the initial seated position to the final seated position after completing five stands. The single sit-to-stand task (time from sitting to standing) (STS-1) was also evaluated as it has been used in assessment scales(Berg et al., 1992, Judge et al., 1996) as a measure of functional mobility, balance and lower limb strength.

- Pick-up-weight test: The ability to reach down and pick up an object from the floor has been included in several mobility assessment scales (Berg et al., 1992, Reuben and Siu, 1990). A bag containing a 5 kg weight with handles that extended 50 cm above the floor was placed on the floor in front of the subject. The subjects were asked to pick up the bag and place it on a table using one hand only. Performance was rated as either able or unable to complete the task.
- Half-turn test: The ability to turn around in an efficient manner has been included in assessments of mobility and balance in older people(Berg et al., 1992, Podsiadlo and Richardson, 1991). Subjects were asked to take a few steps and then turn around to face the opposite direction. The number of steps taken to complete this 180° turn was counted.
- Alternate-step test: The alternate-step test (AST) is a modified version of the Berg stool-stepping task(Berg et al., 1992). It involves weight shifting and provides a measure of lateral stability. This test involved alternatively placing the entire left and right feet (shoes removed) as fast as possible onto a step that was 18 cm high and 40 cm deep. The time taken to complete eight steps, alternating between the left and right feet comprised the test measure.
- Six-metre-walk: Slow gait speed is associated with an increased risk of falls (Imms and Edholm, 1981, Bootsma-van der Wiel et al., 2002) and is a measure included in fall risk assessment scales (Podsiadlo and Richardson, 1991, Piotrowski and Cole, 1994). Subjects completed a six-metre-walk test (SMWT) measured in seconds along a corridor at their normal walking speed. A 2-m approach and a further 2 m beyond the measured 6-m distance ensured that walking speed was constant across the 6 m.
- Stair ascent and descent: The inability to negotiate stairs is a marker of functional decline in older people (Guralnik et al., 1994) and many falls occur during this task(Facts, 1996). The test stairs were indoors, had a handrail, were covered with linoleum and well lit. The subjects started the stair-ascent test at the bottom of eight steps (15 cm high, 27.5 cm deep). Subjects could use the handrail if preferred and a walking aid if they normally used one. Timing commenced for the stair-ascent test when the subject raised their foot off the ground to climb the first step and stopped when both feet were placed on the eighth step (which was a landing). After a brief rest, the subject was asked to descend the stairs. Timing was started when they raised their foot off the ground for the first step and stopped when they

completed the last step. Time taken to complete the ascent and descent tests was recorded.

A recent study (Tiedemann et al., 2008) compared these functional tests and showed that, when dichotomised, the AST was the best test for discriminating between the faller groups. An AST cut-off point of 10 s was associated with a 130% increased risk, with 69% sensitivity and 56% specificity with respect to identifying multiple fallers. At identified cut-off points, the STS-5 (12 s), the SMWT (6 s), the stair-descent test (5 s) and the stair-ascent test (5 s) could also significantly predict subjects who suffered multiple falls with sensitivities and specificities above 50%.

2 Databases

In the current chapter, the characteristics of the ECG holter databases that have been used for this thesis work are presented. Table 2.1 reported the summary properties of each database that will be then detailed in the following sections.

Table 2.1 Summary of the adopted database

Database	Number of subjects	Clinical Condition	Availability
Congestive Heart Failure RR Interval Database	29 (aged 34 to 79; 8 male, 2 female)	CHF	www.physionet.org (PhysioBank: Public data archives)
BIDMC Congestive Heart Failure Database.	15 (aged 22 to 71; 11 male, 4 female)	CHF	www.physionet.org (PhysioBank: Public data archives)
ECG Holter database for Vascular Events	139 (age: 72 ± 7 years; 90 male, 49 female)	Hypertension with or without vascular events	www.physionet.org (PhysioNetWorks, for registered users)
ECG Holter database for Fall Risk	168 (age: 72 ± 8 years; 108 male, 60 female)	Hypertension with or without history of fall	progettoshare.it (by request)

2.1 Congestive Heart Failure Holter databases

2.1.1 Background and rationale

For the investigation of ECG holter in CHF patients, two databases are freely available from physionet.org(Goldberger et al., 2000):

- Congestive Heart Failure RR Interval Database
- BIDMC Congestive Heart Failure Database.

2.1.2 Population

The Congestive Heart Failure RR Interval Database provides the RR time-series for 29 long-term ECG recordings of subjects aged 34 to 79, with CHF (NYHA classes I, II, and III). Subjects included 8 men and 2 women; gender is not known for the remaining 21 subjects. The BIDMC Congestive Heart Failure Database includes long-term ECG recordings from 15 subjects (11 men, aged 22 to 71, and 4 women, aged 54 to 63) with severe congestive heart failure (NYHA class 3-4).

2.1.3 Protocol and measurement system

The original ECG recordings, even if are not available, of the Congestive Heart Failure RR Interval Database were digitized at 128 samples per second, and the beat annotations were obtained by automated analysis with manual review and correction. The database is contributed by Rochelle Goldsmith, of Columbia-Presbyterian Medical Center, New York. The individual recordings of the BIDMC Congestive Heart Failure Database are each about 20 hours in duration, and contain two ECG signals each sampled at 250 samples per second with 12-bit resolution over a range of ±10 millivolts. The original

analog recordings were made at Boston's Beth Israel Hospital (now the Beth Israel Deaconess Medical Center) using ambulatory ECG recorders with a typical recording bandwidth of approximately 0.1 Hz to 40 Hz. The RR time-series were obtained using an automated detector (without manual review and correction)

2.2 ECG Holter database for Vascular Events

2.2.1 Background and rationale

Previous studies showed that HRV could be an independent risk factor for vascular events: Sajadieh et al. showed that subjects with familial predisposition to premature heart attack and sudden death have reduced HRV(Sajadieh et al., 2003); Dekker et al. concluded that low HRV is associated with increased risk of coronary heart disease and death from several causes (Dekker et al., 2000). Binici et al. demonstrated that depressed nocturnal heart rate variability is a strong marker for the development of stroke in apparently healthy subject (Binici et al., 2011). Since hypertension is a risk factor for vascular events and to the best of authors' knowledge, no public database of hypertensive patients with a follow-up after the recording is freely available, a database of ECG holter recorded in hypertensive patients were collected *ad hoc* in order to investigate future vascular events in a twelve month follow-up.

2.2.2 Population

The records have been collected among the hypertensive patients aged 55 or over, followed up by the outpatient hypertension centre of the University Hospital of Naples Federico II. The recordings have been performed between 1 January 2012 and 10 November 2012.

The following exclusion criteria have been adopted:

- refusal of written informed consent;
- severe ocular disease;
- deafness in alone living subject;
- chronic obstructive pulmonary disease, (pre)dementia, or other disease which may reduce life expectancy.

The dataset consists of 139 hypertensive patients (including 49 female and 90 male, age 72 ± 7 years). Clinical and demographic features of the included subjects are reported in Table 2.2. Among the study sample, in the 12-month follow-up after recordings, 17 patients experienced a recorded event (11 myocardial infarctions, 3 strokes, 3 syncopal events) and for that reason, were considered as high-risk subjects, while the remaining ones as low-risk subjects.

Table 2.2 Clinical and demographic feature of the subjects included in the ECG Holter database for Vascular Events

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
1911	M	56	105	180	2.29	32.41	yes	no	no	140	80	4	123	66	none
2012	M	72	83	169	1.97	29.06	no	no	no	130	75	n/a	121	69	none
2019	F	80	80	165	1.91	29.38	no	no	no	177	75	2.5	164	56	none
2020	M	77	88	178	2.09	27.77	no	no	no	140	85	2.7	115	67	none
2025	F	66	80	174	1.97	26.42	no	no	no	110	65	1.5	98	66	none
2031	M	84	72	170	1.84	24.91	no	no	no	120	70	2.6	147	51	none
2032	F	66	85	160	1.94	33.20	no	no	no	150	65	1.6	178	53	none
2033	M	77	82	169	1.96	28.71	no	no	yes	115	80	n/a	144	42	myocardial infarction
2035	M	77	80	162	1.90	30.48	no	yes	yes	160	75	n/a	123	70	none
2037	F	69	90	154	1.96	37.95	no	yes	no	110	65	1.5	124	64	none
2041	M	85	97	165	2.11	35.63	no	no	no	135	75	3	159	50	none
2047	F	69	83	173	2.00	27.73	no	no	no	146	80	1.9	86	68	none
2050	M	73	68	167	1.78	24.38	no	yes	no	105	70	1.7	202	43	none
2055	M	65	72	167	1.83	25.82	no	no	no	130	85	2.3	106	68	none
2057	F	66	72	176	1.88	23.24	no	yes	no	130	85	2	117	66	none
2059	F	75	80	150	1.83	35.56	no	no	no	170	80	n/a	154	71	myocardial infarction
2062	M	72	93	187	2.20	26.59	no	no	no	120	80	1.4	126	65	none
2063	M	70	82	178	2.01	25.88	no	yes	no	162	100	1.6	153	62	none
2065	F	69	81	170	1.96	28.03	no	yes	yes	135	65	2.7	105	66	none

[1] Body surface area
[2] Body Mass index
[3] Family history of hypertension
[4] Family history of stroke
[5] Systolic arterial pressure
[6] Diastolic arterial pressure
[7] Intima media thickness
[8] Left ventricular mass index
[9] Ejection fraction

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
2066	M	74	74	165	1.84	27.18	no	no	no	130	80	3.1	121	63	none
2068	M	67	72	171	1.85	24.62	yes	yes	no	120	85	n/a	144	61	none
2069	M	64	86	178	2.06	27.14	no	no	no	115	75	2.2	111	61	none
2072	M	73	64	174	1.76	21.14	yes	no	no	125	75	1.2	119	67	none
2073	M	73	60	167	1.67	21.51	no	no	no	195	95	2.4	141	32	none
2076	M	68	62	165	1.69	22.77	yes	no	no	143	62	3.7	168	33	none
2078	M	74	85	180	2.06	26.23	yes	yes	no	150	75	1.7	140	67	none
2079	M	71	113	168	2.30	40.04	no	no	no	150	85	2.6	156	67	none
2082	M	58	92	175	2.11	30.04	yes	yes	no	135	70	1.6	98	69	none
2084	F	70	93	165	2.06	34.16	no	yes	no	140	70	2.2	n/a	n/a	none
2087	F	71	74	172	1.88	25.01	no	yes	no	160	75	2.3	126	65	none
2089	F	75	68	156	1.72	27.94	yes	no	no	135	65	1.7	93	64	none
2092	F	73	98	170	2.15	33.91	no	yes	no	155	78	2.9	129	65	none
2097	M	79	81	172	1.97	27.38	yes	no	no	110	80	2.4	125	46	none
2100	F	64	83	155	1.89	34.55	yes	no	no	200	80	3.3	156	62	none
2102	M	74	74	172	1.88	25.01	no	yes	no	150	90	n/a	n/a	n/a	none
2107	M	76	70	160	1.76	27.34	no	yes	yes	145	75	3	146	60	none
2108	M	84	70	170	1.82	24.22	yes	no	no	164	54	3.5	194	63	myocardial infarction
2114	F	72	55	160	1.56	21.48	yes	yes	no	160	80	3	99	65	none
2115	M	75	75	172	1.89	25.35	yes	no	no	122	74	3.3	121	68	none
2116	M	65	98	171	2.16	33.51	no	no	no	130	80	1.7	125	54	none
2117	M	69	65	175	1.78	21.22	no	yes	no	140	80	2.3	113	38	none
2119	F	74	91	162	2.02	34.67	no	no	no	140	80	2.3	101	72	stroke
2120	F	81	76	158	1.83	30.44	no	yes	no	160	80	2	163	66	none
2121	M	81	93	170	2.10	32.18	yes	no	no	170	75	5	159	62	myocardial infarction
2125	F	72	78	158	1.85	31.24	no	yes	no	190	80	4.2	154	72	none
2134	F	86	78	160	1.86	30.47	no	yes	no	145	55	2.2	122	59	none
2136	M	77	84	173	2.01	28.07	no	no	yes	155	85	2	154	66	none

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
2139	M	64	75	165	1.85	27.55	no	no	no	140	90	2.1	113	64	none
2140	M	70	91	187	2.17	26.02	no	no	no	145	85	2.3	127	65	none
2142	M	71	80	160	1.89	31.25	no	no	yes	165	80	3.3	152	53	none
2148	F	66	64	156	1.67	26.30	no	no	no	130	75	2	129	60	myocardial infarction
2150	M	59	68	164	1.76	25.28	yes	no	yes	100	60	1.4	98	69	none
2152	F	82	64	156	1.67	26.30	no	no	no	110	70	1.6	159	65	none
2154	M	80	75	167	1.87	26.89	yes	no	no	105	65	2.3	117	52	none
2156	M	69	80	165	1.91	29.38	yes	no	no	150	90	2.5	n/a	n/a	none
2159	M	75	68	169	1.79	23.81	no	yes	no	160	90	2.7	107	70	none
2161	M	74	78	166	1.90	28.31	no	yes	no	130	70	2.4	122	56	none
2167	M	77	80	169	1.94	28.01	yes	no	no	170	70	3	128	62	none
2168	M	83	75	170	1.88	25.95	no	no	no	145	70	3.3	129	58	none
2170	F	65	59	154	1.59	24.88	no	no	no	145	65	1.8	n/a	n/a	none
2171	M	77	89	163	2.01	33.50	no	no	no	125	80	1	118	69	none
2175	M	69	75	169	1.88	26.26	yes	no	no	150	86	2.2	n/a	n/a	none
2180	M	69	88	171	2.04	30.09	no	yes	no	120	70	1.7	133	62	none
2184	F	68	55	165	1.59	20.20	no	yes	no	110	70	1.35	98	68	myocardial infarction
2185	M	81	72	171	1.85	24.62	yes	yes	no	145	80	2.9	148	60	myocardial infarction
2186	F	65	67	159	1.72	26.50	no	yes	no	135	75	3.6	116	73	none
2188	F	85	75	160	1.83	29.30	no	no	no	130	80	3.5	131	36	none
2191	M	73	92	173	2.10	30.74	no	yes	yes	155	85	3.6	139	52	none
2194	F	68	95	162	2.07	36.20	no	yes	no	145	75	1.8	118	72	none
2202	M	63	72	168	1.83	25.51	no	yes	yes	135	85	1.4	n/a	n/a	none
2210	F	80	58	153	1.57	24.78	no	no	no	nan	nan	n/a	n/a	n/a	none
2213	M	65	82	175	2.00	26.78	no	yes	no	120	80	2.5	154	56	none
2215	m	92	62	165	1.69	22.77	no	no	no	120	80	3	126	57	none
2218	F	77	64	160	1.69	25.00	no	yes	no	110	60	1.5	146	70	syncope
2219	F	75	72	162	1.80	27.43	no	no	no	150	75	1.4	149	45	none

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
2220	M	73	87	178	2.07	27.46	no	yes	no	175	65	1.8	233	53	none
2226	M	65	83	165	1.95	30.49	yes	no	no	125	80	3.4	151	49	none
2227	M	65	70	163	1.78	26.35	yes	yes	no	150	80	n/a	108	72	none
2229	M	64	80	164	1.91	29.74	no	no	no	170	95	2.2	175	42	none
2230	F	67	65	159	1.69	25.71	yes	no	no	100	60	2.5	116	67	none
2231	F	69	80	159	1.88	31.64	no	no	no	142	82	2.2	133	66	none
2244	M	86	73	168	1.85	25.86	yes	no	no	125	60	2.6	146	57	none
2245	M	68	70	165	1.79	25.71	no	no	no	120	70	2.1	119	72	none
2248	F	69	76	158	1.83	30.44	no	yes	no	150	90	2.5	126	66	none
2249	F	66	89	167	2.03	31.91	no	no	no	120	70	1.9	175	28	none
2250	M	66	100	170	2.17	34.60	no	no	no	135	75	1.6	166	47	none
2251	M	84	83	181	2.04	25.34	yes	no	no	140	75	2.6	140	68	none
2258	M	72	92	170	2.08	31.83	no	no	no	115	65	3.2	143	32	none
2259	M	78	68	162	1.75	25.91	no	no	no	130	70	2	131	67	none
2269	M	66	86	167	2.00	30.84	yes	yes	no	140	60	2.8	142	62	none
2274	F	68	58	158	1.60	23.23	yes	yes	no	130	70	2.1	120	53	none
2275	M	68	78	172	1.93	26.37	yes	no	no	135	85	1.6	127	52	none
2276	F	77	54	160	1.55	21.09	no	yes	no	136	75	2	201	60	none
2278	M	77	87	170	2.03	30.10	no	yes	yes	120	75	1.8	135	59	none
2282	F	65	60	150	1.58	26.67	no	no	no	165	90	2	113	67	none
2284	M	79	70	170	1.82	24.22	no	no	no	135	80	2.8	n/a	n/a	none
2285	F	69	60	167	1.67	21.51	no	yes	no	110	80	1.6	90	68	none
2289	F	64	98	165	2.12	36.00	no	no	yes	175	80	1.9	130	62	myocardial infarction
2291	M	74	75	170	1.88	25.95	yes	no	no	145	85	2.2	144	62	none
2293	M	81	68	166	1.77	24.68	no	no	no	130	85	2.3	141	33	none
2294	M	67	61	165	1.67	22.41	no	no	no	120	80	2.8	126	25	stroke
2295	M	64	88	173	2.06	29.40	yes	no	yes	115	60	2.3	n/a	n/a	none
2296	M	74	83	170	1.98	28.72	no	no	no	145	85	1.5	120	48	none

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
2298	F	66	64	160	1.69	25.00	no	no	no	140	60	3	96	69	none
2299	F	78	50	165	1.51	18.37	no	no	no	110	60	1.1	91	69	none
2304	F	84	75	160	1.83	29.30	no	yes	yes	170	80	0.95	154	59	myocardial infarction
2306	M	66	86	165	1.99	31.59	no	no	no	125	70	1.5	118	62	none
2307	F	65	50	156	1.47	20.55	yes	yes	no	100	60	1	92	62	none
2309	M	74	79	172	1.94	26.70	no	no	no	100	60	n/a	113	64	none
2312	F	63	75	168	1.87	26.57	no	no	no	120	80	1.1	99	72	none
2315	M	73	80	178	1.99	25.25	no	no	no	135	80	2.4	103	67	none
2319	F	69	68	160	1.74	26.56	no	no	no	120	70	3.2	105	64	none
2321	M	63	83	178	2.03	26.20	yes	yes	no	140	80	1.5	161	43	none
2323	M	77	77	168	1.90	27.28	no	no	no	125	85	n/a	n/a	n/a	none
2328	M	46	77	172	1.92	26.03	yes	no	no	145	75	3.3	108	68	none
2332	M	78	72	174	1.87	23.78	no	no	no	155	75	2	127	66	none
2334	F	73	63	173	1.74	21.05	no	yes	no	140	70	2	137	60	none
2337	M	65	84	168	1.98	29.76	yes	yes	no	150	90	2.8	167	38	none
2338	M	76	74	170	1.87	25.61	no	yes	no	115	70	1.9	113	61	none
2339	M	76	85	172	2.02	28.73	yes	no	no	120	70	3.8	184	33	syncope
2348	M	72	65	168	1.74	23.03	yes	yes	no	135	70	2.5	118	62	stroke
2349	M	65	107	170	2.25	37.02	no	no	no	130	85	2	146	64	none
2350	F	81	94	162	2.06	35.82	yes	no	no	130	80	3.2	102	63	none
2352	M	75	90	182	2.13	27.17	no	no	no	150	80	n/a	111	66	none
2355	F	69	85	165	1.97	31.22	no	no	no	120	66	1.8	109	62	none
2357	M	74	82	173	1.99	27.40	no	no	no	145	80	2.4	104	65	none
2359	M	69	69	165	1.78	25.34	yes	no	no	135	75	3	125	60	none
2370	F	64	63	162	1.68	24.01	yes	no	no	135	80	n/a	75	76	none
2373	M	66	88	173	2.06	29.40	no	no	no	135	80	1.3	132	55	myocardial infarction
2384	M	83	76	180	1.95	23.46	no	no	no	110	70	3.3	161	47	none
2387	M	68	84	180	2.05	25.93	yes	no	no	155	85	2.6	121	33	none

ID	Sex	Age	Weight	Height	BSA[1]	BMI[2]	Smoker	F hyp[3]	F stroke[4]	SP[5]	DP[6]	IMT[7]	LVMi[8]	EF[9]	Vascular event
2392	M	70	76	172	1.91	25.69	no	no	no	120	80	3.1	140	54	none
2396	M	69	90	165	2.03	33.06	no	no	no	150	90	4	124	61	none
2399	F	65	72	159	1.78	28.48	no	yes	no	150	90	3	105	67	none
2403	F	78	55	157	1.55	22.31	no	yes	no	170	60	2.3	136	64	syncope
2412	M	70	98	176	2.19	31.64	no	yes	no	130	75	2.2	131	54	myocardial infarction
2413	M	78	74	170	1.87	25.61	no	no	no	125	65	2.3	170	32	none
2417	M	65	93	175	2.13	30.37	no	no	no	120	80	1.7	112	65	none
2425	M	67	67	170	1.78	23.18	yes	no	no	120	80	n/a	n/a	n/a	none

2.2.3 Protocol and measurement system

The ECG Holter was performed after a one-month antihypertensive therapy wash-out. On 2 consecutive days, patients underwent a 24-hour ECG Holter recording. The recorders were applied between 9 and 11 AM on a working day, and the patients were asked to follow as closely as possible their usual daily activities during each monitoring session. They were asked to stay in bed from 11 PM to 7 AM. The patients were followed up for 12 months after the recordings in order to record major cardiovascular and cerebrovascular events, i.e. fatal or non-fatal acute coronary syndrome including myocardial infarctions, syncopal events, coronary revascularization, fatal or non-fatal stroke and transient ischemic attack. All the events were adjudicated by the Committee for Event Adjudication in the Hypertension Center. Adjudication was based on patient history, contact with the reference general practitioner and clinical records documenting the occurrence of the event/arrhythmia (De Luca et al., 2005, Izzo et al., 2013). Moreover, the patients were evaluated by a cardiac and carotid ultrasonography. Left ventricular mass was determined by using the formula developed by Devereux(Devereux et al., 1986) as recommend by American Society of Echocardiography (ASE)(Lang et al., 2005) and divided by the body surface area to calculate left ventricular mass index (LVMi, g/m^2). B-mode ultrasonography of carotid arteries was performed in order to compute the maximum IMT (mm). Further details about the ECG recording, the cardioecographic and carotid ultrasonographic procedures can be found in a previous report(Melillo et al., 2012). The current study was approved by the Ethics Committee of Federico II University Hospital Trust and the data were collected by the Department of Translational Medical science of the University of Naples Federico II in the framework of the Smart Health and Artificial intelligence for Risk Estimation (SHARE) project.

2.3 ECG Holter database for Fall Risk

2.3.1 Background and rationale

ANS disturbance and cardiovascular disorders including carotid sinus hypersensitivity, serious arrhythmias, severe valvular heart disease, and coronary heart disease may be underestimated causes of falls(Isik et al., 2012). To investigate the relationship between abnormal HRV and fall risk, a database of ECG holter recorded in hypertensive patients with and without history of falls were collected *ad hoc*.

2.3.2 Population

The records have been collected among the hypertensive patients aged 55 or over, followed up by the outpatient hypertension centre of the University Hospital of Naples Federico II. The recordings were performed between January 2008 and December 2012. Clinical and demographic features of the included subjects are reported in Table 2.3.

Table 2.3 Clinical and demographic feature of the subjects included in the ECG Holter database for fall risk

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
636	F	78	55	157	1.55	22.31	no	yes	no	170	60	2.3	136	64	yes
782	M	76	70	160	1.76	27.34	no	yes	yes	145	75	3	146	60	no
868	M	64	75	165	1.85	27.55	no	no	no	140	90	2.1	113	64	no
2387	M	69	86	178	2.06	27.14	no	yes	no	143	75	1.9	128	64	yes
2668	F	69	68	160	1.74	26.56	no	no	no	120	70	3.2	105	64	no
2763	M	69	88	171	2.04	30.09	no	yes	no	120	70	1.7	133	62	no
2841	F	77	84	165	1.96	30.85	no	no	no	170	85	2.4	120	68	yes
2984	M	64	80	177	1.98	25.54	yes	no	no	110	60	3	121	57	yes
2991	F	73	63	173	1.74	21.05	no	yes	no	140	70	2	137	60	no
3340	M	65	107	170	2.25	37.02	no	no	no	130	85	2	146	64	no
3495	F	84	75	160	1.83	29.30	no	yes	yes	170	80	0.95	154	59	no
3534	M	77	84	173	2.01	28.07	no	no	yes	155	85	2	154	66	no
3662	F	71	70	168	1.81	24.80	no	no	no	130	70	2	133	66	yes
4609	M	77	89	163	2.01	33.50	no	no	no	125	80	1	118	69	no
4668	F	69	80	159	1.88	31.64	no	no	no	142	82	2.2	133	66	no
5016	F	66	64	156	1.67	26.30	no	no	no	130	75	2	129	60	no
5222	M	65	100	173	2.19	33.41	no	yes	no	180	100	1.3	188	55	yes
5400	M	73	80	178	1.99	25.25	no	no	no	135	80	2.4	103	67	no
5431	F	84	48	160	1.46	18.75	no	yes	no	115	60	1.6	119	73	yes

[10] Body surface area
[11] Body Mass index
[12] Family history of hypertension
[13] Family history of stroke
[14] Systolic arterial pressure
[15] Diastolic arterial pressure
[16] Intima media thickness
[17] Left ventricular mass index
[18] Ejection fraction

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
5451	F	81	76	158	1.83	30.44	no	yes	no	160	80	2	163	66	no
5940	M	64	82	173	1.99	27.40	yes	yes	no	135	80	2	93	67	yes
6106	M	73	92	173	2.10	30.74	no	yes	yes	155	85	3.6	139	52	no
6215	M	75	84	170	1.99	29.07	no	no	no	140	85	2.2	172	44	yes
6666	M	77	87	170	2.03	30.10	no	yes	yes	120	75	1.8	135	59	no
7014	M	62	77	160	1.85	30.08	no	no	no	130	70	1.8	123	70	no
7605	F	86	78	160	1.86	30.47	no	yes	no	145	55	2.2	122	59	no
7633	F	68	54	152	1.51	23.37	no	yes	no	140	60	1.75	98	68	yes
7842	M	63	89	160	1.99	34.77	no	no	no	125	75	3	127	68	yes
7938	F	69	90	154	1.96	37.95	no	yes	no	110	65	1.5	124	64	no
8500	F	63	75	168	1.87	26.57	no	no	no	120	80	1.1	99	72	no
9205	M	65	72	167	1.83	25.82	no	no	no	130	85	2.3	106	68	no
9278	F	64	98	165	2.12	36.00	no	no	yes	175	80	1.9	130	62	no
9516	M	84	70	170	1.82	24.22	yes	no	no	164	54	3.5	194	63	no
9629	M	85	70	170	1.82	24.22	no	no	no	147	65	1.8	129	65	yes
9683	M	59	71	178	1.87	22.41	no	yes	no	150	90	1.4	144	71	yes
9740	F	69	83	173	2.00	27.73	no	no	no	146	80	1.9	86	68	no
10121	F	65	50	156	1.47	20.55	yes	yes	no	100	60	1	92	62	no
10169	F	65	60	150	1.58	26.67	no	no	no	165	90	2	113	67	no
10346	M	81	64	163	1.70	24.09	no	yes	yes	147	67	2.65	123	67	yes
30061	M	71	80	160	1.89	31.25	no	no	yes	165	80	3.3	152	53	no
30343	M	73	64	174	1.76	21.14	yes	no	no	125	75	1.2	119	67	no
30415	M	74	82	173	1.99	27.40	no	no	no	145	80	2.4	104	65	no
30472	F	80	80	165	1.91	29.38	no	no	no	177	75	2.5	164	56	no
30521	F	72	55	160	1.56	21.48	yes	yes	no	160	80	3	99	65	no
30671	M	68	62	165	1.69	22.77	yes	no	no	143	62	3.7	168	33	no
30795	F	82	64	156	1.67	26.30	no	no	no	110	70	1.6	159	65	no
30945	M	64	86	178	2.06	27.14	no	no	no	115	75	2.2	111	61	no

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
31663	F	68	95	162	2.07	36.20	no	yes	no	145	75	1.8	118	72	no
31707	M	74	75	170	1.88	25.95	yes	no	no	145	85	2.2	144	62	no
31769	M	86	73	168	1.85	25.86	yes	no	no	125	60	2.6	146	57	no
31870	M	80	75	167	1.87	26.89	yes	no	no	105	65	2.3	117	52	no
32713	M	74	83	170	1.98	28.72	no	no	no	145	85	1.5	120	48	no
32750	F	75	68	156	1.72	27.94	yes	no	no	135	65	1.7	93	64	no
32811	M	67	61	165	1.67	22.41	no	no	no	120	80	2.8	126	25	no
32812	M	74	85	180	2.06	26.23	yes	yes	no	150	75	1.7	140	67	no
33804	M	66	86	165	1.99	31.59	no	no	no	125	70	1.5	118	62	no
33862	M	83	76	180	1.95	23.46	no	no	no	110	70	3.3	161	47	no
34275	M	74	74	165	1.84	27.18	no	no	no	130	80	3.1	121	63	no
34281	F	59	65	158	1.69	26.04	no	no	no	120	80	1.3	126	63	yes
34538	M	65	93	175	2.13	30.37	no	no	no	120	80	1.7	112	65	no
34647	M	91	85	172	2.02	28.73	no	no	no	130	60	4.6	180	59	yes
35022	M	81	72	171	1.85	24.62	yes	yes	no	145	80	2.9	148	60	no
35063	F	66	72	176	1.88	23.24	no	yes	no	130	85	2	117	66	no
35325	M	66	86	167	2.00	30.84	yes	yes	no	140	60	2.8	142	62	no
35693	M	70	98	176	2.19	31.64	no	yes	no	130	75	2.2	131	54	no
35728	M	66	88	173	2.06	29.40	no	no	no	135	80	1.3	132	55	no
36052	M	65	98	171	2.16	33.51	no	no	no	130	80	1.7	125	54	no
36570	M	74	92	182	2.16	27.77	no	no	no	120	75	2.5	103	67	yes
36886	M	73	68	167	1.78	24.38	no	yes	no	105	70	1.7	202	43	no
36970	F	65	72	159	1.78	28.48	no	yes	no	150	90	3	105	67	no
37293	M	78	68	162	1.75	25.91	no	no	no	130	70	2	131	67	no
37314	M	69	65	175	1.78	21.22	no	yes	no	140	80	2.3	113	38	no
37478	F	77	64	160	1.69	25.00	no	yes	no	110	60	1.5	146	70	no
37511	M	81	68	166	1.77	24.68	no	no	no	130	85	2.3	141	33	no
37591	F	80	58	153	1.57	24.78	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	no

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
38177	M	70	91	187	2.17	26.02	no	no	no	145	85	2.3	127	65	no
38187	M	76	85	172	2.02	28.73	yes	no	no	120	70	3.8	184	33	no
38668	M	70	76	172	1.91	25.69	no	no	no	120	80	3.1	140	54	no
38719	F	71	74	172	1.88	25.01	no	yes	no	160	75	2.3	126	65	no
38821	F	66	80	174	1.97	26.42	no	no	no	110	65	1.5	98	66	no
39013	F	74	68	160	1.74	26.56	no	yes	no	160	65	4.6	115	70	yes
39205	M	57	125	175	2.47	40.82	no	no	no	116	70	1.2	146	61	yes
39666	M	64	112	181	2.37	34.19	no	no	no	145	80	1.9	114	63	yes
40079	M	73	87	178	2.07	27.46	no	yes	no	175	65	1.8	233	53	no
40121	F	65	67	159	1.72	26.50	no	yes	no	135	75	3.6	116	73	no
40206	M	60	68	160	1.74	26.56	no	no	no	142	76	2.2	115	70	yes
40578	M	67	72	171	1.85	24.62	yes	yes	no	120	85	n/a	144	61	no
40972	M	68	87	170	2.03	30.10	no	no	no	155	80	1.6	136	64	yes
41335	F	72	78	158	1.85	31.24	no	yes	no	190	80	4.2	154	72	no
41647	M	74	78	166	1.90	28.31	no	yes	no	130	70	2.4	122	56	no
41739	M	72	65	168	1.74	23.03	yes	yes	no	135	70	2.5	118	62	no
42022	M	77	88	178	2.09	27.77	no	no	no	140	85	2.7	115	67	no
42120	M	71	113	168	2.30	40.04	no	no	no	150	85	2.6	156	67	no
42253	M	65	82	175	2.00	26.78	no	yes	no	120	80	2.5	154	56	no
42494	F	72	70	165	1.79	25.71	no	yes	no	155	80	2.3	115	70	yes
42617	M	61	74	171	1.87	25.31	no	no	no	130	80	1.25	139	61	yes
43054	M	59	90	178	2.11	28.41	no	no	no	130	65	1.3	166	69	yes
43375	M	76	91	185	2.16	26.59	no	no	no	110	65	2.8	121	45	yes
43397	M	72	92	170	2.08	31.83	no	no	no	115	65	3.2	143	32	no
43534	M	76	60	160	1.63	23.44	no	no	no	170	80	3.6	139	63	yes
43582	M	81	93	170	2.10	32.18	yes	no	no	170	75	5	159	62	no
43803	M	57	85	176	2.04	27.44	no	no	no	170	110	1.5	174	64	yes
44058	F	64	83	155	1.89	34.55	yes	no	no	200	80	3.3	156	62	no

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
44089	F	67	65	159	1.69	25.71	yes	no	no	100	60	2.5	116	67	no
44162	M	76	74	170	1.87	25.61	no	yes	no	115	70	1.9	113	61	no
44310	M	59	68	164	1.76	25.28	yes	no	yes	100	60	1.4	98	69	no
44349	F	74	91	162	2.02	34.67	no	no	no	140	80	2.3	101	72	no
44372	F	77	54	160	1.55	21.09	no	yes	no	136	75	2	201	60	no
44559	M	69	90	170	2.06	31.14	no	no	no	130	75	n/a	n/a	n/a	yes
44677	M	75	75	172	1.89	25.35	yes	no	no	122	74	3.3	121	68	no
44729	M	84	83	181	2.04	25.34	yes	no	no	140	75	2.6	140	68	no
44775	F	66	85	160	1.94	33.20	no	no	no	150	65	1.6	178	53	no
44987	M	58	72	170	1.84	24.91	yes	yes	yes	150	75	3.8	142	56	yes
45047	M	77	77	168	1.90	27.28	no	no	no	125	85	n/a	n/a	n/a	no
45065	M	79	81	172	1.97	27.38	yes	no	no	110	80	2.4	125	46	no
45300	F	78	50	165	1.51	18.37	no	no	no	110	60	1.1	91	69	no
45379	F	69	85	165	1.97	31.22	no	no	no	120	66	1.8	109	62	no
45411	M	73	60	167	1.67	21.51	no	no	no	195	95	2.4	141	32	no
45431	M	58	92	175	2.11	30.04	yes	yes	no	135	70	1.6	98	69	no
45540	F	92	80	163	1.90	30.11	n/a	n/a	n/a	150	90	n/a	n/a	n/a	yes
45780	M	68	70	165	1.79	25.71	no	no	no	120	70	2.1	119	72	no
45786	F	71	65	160	1.70	25.39	no	no	no	160	65	2.7	127	66	yes
45854	F	69	60	167	1.67	21.51	no	yes	no	110	80	1.6	90	68	no
45979	F	69	81	170	1.96	28.03	no	yes	yes	135	65	2.7	105	66	no
46004	M	72	93	187	2.20	26.59	no	no	no	120	80	1.4	126	65	no
46063	F	81	65	165	1.73	23.88	no	no	no	195	90	1.7	167	59	yes
46087	M	75	75	176	1.91	24.21	yes	no	no	185	85	2.2	143	59	yes
46123	M	70	82	178	2.01	25.88	no	yes	no	162	100	1.6	153	62	no
46193	M	56	105	180	2.29	32.41	yes	no	no	140	80	4	123	66	no
46198	M	84	72	170	1.84	24.91	no	no	no	120	70	2.6	147	51	no
46354	F	68	55	165	1.59	20.20	no	yes	no	110	70	1.35	98	68	no

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
46480	F	76	70	160	1.76	27.34	no	yes	no	130	70	2.2	122	65	yes
46527	M	59	89	175	2.08	29.06	no	no	no	145	85	1.15	122	67	yes
46770	M	77	80	162	1.90	30.48	no	yes	yes	160	75	n/a	123	70	no
46862	F	75	80	150	1.83	35.56	no	no	no	170	80	n/a	154	71	no
46880	F	73	98	170	2.15	33.91	no	yes	no	155	78	2.9	129	65	no
46971	M	74	74	172	1.88	25.01	no	yes	no	150	90	n/a	n/a	n/a	no
46978	F	70	93	165	2.06	34.16	no	yes	no	140	70	2.2	n/a	n/a	no
46989	M	75	68	169	1.79	23.81	no	yes	no	160	90	2.7	107	70	no
47017	F	69	76	158	1.83	30.44	no	yes	no	150	90	2.5	126	66	no
47019	M	69	75	169	1.88	26.26	yes	no	no	150	86	2.2	n/a	n/a	no
47086	M	65	70	163	1.78	26.35	yes	yes	no	150	80	n/a	108	72	no
47173	F	64	63	162	1.68	24.01	yes	n/a	n/a	135	80	n/a	75	76	no
47204	M	68	84	180	2.05	25.93	yes	no	no	155	85	2.6	121	33	no
47296	M	65	84	168	1.98	29.76	yes	yes	no	150	90	2.8	167	38	no
47347	M	77	80	169	1.94	28.01	yes	no	no	170	70	3	128	62	no
47356	F	65	59	154	1.59	24.88	no	no	no	145	65	1.8	n/a	n/a	no
47357	M	69	80	165	1.91	29.38	yes	no	no	150	90	2.5	n/a	n/a	no
47448	M	63	72	168	1.83	25.51	no	yes	yes	135	85	1.4	n/a	n/a	no
47457	M	66	100	170	2.17	34.60	no	no	no	135	75	1.6	166	47	no
47476	M	65	83	165	1.95	30.49	yes	no	no	125	80	3.4	151	49	no
47502	F	85	75	160	1.83	29.30	no	no	no	130	80	3.5	131	36	no
47879	M	74	79	172	1.94	26.70	n/a	n/a	n/a	100	60	n/a	113	64	no
47899	M	64	88	173	2.06	29.40	yes	no	yes	115	60	2.3	n/a	n/a	no
47987	F	68	58	158	1.60	23.23	yes	yes	no	130	70	2.1	120	53	no
48002	M	63	83	178	2.03	26.20	yes	yes	no	140	80	1.5	161	43	no
48006	M	68	78	172	1.93	26.37	yes	no	no	135	85	1.6	127	52	no
48040	M	79	70	170	1.82	24.22	no	no	no	135	80	2.8	n/a	n/a	no
48128	F	66	64	160	1.69	25.00	no	no	no	140	60	3	96	69	no

ID	Sex	Age	Weight	Height	BSA[10]	BMI[11]	Smoker	F hyp[12]	F stroke[13]	SP[14]	DP[15]	IMT[16]	LVMi[17]	EF[18]	Fall
48355	M	46	77	172	1.92	26.03	yes	no	no	145	75	3.3	108	68	no
48366	M	78	72	174	1.87	23.78	no	no	no	155	75	2	127	66	no
48396	M	77	82	169	1.96	28.71	no	no	yes	115	80	n/a	144	42	no
48410	F	81	94	162	2.06	35.82	yes	no	no	130	80	3.2	102	63	no
48526	M	69	69	165	1.78	25.34	yes	no	no	135	75	3	125	60	no
48576	M	69	90	165	2.03	33.06	no	no	no	150	90	4	124	61	no
48681	M	67	67	170	1.78	23.18	yes	no	no	120	80	n/a	n/a	n/a	no
48710	M	78	74	170	1.87	25.61	no	no	no	125	65	2.3	170	32	no
50965	M	75	90	182	2.13	27.17	n/a	n/a	n/a	150	80	n/a	111	66	no
51402	M	72	83	169	1.97	29.06	n/a	n/a	n/a	130	75	n/a	121	69	no
100-1046	M	85	97	165	2.11	35.63	no	no	no	135	70	3	146	56	no
100-1046	M	85	97	165	2.11	35.63	no	no	no	135	75	3	159	50	no
100-1070	F	75	72	162	1.80	27.43	no	no	no	150	75	1.4	149	45	no
100-200	M	83	75	170	1.88	25.95	no	no	no	145	70	3.3	129	58	no
100-467	m	92	62	165	1.69	22.77	no	no	no	120	80	3	126	57	no
100-959	F	66	89	167	2.03	31.91	no	no	no	120	70	1.9	175	28	no
100-97	M	64	80	164	1.91	29.74	no	no	no	170	95	2.2	175	42	no

The following exclusion criteria have been adopted:

- refusal of written informed consent;
- severe ocular disease;
- deafness in alone living subject;
- chronic obstructive pulmonary disease, (pre)dementia, or other disease which may reduce life expectancy.

The dataset consists of 168 hypertensive patients (including 60 female and 108 male, age 72 ± 8 years). Among the study sample, 47 subjects experienced a fall during 3 months within the registration.

2.3.3 Protocol and measurement system

The ECG Holter was performed after a one-month antihypertensive therapy wash-out. On 2 consecutive days, patients underwent a 24-hour ECG Holter recording. The recorders were applied between 9 and 11 AM on a working day, and the patients were asked to follow as closely as possible their usual daily activities during each monitoring session. They were asked to stay in bed from 11 PM to 7 AM, Moreover, the patients were evaluated by a cardiac and carotid ultrasonography, as described in section 2.2.3. The study was approved by the Ethics Committee of Federico II University Hospital Trust and the data were collected by the Department of Translational Medical science of the University of Naples Federico II in the framework of the Smart Health and Artificial intelligence for Risk Estimation (SHARE) project.

3 Data-mining

Data mining can be defined as "*the analysis of (often large) observational data sets to find unsuspected relationships and to summarize the data in novel ways that are both understandable and useful to the data owner*". It is an increasingly popular field including statistical, visualization, machine learning, and other data manipulation and knowledge extraction techniques aimed at gaining an insight into the relationships and patterns hidden in the data (Lavrač, 1999). The process of data mining includes the steps of data processing, feature extraction, feature selection, development of an algorithm, interpretation and evaluation. The data mining techniques could be distinguished in supervised (i.e. the algorithm infer a function from a labelled training data) and unsupervised (i.e. no a priori information is required and the technique is used to fit groups of instances characterized by homogeneous patterns). Formally, data represented in a table may be collected from measurements or acquired from experts. Rows in the table correspond to objects (training examples) to be analysed in terms of their properties (attributes) and the class (concept) to which they belong. In a medical setting, a concept of interest could be a set of patients with a certain disease or outcome. Supervised learning assumes that training examples are classified whereas unsupervised learning concerns the analysis of unclassified examples. Furthermore, the supervised learning techniques are usually distinguished in classification algorithms, which provide discrete output (e.g. binary class, such as health or disease condition; multiclass label for disease severity), and regression algorithms, which provide a continuous output (e.g. the risk of developing a disease condition). The current chapter provides an overview of the data-mining techniques that were used in this thesis.

3.1 Data-processing and feature extraction

The RR time-series in the selected databases were analysed in order to extract HRV measures, which were used as input of classification algorithms. The length of the recordings was selected according to the aim:

- nominal 24-hours (standard length for long-term HRV analysis)(Malik et al., 1996) for CHF severity assessment;
- 5 minutes (standard length for short-term HRV analysis)(Malik et al., 1996) for fast assessment of risk of developing vascular events;
- 30 minutes (concurrent analysis of nominal 24-hour recordings in non-overlapping 30 minute segments) (Hautala et al., 2010) for assessment of fall risk.

All the extracted features are reported in Table 3.1.

Table 3.1 HRV measures computed in this thesis

Abbreviation	Description	CHF	CV	Fall	Ref.
AVNN	Average of all the NN intervals	Yes	Yes	Yes	(Malik et al., 1996)
SDNN	Standard deviation of all NN intervals	Yes	Yes	Yes	(Malik et al., 1996)
SDANN	Standard deviation of the averages of NN intervals in all 5-minute segments	Yes			(Malik et al., 1996)
SDNN IDX	Mean of the standard deviations of NN intervals in all 5-minute segments	Yes			(Malik et al., 1996)
RMSSD	square root of the mean of the sum of the squares of differences between adjacent NN intervals	Yes	Yes	Yes	(Malik et al., 1996)
NN50	number of differences between adjacent RR intervals that are longer than 50 ms		Yes	Yes	(Mietus et al., 2002)
pNN50	percentage of differences between adjacent NN intervals that are longer than 50 ms	Yes	Yes	Yes	(Malik et al., 1996)
pNN10	percentage of differences between adjacent NN intervals that are longer than 10 ms	Yes			(Mietus et al., 2002)
HRVTi	HRV triangular index		Yes	Yes	(Malik et al., 1996)
TINN	triangular interpolation of RR interval histogram		Yes	Yes	(Malik et al., 1996)
TOTPWR / TP	Total spectral power up to 0.4 Hz	Yes	Yes	Yes	(Clifford and Tarassenko, 2005)
ULF	Spectral power between 0 and 0.003 Hz	Yes			(Clifford and Tarassenko, 2005)
VLF	Spectral power between 0.003 and 0.04 Hz	Yes	Yes	Yes	(Clifford and Tarassenko, 2005)
LF	Spectral power between 0.04 and 0.15 Hz	Yes	Yes	Yes	(Clifford and Tarassenko, 2005)
HF	Spectral power between 0.15 and 0.4 Hz	Yes	Yes	Yes	(Clifford and Tarassenko, 2005)
LF/HF	Ratio of low to high frequency power	Yes	Yes	Yes	(Clifford and Tarassenko, 2005)
VLF%	relative power in very low frequency band (0 - 0.04 Hz)		Yes	Yes	(Malik et al., 1996)
LF%	relative power in low frequency band (0.04 – 0.15 Hz)		Yes	Yes	(Malik et al., 1996)
HF%	relative power in high frequency band (0.15– 0.4 Hz)		Yes	Yes	(Malik et al., 1996)
VLF_{peak}	peak frequency of VLF band		Yes	Yes	(Malik et al., 1996)
LF_{peak}	peak frequency of LF band		Yes	Yes	(Malik et al., 1996)
HF_{peak}	peak frequency of HF band		Yes	Yes	(Malik et al., 1996)
HF_{nu}	power in high frequency band (0.15– 0.4 Hz), expressed in normalized unit		Yes	Yes	(Malik et al., 1996)
LF_{nu}	power in low frequency band (0.04 – 0.15 Hz), expressed in normalized unit		Yes	Yes	(Malik et al., 1996)
SD_1	short-term variability in Poincaré Plot		Yes	Yes	(Brennan et al., 2001)
SD_2	long-term variability in Poincaré Plot		Yes	Yes	(Brennan et al., 2001)
AppEn	Approximate Entropy		Yes	Yes	(Pincus, 1991)
SampEn	Sample Entropy		Yes	Yes	(Richman and Moorman, 2000)
CD	Correlation dimension		Yes	Yes	(Carvajal et al., 2005)
$Alpha_1$	short-term fluctuations in Detrended Fluctuation Analysis		Yes	Yes	(Penzel et al., 2003)
$Alpha_2$	long-term fluctuations in Detrended Fluctuation Analysis		Yes	Yes	(Penzel et al., 2003)
DET	determinism		Yes	Yes	(Eckmann et al., 1987)
REC	recurrence rate		Yes	Yes	(Eckmann et al., 1987)
L_{mean}	mean length of lines in recurrence plot		Yes	Yes	(Eckmann et al., 1987)
L_{max}	maximal length of lines in recurrence plot		Yes	Yes	(Eckmann et al., 1987)
DIV	Divergence		Yes	Yes	(Eckmann et al., 1987)
ShanEn	Shannon Entropy		Yes	Yes	(Eckmann et al., 1987)

In the current section, the computation details for each feature are briefly reported, considering the following notation: RR_j denotes the value of *j*'th *RR* interval and *N* is the total number of successive intervals.

3.1.1 Time-domain HRV measures

The most simple feature is the mean value of the RR interval time-series, referred as AVNN, and computed as in the following equation:

$$(1) AVNN = \frac{1}{N}\sum_{j=1}^{N} RR_j.$$

The standard deviation of the RR intervals (*SDNN*) is computed as follows:

$$(2) SDNN = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}(RR_j - AVNN)^2}.$$

The root mean square of successive differences (RMSSD) is given by:

$$(3) RMSSD = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}(RR_{j+1} - RR_j)^2}.$$

Another measure calculated from successive RR interval differences is the *NN50* which is the number of successive intervals differing more than 50 ms and the corresponding relative amount pNN50:

$$(4) pNN50 = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\vartheta(\left|RR_{j+1} - RR_j\right| > 50\, ms)}$$

where $\vartheta()$ is the heaviside step function (i.e., the discontinuous function whose value is zero for negative argument and one for positive argument, formally $\vartheta(x) = 0$ if $x < 0$, otherwise $\vartheta(x) = 1$) and $|\ |$ is the absolute value operator.

Similarly, the pNN10 is computed as follows:

$$(5) pNN10 = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}\vartheta(\left|RR_{j+1} - RR_j\right| > 10\, ms)}$$

Moreover, in long-term analysis (segments longer than 5 minutes), two other parameters were computed: SDANN, i.e. the standard deviation of the averages of NN intervals in all 5-minute segments; SDNN IDX, i.e. the mean of the standard deviations of NN intervals in all 5-minute segments.

In addition to the above statistical measures, there are some geometric measures that are calculated from the RR interval histogram. The HRV triangular index (HRVTi) is

obtained as the integral of the histogram (i.e. total number of *RR* intervals) divided by the height of the histogram which depends on the selected bin width. In order to obtain comparable results, a bin width of 1/128 seconds is recommended by International Guidelines(Malik et al., 1996). Another geometric measure is the *TINN* which is the baseline width of the RR histogram evaluated through triangular interpolation by least square methods(Malik et al., 1996).

3.1.2 Frequency-domain HRV measures

The frequency-domain HRV measures rely on the estimation of power spectral density (PSD), which could be computed with several methods. In this thesis Welch periodogram, AR method and Lomb-Scamble periodogram were adopted, for the following reason:

- Welch's periodgram has been previously adopted in the studies investigating discrimination ability of frequency-domain HRV measures between healthy and CHF patients(Asyali, 2003, Isler and Kuntalp, 2007, Melillo et al., 2011b), and, for that reason, it is considered as benchmark method. Moreover, the choice of parameters was performed according to these studies(Asyali, 2003, Melillo et al., 2011b), that is, the NN interval was first interpolated with cubic spline interpolation at 4 Hz, then, the interpolated series was divided into overlapping segments of length 256 points (with a 50% overlap) and each segment was Hamming windowed.
- AR model is the most widely used parametric method for HRV analysis, particularly with order model set to 16(Acharya et al., 2006).
- Lomb-Scamble periodogram has been shown to provide a superior PSD estimate of RR series compared to FFT techniques, with reference to ectopy removal or replacement (Clifford and Tarassenko, 2005). This was due to the fact the Lomb-Scamble periodgram did not require an evenly sampled time-series and consequently interpolation of the unevenly sampled RR times-series nor the replacement of missing beats.

The generalized frequency bands in case of short-term HRV recordings are the very low frequency (VLF, 0-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.4 Hz). The frequency-domain measures extracted from the PSD estimate for each frequency band include absolute and relative powers of VLF, LF, and HF bands, LF and HF band powers in normalized units, the LF/HF power ratio, and peak frequencies for each band.(Malik et al., 1996)

3.1.3 Nonlinear HRV measures

3.1.3.1 Poincare Plot

The two parameters of the Poincarè Plot SD_1 and SD_2 were computed according to the following formulae proposed by Brennan et al. (Brennan et al., 2001):

(6) $SD_1 = \frac{SDSD}{\sqrt{2}}$

(7) $SD_2 = \sqrt{2SDNN^2 - \frac{1}{2}SDSD^2}$

where *SDSD* is the standard deviation of the difference of RR interval time series.

3.1.3.2 Approximate Entropy

The *AppEn* was computed according to the algorithm here described.

A series of vector of length *m* $X_1, X_2, \ldots, X_{N-m+1}$ is constructed from the *RR* intervals as follows:

$X_i = [RR_i, RR_{i+1} \ldots RR_{i+m-1}]$.

The distance $d[X_i, X_j]$ between vectors X_i and X_j is defined as the maximum absolute difference between their respective scalar components. For each vector X_i, the relative number of vectors X_j for which $d[X_i, X_j] \le r$, $C_i^m(r)$ is computed where *r* is referred as a tolerance value (see the following equation).

$$C_i^m(r) = \frac{number\ of\ \{d[X_i, X_j] \le r\}}{N - m + 1} \quad \forall j \tag{8}$$

Then, the following index $\Phi^m(r)$ is computing by taking natural logarithm of each $C_i^m(r)$ and averaging them over *i*.

$$\Phi^m(r) = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} \ln C_i^m(r) \tag{9}$$

Finally, the approximate entropy is computed as:

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \tag{10}$$

.

Since several clinical studies(Pincus, 1991, Niskanen et al., 2004, Ho et al., 1997) have shown that either *m*=1 or 2 and *r* between 0.1 and 0.2 times the *SDNN* are suitable to provide valid value of *AppEn*, in the current thesis, *m*=1 and *r*=0.2 times the *SDNN* was adopted.

3.1.3.3 Sample Entropy

SampEntropy computation is very similar to *AppEn*, with two important differences in its calculation: first, in the computation of $C_i^m(r)$ the comparison of the vector *X(i)* with itself is included in the count for *AppEn* (self-match problem), while this comparison is excluded for *SampEn*; secondly, the logarithm is applied instead of subtraction in the final step. These changes aims to remove the bias in *AppEn*, as the count of the self-comparison in *AppEn* lower its value and the signals are interpreted as more regular than they are.

Formally, the three steps of *SampEn* computation are described by the following equations:

$$C_i^m(r) = \frac{number\ of\ \{d[X_i, X_j] \le r\}}{N-m+1} \quad \forall j \neq i \tag{11}$$

$$\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_i^m(r) \tag{12}$$

$$SampEn(m, r, N) = \log \frac{\Phi^m(r)}{\Phi^{m+1}(r)} \tag{13}$$

3.1.3.4 Correlation dimension

Also, the *CD* is computed similarly to *AppEn*. The reconstruction of the attractor is the first step, that is, a series of vector of length *m* $X_1, X_2, \ldots, X_{N-m+1}$ is constructed from the *RR* intervals as follows:

$X_i = [RR_i, RR_{i+\tau} \ldots RR_{i+\tau(m-1)}]$

where τ is the time delay and *m* is the embedding dimension. The second step is the estimation of Euclidean distances between each couple of vectors:

$$d[X_i, X_j] = \sqrt{\sum_{k=1}^{m} (X_i(k) - X_j(k))^2} \tag{14}$$

Then, the idea is to construct a function which estimates the probability that two arbitrary points on the orbit are close than *r*. So, the correlation integral function is determined by the following formula

$$C_m(r) = \frac{1}{N_m(N_m - 1)} \sum_{i}^{N_m} \sum_{j=1}^{N_m} \vartheta(r - d[X_i, X_j]) \tag{15}$$

where $N_m = N - \tau(m-1)$ and ϑ is the Heaviside function.

The correlation dimension is defined as the following limit value:

$$CD(m) = \lim_{r \to 0} \lim_{N \to \infty} \frac{\log C^m(r)}{\log r} \quad (16)$$

In practice, this limit value is approximated by the slope of the regression curve ($\log r$, $\log C^m(r)$).

The appropriate value of τ could be chosen using the minimal mutual information technique(Fraser and Swinney, 1986, Fraser, 1989), while the value of *m* could be estimated with the methods proposed by Grossberger and Procaccia(Grassberger and Procaccia, 1983); in HRV analysis the values of 1 and 10 are widely used value for τ and *m*, respectively and for that reason they are adopted in the current thesis.

3.1.3.5 Detrended fluctuation analysis

The DFA consisted in the following steps:

1) The average $\overline{RR}$ of the *RR* interval series is calculated on all the *N* samples. The alternate component of *RR* interval series, which is defined as *RR* minus its average value $\overline{RR}$, is integrated:

$$y(k) = \sum_{j=1}^{k} (RR_j - \overline{RR}), k = 1,...., N \quad (17)$$

.

2) The integrated series is divided into non-overlapping segments of equal length *n*. A least square line is fitted within each segment, representing the local trends with a broken line. This broken line is referred as $y_n(k)$, where *n* denotes the length of each segment.

3) The integrated time series is detrended as follows: $y(k) - y_n(k)$. The root-mean-square fluctuation of the detrended time series is computed according to the following formula:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} (y(k) - y_n(k))^2} \quad (18)$$

.

4) The steps from 2 to 4 are repeated for *n* from 4 to 64.

Representing the function *F(n)* in a log-log diagram, two parameters are computed: short-term fluctuations (*Alpha1*) as the slope of the regression line relating $\log(F(n))$ to $\log(n)$ with *n* within 4-16; long-term fluctuations (*Alpha2*) as the slope of the regression line relating $\log(F(n))$ to $\log(n)$ with *n* within 16-64.

3.1.3.6 Recurrence Plot

The Recurrence Plot is designed according to the following steps.

As in *CD* computation, vectors $X_i = (RR_i, RR_{i+\tau}, ..., RR_{i+(m-1)\tau})$, with $i=1,..., K$, with $K=[N-(m-1)\tau]$, where *m* is the embedding dimension and τ is the embedding lag, are defined.

The Recurrence Plot is a K-dimensional matrix of dots, where a dot is placed if the Euclidean distance between X_i and X_j is lower than a threshold value *r*.

Formally, the following steps are suggested for achieving the Recurrence Plot:

1) A *K*-dimensional square matrix M_1 is calculated computing the Euclidean distances of each vector X_i from all the others.

2) A *K*-dimensional square matrix M_2 is calculated as the matrix whose elements $M_2(i,j)$ are defined as:

$$M_2(i,j) = \begin{cases} 1 & if \quad M_1(i,j) < r \\ 0 & if \quad M_1(i,j) > r \end{cases} \tag{19}$$

The Recurrence Plot is the representation of the matrix M_2 in which a dot is associated to one value, that is, an image in which black pixels correspond to ones and white pixels to zeros. M_1 is a symmetrical matrix as the distance between X_i and X_j is equal to the one between X_j and X_i and consequently, Recurrence Plot is a symmetric image along the diagonal.

According to findings by Niskander et al. and Dabire et al.(Dabire et al., 1998, Niskanen et al., 2004), the following values of the parameters should be chosen: $m = 10; \tau = 1; r = \sqrt{m} * SDRR$.

In the Recurrence Plot, lines are defined as series of diagonally adjacent black points with no white space. The length *l* of a line is the number of points which the line consists of.

Moreover, some measures of Recurrence Plot are widely computed: recurrence rate *(REC)* defined in equation 20; maximal length of lines (l_{max}); mean length of lines (l_{mean}); the determinism (*DET*) defined in equation 21; the Shannon Entropy (*ShEn*) defined in equation 22.

$$REC = \frac{1}{K^2}\sum_{i=1}^{K}\sum_{j=1}^{K} M_2(i,j) \quad (20)$$

$$DET = \frac{\sum_{l=2}^{l_{\max}} l * N_l}{\sum_{i=1}^{K}\sum_{j=1}^{K} M_2(i,j)} \quad (21)$$

, with N_l = number of lines of length l

$$ShEn = \sum_{l=l_{\min}}^{l_{\max}} n_l * \ln n_l \quad (22)$$

, with n_l = percentage of N_l over all the number of lines.

3.1.4 Commentary on the selected features

In this thesis, the conventional time-domain and frequency domain HRV measures have been computed, since they are widely used in medical domain studies, and this enables the comparison with the results of previous studies (Casolo et al., 1995, Panina et al., 1996, Sajadieh et al., 2003, Dekker et al., 2000, Binici et al., 2011, Arbolishvili et al., 2006). Moreover, the nonlinear parameters which have been shown to change in pathophysiological cardiac condition(Acharya et al., 2004a, Acharya et al., 2004b, Acharya et al., 2006, Chua et al., 2008), have been selected:

- Poincarè Plot parameters varied in case of premature ventricular complexes, atrial fibrillation, sick sinus rhythm and ventricular fibrillation;
- AppEn showed smaller values for cardiac abnormal cases, indicating smaller variability in the beat to beat, but, for sick sinus rhythm, it is higher compared to normal subjects;
- SampEn has been introduced in order to remove the bias, which exists in the computation of AppEn(Melillo et al., 2014);
- CD has been shown to decrease for different cardiac condition;
- DFA slopes are decreased in very highly varying signals like premature ventricular complexes, left bundle branch block, atrial fibrillation and ventricular fibrillation;
- RP plot showed, in normal cases, diagonal line and less squares indicating more variation indicating high variation in the heart rate. Abnormalities, like complete heart block and ischemic or dilated cardiomyopathy cases, show more squares in the RP plot indicating inherent periodicity and lower heart rate variation.

3.2 Feature selection

In this thesis, several features (measures) were extracted from ECG signals. Since the number of instances was relatively large compared to the number of available instances

for the training, feature selection techniques can be used to find the relevant features and discard the irrelevant or redundant ones in order to:

- achieve a faster implementation of the algorithms (less time and memory are required to build a classifier if there are fewer features);
- reduce or avoid the risk of over-fitting (models built on several features tend to be specific to the training set and, for that reason, less generalizable);
- improve the performances (irrelevant features could degrade the performance of the algorithms);
- improve the intelligibility of the classification models (it is easier to interpret the relations among a reduced number of features);
- avoid the so-called curse of dimensionality, i.e. when the number of dimensions of the problem increases, the amount of instances required for an effective output (e.g. classification) grows exponentially.

Formally, the problem of feature selection is defined as follows: given a set of d features, select a subset of size m that leads to the smallest classification error. The most straightforward approach to the feature selection problem would require: examining all $\binom{d}{m}$ possible subset of size m and selecting the subset with the smallest classification error. However, the number of possible subsets grows combinatorially, making this approach, which is referred as exhaustive search feature selection, impractical for even moderate values of m and d. Two other features selection techniques were adopted in this thesis: a chi-squared statistics(Liu and Setiono, 1995) and a correlation-based (Hall and Smith, 1997) feature selection methods. The first method ranked the features by computing the value of the chi-squared statistic of each feature with respect to the classification problem. The second method scores the worth of subsets of features by taking into account the usefulness of individual features for predicting the class along with the level of intercorrelation among them with the belief that good feature subsets include features highly correlated with the class, yet uncorrelated with each other. Moreover, in some circumstances, the feature importance measures based on Random Forests (RF) were computed(Breiman, 2001).

3.3 Classification algorithms

3.3.1 Classification and Regression Tree

Classification and Regression Tree (CART), developed by Breiman et al. (Breiman, 1984), has been used in several applications of pattern recognition especially for medical diagnosis (Esposito et al., 1997). The CART algorithm iteratively splits the data set, according to a criterion that maximizes the separation of the data, producing a tree-like decision structure (Breiman, 1984). The CART algorithms consists of two stages: tree growing and tree pruning (Breiman, 1984). In the former stage the tree grows by selecting

among all the possible splits, which generate the "purer" child nodes where the purest node is the one containing elements of only one class. The outcome of this step is further referred to as the Large-Tree. Among different functions that have been proposed for the measure of the impurity of each node *t*(Breiman, 1984) we adopted the Gini index criterion(Breiman, 1984), which for binary classification can be computed as follows:

$$Gini\ index(t) = 1 - \left(\frac{n_i}{n}\right)^2 - \left(\frac{n_j}{n}\right)^2 \quad (23)$$

where *t* is the considered node, *i* and *j* are the two class labels, n_i and n_j are the number of subject present at the node belonging to the class *i* or *j*, respectively, and *n* is the number of subject present at the node.

In the latter stage, the Large Tree is pruned according to a minimal cost-complexity function, which relies on the tree size and the misclassification error. The misclassification error is estimated by the inner 10-fold-crossvalidation of the CART. The data set is randomly divided into 10 subsets. One of the subsets is used as independent testing dataset while the other 9 subsets are used as training dataset. The tree growing and pruning procedure is repeated 10 times, each time with one of the 10 different subsets used as a testing set. The misclassification error is calculated as the percentage of misclassified cases averaged over all the 10 subsets.

This procedure is repeated pruning the tree and for each sub-tree the cost complexity function is computed as a linear combination of the number of nodes and of the cross-validated estimated of the misclassification error. The outcome of this stage is referred further to as the Best Sub-Tree, which is the sub-tree achieving the lowest value of the cost-complexity function. Further details about minimal cost-complexity pruning can be found in Breiman (Breiman, 1984).

3.3.2 C4.5

C4.5 is the landmark decision tree algorithm developed by Quinlan et al.(Quinlan, 1993). The feature of each node is selected in order to divide input samples effectively and information gain is used as a measure of effectiveness. After the induction of the decision tree, a pruning method was applied to reduce the tree's size and complexity.

3.3.3 Random forest

RF is a state-of-the-art classifier developed by Breiman(Breiman, 2001). It is composed of a number of decision trees that choose their splitting attributes from a random subset of *k* attributes at each internal node. The best split is taken among these randomly chosen attributes and the trees are built without pruning, as opposed to C4.5. One of the most relevant downsides of using RF, particularly in medical domain data-mining, is that its model is not easily understandable as a single tree.

3.3.4 Rotation forest

Rotation forest (RTF) is an ensemble method capable of both classification and regression, depending on the base classifier (Kuncheva and Rodríguez, 2007). By default, rotation forest uses C4.5 decision trees as the base classifiers, although it is capable of using just about any classifier or combination of classifiers. The algorithm focuses on presenting transformed data to the classifier by using a projection filter such as principal component analysis (PCA), non-parametric discriminant analysis, random projections, and independent component analysis. The most successful projection filter is the PCA filter (Kuncheva and Rodríguez, 2007). The algorithm uses the boostrap method for creating the training set for each base classifier. The feature set is randomly split into M subsets and principal component analysis is applied to each subset. All of the eigenvectors are retained as the new features in order to preserve the variance in the data. The idea why these M data transformations are performed is to encourage simultaneously individual accuracy and overall diversity of classifiers within the ensemble, as this is the most important precondition for a successful ensemble (Breiman, 2001).

3.3.5 Naïve Bayes classifier

Naïve Bayes Classifier (NB) uses the naive Bayes formula to calculate the probability of each class given the values of all the attributes and assuming the conditional independence of the attributes(John and Langley, 1995). A new instance is classified into the class with maximum calculated probability.

3.3.6 AdaBoost

AdaBoost (AB) is a meta-learning algorithm which works by incrementally running classifiers on samples of data instances and combining them into an aggregate model.(Freund and Schapire, 1996) Each individual or weak classifier contributes to the aggregate model in proportion to its accuracy. After each iteration, data instances are reweighted based on incorrect aggregate classifications. This boosts the emphasis of misclassified instances, refining the construction of weak classifiers in future iterations. In the current study, C4.5 was adopted as weak classifier in the AB algorithm.

3.3.7 Support Vector Machine

Support Vector Machine (SVM) belong to a general field of kernel-based machine learning methods and are used to efficiently classify both linearly separable and linearly inseparable data.(Vapnik, 1998) When the data are not linearly separable, they could be transformed to a higher dimensional space by using a transformation function, which is the so-called kernel function.

3.3.8 Multilayer perceptron

Multilayer perceptron (MLP) is one of the most popular neural network models due to its clear architecture and the simplicity of the algorithm(Bishop, 1995). It consists of a network of nodes (processing elements) arranged in layers. The principle of the network is that when data are presented at the input layer, the network nodes perform calculations in the successive layers until an output value is obtained at each of the output nodes. This output signal should be able to indicate the appropriate class for the input data.

3.3.9 MultiBoost

MultiBoost (MB) is regarded as an extension to AdaBoost that combines the AB algorithm with the wagging procedure, which is itself extension of the basic bagging method(Webb, 2000). Instead of K single classifiers used by the AB algorithm, MB constructs a number of sub-committees consisting of a number of trees. Each sub-committee has its own specific iteration in which it terminates. Sub-committee is formed by AB using wagging instead of bootstrap. Wagging works by setting random weights of instances to those drawn from an approximation of the continuous Poisson distribution. After the weights are assigned, the vector of weights is always standardized to sum to N. All instances in the training set are used to train the base classifier using the designated weights. Using C4.5 as the base classifier for MB is straightforward, as C4.5 handles weights associated to instances. Wagging is shown to be particularly successful in reducing the variance error.

3.3.10 RUSBoost and PCA

RUSBoost (RB) is a hybrid approach recently proposed by Seiffert et al. (Seiffert et al., 2010) to handle class imbalance. RB relies on the Random Under-Sampling technique and AB as boosting algorithm. CART was adopted as weak learner. RUS is one of the most common data sampling techniques, and simply removes examples from the majority class at random until a desired class distribution is achieved. However, since HRV features have been shown to be correlated, there is the risk that some of the computed features might be redundant and could worsen the classifier performance by increasing the running time and reducing its generalization ability. In order to find the optimal feature space, we adopted the PCA method (Kuncheva and Rodríguez, 2007) and we tested the proposed classifier with different number of dimensions.

3.3.11 Synthetic minority over-sampling technique (SMOTE)

SMOTE is an over-sampling approach in which the minority class is over-sampled by creating “synthetic” examples rather than by over-sampling with replacement(Chawla et al., 2002). The rare class was over-sampled by creating new synthetic rare class samples according to each rare class sample and its nearest neighbours.

3.4 Commentary on the selected data-mining methods

The data mining methods employed in this thesis have been applied for intelligent data analysis in medicine. In particular, machine learning algorithms are usually classified in three group and at least one algorithm for each group has been selected:

- Decision trees for inductive learning of symbolic rules;
- Bayesian classifier and SVM for statistical or pattern-recognition methods;
- MLP for artificial neural networks groups.

Since in medical domain it is crucial that any computerised system is able to explain and justify its decisions, methods which provided intelligible models are preferred. For examples, decision tree classifier often give an appropriate explanation: induced decision trees are fairly easy to understand: positions of attributes in the tree, especially the top (most informative) ones, often directly correspond to domain expert's knowledge(Lavrač, 1999).For that reason, in all the application described CART or C4.5, that are the most used decision tree algorithm, were employed. However, even if these methods performed an inner feature selection, they showed weak performance when the number of features is higher than instances, the features are strongly correlated and the dataset is unbalanced, such as the databases employed in the current study. To deal with these issues, the author proposed novel strategies, based on a feature selection step and/or an oversampling method. This enabled to obtain intelligible models with comparable performance of other up-to-date classifiers (such as RF or MLP), which provide models difficult to interpret.

The main problem with all the data-mining method is model shrinkage(Cooney et al., 2009), that is, their predictive ability declines sharply once the model is applied to an external dataset, which limits their utility in clinical practice. Validating a classifier involves testing it on a set of subjects (the test set) that is independent of the training set. When the dataset is large, one can simply divide it into a training and test set (hold-out method). An effective and statistically justified validation method that can be used with smaller datasets is the cross-validation. The quality of the biomedical engineering literature on these topics is extremely varied: at the low end of the quality scale, one can find many papers that report no validation studies at all, but merely show that the classifier works well on the training set, which tells nothing about the predictive value of the classifier when faced with new data; many other paper lack sufficiently clear description of the validation methods to enable readers to judge the validity of the work(Foster et al., 2014).

The author of the present thesis proposed and strongly recommend a methodology to estimate the classification performances, based on a nest cross-validation approach. First of all, the hold-out approach should be adopted to split the dataset in a test set and a training set. The training set should be used for the classifier training, including the tuning of algorithm parameters. The optimal parameter and feature should be chosen according

to cross-validated estimation of the classifier performances. Finally, in order to increase the external validity of the develop model, data from multiple medical sites should be preferred, and this could be a further development of the clinical studies described in this thesis.

3.5 Cloud-based architecture

In order to provide the advanced functionality of ECG processing and the classification models, a web-based architecture was developed in the framework of the in the framework of the UE-funded research project "Smart health and artificial intel-ligence for Risk Estimation" (SHARE). The SHARE platform aims to integrate recording device and a Cloud infrastructure and consists of several basic services as shown in Figure 3.1.

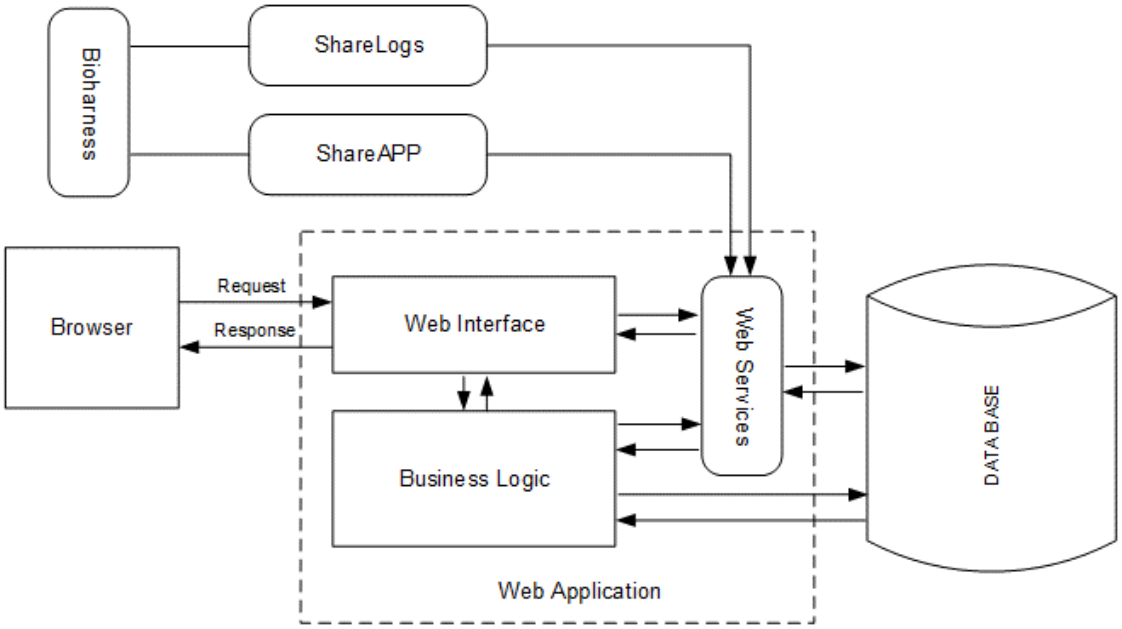

Figure 3.1 The system architecture of the SHARE platform

In the architecture design, the following requirements were considered:

- management of biomedical signal and data acquired in a highly seamless manner;
- set up a scalable framework to support the processing of multiple data streams for concurrent application services.
- persistent storage and exchange of data, their automatic analysis and availability everywhere to enable further decision making.

It would provide a framework supporting data management, concurrent application execution, and data analysis. For that reason, a Cloud environment providing storage and Virtual Machine (VM)-based approach for computational process was adopted. Each component of the system was briefly described in this section.

The Bioharness™ (vers. 3 BH3, Zephyr Technology) is a state-of-art commercial wearable multi-sensing device, which enables long-term recordings of several biomedical signals and data. The BH3 is worn in epidermal contact with an elasticated strap at the chest (50 g, 50 mm width). The monitoring device (weight 35 g, 80x40x15mm) acts as a data logger or transmitter, has a memory of up to 480 hours and battery life of up to 24 hours. Particularly, it can record one-lead ECG, breathing signal and respiration rate, posture, temperature, accelerometer signals along the 3 orthogonal axes. BH3 was chosen since it appeared a cheap and reliable device for health monitoring, useful both for cardiovascular issue and faller detection and since the manufacturer provided SDK.

ShareAPP (referred as Share Cardio Health in Google Play) is an Android application, which has been developed *ad hoc* to provide a user interface for the patients, who could transmit the data acquired by BH3 in real time though a smartphone. The App was designed in order to minimize the user interaction. Moreover, it enables the physician to submit a daily questionnaire to the patients.

ShareLogs is an *ad hoc* developed standalone application for Windows, which enables the upload of all the acquired signals by BH3 on the SHARE platform. It has been designed in order to follow the physician's usual workflow: at each planned visit, the physician upload all the data stored on the BH3. This avoid the risk of losing the data that were not stored in real-time (e.g., because the mobile device was offline or out of Bluetooth coverage area or network problems).

The Web Interface consists of a Content Management System (CMS) to show all the public information on the Project and a Restricted Area reserved to the system user, i.e. physician, researchers, patients. The CMS relies on Wordpress while the Restricted Area application was developed in ASP.NET (C#) by using Visual Studio 2013 and MySQL.

The Web Services represent the software interface to store the data, acquired by BH3 and transmitted though the ad hoc applications. Moreover, they provided the most advanced functionality of the system, i.e. remote processing and data mining.

The platform enabled the remote processing of ECG for HRV analysis, computing the feature described in the section 3.1. In particular, time-, frequency domain and nonlinear HRV measures are computed and examples are shown in

Figure 3.2, Figure 3.3, and Figure 3.4. The ECG recording were analysed concurrently in segments of user-specified length. Finally, the SHARE platform provides an automatic assessment of cardiovascular risk, relying on data-mining approach applied to HRV measures. In particular, now a tree-based model is integrated in the web platform and an example of the results is shown in Figure 3.5.

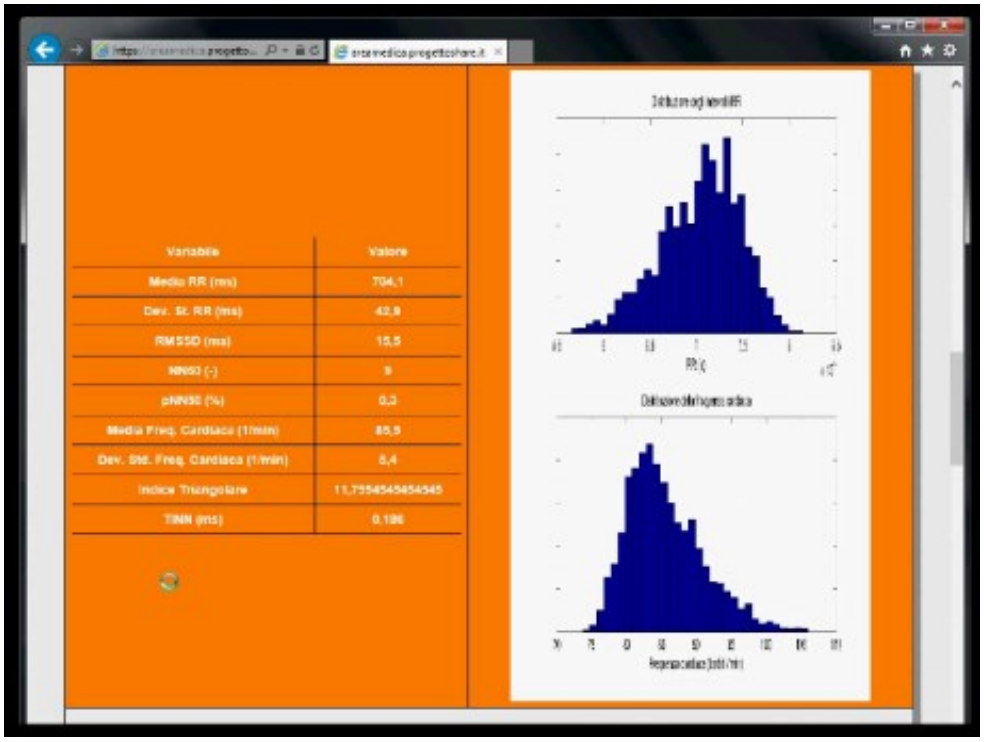

Figure 3.2 An example of HRV analysis in the time-domain as provided by the SHARE platform

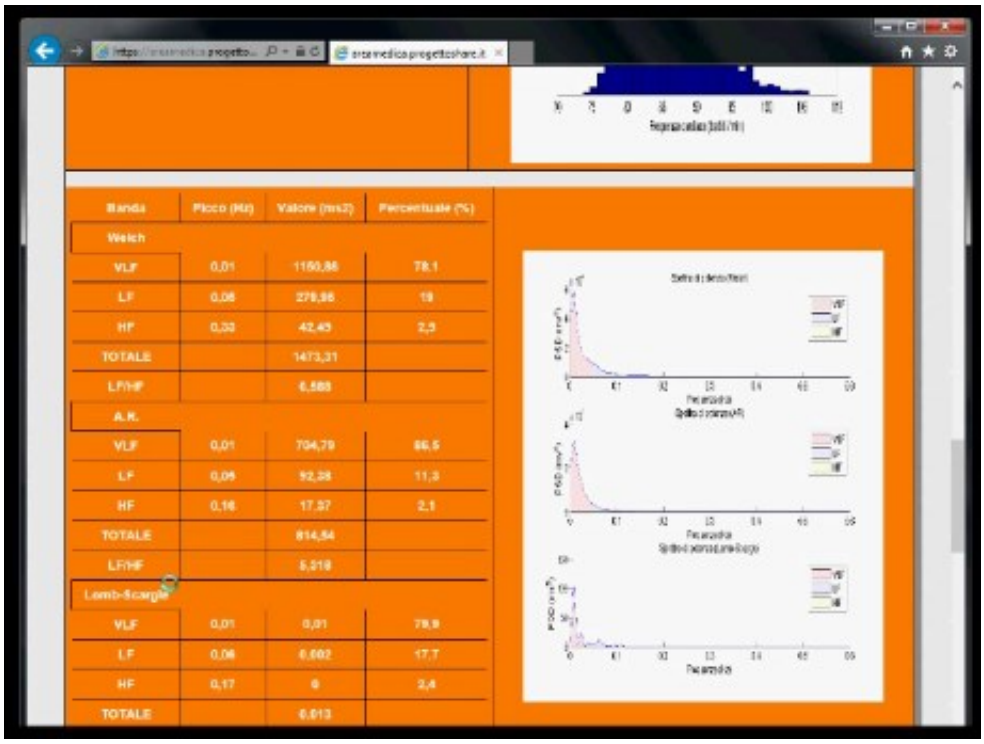

Figure 3.3 An example of HRV analysis in the frequency-domain as provided by the SHARE platform

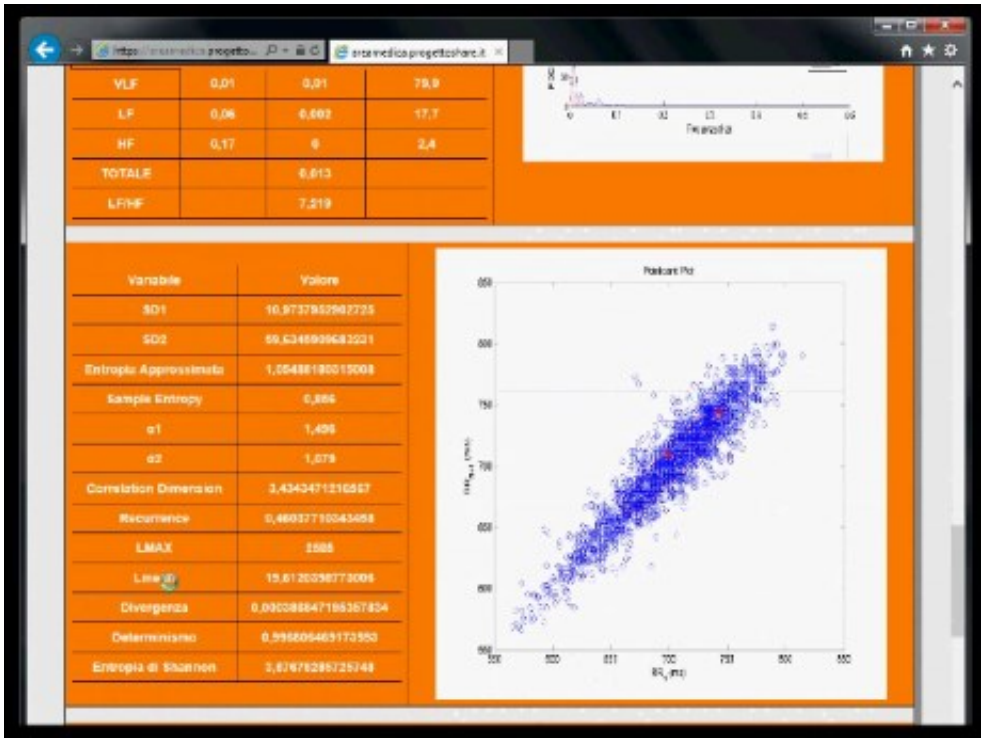

Figure 3.4 An example of nonlinear HRV analysis as provided by the SHARE platform

Figure 3.5 An example of the results of the classification as provided by the SHARE platform

The most important advantages of the implemented system are the following:

- it relies on a commercial multi-sensing wearable device for signal acquisition;
- the most advanced functionalities i.e. ECG processing and automatic classification, were provided by the centralized structure of the system, and the users, i.e. physician, needs only to have a Web browser running in a personal computer and a network connection to access these services;
- the technical programs can be updated and new tools can be easily added without interfering with the medical users. The addition or incorporation of a new technique in the GUI can be a quite simple task: a button is added which acts as a link to the function that runs under MATLAB and performs the corresponding processing. This fact makes the system into an open structure that can easily incorporate new tools as soon as they are developed, and therefore have an immediate presence in the support of clinical diagnosis;
- the proposed architecture overcome the system based on the discontinued MATLAB WEB SERVER toolbox(Garcia et al., 2002), which has been discontinued by the manufactures;
- most system proposed in previous studies focused on ECG storage and processing(Fortino et al., 2012, Hsieh and Hsu, 2012, Pandey et al., 2012), but they did not provide any automatic classification based on data-mining methods.

Moreover, the system appeared to be well accepted by almost all the patients (95%) with a limited amount of data lost (<20%). Finally, the results of the clinical trials could provide the scientific evidences needed for the CE marking of the system as a medical device.

4 Results and discussion

In this chapter the results of the data-mining methods applied to the database described in chapter 2 are shown and discussed.

4.1 Automatic assessment of congestive heart failure severity

The classification models described in this section aimed to discriminate between severe and mild CHF patients. The standard time- and frequency-domain HRV measures were extracted by 24h nominal ECG recordings from the Congestive Heart Failure RR Interval Database and the BIDMC Congestive Heart Failure Database. The patients with NYHA Class I and II were labelled as mild CHF, those with NYHA Class III and IV as severe CHF. CART algorithms with a feature selection algorithm (exhaustive search) was adopted in order to handle a small and unbalanced dataset. The performance of the proposed method was compared with other classifiers based on decision trees, i.e. C4.5 (Quinlan, 1996) and RF (Breiman, 2001), enhanced with SMOTE, a standard data level based method to deal with imbalance. The performance of the models are evaluated by the most common measures for binary classification estimated by 10-fold-crossvalidation.

4.1.1 Results

The performance of the proposed method (i.e. CART with exhaustive search feature selection approach) and benchmarks (i.e. C4.5 and RF, enhance with SMOTE) are reported in Table 4.1.

The proposed method achieved higher values of accuracy than the benchmarks. The higher performances were obtained by two different combinations of features: "TOTPWR, pNN10, pNN50, SDNN IDX" and "ULF, TOTPWR, pNN50".

Table 4.1 Classification performance measurement of the selected classifier estimated by 10-fold-cross-validation for classification of severe versus mild CHF patients

Classifier	Methods to handle class-imbalance	TP #	FN #	TN #	FP #	F1 %	ACC %	PRE %	SEN %	SPE %
CART	**Here proposed**	**28**	**2**	**7**	**4**	**90.3**	**85.4**	**87.5**	**93.3**	**63.6**
RF	SMOTE (k=5)	25	5	18	4	84.7	82.7	86.2	83.3	81.8
C4.5	SMOTE (k=5)	25	5	19	3	86.2	84.6	89.3	83.3	86.4
CART	SMOTE (k=5)	22	8	17	5	77.2	75.0	81.5	73.3	77.3
RF	None	26	4	4	7	82.5	73.2	78.8	86.7	36.4
C4.5	None	22	8	5	6	75.9	65.9	78.6	73.3	45.5
CART	None	29	0	0	11	84.5	73.2	73.2	100.0	0.0

TP: the number of severe CHF patients correctly classified
TN: the number of mild CHF patients correctly classified
FP: the number of mild CHF patients incorrectly classified as severe CHF patients
FN: the number of severe CHF patients incorrectly classified as mild CHF patients
ACC: Accuracy; PRE: Precision; SEN: Sensitivity; SPE: Specificity

The selected Best Sub-trees are represented in Figure 4.1 and Figure 4.2. Each terminal node is the graphical representation of a set of "if … then" rules. For instance, the terminal node 2 in the Figure 4.1 can be read as: "if TOTPWR is lower than 11080.25 ms^2 the subject is classified as a severe CHF patient".

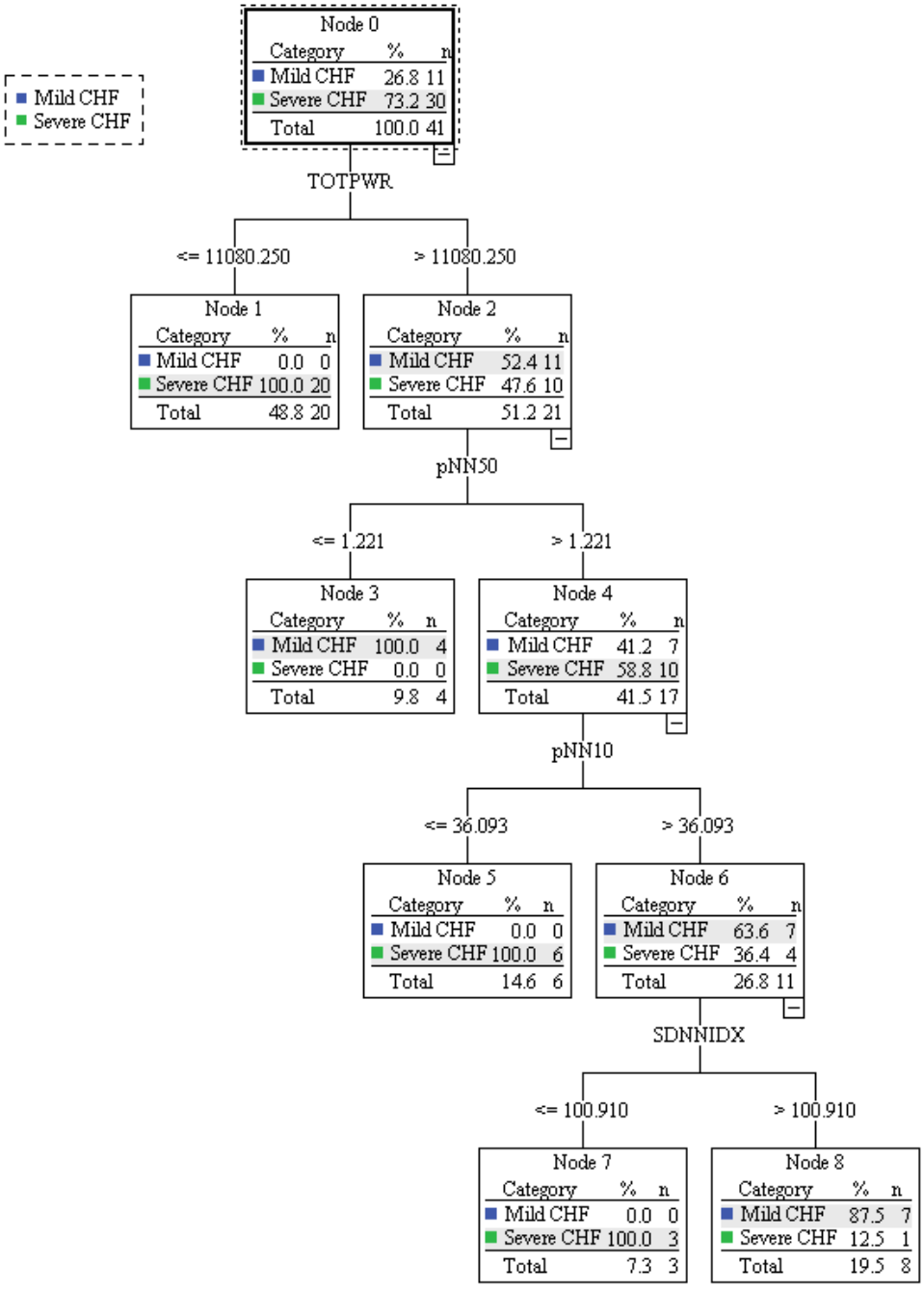

Figure 4.1 The final model tree for the classification of severe versus mild CHF patients based on the combination of HRV features: TOTPWR, pNN50, pNN10, SDNN IDX

In the model shown in Figure 4.1, the initial variable selected by CART (at node 1 split) was TOTPWR. The subjects whose TOTPWR is lower than 11080.25 ms^2 were all

correctly classified as severe CHF patients. CART selected pNN50 for the second node split. In this node split, the subjects whose pNN50 were lower than 1.22% were classified as mild CHF patients. Otherwise, the following classification split was based on pNN10, that is, if it is lower than 36.093%, the subject was classified as severe CHF patient, otherwise a final classification split is based on SDNN IDX with a threshold of 100.910 ms^2.

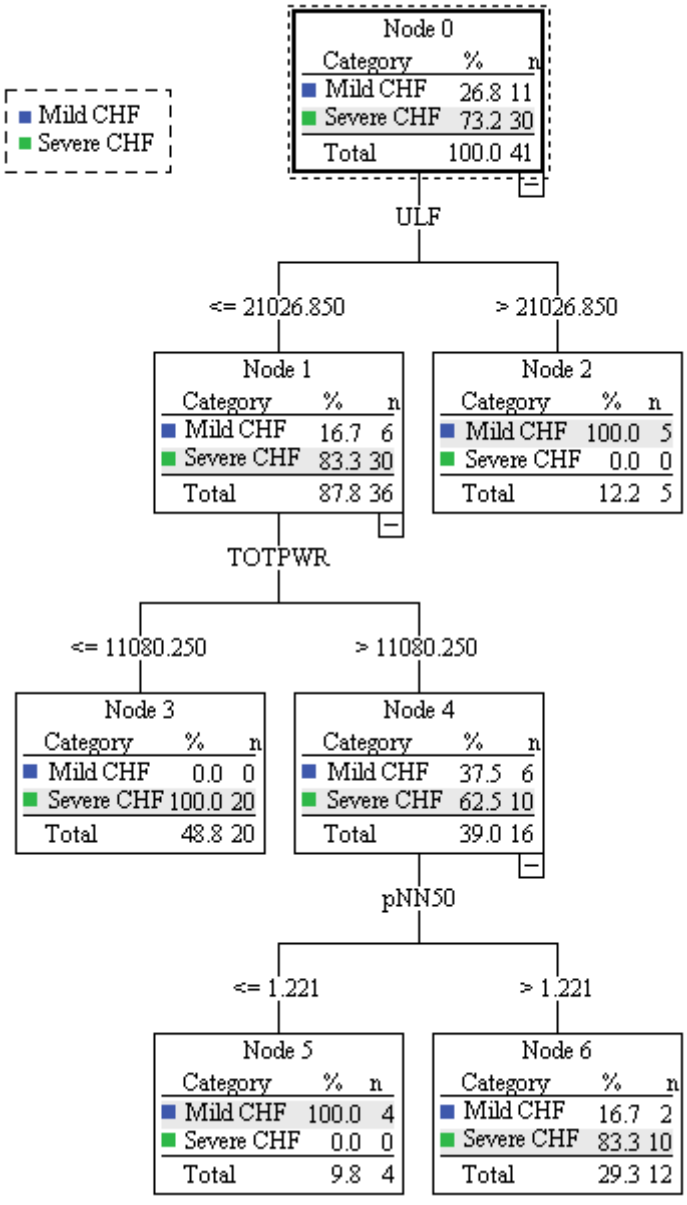

Figure 4.2 The final model tree (CART) for the classification of severe versus mild CHF patients based on the combination of HRV features: ULF, TOTPWR, pNN50

In the model shown in Figure 4.2, the initial variable selected by CART (at node 1 split) was ULF. The subjects whose ULF is higher than 21026.85 ms^2 were correctly classified as mild CHF patients. CART selected TOTPWR for the second node split. In this node split, the subjects who's TOTPWR were lower than 11080.25 ms^2 were classified as severe CHF patients. A final classification split is based on pNN50, that is, if it is lower than 1.22%, the subject was classified as a mild CHF patient, otherwise as a severe CHF patient.

4.1.2 Discussion

The classifiers based on the combinations of standard long-term HRV measures "TOTPWR, pNN10, pNN50, SDNN IDX" and "ULF, TOTPWR, PNN50" enable distinguishing severe from mild CHF patients with an accuracy rate of 85.4%, a sensitivity rate of 93.3% and a specificity rate of 63.6% (10-fold-crossvalidation estimates). The existence of these two best combinations can be explained by the high correlation between HRV measures (Bigger et al., 1992, Malik et al., 1996).

The selection of pNN10 in the best combination would confirm its discrimination power proved by Mietus (Mietus et al., 2002). As concerns pNN50, Mietus et al. (Mietus et al., 2002) showed that pNN50 failed to distinguish the LRPs and HRPs, while pNN50 is used in the Best Sub-Trees (see Figure 4.1 node 2 and Figure 4.2 node 4). This apparent inconsistency may be explained by considering that pNN50 could have a discriminative power only for the subgroups of patients which had high value of TOTPWR (TOTPWR > 11080.25 ms^2), consistent with the absence of statically significant differences between the two patient groups.

The sets of rules of both the models are clinically consistent, even if CART does not use any medical priori knowledge. In fact, the main clinical result of this research is that terminal node classifying as severe CHF are on the left, therefore revealing lower values of the splitting features for severe CHF patients (with the only exception of pNN50). This is coherent with the results showed by Casolo (Casolo et al., 1995), Panina (Panina et al., 1996) and Arbolishvili (Arbolishvili et al., 2006). It should be emphasized that the findings of Casolo (Casolo et al., 1995), Panina (Panina et al., 1996) and Arbolishvili (Arbolishvili et al., 2006) were obtained adopting different methods for power spectral density estimation. Several methods were proposed in literature in order to estimate PSD of RR intervals (Malik et al., 1996, Rajendra Acharya et al., 2006). Particularly, many PSD estimators are based on the hypothesis that the signal under examination is uniformly sampled (Laguna et al., 1998). In contrast, the RR series is unevenly sampled and requires resampling before PSD estimation. In this study, Lomb-Scamble periodogram (Lomb, 1976) was chosen as it estimates PSD of unevenly sampled signals without the requisite of resampling and its estimation has been proven to be more accurate than FFT-based method for RR data (Clifford and Tarassenko, 2005).

In relation to the methodology, the exhaustive research for feature selection improved the classification performance compared to CART model obtained using all the features. Moreover, as the study dataset is imbalanced, the performance of the proposed method are compared with SMOTE and with other two widely used decision tree methods. The proposed method achieved the highest performance in terms of accuracy rate and F1, which is one of the most suitable metrics for rare class problems (Shuli et al., 2009). Compared to a previous study, based on short-term HRV measures (Pecchia et al., 2010), the classifier proposed in the current studies achieved an higher accuracy and sensitivity (85.4% vs 79.3%, 93.3% vs 82.4%, respectively), even if with a lower specificity (75.0% vs 63.6%). This result leaded us to consider long-term HRV measures more effective for the individuation of severe CHF patients than short-term ones.

As regards the other classifier proposed in literature for CHF assessment, Guidi (Guidi et al., 2012) compared different algorithms to automatically classify CHF patients in three groups (mild, moderate and severe) and achieved an accuracy of 86% (independent set estimate; sensitivity and sensibility are not reported) by using neural network. Guiqiu (Guiqiu et al., 2010) proposed a classifier based on support vector machine, which achieved an accuracy of 74% (10-fold-cross-validation estimate) in discriminating between mild CHF (NYHA I) and moderate/severe CHF patients (NYHA II and III). We underline that the classifier proposed by Guidi (Guidi et al., 2012) was based on anamnestic and instrumental data (not including HRV measures), and the one by Guiqiu (Guiqiu et al., 2010) was based on twelve parameters including LF/HF and other parameters from clinical tests (blood test, echocardiography test, electrocardiography test, chest radiography test, six minute walk distance test). For that reason some parameters needed by the automatic classifier proposed by Guidi (Guidi et al., 2012) or Guiqui (Guiqiu et al., 2010) should be entered by physicians, while the adoption of only HRV measures, as in the current study, enables a completely automatic assessment.

The current study had the following limitations related to the employed holter databases: a small and unbalanced dataset, the differences in the sampling frequency of ECG recordings and the different extraction procedures of NN intervals (for instance, some records were not manually reviewed and incorrect RR detections due to artifact may occur). The small sample size could result in biased cross-validated performance estimates, even if appropriate strategies (feature selection and tree pruning) have been adopted to avoid over-fitting and to increase the generalization ability. As regards the imbalanced dataset problem, a standard approach (oversampling) have been adopted as a benchmark to compare the proposed method. As regards the sampling frequency of ECG, it should be remembered that finite sampling frequency introduces an error in the RR interval measurement, as previously shown by Merri (Merri et al., 1990). However, a sampling rate of 128 Hz, which is the lowest sampling rate of the records used in this paper, has been found to be accurate enough to locate the R-peaks and hence compute HRV (Malik et al., 1996).

4.2 Automatic identification of hypertensive patients at high risk of vascular events

The classification models described in this section aimed to identify hypertensive patients at higher risk to develop vascular events in the 12 months following the ECG recordings. Time-, frequency-domain and nonlinear HRV measures were extracted by 5-minute ECG segment randomly chosen from 24h nominal holter recordings. The patients who underwent a vascular event in the one year follow-up after ECG recording were labelled as high-risk, while the subject who were free of vascular event were labelled as low-risk. Several classification algorithms, with two feature selection algorithms, were adopted. In order to assess the generation ability of the models, the hold-out approach was adopted, i.e. the whole dataset was split into two subsets: training set (60% of instances) and test set (the remaining 40% of instances). The training set was used for feature selection and choice of the optimal parameters and SMOTE was adopted in order to handle a small and unbalanced dataset. The choice of the algorithm parameters and best subset of features was based on the performances (i.e. accuracy, then sensitivity and finally specificity) estimated by 10-fold cross-validation. The test set was adopted to evaluate the performance of the developed classifiers (with the features and parameters chosen on training set): ROC curves were constructed to compare the predictive value of each method for predicting vascular events and accuracy, sensitivity, specificity were computed according to standard formulae.

4.2.1 Results

The clinical characteristics of the study sample of patients were reported in Table 4.2. No statistical differences were detected between the two groups of patients in the demographic and clinical features.

Among the 33 HRV features, the chi-squared statistics feature selection method identified as relevant the following features (reported in descending order of ranking): CD, SampEn, SD_2, SDNN, LF, LF_{peak}, HF, HRVTi, TP, $LF_{\%}$, while the correlation-based algorithm selected the subset of the following features: HRVTi, LF, HF, $LF_{\%}$, LF_{peak}, SD_2, SampEn, CD. Figure 4.3 showed the importance of each feature as computed by the RF algorithm. All the features identified by the feature selection methods were ranked among the ten most important features by RF, with the only exception of TP, which was ranked as 13rd.

For each data-mining method, the optimal combination of parameters and the best subset of input features were selected by maximizing the accuracy estimated by 10-fold-crossvalidation as shown in Table 4.3. AB classifiers were developed by varying the number of iteration from 20 to 400 and C4.5 trees (both as single classifier and as base classifier in AB) were developed by varying confidence factor for pruning from 0.05 to 0.5, minimum number of instances per leaf from 5 to 20. MLP were trained by varying the learning rate from 0.3 to 0.9, the momentum from 0.2 to 1 and the number of epoch

form 100 to 2000. RF was constructed using an ensemble of random trees from 20 to 400 with no depth limit and varying the number of randomly chosen features from log2(n)+1 to n, where n is the number of feature. As regards SVM, we used radial basis function kernel, varying gamma from 10^{-5} to 10.

Table 4.2 Clinical and demographic features of the subjects stratified by cardiovascular risk

Clinical Features	Low-risk subjects	High-risk subjects	p-value
Age (years)	71.4±7	74.1±6.5	0.136
Sex (female)	41 (33.6%)	8 (47.1%)	0.277
Family history of hypertension	41 (33.6%)	7 (41.2%)	0.622
Family history of stroke	10 (8.2%)	3 (17.6%)	0.236
Smoking	35 (28.7%)	5 (29.4%)	0.983
Diabetes	18 (14.8%)	3 (17.6%)	0.834
Diastolic Blood Pressure (mmHg)	76.3±9.1	73.5±8.4	0.204
Systolic Blood Pressure (mmHg)	136.6±19.5	141.7±23.5	0.326
Total Cholesterol (mg/dl)	175.7±35.1	182.9±42.7	0.460
Low Density Lipoprotein (mg/dl)	101±30.1	102±34.3	0.907
High Density Lipoprotein (mg/dl)	52.4±13.1	53.3±15.3	0.813
Body Mass Index (kg/m^2)	27.6±3.9	27.9±4.9	0.793
Body Surface Area (m^2)	1.9±0.2	1.9±0.2	0.442
Alpha-blockers	17 (13.9%)	3 (17.6%)	0.782
Beta-blockers	50 (41%)	6 (35.3%)	0.487
ACE inhibitor	37 (30.3%)	8 (47.1%)	0.247
Dihydropyridine	27 (22.1%)	7 (41.2%)	0.131
Intima Media Thickness (mm)	2.3±0.7	2.4±1.1	0.685
Left Ventricular Mass index (g/m^2)	130.1±26.1	140.2±25.1	0.135
Ejection Fracion (%)	59.3±10.9	57.8±13	0.591

Data are expressed as mean and standard deviation for continuous variables (e.g. age) and as count and percentage of patients per each group for categorical variables (e.g. gender).

C4.5 and AB achieved the highest performances with chi squared feature selection algorithm, while MLP and NB with the correlation-based algorithm. SVM and RF performed well with all the features (i.e. without any feature selection step).

The performance measurements estimated on the independent test set are reported in Table 4.4 for each classification algorithm based on HRV features. The RF outperformed the other data-mining methods by achieving the best value of performance measures, i.e., an accuracy of 85.7%, a sensitivity of 71.4%, and a specificity of 87.8%. The prediction based on the echographic parameters, i.e., IMT and LVMi, resulted in a very low sensitivity rate (<45%), as shown in Table 4.4.

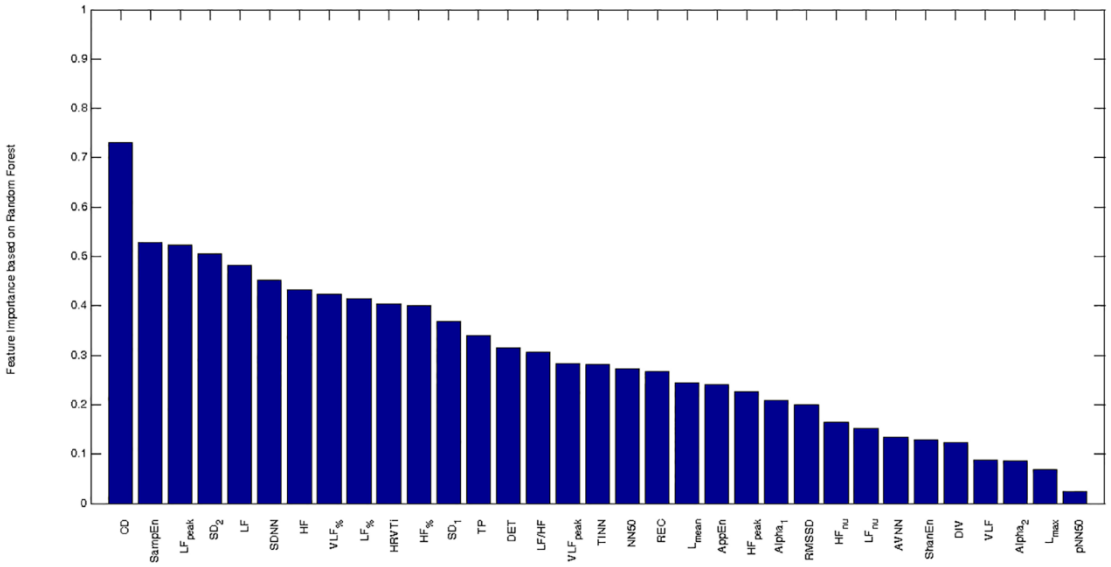

Figure 4.3 Feature importance computed by using Random Forest algorithm.

Table 4.3 Performance measurement (10-fold-crossvalidation estimation) of the proposed algorithms based on HRV features

Classifier	Parameters	Feature selection (# features)	AUC	ACC	SEN	SPE
AB	NI: 220; CF 0.5; MI: 20	None (33)	94.5%	91.8%	93.2%	90.4%
AB	NI: 20; CF: 0.3; MI: 10	CFS (8)	92.2%	85.6%	86.3%	84.9%
AB	**NI: 120; CF: 0.45; MI: 10**	**X^2-FS(10)**	**94.7%**	**89.0%**	**90.4%**	**87.7%**
C4.5	CF: 0.3; MI: 5	None (33)	80.3%	76.7%	78.1%	75.3%
C4.5	CF: 0.3; MI: 5	Correlation (8)	82.8%	80.8%	87.7%	74.0%
C4.5	**CF: 0.1; MI: 5**	**X^2-FS (10)**	**83.0%**	**76.7%**	**76.7%**	**76.7%**
MLP	LR 0.3; M 0.6; NE 200	None (33)	86.7%	82.9%	80.8%	84.9%
MLP	**LR 0.6; M 0.4; NE 200**	**Correlation (8)**	**86.9%**	**78.1%**	**86.3%**	**69.9%**
MLP	LR 0.3; M 0.2; NE 1800	X^2-FS (10)	86.1%	78.8%	82.2%	75.3%
NF	-	None (33)	72.4%	65.8%	76.7%	54.8%
NF	**-**	**Correlation (8)**	**80.1%**	**70.5%**	**78.1%**	**63.0%**
NF	-	X^2-FS (10)	77.8%	71.9%	82.2%	61.6%
RF	**NT 300 NF 5**	**None (33)**	**94.5%**	**88.4%**	**91.8%**	**84.9%**
RF	NT 20 NF 5	Correlation (8)	92.3%	87.7%	90.4%	84.9%
RF	NT 400 NF 4	X^2-FS (10)	93.2%	89.0%	93.2%	84.9%
SVM	**G: 1.4**	**None (33)**	**93.1%**	**89.0%**	**86.3%**	**91.8%**
SVM	G: 2.3	Correlation (8)	89.1%	81.5%	84.9%	78.1%
SVM	G: 1.6	X^2-FS (10)	89.2%	80.8%	86.3%	75.3%

CFS: correlation-based feature selection algorithm (a subset of 8 HRV features)
X^2-FS: chi-squared feature selection algorithm (a subset of 10 HRV features)
NI: number of iteration; ML: minimum number of instances per leaf; CF: confidence factor for pruning;
LR: learning rate; M: momentum; NE: number of epoch;
NT: number of trees; NF: number of randomly chosen features; G: gamma;
AUC: area under the curve; CI: confidence interval; ACC: accuracy; SEN: sensitivity; SPE: specificity;
In bold: the best performances of each classifier.

The ROC curves (estimated on the independent test set) for predicting vascular events over twelve months with HRV or echographic parameters are compared in Figure 4.4. The HRV-based classifier showed higher AUC compared to echographic parameters. Among clinical parameters, the higher AUC was achieved by LVMi, followed by IMT. The other clinical available parameters (e.g. blood pressure, cholesterol) resulted in ROC with AUC lower than 0.5, i.e., worst performance than random choice, and for that reason, they are omitted. Among HRV-based classifier, SVM achieved the highest AUC, followed by RF.

Since AB achieved satisfactory performances, it was interesting to observe the rules obtained from the decision tree with the highest weight, shown in Figure 4.5:

- the subject was classified as low-risk if HRVTi>13.6;
- a depression of HRVTi (<13.6) associated with a decreased SampEn (<0.997) or decreased $LF_{\%}$ (<18.1%) leaded to high-risk classification;
- otherwise, the subject was classified based on LF and CD, in particular, reduced CD (<3.43), although with LF > 0.011 s^2, leaded to high-risk classification, otherwise, the subject was classified as low-risk.

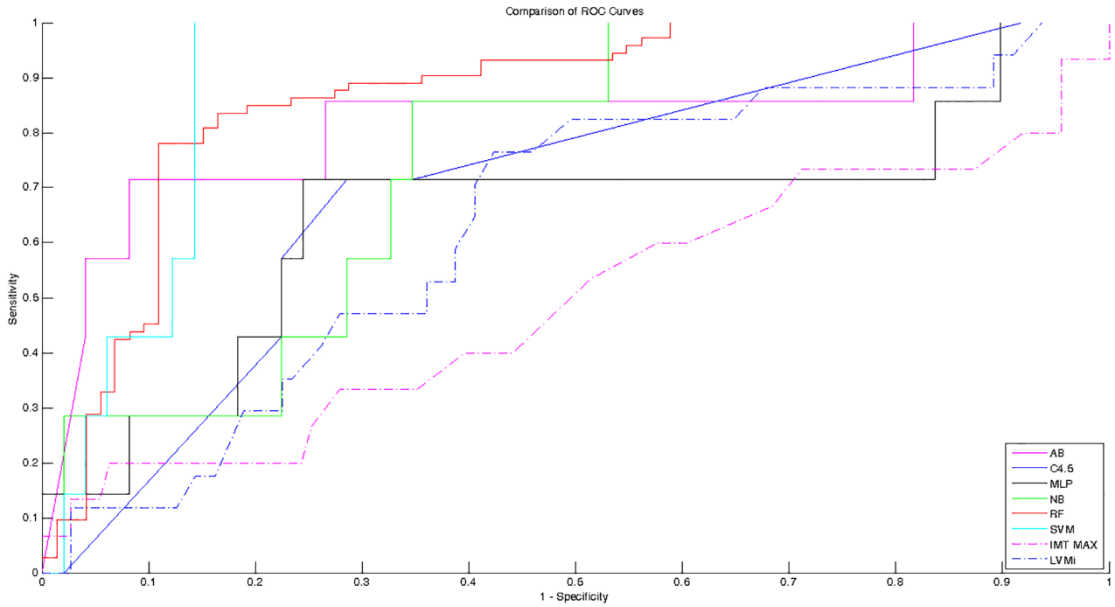

Figure 4.4 Receiver-operator characteristic curves for predicting vascular events by HRV-based classifiers and echographic parameters.
The HRV-based classifiers are able to predict vascular events with higher sensitivity and specificity rate than echographic parameters. Sensitivity is determined from the proportion of patient developing a vascular event identified as high risk; specificity is determined from the proportion of patient free of vascular events identified as low risk. Solid lines represent classifier based on HRV features, dash-dot lines represent classifications based on echographic parameters.

Table 4.4 Performance measurements estimated on the test set (hold-out estimation) of the best classifiers based on HRV features and of classification based on echographic parameters

Classifier / parameter	Area under the curve	Accuracy (95% CI)	Sensitivity	Specificity
AB	81.9%	83.9%(76.9 – 86.6)	71.4%	85.7%
C4.5	69.8%	75.0% (67.7 – 79.1)	57.1%	77.6%
MLP	64.7%	76.8% (69.5 – 80.6)	42.9%	81.6%
NF	74.9%	69.6% (62.4 – 74.4)	57.1%	71.4%
RF	88.8%	85.7% (78.7 – 88.1)	71.4%	87.8%
SVM	90.1%	83.9% (76.9 – 86.6)	71.4%	85.7%
LVMi	63.5%	69.5% (69.9-73.0)	41.2%	73.9%
IMT MAX	49.1%	61.9% (57.3-65.8)	40.0%	64.9%

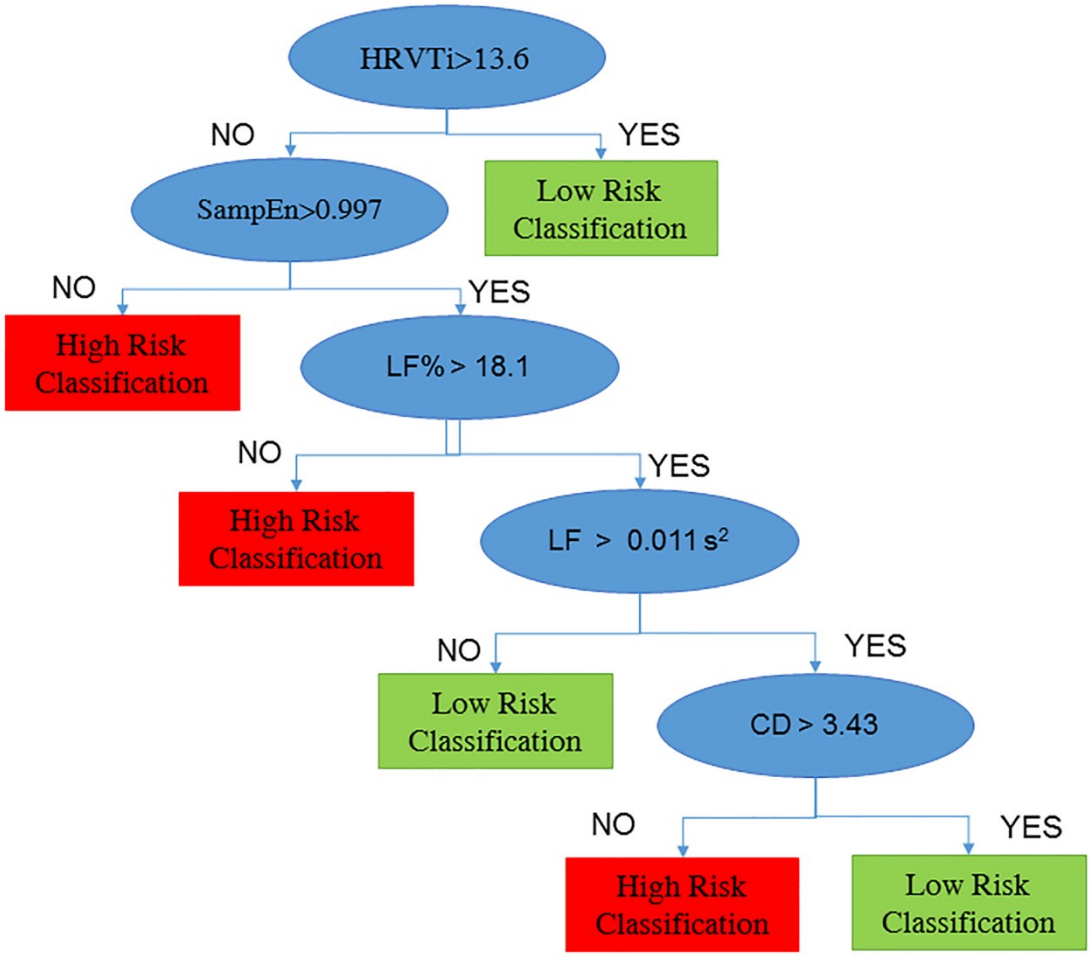

Figure 4.5 Decision tree for prediction of vascular events. The decision tree shows the set of rules adopted for classify high and low risk subjects:

4.2.2 Discussions

HRV features extracted from 5 minutes excerpts of 24 hours clinical ECG database of hypertensive patients were used to develop a computer-aided predictive tool that

improves risk stratification. Tree-based models applied on HRV features resulted effective in identifying high-risk patients among a population of hypertensive patients.

Linear HRV features demonstrated prognostic value for vascular events (Sajadieh et al., 2003, Dekker et al., 2000, Binici et al., 2011). Nevertheless, these traditional measures had only a partial predictive capability. The feature selection and ranking showed that nonlinear features, particularly CD, SampEn and SD_2, increased the discrimination power when they were used in combination with the linear HRV features, such as HRVTi, LF, and HF. As a result, tree-based models showed to be effective at predicting vascular events among hypertensive. Nevertheless, the results clearly showed that the HRV-based classifiers had a better prognostic capacity compared with LVMi and IMT, which are considered as powerful predictors of vascular events (Lorenz et al., 2007, Nagai et al., 2013, Schillaci et al., 2000).

The sensitivity and specificity rates obtained in the current study were comparable with the performances achieved by Ebrahuimzaded et al.(Ebrahimzadeh et al., 2014) and by Song et al.(Song et al., 2014), who recently proposed HRV-based classifier for prediction of sudden cardiac death. However, in the present study none of the cardiovascular and cerebrovascular events occurred over the follow-up was fatal. Moreover, in the current study, we adopted a nested cross-validation approach: an inner 10-fold-crossvalidation loop was performed for model section (i.e., features selection and machine learning parameter optimization), while a hold-out test set was used to obtain almost unbiased estimates of the true classification performances.

The sets of rules of the tree models presented were consistent with the findings of previous studies, even if no medical a priori knowledge was adopted in the data-mining methods. In fact, depressed HRV was showed to be associated with high cardiovascular risk in previous studies(Sajadieh et al., 2003, Dekker et al., 2000, Binici et al., 2011). Since HRV was proven to be the result of changes in heart rate caused by fluctuations in sympathetic and parasympathetic outflow, less compensatory change, as evaluated by depressed HRV, suggested a less adaptive ANS. One of the reasons could be that ANS resulted less sensitive for minor hemodynamic changes in some hypertensive patients, which could have been a direct cause of the vascular event registered in this study. Furthermore, a possible mechanism underlying our findings could be low-grade inflammation: it has been suggested that autonomic imbalance could activate inflammation by influencing the bone marrow and lymphoreticular system and increased inflammation is associated with higher risk of cardiovascular events(Sajadieh et al., 2004). Finally, another possible explanation for the association between HRV and vascular risk was that individuals with low HRV already suffered from subclinical or silent vascular disease, which, if not detected, resulted in cardiovascular events in the following months (Hillebrand et al., 2013).

As regards the comparison of data-mining methods, RF showed extremely good performance in the current study when comparing several methods for diagnosis of congestive heart failure based on HRV features, confirming previous findings (Jovic and Bogunovic, 2011). Moreover, RF and SVM performed well without any feature selection, consistently with the capability of these algorithms to constitute embedded feature selection strategy, as demonstrated in previous studies (Saeys et al., 2008, Maldonado et al., 2011).

The clinical feasibility and uptake of the developed tool are now tested in a prospective study in subjects aged 55 and over recruited by the Centre of Hypertension of the University Hospital of Naples. Moreover, since 5-minute HRV measurement is inexpensive, easy to assess, and non-invasive, future research will focus on the clinical applicability of the system as a screening tool in non-specialized ambulatories (e.g. at General Practitioners'), in order to identify high-risk patients to be shortlisted for more complex (and costly) investigations. Improved identification of individuals at risk for the development of vascular events may result in more targeted and adequate prevention strategies.

4.3 Automatic identification of hypertensive patients with history of fall

The classifier described in this section aimed to identify fallers among hypertensive patients (i.e. subject who referred at least one fall within three months from the ECG recordings). Time-, frequency-domain and nonlinear HRV measures were extracted by concurrent analysis of non-overlapping 30-minute ECG segments from 24h nominal holter recordings [8]. Several tree-based classification algorithms were adopted. In order to assess the performance of the classifiers, the 10-fold person-independent cross-validation[10] was adopted. In the 10-fold person-independent cross-validation method, subjects are partitioned into two subsets in each round (totally 10 rounds): one with 90% subjects for training and the other with 10% subjects for testing. This technique guarantees that each subject appears only once in the testing set and 9 times in the training set and any subject used for testing does not appear in the training set because the partition is based on the subjects rather than the individual excerpts. Since a subject-based classification was required, for each subject, the proportion of excerpts classified as fallers was computed and considered as an estimate of the probability that the subject belongs to fallers. A subject-based ROC curve analysis was performed: for all the cut-points, true and false positive rates were calculated and we selected as best cut-point the one that maximizes the true positive rate, provided a false positive rate lower than 20%.

4.3.1 Results

No significant differences in age and gender distribution were detected between the subjects with and without an history of fall (at least one fall within 3 months from the recordings).

Several classification algorithms have been trained and tested with the parameter values here reported:

- RF was constructed using an ensemble of 100 random trees with no limit to tree depth;
- RTF was constructed of an ensemble of 10 C4.5 trees using PCA filter (all dimensions retained);
- AB was used in combination with C4.5 classifier, the number of iterations was varied between 10 and 200 with steps of 50 iterations; C4.5 decision tree was tested with a variable minimal number of observations in each leaf (2, 5, 10, 20). Confidence factor for pruning was set to default of 0.25;
- MB was used in combination with C4.5 classifier, the number of iterations was varied between 10 and 200 with steps of 50 iterations, C4.5 decision tree was tested with a variable minimal number of observations in each leaf (2, 5, 10, 20). Confidence factor for pruning was set to default of 0.25. The number of sub-committees was set to 30% of the number of iterations (classifiers), as default.
- RB was evaluated with PCA dimension varying between 2 and 20. The number of iterations was varied from 20 to 500 with steps of 20 iterations, and CART was tested with a variable minimal number of observations in each leaf (5, 25, 50 and RB' default) and of misclassification cost ratio (from 1 to 20). Post-sampling 50:50 class distribution was adopted.

The ROC curves of the best classifier for each algorithm are shown in Figure 4.6 and the related performances for the selected cut-points (higher true positive rate, provided a false positive rate lower than 20%) are reported in Table 4.5.

Table 4.5 Best Performance of the Adopted Classification Methods for identification of subjects with history of falls

Classifier	AUC %	ACC %	SEN %	SPE %	PPV %	NPV %	OR (95% CI, p-value)
RF	46.3	67.3	21.3	85.1	35.7	73.6	1.5 (0.6-3.6, 0.32)
RTF	51.5	67.9	21.3	86.0	37.0	73.8	1.6 (0.7-3.9, 0.25)
AB	51.7	68.5	25.5	85.1	40.0	74.6	2.0 (0.9-4.5, 0.10)
MB	54.1	63.7	17.0	81.8	26.7	71.7	0.9 (0.4-2.2, 0.86)
RB	63.9	69.0	40.4	80.2	44.2	77.6	2.7 (1.3-5.7, 0.007)
RB & PCA	67.6	72.0	51.1	80.2	50.0	80.1	4.2 (2.0-8.7, <0.001)

AUC: area under the curve; ACC: accuracy; SEN: sensitivity; SPE: specificity; PPN: positive predictive value; NPV: negative predictive value; OD: odds ratio; CI: confidence interval

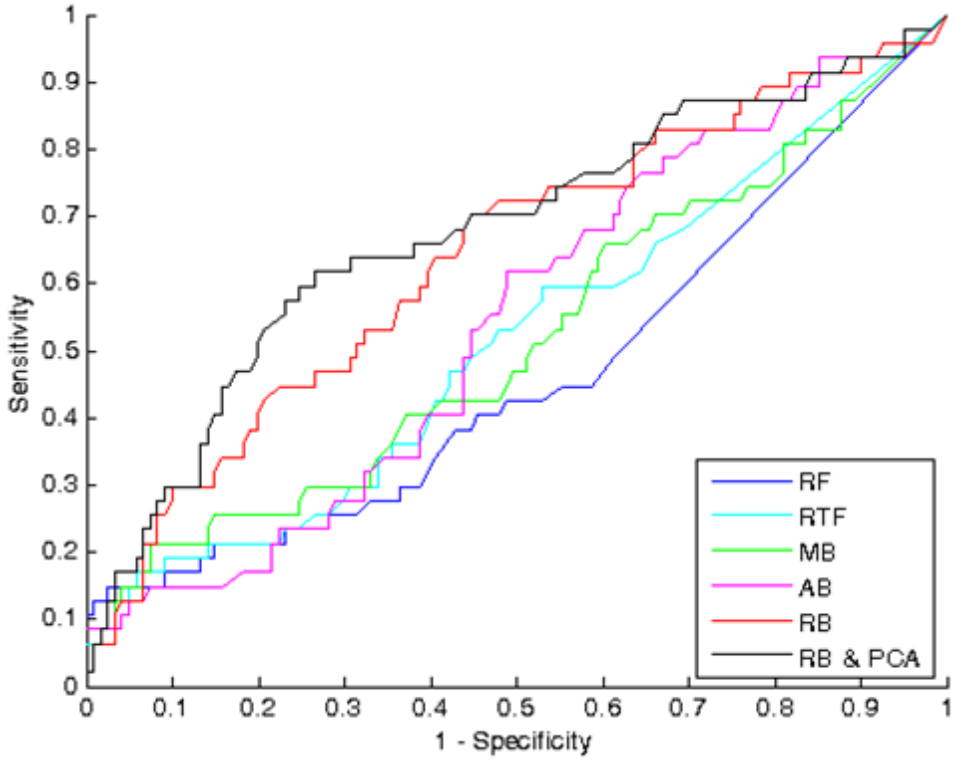

Figure 4.6 Comparison of the ROC curves of automatic classifier for identification of subjects with history of falls

The algorithms based on the boosting approach appeared to be superior to those based on bagging and the method based on RB achieved better performances, in terms of accuracy, sensitivity, positive and negative predictive value, compared to the other classifiers. These results were achieved with the following values of the parameters: 11 PCA dimensions, 180 iterations, learning rate of 0.7, misclassification cost ratio of 5, and 5 minimal observations in leaves. In particular, Random Under-Sampling improved the performance of AB algorithm, increasing the AUC from 51.7% to 63.9% and the sensitivity rate from 25.5% to 40.4% without relevant decrease in specificity rate. Using PCA resulted in a further improvement of the RB performance, by increasing sensitivity rate from 40.4% to 51.1% and AUC from 63.9% to 67.6% (with an unchanged specificity rate of 80.2%).

4.3.2 Discussions

An automatic classifier based on HRV analysis was developed in order to identify subject with a history of fall among hypertensive cardiovascular patients. To the best of authors' knowledge, only another study (Isik et al., 2012) investigated the discrimination power of HRV features for fallers' identification using 24h ECG, but it was a retrospective study and did not proposed an automatic classifier method. Moreover, in that study (Isik et al., 2012), the authors adopted only standard linear HRV methods, such as SDNN, RMSSD,

pNN50, and observed no significant differences in these measures between fallers and non-fallers. The statistical analysis on HRV linear and nonlinear measures of the current dataset showed that frequency and nonlinear measures significantly differed between fallers and non-fallers, suggesting that the choice of only standard linear methods, as done in Isik et al. (Isik et al., 2012) could not be satisfactory.

The best performance presented in this paper was achieved by a hybrid data-mining algorithm, RB, integrated with feature extraction based on PCA. This classifier achieved a relatively high specificity and accuracy (80% and 72% respectively), but low sensitivity (51%). Particularly, the sensitivity rate achieved is consistent with the findings of (Rubenstein, 2006) which highlighted that at least the 42% of falls are due to transient problems, which are related to ANS and cardiovascular system states. Since a limited part of falls are directly caused by cardiovascular system (i.e. syncope), the results presented in the current paper suggested for the first time that ANS / cardiovascular system dysfunctions may be responsible for a temporary reduced capability to react to extrinsic risk factors (i.e. reduced reflex velocity) avoiding falls. Moreover, for the first time this study proved that these dysfunctions are detectable with HRV monitoring. Moreover, the low rate of false positives (1 – specificity, 19.9%) suggested that this approach based on HRV analysis could be successfully used in clinical settings, eventually in combination with other approaches.

Several fall risk assessment tools in elderly population have been proposed in literature and showed a wide variability in the reported diagnostic accuracy: sensitivity varied from 43% to 100% and specificity varied from 38% to 96% (Perell et al., 2001). The method proposed in the current study achieved higher performance than several test for predicting falls: Fig. 2 shows the comparison between ROC curves of the proposed method and those of several functional mobility tests for predicting falls in community-dwelling older people(Tiedemann et al., 2008). The proposed method outperformed all the functional tests, which had relative risk (RR) ranging from 1.3 to 2.3 and sensitivity and specificity scores ranging from 11% to 78%, and 28% to 93%, respectively. More recently, a Stroop Stepping Test (SST) using low-cost computer gaming technology has been proposed to discriminate between older fallers and non-fallers, but the authors provided only the odds ratio (1.7) (Schoene et al., 2014), which is lower than the one here proposed (DOR=4.2, CI95% 2.0-8.7, p-value <0.001). Finally, the method proposed in the present paper is clinically feasible, since it only requires a 24h ECG recording, which is often performed in cardiovascular patients also though wearable devices(Baig et al., 2013). For instance, the method proposed do not require the use of other technologies as wearable accelerometers or pressure matrices, which are not used in everyday clinical practices, not having direct benefits for cardiovascular outpatients. For that reason, the method proposed could be used widely in outpatient settings to identify high-risk patients who need further assessment and could benefit from fall prevention programs or fall detection systems (Mirmahboub et al., 2013, Yun et al., 2014, Evans et al., 2014).

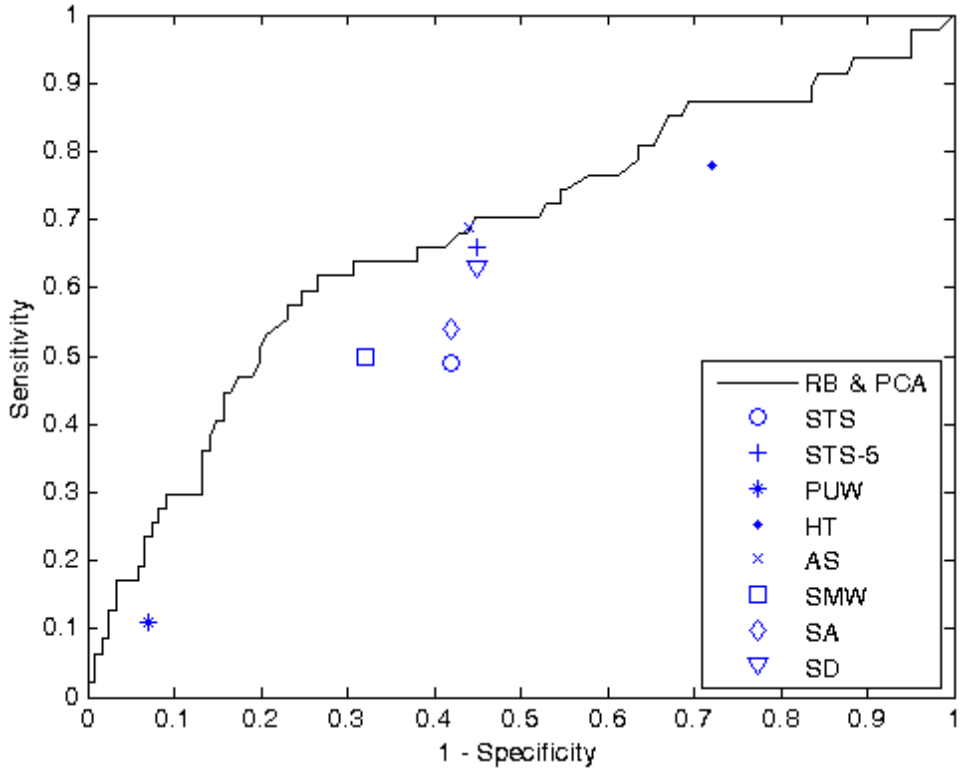

Figure 4.7 Comparison of performance of the proposed method with several functional mobility tests proposed in literature for faller identification (STS: Sit-to-stand once, STS-5: Sit-to-stand five times, HT: Half-turn-test steps, AS: Alternate-step test, SMW: Six-metre walk, SA: Stair ascent, SD: Stair descent)

Regarding the classification data-mining methods, we adopted up-to-date ensemble algorithms based on bagging (i.e. RF, RTF) and boosting (i.e. AB, MB, RB), showing that the latter appeared to be superior to the former, maybe because RF performance could be more affected by the dependency structure of the data (Adler et al., 2011). Moreover, as recently proposed by Seiffert et al. (Seiffert et al., 2010), when the dataset is imbalanced, as in the current study, the performance of boosting algorithm could be improved by integrating it with a data sampling technique. Finally, since previous studies showed the importance of feature selection for learning from small and imbalanced datasets (Zheng et al., 2004), we proposed to integrate RB with a feature extraction method based on PCA and observed that using PCA resulted in higher performances compared to RB and also to bagging classifier adopting PCA filter.

This study had some limits. The dataset used was not specifically designed to study falls. Therefore, important information, such as the exposure to other independent intrinsic risk factors for falls could not be accessed or used to verify independently the results. Moreover, the fall recordings were based on patient self-reports, which are considered not every time reliable as some non-harmful falls can be forgotten and not reported. Therefore, the number of falls could have been underestimated. In addition, the results of the classifiers could be difficult to interpret as the methods employed mixed and masked those HRV features that have an accepted clinical meaning. However, with respect to

maximum achieved accuracy, the opaque models obtained from automatic classifiers have an advantage over those with clear interpretation. It should be noted that automatic systems in this field are sufficient to provide early warning signs before adequate medical assessment can be performed. Finally, the current findings have been obtained in a population of cardiac patients, in which HRV is already known to be depressed compared to healthy people. This suggests that depressed HRV could be a more relevant risk factor for falls in people free of cardiovascular disease.

5 Conclusion

The aim of this thesis was to research and develop automatic methods based on ANS assessment for evaluation of risk in cardiac patients (i.e., affected by CHF or hypertension). HRV analysis have been adopted as non-invasive marker of the ANS status and several data-mining methods have been combined to achieve the following goals:

- Automatic assessment of disease severity in CHF patients;
- Automatic identification of hypertensive patients at higher risk of developing vascular events;
- Automatic identification of hypertensive patients with a history of falls.

Automatic assessment of disease severity in CHF patients: previous studies focused on discrimination of CHF from healthy subjects, and some of the proposed methods relied on HRV measures. Few studies focused on disease severity and they adopted parameters that should be manually entered by the physician. For the first time, a completely automatic method, based on long-term HRV measures (i.e., extracted from nominal 24-h ECG recordings), was proposed in order to automatically assess the CHF severity (mild versus severe CHF). It has been developed by using public databases, freely available from the physionet.org website. Since the dataset is unbalanced, an approach based on feature selection and tree-based classifier was proposed and compared to standard methods to handle the imbalance problem.

Automatic identification of hypertensive patients at high risk of vascular events: previous clinical studies showed that depressed HRV was associated with cardiovascular risk and a few recent studies focused on short-term prediction of sudden cardiac death or other cardiovascular fatal events. For the first time, a completely automatic system was proposed in order to identify hypertensive patients at higher risk to develop vascular events (e.g. stroke, myocardial infarction, syncope) in the 12 months following the recordings. It was based on linear and nonlinear HRV analysis of a 5-minute ECG segment. A rigorous validation method, based on a crossvalidation loop nested in a hold-out splitting, was proposed to compare the performance of several data-mining algorithms, based on different approaches. The algorithms were trained on a database developed ad hoc, which is now available in the PhysioNetWorks area of the physionet.org website. The clinical feasibility and uptake of the developed tool are now tested in a prospective study in subjects aged 55 and over recruited by the Centre of Hypertension of the University Hospital of Naples Federico II. Moreover, since 5-minute HRV measurement is inexpensive, easy to assess, and non-invasive, future research will focus on the clinical applicability of the system as a screening tool in non-specialized

ambulatories (e.g. at General Practitioners'), in order to identify high-risk patients to be shortlisted for more complex (and costly) investigations. Improved identification of individuals at risk for the development of vascular events may result in more targeted and adequate prevention strategies.

Automatic identification of hypertensive patients with history of fall: ANS disturbance and cardiovascular disorders may be underestimated causes of falls. For that reason, it was explored whether an automatic identification of fallers among hypertensive patients based on HRV was feasible. The proposed method outperformed several functional tests which were proposed in literature for faller identification. Moreover, it does not require the use of other technologies as wearable accelerometers or pressure matrices, which are not used in everyday clinical practices, not having direct benefits for cardiovascular outpatients. For that reason, the method proposed could be used widely in outpatient settings to identify high-risk patients who need further assessment and could benefit from fall prevention programs or fall detection systems.

The results obtained in this thesis could have implications both in clinical practice and in clinical research. The system have been designed and developed in order to be clinically feasible. In particular, HRV analysis and the automatic system for identification of high-risk patients are integrated in a web-based platform, developed in the framework of the Smart Health and Artificial Intelligence for Risk estimation (SHARE) project. The platform, now integrated in an open and interoperable cloud computing platform for health and eGovernement (PRISMA), included a standalone software (for Windows operative system) and an Android application to acquire signals from wearable devices. Finally, the findings obtained by the data-mining methods (which did not use any a priori knowledge) reinforce the previous clinical observation that depressed HRV is a marker of cardiovascular risk and, for the first time, showed that it could be also an interesting parameter to be investigated in fall identification and prevention research.

The main limitation of the presented studies is the relatively small sample size of the datasets. This issue could be addressed in the next future by increasing the number of enrolled subjects by Centre of Hypertension of the University Hospital of Naples Federico II. This would make the present findings clinically more relevant. Moreover, the dataset used in the fall identification issue was not specifically designed to study falls. Therefore, important information, such as the exposure to other independent intrinsic risk factors for falls could not be accessed or used to verify independently the results. Moreover, the fall recordings were based on patient self-reports, which are considered not every time reliable as some non-harmful falls can be forgotten and not reported. Therefore, the number of falls could have been underestimated.

Further developments of the current thesis could be the adoption of new HRV measures (e.g. point process time-frequency analysis), strong risk markers extracted from ECG (e.g.

Heart Rate Turbulence or T wave alterations), and other non-invasive measures obtained by wearable sensors (e.g accelerometric signals, breath rate).

List of Figures

List of Tables

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List of abbreviations

The following table describes the meanings of several abbreviations and acronyms used throughout the thesis. The abbreviation adopted in each table are reported in the footnotes. The abbreviation for HRV measures are reported in Table 3.1

Abbreviation	Meaning
ANS	Autonomic Nervous System
HRV	Heart Rate Variability
PSD	Power Spectral Density
FFT	Fast Fourier Transform
CHF	Congestive Heart Failure
ECG	electrocardiographic signals
STS-5	sit-to-stand test with five repetitions
STS-1	single sit-to-stand task
AST	alternate-step test
SMWT	six-metre-walk test
AR	Auto-Regressive
RF	Random Forests
RTF	Rotation forest
CART	Classification and Regression Tree
PCA	principal component analysis
NB	Naïve Bayes Classifier
AB	AdaBoost
SVM	Support Vector Machine
MLP	Multilayer perceptron
MB	MultiBoost
RB	RUSBoost

List of publications

The following is a list of works published by the author during the course of the doctorate.

Many of these works are cited in the text and therefore also appear in the full bibliography.

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National conferences proceedings

1. Melillo P, Bracale U, Mirarchi L, Bracale M, Pecchia L: *Linear and nonlinear Heart Rate Variability analysis for automatic stress detection.* 3° Congresso del Gruppo Nazionale di Bioingegneria, ISBN: 978 88 555 3182-5

Patent Application

1. Pecchia L, Melillo P, Stranges S, De Pietro G, Sannino G, Autonomous Nervous System status detection to predict falls including Heart Rate Variability (HRV) assessment, RM2014A000504, filled on 05/09/2014