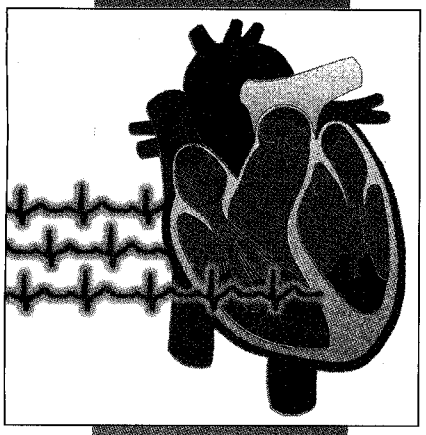

Time-Frequency Analysis of Heart-Rate Variability

An Improved Method for Monitoring and Diagnosing Myocardial Ischemia

J. Vila, F. Palacios*, J. Presedo, M. Fernández-Delgado, P. Felix and S. Barro

Department of Electronics and Computer Science, University of Santiago de Compostela

*General Hospital of Elche

In this article we present the results of a study that shows the viability of a new technique for the diagnosis and monitoring of myocardial ischemia that is based on the utilization of heart-rate variability (HRV) information. Ischemia is understood as being the lack of oxygen supply to the heart, a situation that in an extreme and irreversible case results in acute myocardial infarction (AMI), a reason for which early detection and treatment is of great interest.

When a patient is admitted to a coronary care unit (CCU), a diagnosis is effected based on an evaluation of clinical history and an electrocardiogram (ECG). Results can be confirmed with enzymatic evolution criteria or by way of imaging techniques, such as the bidimensional echocardiograph or coronariography. During the stay in the CCU, the patient's condition will be observed and some possible complications detected by monitoring the electrical activity of the heart. The treatment of ischemia can be approached via the evolution of the ECG, and especially from one of the parameters extracted from it—the ST segment (ECG signal between S and T waves) deviation [1]. The utility of this measure is found in its capacity for detecting abnormalities in the conduction of the cardiac impulse that are associated with the presence of ischemia.

Even when we take into account that this is, at present, the most widespread technique used for the monitoring of ischemia, it presents serious problems due to its low specificity, given that other phenomena such as a simple change of posture can cause similar manifestations in the ST segment [2]. For this reason, the search for new techniques capable of complementing the information obtained from the ST segment and contributing to a more reliable diagnosis of myocardial ischemia is justified.

It should also be pointed out that the ischemia, apart from electrical alterations, also provokes hemodynamic changes in an earlier phase. Thus, the measuring of these alterations may lead to even earlier detection of ischemia. The principal problem is that a direct measurement would imply the use of invasive techniques (introduction of a catheter), which is unacceptable in routine conditions. The information supplied by the heart-rate signal could be useful in this sense.

Although the existence of fluctuations in instantaneous heart rate has been known for some time, there was no serious investigation into the cause of these fluctuations and their possible use in the clinical environment until the 1970s. In 1981, Akselrod published a paper, in *Science* [3], that experimentally demonstrated the presence of different components in the heart-rate spectrum. These were related, in different degrees, to the different components of the cardiovascular control system, as pointed out in Table 1. The discovery of this relationship between HRV and the cardiovascular control system, together with the already well-known fact that the functioning of this control system is seen to be affected by possible alterations in the hemodynamic behavior of the myocardium [4], means that HRV could be utilized as an

Table 1. Spectral components of an HR signal.

Name	Frequency (Hz)	Associated With
HF (high frequency)	0.15-0.4	Parasympathetic
LF (low frequency)	0.05-0.15	Sympathetic and parasympathetic

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The treatment of ischemia can be approached via the evolution of the ECG.

indirect measurement of these alterations. As such, it can also be utilized as a variable to be taken into consideration in the treatment of related pathologies. This is the case of myocardial ischemia, as well as many other cardiovascular complications.

In a work recently published by Malik and Camm [5] dedicated entirely to the study of HRV, there is a review of principal clinical applications; among them being its use for risk stratification in postinfarct patients, its relationship with hypertension or diabetes, and its usefulness in fetal monitoring. Nevertheless, not one chapter is dedicated to ischemia. On the other hand, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology have recently published recommendations on processing techniques to be used in HRV studies [6], also reviewing the present usefulness of this technique, again with no mention of ischemia. This does not mean that up until now there has not been any research in this area, but rather that the experiments carried out were very specific, and the results should be taken with a degree of caution. Thus, the use of this technique in relation to ischemia still has not been established in clinical practice.

The most interesting results have been obtained in analyzing the evolution over time of the power concentrated in the low-frequency (LF) and high-frequency (HF) peaks, and the ratio of these powers. Some authors have pointed out, for example, how the LF/HF ratio tends to increase in certain ischemic episodes [7, 8], while others observe an increase in the power of the LF peak [9,10] and even a global fall in the spectral power [9]. We have confirmed the existence of some HRV patterns by analyzing the usefulness of these techniques in a study of some particular betablocking treatment [11].

The fact that the results of these studies are still fairly incomplete, and not at all generalizable to all types of ischemic episodes, is due fundamentally to two reasons. First is the great diversity with regard to the origin and labeling of the analyzed records. Only two works [8,10] use a widely recognized electrocardiographic signal database, such as the European ST-T Database (ESDB) [1], while other authors have used their own records. The second reason relates to the diversity of processing techniques used, differences being observed with regard to the type of spectral estimator used (classical spectrogram [11], autoregressive modeling [9], wavelets [7], Lomb method [8], etc.), frequency delimitation of the different components, and the temporal demarcation of the ischemic zones, among others.

In the present work, we have aimed to overcome these difficulties by using records from the ESDB, chosen with regard to their clinical annotations, and by using a processing technique especially designed for the analysis of HRV. In this way we hope that the results obtained are more reliable and, at the same time, can easily be verified by other researchers.

Material and Methods

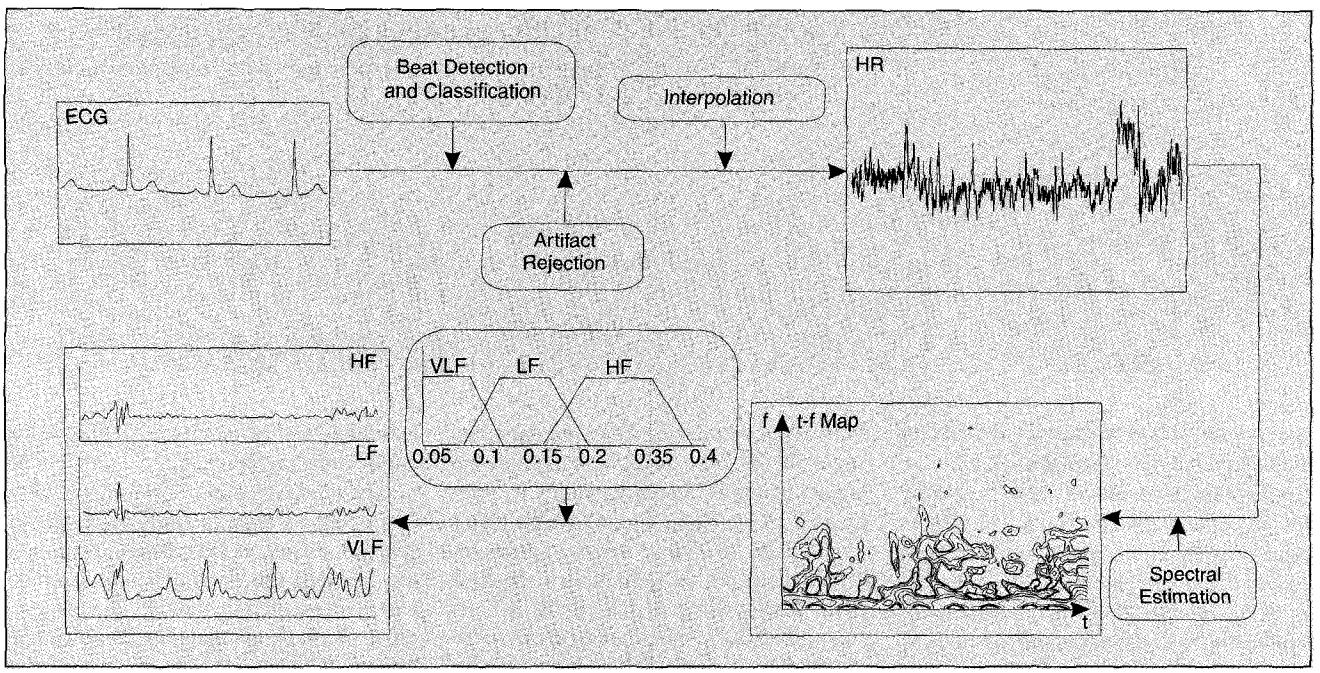
For this analysis we will use a set of records belonging to the ESDB. We have used the clinical information associated with each record of the database in order to select a uniform group of records to be analyzed. The requirements applied for this selection are the following:

- Sinus rhythm
- Exclusion of patients treated with betablockers
- Explicit coronariography, in such a way that only patients with one-vessel disease or without coronariopathy are included
- Effort or rest angina with coronariography (one vessel) and without coronariography (vasospastic angor).

In Table 2, the clinical data corresponding to the 14 records selected are shown. The ages of the patients varied between 40 and 64 years. Sex has not been specifically indicated since all the patients were male. Some patients were not given any type of relevant medication, while others were administered different types of calcium-antagonists and nitrates. The

Table 2. Identification of records used belonging to ESDB (nit=nitrates, ver=verapamil, dil=diltiazem, nif=nifedipine)

Record	Age	Clinical diagnostic	Medication	Episodes
e0115	60	Effort angina, 1-vessel disease		1
e0116	47	Resting angina, Normal coronary arteries	nit, ver	2,3
e0118	51	Resting angina, Normal coronary arteries	nit, ver	4,5,6,7
e0119	51	Resting angina, Normal coronary arteries	nit, nif, dil	8,9,10,11,12
e0121	51	Resting angina, Normal coronary arteries	nit, nif, dil	13
e0122	51	Resting angina, Normal coronary arteries	nit, nif, dil	14
e0127	44	Resting angina, 1-vessel disease		15,16,17,18
e0154	51	Resting angina, 1-vessel disease	nit, dil	19
e0403	40	Resting angina, 1-vessel disease		20,21,22
e0404	54	Resting angina, 1-vessel disease	nif	23,24,25
e0410	41	Resting angina, Normal coronary arteries	nif	26,27
e0411	45	Resting angina, Coronary artery disease		28
e0601	55	Resting angina, Coronary artery disease	dil	29,30
e0612	64	Effort angina, Coronary artery disease		31,32,33



1. Processing steps involved in spectral analysis of a heart-rate signal. The examples of the different domains are only illustrative; they do not correspond to the same record.

14 records contained 33 different ST episodes, according to the notation of the ESDB, with duration between 40 seconds and 12 minutes. The numeration of these episodes, indicated in the final column, will serve as a reference when discussing the results obtained.

The processing methodology followed can be considered as being divided into three stages: the generation of the HR spectrum, extraction of the data relative to each episode, and their statistical analysis.

Generation of the HR Spectrum

Figure 1 shows the steps necessary for obtaining the heart-rate (HR) spectrum. Starting from the ECG signal, the instantaneous HR signal associated with each normal beat will have to be obtained. In order to do this, the correct detection and classification of these beats is required, a task that in our case is solved by starting from an annotated data base. It is then necessary to verify this signal in an automatic or manual manner in order to avoid the inclusion of artifacts. We apply our own automatic filter, called NC-VT (noncausal of variable threshold) [12], whose mode of operation is schematically represented in Fig. 2. This filter includes the best characteristics of those designed by Malik [13] and Sapoznikov [14], researchers who have long worked in this field. Furthermore, given that the spectral estimation technique to be used operates on evenly spaced signals, the application of an interpolation algorithm becomes necessary. In our case, and after having demonstrated its superiority as opposed to other alternatives [15], we use Berger's interpolation method, with a sampling frequency of 4 Hz.

The next step is to obtain the corresponding time-frequency map, using an algorithm for the spectral estimation of nonstationary signals. There are multiple ways of doing this, such as a *classic* spectrum estimation, directly using the short-time Fourier transform (STFT) or *spectrogram*; a *modern* estimation, using an autoregressive modeling of the HR signal; or by using other types of time-frequency distributions (TFDs) other than the spectrogram. Although these alternatives have been used to some degree by researchers in this field, we [12, 17], along with others [18,19], have demonstrated the superiority of the TFD, as opposed to other choices in the case of the HR signal. The classical estimation offers a time-frequency resolution that is insufficient for the type of short-term analysis that we aim for. The modern estimation, on the contrary, offers good resolution but presents many problems for the correct determination of the model and of the order of this model, besides being a technique inadequate for noisy signals, which is typically the case of the HR signal.

Differences among TFDs are found in the choice of kernel, as can be seen in Fig. 3. Although in other domains some authors have demonstrated the advan-

NC-VT Algorithm

```
for i=2 to N-1
  if(abs(HR(i)-HR(L))/HR(L) < u_u OR
    abs(HR(i)-HR(i+1))/HR(L) < u_u OR
    abs(HR(i)-M)/M < u_m)
      accept HR(i)
      every STEP iterations
        update u_u,u_m
  else
    i=i+1
```

2. NC-VT algorithm for artifact filtering. N represents the number of elements of the HR series, L the index of last accepted value, and M the mean of last STEP values. u_n and u_m depend on deviation of last STEP HR values.

Table 3. Results of Friedman's test over different variability indices (p=statistical significance degree).				
Friedman's test	Global	Effort angor	Rest angor	Vasoespastic angor
MAH0, MAH1, MAH2, MAH3				
MAL0, MAL1, MAL2, MAL3	p<0.05	p<0.1	p<0.1	
MAVL0, MAVL1, MAVL2, MAVL3	p<0.05			p<0.05
POH0, POH1, POH2, POH3	p<0.1		p<0.05	
POL0, POL1, POL2, POL3	p<0.01		p<0.1	
POVL0, POVL1, POVL2, POVL3	p<0.01	p<0.1		p<0.1

tages of using kernels capable of adapting themselves to the characteristics of the signals, we have shown their suitability for processing the HR signal [12,17]. In order to reduce the great computational cost of this type of estimator, we have developed an algorithm that is capable of controlling the adaptation process, ensuring it is only carried out in time instances in which the stationarity of the signal changes [20]. The algorithm that we use is called IC-AOK (instantaneous controlled adaptive optimal kernel). It is the result of applying our algorithm for the control of the adaptation instant to AOK distribution, as developed by Baraniuk and Jones [21, 22]. Figure 3 shows the mathematical formulation of this distribution.

Extraction of the Data of Each Episode

As a result of the previous stage, we have a time-frequency map for each record. The next step is the extraction, starting from the aforementioned spectrum, of the power and the maximum in each one of the three bands: very low frequency (VLF), LF, HF. The precise delimitation of each of the spectral bands is difficult, and no consensus has been reached among different researchers. For this reason, we have preferred to employ a more flexible definition of the limits of each band, as is indicated in Fig. 1. The membership degree associated with each band takes the value 1 in a determined range and gently falls toward a 0 value at the extremities.

Given that our objective is the analysis of ischemic episodes, starting from the VLF, LF and HF bands, we will go on to separate the information relative to each episode. This is an important point, given that if we aim to look for patterns associated with the presence of ischemic episodes, it is necessary to define with precision certain areas of interest in relation to each episode. Then we can construct the desired patterns, based on the values of the different variables in each area. Even though in studies carried out up to now there is no uniformity of criterion in this sense, we are going to use the temporal demarcation shown in Fig. 4. The zone labeled 2 corresponds exactly with the time interval in which there exists an ST episode, or at least it was thus annotated in the database. Zones 1 and 3, which we will call "before" and "after" the episode, have a width of two minutes. Lastly, a normality zone (zone 0) has been taken in the five minutes prior to zone 1. In some cases, the durations of zones 0, 1, and 3 have had to be shortened because of the presence of other very close ischemic episodes. In those cases in which there was a sequence of two or more ST episodes separated by less than three minutes, the normality zone for all of these episodes was taken just prior to zone 1 of the first episode of the sequence.

The objective of the definition of these four zones is, first, to study the relationship of the values of the different parameters between the normality zone and the zone corresponding to the ischemic episode. The second objective is to evaluate these parameters in those instances prior to the interval in which the electrical manifestations of the ischemia occurred and in which, predictably, hemodynamic manifestations are produced that can provoke alterations in normal HRV patterns. Third, the aim is to study the persistence of the possible changes in the HRV indices after the electronic manifestations of ischemia. For each of the four zones, the mean and the maximum values of the power are analyzed in each band, as well as the ratio of the LF and HF power peaks, and the ratio of their respective maxi-

Table 4. Results of linear regression analysis on the influence of zone 2 values over zones 0,1, and 3 (S = p<0.05, NS = no statistical significance).				
Linear regression				R (regression coefficient); statistical significance
	MAH0	MAH1	MAH3	
MAH2	S	NS	NS	0.83;S
	MAL0	MAL1	MAL3	
MAL2	S	NS	S	0.86;S
	MAVL0	MAVL1	MAVL3	
MAVL2	NS	NS	S	0.73;S
	POH0	POH1	POH3	
POH2	NS	NS	S	0.76;S
	POL0	POL1	POL3	
POL2	NS	NS	S	0.82;S
	POVL0	POVL1	POVL3	
POVL2	NS	NS	S	0.70;S
	MALH0	MALH1	MALH3	
MALH2	NS	NS	S	0.60;S

There are differences that are statistically significant, or almost significant, for all of the indices.

mums, forming a total of 8 x 4 = 32 data points for each episode. In order to refer to these data, we use the following notation:

$MAH_i, i = 0,1,2,3 \Rightarrow$

Maximum of HF peak in zone i

and identically for the remaining variables with their corresponding prefixes; MAL and MAVL for the maximums in the LF and VLF peaks; POH, POL, and POVL for the power in the corresponding peaks; MALH for the ratio of the maximum in the LF and HF peaks; and POLH for the ratio of the power of these peaks.

Statistical Analysis

The 32 values obtained for each episode, measured over the 33 episodes, form 32 data vectors over which we will carry out a statistical analysis with the following objectives:

- Evaluate the variability indexes on different zones of each ischemic episode, with the aim of verifying the existence of changes, attributable to the ischemic episode, stratifying for each one of the types of angina considered. For this analysis we use Friedman's nonparametric test [23].
- To determine for each variability index which of the remaining zones show statistically significant differences with respect to the normality zone during the ischemic episode. We will apply a multilinear regression analysis [23], where the dependent variable is the measurement in zone 2, and as independent variables we take the values of the variable in zones 0, 1, and 3.
- The determination of behavior patterns of the variability index for the different diagnoses considered.

IC-AOK Algorithm

for each instant t

1) $AF_{HR}(\theta,\tau) = \frac{1}{2\pi}\int HR(t+\tau/2)HR^*(t-\tau/2)e^{j\theta t}dt$

2) *If* HR stationary in t-1

$\Phi_t(\theta,\tau) = \Phi_{t-1}(\theta,\tau)$

else

$\Phi_t(\theta,\tau)$ maximizing

$\iint |A(r,\Psi)\Phi(r,\Psi)|^2 r\, dr\, d\Psi$

with constraints

$\Phi(r,\Psi) = e^{\frac{r^2}{2\sigma^2(\Psi)}}$

$\frac{1}{4\pi^2}\iint |\Phi(r,\Psi)|^2 r\, dr\, d\Psi \le \alpha \quad ; \quad \alpha \ge 0$

3) $TFD_{HR}(t,f) = \iint AF_{HR}(\theta,\tau)\Phi(\theta,\tau)e^{-j\theta}e^{-j2\pi ft}d\theta\, d\tau$

4) Evaluate stationarity of HR

3. IC-AOK algorithm for spectral estimation of nonstationary signals. $AF_{HR}(\theta,\tau)$ is known as the *ambiguity function* of the signal. In step 2, the AOK algorithm, proposed by Baraniuk and Jones [22], is applied if the signal is nonstationary. In other cases the previous kernel is used without modification. The AOK algorithm is described in polar coordinates (r,Ψ).

Results

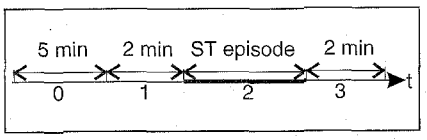
We will now describe the results obtained from the three analyses mentioned above.

Determination of Significant Indexes

With these analyses we aim to determine those HRV indices in the frequency domain that show significant variations among the different zones of each episode. The results obtained are summarized in Table 3. For this analysis, we used Friedman's test, which tests the hypothesis that a set of k variables, measured over a sample of n individuals, comes from populations with similar statistical distributions [23]. In our case, these k variables are the different groups described in the first column; that is, the values of the same variable in the four zones relative to the episode, and the n individuals are those corresponding to the 33 ischemic episodes.

Four different analyses were carried out, with the first one taking globally the data of all the episodes and the other three grouping the data of the episodes with different types of angina: effort, rest, and vasospastic (with normal coronary arteries). Each cell of the table shows the signification level for the hypothesis that each set of variables presents similar distributions. We observe that for the set of records, there are differences that are statistically significant, or almost significant, for all of the indices, except for the high-frequency component. These statistical differences show different behavior patterns for the different diagnoses considered, even if the interpretation of these differences is made difficult by the limitation in the size of the sample. From the results obtained, it is noteworthy that:

- A different behavior between the indices calculated as maximums and those calculated as powers was found. These differences may be related to the size of the sample, or they may indicate a true difference.
- The VLF component, MAVL, maintains statistical significance with those registers that correspond to rest angina with normal coronariopathies (vasospastic angor). This component has been related to the vasomotor activity associated with thermoregulation, considering the finding that relates vasospastic angor with peripheral vasomotor activity to be extremely suggestive.
- Effort angor as well as rest angor with coronariopathy almost reach statistical significance with the LF



4. Definition of zones of interest related to each ST episode.

component, MAL, which, except in decubitus situations, is fundamentally related with the sympathetic regulation of heart rate associated with baroreflex activity. The importance and congruence of this association is reflected by the importance of betablocker treatment for this type of patient. It should be pointed out that in none of the records selected was the existence of betablocker treatment evident.

Relationship Between the Ischemia Zone and the Remaining Zones

In this study we have attempted to evaluate the effect or the relationship of the values of different variables in zones: 0 (normality), 1 (just prior to the episode), and 3 (just after the episode) with the values of the same variable in zone 2 (during the episode). The results of this analysis are summarized in Table 4. A multilinear regression analysis was carried out for each one of the eight variables used. The final column shows their regression coefficient and level of significance. In the three previous columns, the individual level of significance of each one of the independent variables is shown, which indicates whether these variables have a significant contribution to the regression (S) or not (NS).

In view of the results, and as we have previously commented, different behavior among those variables that represent maximum values and those that represent powers becomes clear. We globally evaluated all records, without stratification, due to the limitation in the sample size. The following points particularly attract attention:

- The effect of the measurements in zone 3 is higher than that of zones 0 and 1. We interpret the relationship between zones 2 and 3 as a manifestation of regression, after the end of the changes of the ST, of the neurogenic effects triggered by the ischemia.
- The measurements of MAH and MAL in zone 0 have a statistically significant effect on measurements during the ischemia. The effect of MAH0 on MAH2 is congruent with the fact that there is no MAH difference in the different zones (as was previously proven by means of Friedman's test). It is possible to interpret this result in the sense that the normal, or basal, condition influences the value of this component in all the other zones evaluated.

Patterns According to the Type of Diagnosis

The objective of this new analysis is to try to find behavior patterns related to the different diagnoses considered: rest angor with coronariopathy, effort angor with coronariopathy, and rest angor without coronariopathy. We evaluated the behavior of eight variability indices, comparing zones 0-1, 0-2, 1-2 and 2-3, in an attempt to look for patterns associated with groups of patients with the same diagnoses. The most significant patterns to be found are shown in Table 5. In each row of this table is shown the pattern associated with the group of episodes given in column 2, which presents the diagnosis indicated in column 1. A + sign associated with a variable indicates an increase. On the basis of the patterns shown in this table, we point out that:

- The patterns clearly discriminate among the episodes of rest angor without coronariopathy (vasospastic angor) and the remaining episodes.

Interest goes beyond that recognized as a medium/long-term postmyocardial infarct prediction index.

Vasospastic angor episodes show defined patterns for measurements in zones 0-1 and 2-3 (except two episodes), in that the records with coronariopathy are definable with patterns in zones 0-1 and 1-2.

- All the episodes of vasospastic angor present MAVL-, with the exception of two of them (the same two episodes mentioned as exceptions in the previous point).
- The episodes of rest angor with coronariopathy definable by behavior in zones 0-1 and 2-3, in the same way as vasospastic angina, show MAVL- in zone 0-1.
- Generalizing about the previous points, any one which may be the diagnosis, in the case of there being MAVL- in zone 1, the patterns are defined between zones 0-1 and 2-3. On the contrary, when there is MAVL+ in zone 0-1, the pattern is defined by 0-1 and 0-2. On the other hand, MAVL- in zone 0-1 appears to be associated with vasospasticity, a generalization of those episodes of vasospastic angor, and only present in rest angor with coronariopathy, a

Table 5. Patterns of HRV index related to different diagnoses. (1-Resting angina with normal coronary arteries; 2-Resting angina with conorariopathy; 3-Effort angina with coronariopathy).

Diagnostic	Episodes	0-1	0-2	1-2	2-3
1	22,23,26,27,28,29,31	MAVL-			MAH-
2	10,11,14,17,18	MAVL-			MAH+,MAVL-
1	24,25,53	MAVL-			MAH+
1	30,32	MAVL+	MAL-		
2	5,6,7	MAVL+,MAL-,MAH-	MAL+		
3	1,3,4	MAVL+,MAL-,MAH+	MAL+		
2	8,13,15,16	MAVL+, MAL+	MAL+		

situation in which one cannot discount a vasospasm component.

- There are patterns that are clearly different in those cases in which MAVL+ is given in zone 1. In these cases, MAL+ is present in zone 0-2 (except in episodes 30 and 32, previously mentioned as exceptions), which reflects an increase in sympathetic activity. Complementary patterns are also noted in zone 0-1, which are clearly different among the records, with coronariopathy corresponding to rest and effort angina.
- Lastly, the relevance of zone 0-1 is noteworthy in all cases. Independent of the cardiogenic reflexes set off by the ischemia, and to which we have alluded, this can be interpreted in the sense that the changes in HRV precede the observable ST changes.

Conclusions

The number of patients and the technical limitations of this analysis (ignorance of the fundamental clinical data) means that the results should be treated with a certain degree of caution. Nevertheless, because of these results, it seems reasonable that a wider study with greater controls could give more definitive results with regard to the behavior of the different HRV indices in relation to ischemia, and at the same time enable us to verify the influence of diverse clinical conditioners.

In any case, we believe that the results herein described are, on their own, already of undeniable value, confirming the relationship between HRV, neurovegetative heart control, and ischemia. As a general evaluation of the previous results, regarding the study of HRV in the frequency domain we note that:

- It is an analysis technique for information derived from ECG monitoring, of clear clinical interest in the field of cardiac ischemia, especially if we take into account its noninvasive character.
- This interest goes beyond that recognized as a medium/long-term post-myocardial infarct prediction index.
- Its real-time evaluation contributes diagnostic information of great interest, especially for those ST changes that are registered without angina and that do not present some unmistakable criteria of ischemic origin. Thus, it may be an important tool in the diagnosis and interpretation of those phenomena clinically called anginous equivalents.
- The additional information furnished by this type of analysis has a clear role to play in research into the physiopathological effects of myocardial ischemia. This is an area that has still not been investigated in clinical studies.
- The importance of knowledge of physiopathological aspects and behavior patterns of ischemia in the individual patient could have important repercussions in the personalized adjustment of ischemic cardiopathy treatment. This aspect is of major importance.
- The appearance of relevant patterns in the zone prior to electrical manifestations confirm the usefulness of this technique for the early diagnosis of ischemia.

Acknowledgments

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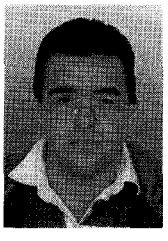
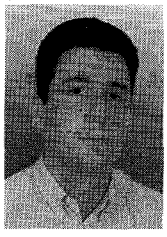
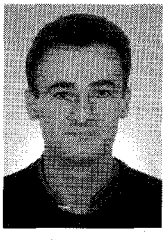


Jose Antonio Vila Sobrino was born in 1968 in Orense, Spain. He received the B.Sc. in Physics in June 1991 from the University of Santiago de Compostela. Since November 1992 he has been an assistant professor at the University of Santiago de Compostela in the Mathematics and Physics Faculties, where he is teaching undergraduate courses related to computer science and digital signal processing. He received the Ph.D. in 1997 from this university. His research interest is in digital signal processing of biomedical signals, especially spectral estimation.

Francisco Palacios Ortega was born in 1955 and received the B.Sc. in Medicine from the University Autonoma de Madrid, Spain, in 1979. Since 1983 he has been a specialist in intensive medicine at the University of Pais Vasco, Spain. He received the Ph.D. in Medicine from the University of Alicante, Spain, in 1993 with a dissertation on the application of heart rate variability to different diagnoses. He is also the head investigator of the General Hospital of the University of Elche, Spain.

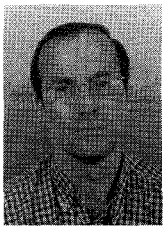


Jesus Maria Rodriguez Presedo was born in Santiago de Compostela, Spain, in 1967. He received the B.S. and Ph.D. (with honors) in physics from the University of Santiago de Compostela, Spain, in 1989 and 1994, respectively. From March 1991 to September 1994 he was an assistant professor at the Faculty of Computer Science in the University of A Coruna. Since October 1994 he has been an associated professor of computer science at the University of Santiago de Compostela, teaching undergraduate and graduate courses within the Mathematics and Physics Faculties related to computer science, digital control and robotics, and digital signal processing of biomedical signals. His research interest is in the field of digital signal processing of biomedical signals, specifically intelligent monitoring of patients with ischemic cardiopathies in real time.



Manuel Fernandez Delgado was born in A Coruna, Spain in 1971. He received the B.S. in physics from the University of Santiago de Compostela in 1994. He is a predoctoral research student in the Department of Electronics and Computing and a Ph.D. candidate at this university. His research fields are neuronal computing and intelligent monitoring of physiological signals (mainly ECG).

Paulo Felix Lamas was born in Vigo, Spain, in 1970. He received the B.S. in physics from the University of Santiago de Compostela in 1993. He is a predoctoral research student in the Department of Electronics and Computing and Ph.D. candidate at this university. His research fields are intelligent fuzzy systems and signal and knowledge processing.



Senén Barro Ameneiro was born in A Coruna, Spain in 1962. He received the B.S. and Ph.D. (with honors) in physics from the University of Santiago de Compostela, Spain, in 1985 and 1988, respec-

tively. He is a professor of computer science and head of the Department of Electronics and Computing at the University of Santiago de Compostela. Before joining this university in 1989, he was an associate professor at the Faculty of Informatics, University of A Coruna, Spain. His research focuses on signal and knowledge processing (mainly in medical domains), real-time systems, intelligent fuzzy systems, and artificial neural networks (applications and biological modeling). He is the editor of three books and author of over 60 scientific papers in these fields. Professor Barro is a member of the Spanish societies APIA, AEPIA, and FLAT (of which he is a member of the management board) and the international societies AAAI, ACM, IEEE, and INNS.

Address for Correspondence: Jose Antonio Vila Sobrino, Depto. Electronica y Computacion, Univ. Santiago de Compostela, 15706 Santiago de Compostela, Spain. Tel: +34 81 563100, ext. 13565. fax: +34 81 599412. E-mail: elvila@usc.es

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