Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis

Eran Toledo, Osnat Gurevitz, Hanoch Hod, Michael Eldar, and Solange Akselrod. Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. Am J Physiol Regul Integr Comp Physiol 284: R1079–R1091, 2003. First published November 27, 2002; 10.1152/ajpregu.00287.2002.—Myocardial infarction (MI) is known to elicit activation of the autonomic nervous system. Reperfusion, induced by thrombolysis, is thus expected to bring about a shift in the balance between the sympathetic and vagal systems, according to the infarct location. In this study, we explored the correlation between reperfusion and the spectral components of heart rate (HR) variability (HRV), which are associated with autonomic cardiac control. We analyzed the HR of patients during thrombolysis: nine anterior wall MI (AW-MI) and eight inferoposterior wall MI (IW-MI). Reperfusion was determined from changes in ST levels and reported pain. Reocclusion was detected in four patients. HRV was analyzed using a modified continuous wavelet transform, which provided time-dependent versions of the typically used low-frequency (LF) and high-frequency (HF) peaks and of their ratio, LF/HF. Marked alterations in at least one of the HRV parameters was found in all 18 reperfusion events. Patterns of HRV, compatible with a shift toward relative sympathetic enhancement, were found in all of the nine reperfusion events in IW-MI patients and in three AW-MI patients. Patterns of HRV compatible with relative vagal enhancement were found in six AW-MI patients, which we attribute to vagal saturation.

wavelet transform; myocardial infarction; spectral analysis; heart rate variability

IN ACUTE MYOCARDIAL INFARCTION (AMI) patients, thrombolysis using streptokinase or recombinant tissue plasminogen activator (rtPA) is a widely used procedure. The occurrence and timing of reperfusion have crucial clinical implications, both for prognosis and for subsequent treatment. Reperfusion is typically determined by examining the changes in the ST segment and in the pain as reported by the patient. The principal aim of this study was characterizing the patterns of heart rate (HR) fluctuations, which appear in synchrony with reperfusion. Such characterization would reveal the behavior of the autonomic nervous system (ANS) during AMI and may lay the basis for a HR-based marker of reperfusion, which would be independent of current markers.

The basic concept that underlies this study is the activation of cardiovascular reflexes by altered myocardial blood supply. It has been shown in animal models that myocardial ischemia induces strong autonomic reflexes: left anterior wall ischemia tends to induce sympathetic activation (43, 54), whereas ischemia of the inferoposterior wall tends to induce parasympathetic activation (23, 54). These findings have been corroborated in humans too (1, 2, 23, 54). The bimodal autonomic activation has been observed in humans during AMI: anterior wall MI (AW-MI) was found to stimulate mostly sympathetic activity, whereas inferior wall MI (IW-MI) was shown to stimulate marked parasympathetic activity (23, 54, 59). Alterations of cardiac control have been observed after reperfusion (4) and were correlated with mortality (37).

In this research, we studied the effect of alteration in myocardial perfusion on autonomic cardiac rate control by applying a continuous time-dependent analysis to HR fluctuations, focusing on the several minutes before and after reperfusion. Cardiac autonomic activity cannot be directly investigated in clinical scenarios. Therefore, a noninvasive tool, which does not interfere with the system under study, is needed. Such a tool, although not without drawbacks, is the spectral analysis of HR variability (HRV). The typical spectral pattern of HRV includes two main spectral peaks: a low-frequency (LF) region, reaching up to 0.18 Hz, affected by both sympathetic and parasympathetic activity, and a high-frequency (HF) peak centered at the respiratory frequency, which is associated with parasympathetic activity (3, 6, 33).

Standard approaches to the spectral analysis of HRV are based on the assumption of steady-state conditions (47). This assumption discards any dynamics in the power spectrum. Therefore, standard approaches are inapplicable when examining nonstationary conditions, as expected in the case of thrombolysis. More-
over, the lack of dynamics in the standard analysis is profoundly inconsistent with the intrinsically dynamic nature of the thrombolysis procedure. Several approaches have been used to cope with the need to assess a time-varying power spectrum. The short-time Fourier transform (18, 47), time-dependent autoregressive models (16, 18), Wigner-Ville distribution (18, 19, 44, 46), discrete wavelet transform (DWT; Ref. 21), the Hilbert transform (10, 11, 22, 32, 36, 41, 51, 58), and the selective-discrete-Fourier transform algorithm (SDA) (7, 34, 35) have been used to obtain time-dependent spectral analysis.

In this study, we apply a special form of the continuous wavelet transform (CWT; Ref. 55). This wavelet transform inherits many features of the SDA, which was developed in our laboratory (34). The CWT of the HR signal performs a time-frequency decomposition of the signal and yields a time-dependent version of the typical LF and HF peaks. Hence, this approach provides an insight into the dynamics of cardiac autonomic control, as reflected by HRV.

As described below, the application of the wavelet transform to HR traces obtained during thrombolytic therapy reveals the rich and complex dynamics of autonomic activity, in relation to reperfusion, and in some cases to reocclusion.

**METHODS**

**Patients and Clinical Conditions**

Forty AMI patients were included in this study. Diagnosis of MI was based on the presence of typical chest pain lasting at least 30 min, accompanied by an ST-segment elevation of ≥1 mm in at least two electrocardiographic leads. Diagnosis was later confirmed by serum Creatine Phospho Kinase MB levels of at least twice the upper limit of normal values and the development of new pathological Q waves. This work fully conforms with the “Guidelines for Research Involving Animals and Human Beings” of the American Physiological Society.

The patients were classified according to the location of the infarct: IW-MI and AW-MI. MI location was determined by the Minnesota Code (20) as follows: anterior (V1 through V5), inferior (L2, L3, or aVF), or lateral (L4, aVL, or V6). ECG was recorded during thrombolytic therapy (streptokinase or rtPA) from the bedside monitor (Horizon 1000, Mennen Medical) to an analog magnetic tape (FM recorder, XR-30 cassette data recorder, TEAC) and later digitized at a sampling rate of 500 Hz at a 16-bit resolution (MP100, Biopac).

Recordings started on admission to the Intensive Cardiac Care Unit (ICCU) and lasted for 3 h. Oral remarks concerning therapeutic interventions, pain described by the patient on a scale of 0–10, and ST elevations were recorded by the physician on the audio channel of the tape and later extracted digitally. We were therefore able to synchronize the events with the ECG. The occurrence and timing of reperfusion were determined by the attending physician: the criterion was a reduction of 50% in ST elevations compared with ST elevations at admission. The time resolution of detecting a 50% change in ST elevation was ~1 min. R-waves were detected offline, and corrections were made for arrhythmias.

The criteria for inclusion in this study were that 1) reperfusion was determined according to the aforementioned criteria; 2) reperfusion occurred during the recording session; 3) opiates were not administered before reperfusion; 4) medications were not administered 1 h before reperfusion; and 5) patients exhibited only infrequent and isolated arrhythmias, which were corrected offline.

Based on the above criteria, 17 patients were included in this study. Nine patients (7 men, 2 women, age 55.8 ± 12.0 yr) were diagnosed with AW-MI, and eight patients (7 men, 1 woman, age 65.9 ± 11.1 yr) were diagnosed with IW-MI. Relevant information about the patients is available in Table 1. One IW-MI patient (T28 in Table 1) exhibited two events of reperfusion, separated by an event of reocclusion. Seven patients were on chronic therapy with β-blockers, and five patients received β-blockers in the ICCU (3 of those patients were on chronic therapy with β-blockers). One patient was on chronic therapy with an α2-agonist drug (T28 in Table 1). Two patients received atropine (T28 and T26 in Table 1), yet the fact that a significant HF peak was observed in both cases, as well as the administered dosage (8), negates the possibility of full cholinergic blockade. Reocclusion, manifested by increase in ST elevations and chest pains, was detected in four recordings.

Because the interpretation of HRV indexes and the mathematical analysis are not performed in the typical manner, we choose to elaborate on those issues in the following two subsections.

**Physiological Interpretation of HRV**

The association between the spectral peaks of HRV and the different branches of autonomic activity is far from simple, and, consequently, interpretation of changes in HRV parameters in terms of ANS activity is not straightforward. Of the two spectral peaks, the HF peak is easier to interpret. The HF peak has been shown to correlate with vagal activity in most cases (3, 5, 6, 28, 42). However, there are several (patho-) physiological conditions in which the last claim does not hold. A change in the HF peak may be caused by changes of respiratory volume or rate (14, 30, 52); a rise in tidal volume can markedly increase the HF peak although vagal activity is constant. Similarly, a reduction in breathing frequency may increase the HF peak. A more extreme condition, in which vagal activity is uncorrelated with the HF peak, is the case of vagal denervation, either surgical or by pharmacological means. Denervation results in a markedly reduced HF peak (14, 56, 57); the residual HF peak is then essentially caused by the mechanical stretching effect of respiration on the sinoatrial (SA) node (50). Lack of correlation between vagal activity and the HF peak has also been observed in conditions that involve a strong vagal activation. Intense vagal activation has been shown to elicit a response in HRV similar to the one caused by vagal denervation, probably as a result of saturation in either the neural traffic or receptors (26, 27). Summarizing these effects, an increase in the power of the HF peak may indicate one of the following possibilities: 1) an increase in vagal activity; 2) an increase in tidal volume; 3) a reduction in breathing rate; or 4) a decrease in vagal activity, which pulls the autonomic system out of vagal saturation.

The LF peak has more complex relations with the ANS because it is affected by both the sympathetic and parasympathetic activation (3). Again, as for the HF peak, sympathetic denervation, either surgical (14, 15, 56, 57) or pharmacological (6, 8, 31), results in a markedly reduced, yet still measurable, LF peak. In the case of sympathetic denervation, the LF peak is probably caused by the mechanical effect of LF fluctuations in the arterial pressure (50, 56). Intense
sympathetic activation, such as during an exercise test (15, 49), results in a diminished LF peak, similar to the one found in the denervated system. During an exercise test, the increase of sympathetic activity in response to an increased workload is first manifested by an increase of the LF power, which then decreases abruptly as the workload further increases (49).

Changes of the LF peak cannot be interpreted independently of the HF peak. Therefore, when associating changes in the LF and HF peaks to changes in ANS activity, one must consider the effect of the sympathetic and vagal activities on the indexes of HRV. A change in vagal activity is reflected by a parallel change in both the LF and HF peaks, when the sympathetic activity does not change (5, 6). However, a change in sympathetic activity is reflected mainly by a change in the HF peak (3, 5, 6, 13, 52).

Therefore, the effect of alterations in autonomic activity on the LF and HF peaks can be summarized as follows: 1) a change in vagal activity without a significant change in sympathetic activity is reflected by a parallel change in both the LF and HF peaks; and 2) opposite changes of sympathetic and vagal activities can be reflected by a change in the HF peak either without any change in the LF peak or with an opposite change in the LF peak.

The second pattern can be identified by inspecting the ratio between the LF and HF peaks. This ratio has been claimed to reflect the sympathovagal balance under a variety of physiological conditions (17, 45, 48). Yet, another hurdle complicates this analysis. Although the sympathetic and parasympathetic systems usually act in opposing directions, the two systems may change their activity concordantly (38), and indeed, overactivity of both systems has been observed during AMI (59). Therefore, we expect that overactivity of both the sympathetic and vagal branches would result in an increase of both the LF and HF peaks, while the LF peak should increase more than the HF peak. This kind of dual increase would result in an increase of the ratio between the LF and HF peak.

Another issue, which must be addressed, is the intricate autonomic response to inhibitory and excitatory provocations. Stimulation of the autonomic system, aimed at increasing HR, can induce either an increase in sympathetic activity or a reduction in vagal activity, or both. Similarly, HR reduction is mediated by either sympathetic withdrawal or an increase in vagal activity, or both. We categorized the various HRV responses to reperfusion into two classes, which reflect the excitatory and inhibitory stimulations, either of which may be induced by changes in myocardial perfusion. These classes comprise the complex relations between the ANS activity and HRV indexes. We categorized the changes of the LF and HF peaks into two classes (class 1 and class 2), assuming no change in respiratory rate or tidal volume has occurred.

Class 1. The changes in HRV parameters comply with one of the following patterns, indicating a shift in balance toward relative vagal enhancement. 1a) LF decreases and HF is unchanged or increased, indicating a reduction in sympathetic activity; vagal activity is unchanged or increased, depending on the change in HF. 1b) Both LF and HF increase, but their ratio is unchanged or reduced, indicating increased vagal activity and unchanged or reduced sympathetic activity, respectively. 1c) Both LF and HF decrease, and their ratio decreases, indicating decreased vagal and sympathetic activities, with a shift in balance toward relative vagal enhancement.

Class 2. The changes in HRV parameters comply with one of the following patterns, indicating a shift in balance toward relative sympathetic enhancement. 2a) LF decreases and LF increases or is unchanged, indicating a reduction in vagal activity and increase in sympathetic activity. 2b) LF increases and HF is unchanged, indicating increased sympathetic activity and unchanged vagal activity. 2c) Both LF and HF decrease, and their ratio is unchanged, indicating reduction of vagal activity without considerable change of sympa-
thetic activity. 2d) Both LF and HF increase and their ratio increases, indicating increased vagal and sympathetic activities, with a shift in balance toward relative sympathetic enhancement.

Class 1d and class 2d represent a complex pattern, in which both the sympathetic and vagal activities change. In those cases, we chose to determine the direction of change according to the LF/HF ratio, which reflects the sympathetic-vagal balance (3).

In this study, we examined the changes in the LF and HF peaks in relation to reperfusion, and therefore, a time-dependent quantification of the LF and HF peaks was needed. The dynamics of HRV was studied using the CWT.

Mathematical Analysis

We used a modified version of the CWT to assess the time-dependent power spectrum of HR fluctuations. Typical methods of time-frequency decomposition such as the short-time Fourier transform (47), Wigner-Ville (19), or the time-dependent parametric models (16) are generally based on dividing the time trace into successive windows and then assessing the power spectrum in every window. Thus the dynamics of the spectral components of the analyzed signal can be determined from changes in those components between successive windows.

The main difference between the above-mentioned time-frequency decomposition methods and the CWT lies in time resolution and frequency resolution. Time resolution (\( \Delta t \)) is the minimal time difference between two events that are differentiable using a specific time-frequency method. Any two events that are closer than \( \Delta t \) would be detected as one event. Accordingly, frequency resolution (\( \Delta f \)) is the minimal detectable frequency difference between two spectral peaks. The length of the windows directly determines the time resolution: short windows provide high time resolution, whereas long ones impose low resolution. Interestingly, in all time-frequency decomposition methods (including the CWT), time and frequency resolutions are linked according to the Heisenberg uncertainty principle: \( \Delta t \Delta f \geq 2 \pi \), which means that high time resolution imposes low frequency resolution and vice versa. Although this shortcoming cannot be circumvented, the CWT presents a unique solution to it using a variable window length. In the CWT and the SDA, the duration of the time window is inversely proportional to the frequency of interest, unlike most methods of time-frequency decomposition

\[
\Delta t \sim 1/\Delta f
\]

Thus it is long for low frequencies and short for high frequencies. Combining the Heisenberg uncertainty principle and the proportion rule in Eq. 1 results in frequency-dependent time and frequency resolutions of the time-frequency decomposition of a signal

\[
\Delta t \sim 1/\Delta f
\]
\[\Delta t \Delta f = 2 \pi \Rightarrow \Delta f / \Delta t \]

Therefore, the CWT has high frequency resolution (small \( \Delta f \)) with low time resolution (large \( \Delta t \)) in the LF range and low frequency resolution with high time resolution in the HF range.

In contrast to the Fourier transform, which expresses a signal as a sum of waves (sines and cosines), the CWT expresses a signal as a sum of limited-duration waves, termed wavelets. The shape of those wavelets is determined by the wavelet function \( \psi(t) \), which defines the CWT. The definition of the general CWT of a signal \( s(t) \) is (21)

\[
W_{\text{CWT}}(t,f) = \int_{-\infty}^{\infty} s(\tau) \sqrt{f} \cdot \psi^* [f(t - \tau)] d\tau
\]

where \( W_{\text{CWT}}(t,f) \) is the CWT at time \( t \) and frequency \( f \), and the superscript asterisk denotes the complex conjugate. As our wavelet function, we chose the complex sum of a sine and a cosine

\[
\psi(t) = \begin{cases} \frac{1}{\sqrt{k}} e^{2\pi j f t} & |t| \leq \frac{k}{2} \\ 0 & \left| t \right| > \frac{k}{2} \end{cases}
\]

where the factor \( k \) is a parameter of analysis (the superscript \( H \) stands for harmonic). Inserting Eq. 4 into Eq. 3 provides the explicit form of the CWT that we used

\[
W_{\text{CWT}}^H(t,f) = \int_{-\infty}^{\infty} s(\tau) e^{2\pi j f \tau} d\tau = \int_{-\infty}^{\infty} \left[ \frac{k}{\sqrt{k}} \right] e^{2\pi j f \tau} s(\tau + t) e^{2\pi j f \tau} d\tau
\]

Equation 5 means that \( W_{\text{CWT}}^H(t,f) \), which is the CWT of \( s(t) \) at time \( t \) and frequency \( f \), is the Fourier transform of the product of \( s(t) \) with a time window centered at time \( t \) and of duration \( kf \). Thus \( W_{\text{CWT}}^H(t,f) \) provides a time-frequency decomposition of the signal. The power in frequency bands (such as the HF and the LF bands) can be assessed by integrating \( |W_{\text{CWT}}^H(t,f)|^2 \) over the desired frequency band. A more detailed mathematical analysis is presented in the appendix.

Computation of HRV Parameters

R-waves were extracted from the ECG and corrected for arrhythmias. The R-R interval trace was resampled to produce a uniformly sampled HR signal (12). The HR traces were filtered using a moving median filter (7, 34, 35). This filter is a nonlinear high-pass filter, which preserves the transients in the signal.

Time-dependent spectral analysis of the HR traces was performed with the wavelet transform using Eq. 5. The respiratory frequency band was detected from the wavelet transform of the HR signal (see, e.g., Figs. 2 and 3). The time-dependent power of the HF peak, HFP(t), was computed using Eq. 9 (see APPENDIX), by setting the limits of integration according to the respiratory frequency band. The time-dependent LF peak, LFP(t), was computed using Eq. 9, by setting the frequency limits of integration to 0.04 and 0.18 Hz. This procedure is exemplified in Fig. 1.

Both resulting traces, the time-dependent LFP(t) and HFP(t) traces, were then filtered, using a moving median filter 3 s long to reduce short-term outliers. The median-filtered versions are denoted by LFP_{M}(t) and HFP_{M}(t), respectively. Their ratio, R(t) = LFP_{M}(t)/HFP_{M}(t), was computed (see Fig. 1). This ratio reflects the dynamic time-dependent version of the widely used LF/HF ratio. In our analysis, we considered four time-dependent parameters: HR(t), LFP_{M}(t), HFP_{M}(t), and R(t). These parameters reflect the dynamics of HRV and HR control.

Data Analysis: Reperfusion

Two epochs, 300 s long each, were selected: the first epoch is 150–450 s before the time of reperfusion (labeled BR), and the second epoch is 150–450 s after the reported time of reperfusion (labeled AR). The two epochs are shown in Fig. 1.
The difference between the average values of the four parameters during the two epochs was computed, for example, as follows for the change in heart rate ($\Delta_{HR}$):

$$\Delta_{HR} = \langle HR(AR) \rangle - \langle HR(BR) \rangle$$

where the angled brackets denote taking the average. The changes in LFPm($t$), HFPm($t$), and R($t$), i.e., $\Delta_{LF}$, $\Delta_{HF}$, and $\Delta_{R}$, were similarly computed.

In addition, we computed the SD of each of the four parameters in the 3,000-s epoch centered around the reported time of reperfusion: $\sigma_{HR}$, $\sigma_{LF}$, $\sigma_{HF}$, and $\sigma_{R}$. The difference in the four parameters ($\Delta_{HR}$, $\Delta_{LF}$, $\Delta_{HF}$, $\Delta_{R}$) between the two epochs was compared with their corresponding SD ($\sigma_{HR}$, $\sigma_{LF}$, $\sigma_{HF}$, and $\sigma_{R}$, respectively). A change in each of the parameters was considered significant when the difference was larger than the SD: e.g., $|\Delta_{HR}| > \sigma_{HR}$. In other cases ($-\sigma_{HR} \leq \Delta_{HR} \leq \sigma_{HR}$), the change in the parameter was considered nonsignificant.

As a result, each parameter was classified as one of three options: increase, decrease, or unchanged at reperfusion. This approach prevents random changes of the parameters from being considered as real changes.

We examined this approach by considering the traces of 15 patients. In each patient, we select, at random and well before diagnosed reperfusion, a time of “false reperfusion.” We then chose two epochs: before the false reperfusion and after the false reperfusion, exactly as we did around the time of true reperfusion. If, as we claim, our statistical test has high specificity, then it should not detect significant changes in the HRV parameters and/or in the HR between the two epochs (before and after the false reperfusion). Applying the test to the LFPm($t$), HFPm($t$), and R($t$) using these paired epochs around the false reperfusion time resulted only in a single detection of significant change (false positive) in each of the HRV parameters ($P < 0.001$). These three misdetections of the HRV parameters occurred all in one single patient (T02 in Table 1). However, applying the same test to the HR data of all 15 patients resulted in the detection of a significant change in 5 patients ($P > 0.15$). Therefore, we conclude that the test we chose has a low rate of type 1 errors (false positive) for the HRV parameters (6%) and that this test is not reliable for the HR signal. We discuss the type-2 error rate (false negative) of this test in the DISCUSSION.

Each reperfusion event was classified into one of the two classes mentioned in the previous section, namely, vagal or sympathetic relative enhancement, according to the combined change in LFPm($t$), HFPm($t$), and R($t$).

The relative change (D) in HR and HRV parameters was expressed as the percent change between the level of the parameter after reperfusion and the level before reperfusion, computed as follows, for example, for HR

$$D_{HR} = |(HR(AR))/HR(BR)) - 1| \times 100\%$$

The relative changes in LFPm($t$), HFPm($t$), and R($t$), i.e., $D_{LF}$, $D_{HF}$, and $D_{R}$, were similarly computed.

The instantaneous respiratory rate was determined from the wavelet transform of the HR trace (see Figs. 2 and 3). At every instant $t$, respiratory rate is the frequency at which $|\text{CWT}(t,f)|$ is maximal within the HF range of frequencies. SD of the respiratory rate was also evaluated. Changes in respiratory rate were considered significant when the difference was larger than the SD (similarly to the analysis of HR and HRV parameters).

**Data Analysis: Reocclusion**

We examined the changes in the HR and its three HRV parameters during the four events of reocclusion. The quantitative analysis was similar to that of the reperfusion events.
**RESULTS**

Changes in HR and HRV Parameters at Reperfusion

Marked alterations in HRV parameters were found around the time of reperfusion. A marked change in at least one of the three HRV parameters \([\text{LFP}_m(t), \text{HFP}_m(t), \text{R}(t)]\) was observed in synchrony with clinical reperfusion in all 18 events of reperfusion. The absolute value of the relative change in LF fluctuations \((|D_{LF}|)\) was on average 119% ± 172, the absolute value of the relative change in the HF fluctuations \((|D_{HF}|)\) was on average 44% ± 34, and the average change in the ratio \((|D_{HR}|)\) was 170% ± 360 \((n = 18)\). All significant changes in the HRV parameters were >10% in absolute values.

HR exhibited significant changes in 14 of 18 reperfusion events. The absolute value of relative change in HR \((|D_{HR}|)\) was 5.3% ± 4.4 \((n = 18)\).

Among the nine AW-MI patients, HR increased in seven cases (only 5 were significant) and decreased in two cases (only 1 was significant). Among the nine IW-MI events, HR increased in four cases and decreased in five cases (HR decrease was not significant in 1 case). The classification of HR change according to MI location was not significant \((P > 0.3, \text{Fisher exact test})\). No correlation was found between the changes of HRV parameters and MI location: ANOVA of \(\text{LFP}_m(t), \text{HFP}_m(t), \text{R}(t)\) with respect to MI location and time of reperfusion (the epochs BR and AR) did not exhibit any significant effect.

However, an important observation was made: the type of HRV alteration \((\text{class 1} \text{ or } \text{class 2})\) was unequivocally associated with the respective MI location. Individual responses of HRV parameters are detailed in Table 1.

Classification According to MI Location

Class 1 HRV responses were observed in six of the nine AW-MI patients and in one of the nine IW-MI episodes \((P < 0.03, \text{Fisher exact test})\). Figure 2 shows an example of this class 1 behavior, exhibited by an AW-MI patient \((T30 \text{ in Table 1})\). In this example, reperfusion was detected at \(t = 2,900 \text{ s}\) and was accompanied by a biphasic alteration of the HRV spectral pattern. First, a reduction of both \(\text{LFP}_m(t)\) (95%) and \(\text{HFP}_m(t)\) (78%) and of \(\text{R}(t)\) (70%), corresponding to class 1\(d\), occurs immediately after reperfusion. Then \(\text{HFP}_m(t)\) increased monotonically, while \(\text{LFP}_m(t)\) remained constant, corresponding to class 1\(b\).

HRV responses classified as class 2 were observed in three AW-MI patients and in eight episodes of reperfusion found in seven IW-MI patients \((P < 0.03, \text{Fisher exact test})\). An example of the analysis of HR fluctuations for an IW-MI patient \((T26 \text{ in Table 1})\) during reperfusion is shown in Fig. 3. In this case, reperfusion was detected at \(t = 1,400 \text{ s}\). Clinical reperfusion was preceded by a marked increase in both \(\text{LFP}_m(t)\) (380%) and \(\text{R}(t)\) (480%), followed by an additional monotonic increase of these two parameters. The \(\text{HFP}_m(t)\) increased only slightly (9%). This behavior complies...
with class 2b. The HR decreased only slightly (2 beats/min; 2%).

Interestingly, we found no correlation between the class of HRV response and the HR response (P/Fisher exact test; cases in which HR was not changed significantly were excluded from the statistical test).

Roughly summarizing, we might say that the class 1 response to reperfusion occurs mainly in AW-MI, whereas the class 2 response is dominant in IW-MI.

**Paradoxical Relation Between HR and HRV**

Two IW-MI patients (T02 and T14 in Table 1) exhibited a highly remarkable paradoxical HR-HRV correlation. The phenomenon can be described as "shutdown" of HR fluctuations in response to HR reduction, followed, during thrombolysis, by a "turn-on" of HR fluctuations in response to an increase of HR.

Figure 4 shows an example of this phenomenon, obtained from patient T14, with IW-MI. The shutdown occurred at t = 3,500 s: average HR decreased by 7 beats/min accompanied by a 90% reduction in both LFP_m(t) and HFP_m(t). On the other hand, the turn-on of HR fluctuations occurred 70 min later at t = 7,700 s: an increase of HR by 2 beats/min was accompanied by an increase in both LFP_m(t) and HFP_m(t) (485 and 4,160%, respectively).

In the other case, which exhibited a similar phenomenon (T02, again an IW-MI), a HR decrease of 19 beats/min was accompanied by a reduction in HFP_m(t) by 73%. Later, a HR increase of 6 beats/min was accompanied by an increase in HFP_m(t) by 368%.

**Reocclusion**

In all of the four events of reocclusion, significant changes were observed in the HRV parameters. HR did not change considerably in three cases. Figure 5 shows an example obtained from an IW-MI patient (T28) in which reperfusion was diagnosed, later reocclusion occurred, and then another reperfusion event was observed.

**Respiratory Rate**

Only two patients exhibited a significant change in respiratory rate between the BR and AR epochs. These patients are marked in Table 1: T27 exhibited an increase of 46.0% in respiratory rate, and T02 exhibited a decrease of 11.0%. All other patients exhibited a small and insignificant change in respiratory rate after reperfusion (and reocclusion).

**DISCUSSION**

The principal result of this study is the finding of marked alterations in the HRV components in relation to myocardial perfusion. While the average changes in HRV parameters were not significantly different between the two study groups, a case-by-case examination detected substantial alterations. By itself, this result is clinically important, because it indicates that continuous assessment of HR fluctuations may provide a marker of reperfusion, independent of the currently used markers. As for the type of changes found in the HRV patterns, these can be explained in terms of alterations in cardiac autonomic control of heart rate.
In this study, we link the time-dependent change in the spectral pattern of HRV to changes in activity of the ANS. It is known that stimulation of sympathetic afferents causes either one or both of the following reactions: increase of firing rate of sympathetic efferents and reduction of firing rate of vagal efferents (25, 29, 38, 39, 53). Therefore, the mutually opposed effect of sympathetic (or parasympathetic) stimulation has to be accounted for when interpreting the changes in the power of the spectral components of HRV. On the other hand, MI may stimulate a parallel activation of the sympathetic and parasympathetic systems (59). Such complex responses of the vagal and sympathetic systems to ischemia are most probably the reason for the
lack of correlation between the average changes of HRV parameters and MI location in this study.

The classification of HRV response into the two classes, described in Methods, enabled us to incorporate several complex autonomic responses into a coherent picture. Indeed, we found a significant correlation between the location of the infarct and the type of autonomic activation (class 1 or class 2) at reperfusion (and reocclusion), as reflected by HRV. In terms of the parameters of HRV analysis introduced above, a shift in balance toward relative sympathetic enhancement (class 2) was found in all nine reperfusion episodes of IW-MI patients (the reperfusion episodes of the patients who exhibited the paradoxical HR-HRV correlation are discussed in the following subsection). The AW-MI patients presented a less uniform behavior: six of nine patients exhibited a shift in balance toward relative vagal enhancement (class 1).

Other studies, focusing on the time before reperfusion, have also found that the proportion of IW-MI patients exhibiting vagal dominance (and therefore expected according to our hypothesis to shift toward relative sympathetic enhancement after reperfusion) is higher than the proportion of AW-MI exhibiting sympathetic dominance (4, 40, 59). The proportions in those studies were lower than the ones we found, namely, 100% for IW-MI and 66% for AW-MI.

It is important to note that we do not speak of vagal or sympathetic overactivity, as referred to in several studies (40, 59, 60), since we did not assess the baseline ANS activity. Moreover, our hypothesis deals only with changes related to alteration of myocardial perfusion. This restrictive assumption stems from the diversity of clinical conditions, which we encountered in this study: some patients received medication directly affecting their baseline HRV, whereas others were hypertensive and were medicated accordingly. Yet, we assume that 1 h after taking any medication (see inclusion criteria), its concentration is in steady state, and therefore any changes in HRV can be attributed to changes in ANS activity rather than to the effect of the medication.

Surprisingly, the changes of HR correlated neither with HRV, nor with MI location. Correlations may become statistically significant in a larger patient population, yet even at this stage, it is clear from the magnitude of HR changes and from the directions of the changes, that HR itself is a poor marker of reperfusion. This finding conflicts with previous studies, which used the HR to study ANS activity during myocardial ischemia and infarction (24, 40, 59, 60). However, considering in our case the diversity of the patients, in terms of initial clinical condition, the chronic use of medications and the medications given during the thrombolysis (especially β-blockers), it is reasonable to assume that HR is determined not only by the ANS, but by other factors.

Paradoxical Correlation between HR and HRV

The paradoxical relation between HR and HRV observed in two patients is remarkable. In those patients, we observed events that we refer to as shutdown and turn-on of HRV. Those events are characterized by two puzzling observations: 1) HR changed in the opposite direction from that predicted by the type of HRV alteration, and 2) the marked change in both HF and LF peaks should have indicated an intense change in cardiac autonomic activity, which probably did not occur.

The second observation is crucial for the understanding of this phenomenon, because if such an intense change in ANS activity occurred, it could explain the pattern of HRV. Yet, the occurrence of such an intense alteration of ANS activity is contradicted by two facts. Reperfusion, which might have induced such an alteration, did not occur at that stage and in fact occurred much later in both patients. Second, mean HR changed only slightly during the abrupt HRV changes, and, moreover, the HR changed in the direction opposite from that predicted by the type of HRV alteration. By itself, the slight and opposing HR change does not prove, but only supports, the lack of an intense autonomic stimulation, because we found in the current study that in many cases, mean HR did not correlate with HRV. We explain this result in terms of vagal saturation, of either the cholinergic receptors in the SA node, or of the nerve fibers. Vagal saturation has been observed by Goldberger and coworkers (26–28) in normal subjects under β-blockade, in which vagal activity was gradually increased using phenylephrine. In those studies, the gradually increased vagal activity resulted in a monotonic HR reduction and a gradual increase of the HF peak. However, at a certain level, the HF peak decreased dramatically, whereas HR continued to decrease. This phenomenon has been attributed to saturation of the vagal system.

In this view, when the vagal system is highly active, and its level is close to the saturation threshold, a slight increase of vagal activity causes the mean HR to slightly decrease but may drive the SA node into a state of saturation, which inhibits the fluctuations of the HR caused by modulation of vagal activity. In that case, only the mechanically induced fluctuations remain effective. When the vagal activity is reduced to a level below the saturation threshold, then mean HR slightly increases and HRV parameters may exhibit a two-order-of-magnitude increase.

In the case of IW-MI patients, such explanation is highly plausible. Therefore, under vagal saturation, a small and gradual reduction in vagal activity results in an abrupt increase in the HF peak. In both patients who exhibited the saturation phenomenon, both the LF and HF peaks increased after reperfusion. This increase in the HF peak reflects a reduction of vagal activity, and the increase in the LF peak suggests an increase in sympathetic activity, i.e., a pattern of shift in balance toward relative sympathetic enhancement.

Incorporating this modification of HRV interpretation to the classification of HRV patterns according to MI location indicates that all of the nine reperfusion episodes of IW-MI patients were associated with a shift in balance toward relative sympathetic enhancement (P < 0.001, Fisher exact test).
Impact of Respiratory Rate

Changes in the respiratory rate are known to have an effect on HRV. It was shown in several studies that respiratory rate is inversely correlated with the power of the HF peak (14, 30, 52). Therefore, an increase of the HF peak, while the breathing rate increases, indicates an increase in vagal activity, which is larger than estimated if one would disregard the change in respiratory rate. One patient (T27) exhibited this condition: both the HF peak and the respiratory rate increased after reperfusion. Therefore, in this case, the original interpretation of HRV (class 2d) should be altered. Taking into account the fact that the increase in the respiratory rate prompts us to conclude that the ratio LF/HF is skewed toward sympathetic activity in this case. Therefore, the “true” pattern of HRV change in this patient is either class 2d or class 1c, and the shift in autonomic activation cannot be uniquely determined from the HRV in this case.

In contrast, patient T02, in whom respiratory rate decreased, exhibited paradoxical HR-HRV relations. In this case, the HF peak is determined mostly by the mechanical coupling in the cardiorespiratory system, which is less influenced by changes in respiratory rate, as shown by Bernardi and coworkers (14).

Reocclusion

Interestingly, reocclusion in the four patients was accompanied, and in one case even preceded, by marked alterations of HRV indexes. In three of four cases, these changes correlated with MI location. This result indicates that during thrombolysis and notwithstanding the clinical limitations, the time-frequency HRV analysis reflects not only the renewal of myocardial blood supply, but also the ischemia caused by coronary occlusion.

Mathematical Analysis

The use of the CWT was beneficial in three aspects. By using a time-dependent spectral analysis, we were able to quantify dynamic changes in the HRV indexes and then to use them for deducing the alterations of ANS activity. The assessment of the LFPm(t) and HFPm(t) enabled us to obtain a measure of the intersubject variability of those peaks, rather than inter-subject variability. The intrasubject variability was used to determine a patient-specific threshold, which was considered as the intrinsic level of noise of the computed parameter in this individuum. This approach is most valuable when examining complex patterns of HRV alterations related to transitional physiological conditions. Moreover, it seems that the most important advantage of using the wavelet transform is the ability to obtain a comprehensive description of the HRV evolution throughout the recording session, rather than focusing on a specific event.

In general, when implementing such a threshold approach, fine-tuning of the threshold value and/or of the trace duration used for the assessment of the intrinsic level of noise of the relevant HRV parameter should be performed according to the specific experimental or clinical setup. In our case, when applying it to subtraces where no reperfusion had occurred (see METHODS), we found that this threshold test is very reliable for the HRV parameters in terms of type-1 error (false positive detection rate). Therefore, we may conclude that the changes in HRV parameters considered as significant according to this test most likely reflect true physiological changes, in this case, reperfusion or reocclusion. The correlation between the location of the infarct and the type of HRV response confirms that this test also has low rates of type-2 error, because the specific HRV changes were closely correlated with changes in myocardial perfusion. Our test was found unreliable, leading to many false-positive detections when applied to the HR signal. This finding is in accordance with the lack of correlation between the HR response and the infarct location, indicating that this test applied to the HR has also high false-negative detection rate.

Focusing on the dynamic changes, we were also able to observe events of shutdown and turn-on of the HRV, which probably reflect saturation effects of the vagal system. Overlooking this effect would increase the intersubject variability of the measured parameters, thus masking the true behavior of ANS activity. In addition, the continuous analysis enabled us to observe autonomic changes related to reocclusion.

Limitations of the Study

The experiment was performed in the clinical setting, where the patient’s care is of utmost priority. Indeed, we were unable to control or limit the administration of medications. Administration of β-blockers and atropine is of special concern because these medications have a chronotropic effect. Moreover, administration of β-blockers during AMI has been shown to affect the pattern of ANS activity during coronary occlusion (2), probably due to the resulting reduction of the infarct size. We addressed this limitation by considering changes in HRV in a patient, relatively to baseline condition of that specific patient.

The clear correlation between the types of HRV response to reperfusion (class 1 and class 2) and the location of infarct (IW-MI or AW-MI) indicates that the effect of changes in tidal volume that occur at reperfusion is insignificant, relative to reperfusion itself. This assumption is also supported by the fact that respiratory rate, as reflected by the frequency of the HF peak, did not change considerably in most patients, thus lowering the possibility that respiratory volume may have changed.

Conclusions

We found that time-dependent spectral analysis of HRV, using the CWT, enabled us to detect patterns of alteration in HRV, which were directly associated with changes in myocardial perfusion. Marked alteration in
HRV parameters was found during reperfusion and during reocclusion. Interestingly, significant correlation was found between infarct location and the type of ANS response to reperfusion, as reflected by HRV. This result is highly important in view of the diversity of clinical conditions exhibited by the patients, in terms of the infarct location and size, medication, and age. In contrast, HR itself was found to be a poor marker of reperfusion correlated neither with HRV response nor with MI location. The continuous HRV spectral analysis also enabled us to observe events of shutdown and turn-on of HRV, which we attribute to saturation of the vagal system.

The CWT, although more complicated mathematically than standard spectral analysis, provides a rich description of the time-dependent evolution of HRV and the autonomic control branches involved during extreme physiological conditions and in a complex clinical setting.

APPENDIX

We used a modified version of the CWT to assess the time-dependent power spectrum of HR fluctuations. The CWT provides a time-frequency decomposition of a continuous signal. A basic notion of wavelet analysis is the wavelet function, denoted here as \( \psi(t) \). This function, which is used to decompose the analyzed signal in the time-frequency plane, must comply with specific constraints (22). It should be localized both in time and in frequency, meaning that it must have the spectral pattern of a bandpass filter. The definition of the general CWT of a signal \( s(t) \) is (21)

\[
W_{\text{CWT}}(t,f) = \int_{-\infty}^{\infty} s(\tau) \psi^*([\tau - t]) d\tau
\]

where \( W_{\text{CWT}}(t,f) \) is the CWT at time \( t \) and frequency \( f \), and the superscript asterisk denotes the complex conjugate. Obviously, we deal with discrete-time signals, and this issue is explained later. As our wavelet function, we chose the complex sum of a sine and a cosine

\[
\psi^h(t) = \begin{cases} \frac{1}{\sqrt{k}} e^{2\pi i ft} & |t| \leq \frac{k}{2} \\ 0 & |t| > \frac{k}{2} \end{cases}
\]

where the factor \( k \) is a parameter of analysis (the superscript \( H \) stands for harmonic). Inserting Eq. 7 into Eq. 6 provides the explicit form of the CWT that we used

\[
W^h_{\text{CWT}}(t,f) = \int_{-\infty}^{\infty} s(\tau) e^{2\pi i [ft-\tau]} d\tau = \int_{-\infty}^{\infty} s(\tau + t) e^{2\pi i ft} d\tau
\]

Equation 8 means that the CWT of \( s(t) \) at time \( t \) and frequency \( f \) is the Fourier transform of the product \( s(t) \) and a time window centered at time \( t \) and of duration \( k/f \).

This time window is frequency dependent: for low frequencies and short for high frequencies, unlike most methods of time-frequency decomposition, such as the short-time Fourier transform (47), Wigner-Ville (19), or the time-dependent parametric models (16). The frequency-dependent window length results in frequency-dependent time and frequency resolutions. The CWT shares this property with the SDA (34). The factor \( k \) in Eq. 7 determines the number of periods of the sine and cosine, which constitute the wavelet function \( \psi^h(t) \). Setting \( k = 1 \) provides maximal time resolution but little noise robustness. Increasing the parameter \( k \) widens the time window, resulting in better robustness but reduced time resolution. We chose to set \( k = 10 \) in our analysis (34).

Figure 1 shows an example of this analysis. A simulated HR, with constant mean value but abruptly changing spectral components, is shown in Fig. 1a. The wavelet transform \( |W^h_{\text{CWT}}(t,f)|^2 \) of this HR signal is shown in Fig. 1b, coded in gray scale. The LF component (~0.1 Hz), as a function of time, appears as a sharp peak in frequency, and its change in amplitude is easily detectable. The HF component (between 0.2 and 0.8 Hz), as a function of time, appears as a wider spectral peak, in accordance with the frequency dependence of the spectral resolution, expressed by Eq. 2. The changes in amplitude and in center frequency are clearly detectable (in Fig. 1).

In the case of HRV, essentially only one spectral component exists at frequencies >0.18 Hz (an exception is discussed in Ref. 56). Therefore, we may choose to trade frequency resolution for time resolution in this frequency range. On the other hand, a frequency below 0.18 Hz usually includes more than one peak and a high spectral resolution is required (3). Our wavelet transform intrinsically fulfills such time and frequency resolution requirements.

The time-frequency decomposition of the signal, expressed by Eq. 8, does not provide a quantitative measure of the power in the LF and HF bands. However, due to the Parseval equality, which holds here (Ref. 21), the CWT can be understood in terms of “power”: \( |W^h_{\text{CWT}}(t,f)|^2 \) is the power of \( s(t) \) at time \( t \) and frequency \( f \). Moreover, integrating \( |W^h_{\text{CWT}}(t,f)|^2 \) over a specific frequency band provides the time-dependent power of the signal in that frequency band

\[
B(t)|_{f_l}^{f_u} = \int_{f_l}^{f_u} |W^h_{\text{CWT}}(t,f)|^2 df
\]

where \( B(t)|_{f_l}^{f_u} \) denotes the power [in (beats/min)^2] in a specific frequency band, delimited by \( f_l \) and \( f_u \).

To obtain a quantitative measure of LF fluctuations, we set \( f_l = 0.04 \) Hz and \( f_u = 0.18 \) Hz. Therefore, integrating over this frequency range results in a dynamic, time-dependent measure of the LF fluctuations

\[
\text{LFP}(t) = \int_{0.04}^{0.18} |W^h_{\text{CWT}}(t,f)|^2 df
\]

The HFP(t) is computed in the same manner, by setting the frequency limits according to the respiratory frequency. Similarly, the HFP(t) can be understood as a dynamic measure of the HF power. Figure 1 shows the LF power and HF power as a function of time for the example mentioned above. The LFP(t), shown in Fig. 1c, clearly follows the change of power of the 0.11-Hz component, whereas the HFP(t) (Fig. 1d) reduced time change in power of the HF component. It is interesting to compare the time-dependent assessment of the LF and HF peaks obtained using the wavelet transform to the typically computed “steady-state” LF and HF peaks obtained using the power spectrum (such as by fast Fourier transform or autoregressive models). In typical HRV
studies, the focus is on the power of the LF and HF fluctuations, obtained by integrating the power spectrum over this frequency range. Therefore, the typical LF and HF peaks can be approximated by computing the average values of LFP(t) and HFP(t), respectively, over the entire trace.

As mentioned, in the standard spectral analysis performed over the entire trace, one obtains a single value for the LF and for the HF peaks, each of which can be regarded as a time-averaged version of the time-dependent integrals LFP(t) and HFP(t) obtained along the trace, respectively. This time-averaging feature has a smoothing effect, which cancels out short transients and outliers. The extent of the smoothing depends on the trace length. As opposed to this feature, the LFP(t) and HFP(t), which are the dynamic version of the standard LF and HF peaks, obtained from the CWT, exhibit sometimes extremely large or small values in the vicinity of such transients. Moreover, the ratio between these two functions LFP(t)/HFP(t) may exhibit spurious large values when HFP(t) exhibits transitory low values. To avoid this, we filter the integrals LFP(t) and HFP(t) using a moving-window filter, with a window of 3 s: at every instant t, the output of the filter is the median value within the 3 s around the time t. This filter reduces outliers, yet keeps the transients in the signal intact.

In Eqs. 6–10, the time variable is continuous, yet in practical computation schemes the time has to be discrete. To compute Eq. 8, we use the relations between the discrete Fourier transform and the Fourier transform of a continuous signal (47)

$$W_{CWT}^{H}(nT_s) = \sum_{k} \frac{1}{\sqrt{T_s}} s(\tau + nT_s) e^{-j2\pi nkT_s} d\tau = \frac{f}{\sqrt{T_s}} \int_{T_s} s(m + nT_s) e^{-j2\pi nkT_s} dm$$ (11)

where $T_s$ is the sampling interval. Therefore, the computation of the CWT of a discrete signal should be understood in the following sense: the discrete-time signal represents the samples of a continuous-time signal, and we sample, both in time and in frequency, the CWT of that continuous signal.

The straightforward implementation of Eq. 11 has high computational complexity. To expedite the computation, we use a recursion rule (9), which relates $W_{CWT}^{H}(nT_s/f)$ to $W_{CWT}^{H}(nT_s/f)$.

It is important to note that the formulation of the CWT shown here is not the typical one. The typical wavelet formulation is of “time scale” (scale is usually marked by a), rather than of “time frequency” (21). Yet, by substituting the scale parameter a by $1/2\pi f$, we obtain Eq. 6. This formulation is much more intuitive than the one of time scale and relates directly the CWT to the typical spectral components of HRV (see also Ref. 34).

Another point to be noticed is that, usually, the analysis of discrete-time signals is performed using the DWT (11, 32, 36, 51, 58), which is computationally efficient (21, 22). However, the DWT enables the assessment of the spectral power in several predetermined frequency bands. The structure of those frequency bands depends on the sampling frequency of the signal (21). Therefore, when peaks change their frequencies, they might shift from one band to another, complicating the analysis and interpretation.

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