Thrombolysis in the Eyes of the Continuous Wavelet Transform

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Abstract

Acute myocardial infarction (MI) is known to elicit autonomic responses, depending on its location: inferior-wall MI (Inf-MI) promotes vagal activation, and anterior-wall MI (Ant-MI) promotes sympathetic activation. Reperfusion is thus expected to induce an opposite shift in autonomic balance. We studied the patterns of heart rate variability (HRV), which reflect the autonomic response to reperfusion by applying a continuous wavelet transform (CWT). ECG traces, 3 h long, were obtained from 9 Ant-MI and 8 Inf-MI patients during acute MI. Marked alterations in HRV occured in all reperfusion events. A shift in balance towards sympathetic predominance was found in all Inf-MI patients, and in 3 Ant-MI patients, while a shift towards vagal predominance was found in 6 Ant-MI patients ($p<0.001$). The CWT thus enables to study cardiac control during non-steady-state conditions, as exhibited during thrombolysis.

1. Introduction

Occlusion of coronary blood vessels, which causes myocardial infarction (MI), is frequently treated using thrombolytic agents. The occurrence of reperfusion is determined according to clinical criteria. In this study, we aim at characterizing the patterns of heart rate variability (HRV), which appear in synchrony with reperfusion. The basic concept that underlies this study is that myocardial ischemia and acute infarction induce strong autonomic reflex responses. Left anterior wall ischemia/infarction tends to induce sympathetic activation, whereas ischemia or infarction of the inferoposterior wall tends to induce parasympathetic activation [1]. We chose to study cardiac autonomic control by spectral analysis of HRV. Standard approaches to the HR spectral analysis are based on the assumption of steady-state conditions, which disregards the presence of any dynamics in the power spectrum. These approaches are therefore inapplicable when examining transient conditions, as expected in the case of thrombolysis. In this study, we apply a special form of the Continuous Wavelet Transform (CWT) to the analysis of HRV during thrombolysis [2]. This wavelet transform inherits many features of the SDA developed in our laboratory [3]. The CWT of the HR trace provides a time-frequency decomposition of the signal and yields a time-dependent version of the typical LF and HF peaks. Hence, this approach can provide an insight into the dynamics of cardiac autonomic control as reflected by HRV.

2. Mathematical analysis

We used a modified version of the CWT to assess the time-dependent power spectrum of HR fluctuations. The definition of the general CWT of a signal $s(t)$ is [4]:

$$W_{CWT}(t,f) \equiv \int_{-\infty}^{\infty} s(\tau)\sqrt{f}\cdot\psi^{*}\left(f(\tau-t)\right)d\tau \qquad [1]$$

where $W_{CWT}(t,f)$ is the CWT at time t and frequency f and $\psi(t)$ is the wavelet function. As our wavelet function, we chose a complex sum of a sine and a cosine:

$$\psi^{H}(t) = \sqrt{\tfrac{1}{k}}e^{2\pi i t} \text{ for } |t| \le \tfrac{k}{2},\ \psi^{H}(t) = 0 \text{ for } |t| > \tfrac{k}{2} \qquad [2]$$

where the factor k is a free parameter of analysis. We chose to set k=10 in our analysis [3]. Inserting Equation [2] into Equation [1] provides the explicit form of the CWT applied in this study:

$$\begin{aligned} W^{H}_{CWT}(t,f) &= \sqrt{\tfrac{f}{k}}\int_{t-k/2f}^{t+k/2f} s(\tau)e^{2\pi i f(\tau-t)}\,d\tau = \\ &= \sqrt{\tfrac{f}{k}}\int_{-k/2f}^{k/2f} s(\tau+t)e^{2\pi i f\tau}\,d\tau \end{aligned} \qquad [3]$$

Equation [3] means that the CWT of $s(t)$ at time t and frequency f is the conventional Fourier transform of $s(t)$ multiplied by a time window, centered at time t, and of duration k/f. This time window is frequency dependent: it is long for low frequencies and short for high frequencies. The frequency-dependent window length results in frequency-dependent time and frequency resolutions (Δt and Δf):

$$\Delta t \propto 1/f \Rightarrow \Delta f / f \approx 1 \Rightarrow \Delta f \propto f \qquad [4]$$

In the case of HRV, essentially only one spectral component exists at frequencies above 0.18 Hz (an exception is discussed in [5]). Therefore, we may choose to trade Δf for Δt in this frequency range. On the other hand, the frequency band below 0.18 Hz, usually includes more than one peak and a high spectral resolution is required [6]. Our wavelet transform intrinsically fulfills such time and frequency resolutions requirements.

Time-dependent versions of the LF and HF peaks, $LFP(t)$ and $HFP(t)$, were computed by integrating $\left|W_{CWT}^{H}(t,f)\right|^2$ over the relevant frequency bands. They were then smoothed using a 3 sec moving-median filter and their ratio was computed: $R(t)= LFP(t)/HFP(t)$.

3. Data set and analytical procedure

Nine Ant-MI patients (7 men, 2 women, age= 55.8±12.0) and 8 Inf-MI patients (7 men, 1 woman, age= 65.9±11.1) were included in this study. ECG was recorded for 3 hours during thrombolytic therapy (Streptokinase or rtPA) from the bedside monitor and later digitized at a sampling rate of 500 Hz at a 16 bits resolution. The occurrence and timing of reperfusion were determined by the attending physician (criteria were 50% reduction in changes of ST-segment and relief of pain). The criteria for inclusion in this study were: reperfusion was determined according to the aforementioned criteria, reperfusion occurred during the recording session, opiates were not administered prior to reperfusion, medications were not administered one hour prior to reperfusion, patients exhibited only infrequent and isolated arrhythmias, which were correctable.

In this study, HRV patterns were divided into two classes: patterns associated with relative enhancement of vagal activity and those associated with relative enhancement of sympathetic activity:

Class 1: **a shift toward relative vagal enhancement**:

1a. LF decreases and HF is unchanged or increased, reflecting a reduction in sympathetic activity, while vagal activity is unchanged or increased, depending on the change in HF.

1b. LF is unchanged, HF increases, reflecting a reduction in sympathetic activity and an increase in vagal activity.

1c. Both LF and HF increase but their ratio is unchanged or reduced – reflecting increased vagal activity and unchanged or reduced sympathetic activity respectively.

1d. Both LF and HF decrease and their ratio decreases, reflecting reduced vagal and sympathetic activities, with a shift in balance toward relative vagal enhancement.

Class 2: **shift toward relative sympathetic enhancement**:

2a. HF decreases, LF increases or is unchanged, reflecting a reduction in vagal activity and an increase in sympathetic activity.

2b. LF increases, HF is unchanged, reflecting increased sympathetic activity and unchanged vagal activity.

2c. Both LF and HF decrease, and their ratio is unchanged, reflecting a reduction in vagal activity without considerable change in sympathetic activity.

2d. Both LF and HF increase and their ratio increases, reflecting increased vagal and sympathetic activities, with a shift toward relative sympathetic enhancement.

A subtrace of 3000 sec, centered at reported time of reperfusion, was considered for analysis. Two epochs, 300 sec long each, were selected around reported reperfusion time: 150-450 sec before the time of reperfusion 150-450 after reperfusion. The difference between the average values of the HR, $LFP(t)$, $HFP(t)$ and $R(t)$ during these two epochs was computed: Δ_{HR}, Δ_{LF}, Δ_{HF} and Δ_{R}. Each difference was compared to the standard deviation of the relevant parameter, computed over the entire 3000 sec subtrace. A change in each of the parameters was considered significant when its absolute valued difference was larger than its standard deviation. Otherwise, the change was considered nonsignificant.

4. Results

The classification of HRV responses to reperfusion exhibited a significant correlation with MI location: Class 1 HRV responses were observed in 6 out of the 9 Ant-MI patients and in one out of the 9 Inf-MI episodes, while Class 2 responses were observed in 3 Ant-MI patients and in 8 episodes of reperfusion found in 7 Inf-MI patients ($p<0.03$, Fisher exact test). Figure 1 displays the analysis of HR fluctuations for an Inf-MI patient during reperfusion.

Interestingly, HR changes correlated neither with the class of HRV response ($p>0.2$, Fisher exact test), nor with the infarct location. Analysis of variance of $LFP(t)$, $HFP(t)$ and $R(t)$ with respect to MI location and time of reperfusion did not disclose any significant effect.

Two Inf-MI patients exhibited a highly paradoxical HR-HRV correlation. This 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 2 shows an example of the turn-on phenomenon.

5. Discussion

The main finding of this study is the direct link observed between the type of HRV changes (Class 1 or 2), representing opposing autonomic responses to reperfusion, and the corresponding MI location. The classification of HRV responses into the two classes enabled us to incorporate several complex autonomic responses into a coherent picture. For example, in this framework, a pattern of vagal withdrawal and unchanged sympathetic activity becomes equivalent to an increase in sympathetic activity while the vagal one is unchanged.

Without this classification approach, the observed complexity explains why the average changes in HRV parameters were not significantly different between the two study groups, while a case-by-case examination and the resulting classification (Class 1 or 2) detected substantial and coherent alterations. This result may lay the basis for a detection scheme for reperfusion, to be based on HRV patterns in clinical conditions.

Another important finding is the paradoxical relation between HR and HRV observed in two patients. In those patients, we observed events, which we refer to as "shutdown" and "turn-on" of HRV. We explain this result in terms of vagal saturation either of the cholinergic receptors in the SA node, or of the nerve fibers. Vagal saturation has been observed by Goldberger et al. in a controlled experiment [7]. In the case of Inf-MI patients, such saturation explanation is highly plausible. Indeed, under conditions of vagal saturation, a small and gradual reduction in vagal activity then 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. Hence, this increase in the HF peak reflects a reduction of vagal activity, corresponding to a shift in balance toward relative sympathetic enhancement.

Overlooking this effect would increase the inter-subject variability of the measured parameters and lead to misinterpretation of the results, thus masking the true behavior of ANS activity. It is also possible that misinterpreted vagal saturation is the cause for conflicting results found in many other HRV studies. Incorporating this modification of HRV interpretation into the classification of HRV patterns according to MI location indicates that all the 9 reperfusion episodes of Inf-MI patients were indeed associated with a shift in balance toward relative sympathetic enhancement ($p<0.001$,

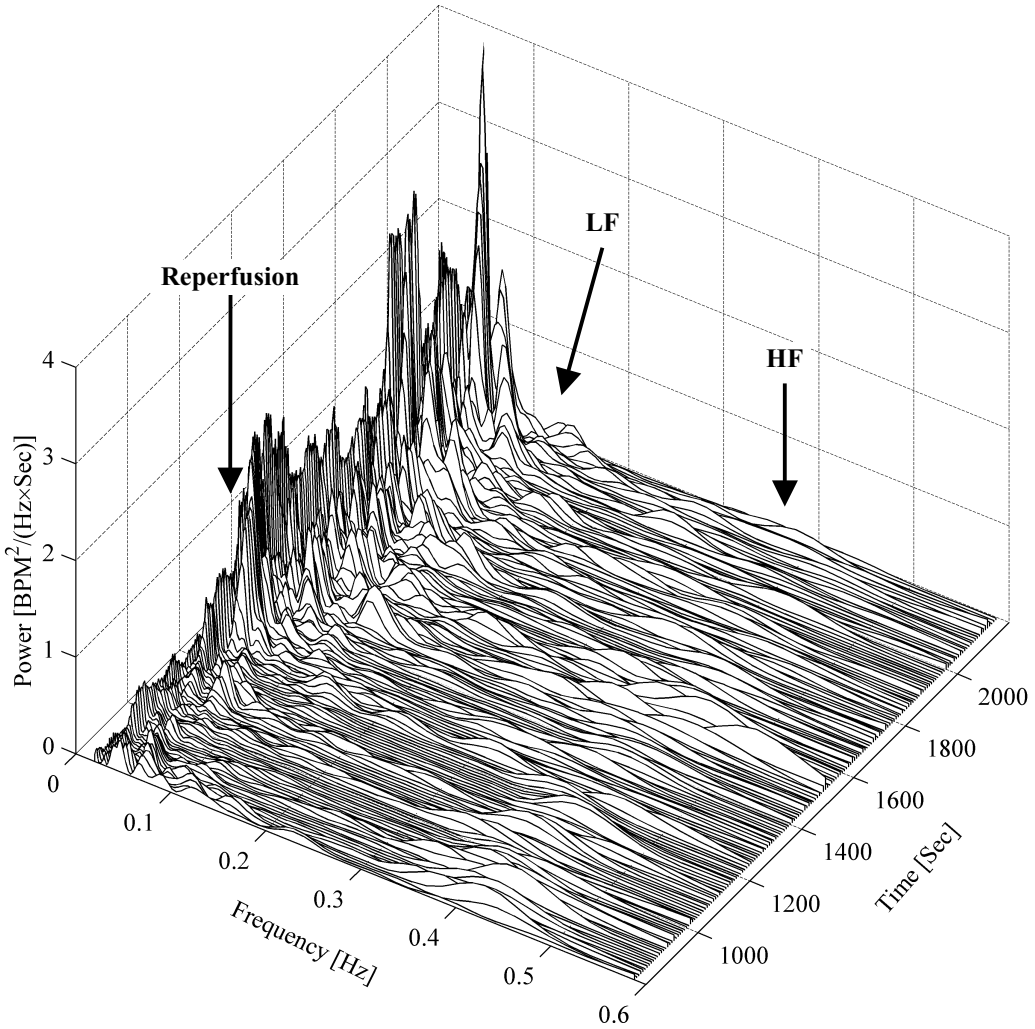

Figure 1: Example of the CWT of an Inf-MI patient. Reperfusion was clinically detected at t=1400 sec and was accompanied by a 380% increase of $LFP(t)$ and a 7% reduction of $HFP(t)$, corresponding to class 1a, suggesting a shift in cardiac autonomic activity toward sympathetic enhancement. Conversely, HR has reduced only by 2 BPM (2%).

Fisher exact test).

In conclusion, the continuous wavelet transform, 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 complex clinical settings.

Acknowledgements

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References

[1] Thames MD, Dibner-Dunlap ME, Minisi AJ. Cardiovascular reflexes during myocardial ischemia and infarction. In: Cardiovascular reflex control in health and disease, Hainsworth R, Mark AL Eds. London: Saunders, 1993, pp. 235-256.

[2] Toledo E, Gurevitz O, Hod H, Eldar M, Akselrod S. Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. Am J Physiol Regul Integr Comp Physiol. In Press.

[3] Keselbrener L, Akselrod S. Selective discrete Fourier transform algorithm for time-frequency analysis: method and application on simulated and cardiovascular signals. IEEE Trans Biomed Eng 1996;43:789-802.

[4] Daubechies I. The wavelet transform, time-frequency localization and signal analysis. IEEE T Inform Theory 1990;36:961-1005.

[5] Toledo E, Pinhas I, Almog Y, Aravot D, Akselrod S. Functional Restitution of Cardiac Control in Heart Transplant Patients. Am J Physiol Regulatory Integrative Comp Physiol 2002;282:R900-R908.

[6] Akselrod S. Components of heart rate variability: basic studies. In: Heart rate variability, Malik M, Camm AJ Eds. Armonk NY: Futura publishing, 1995, pp. 147-164.

[7] Goldberger JJ, Challapalli S, Tung R, Parker MA et al. Relationship of heart rate variability to parasympathetic effect. Circulation 2001;103:1977-1983.

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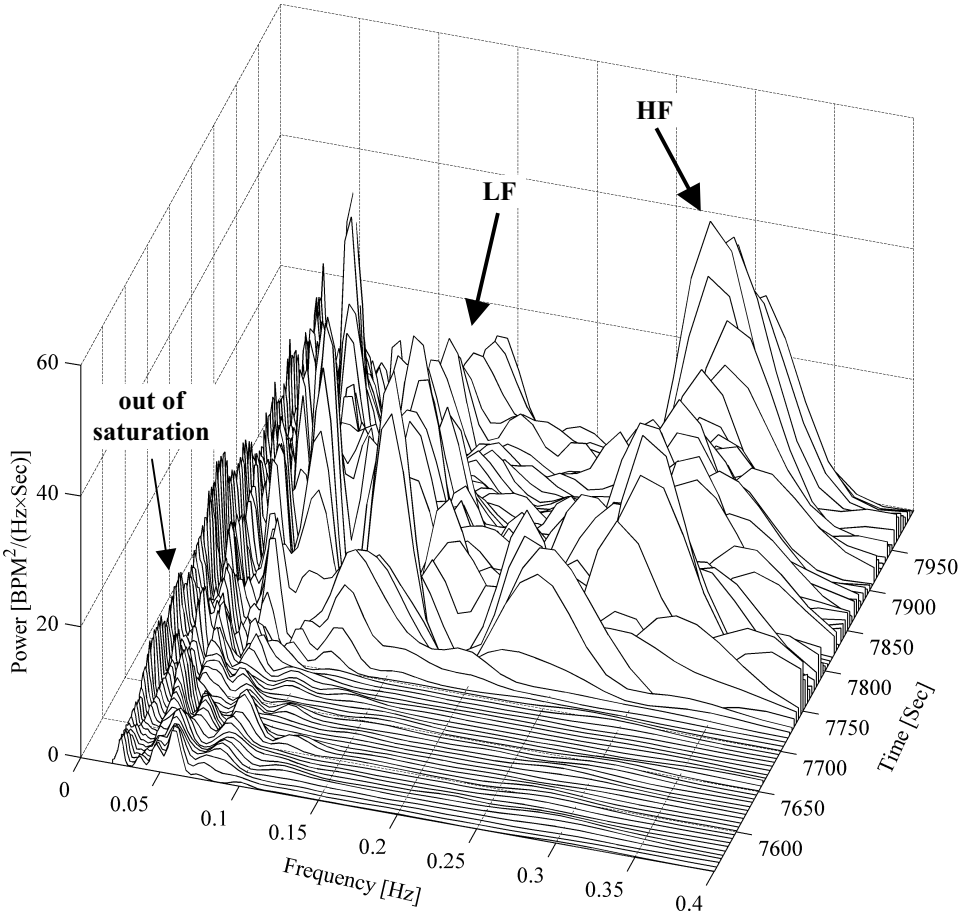

Figure 2: An example of the *turn-on* phenomenon at t=7750 sec: a slight HR increase (2 BMP, 3%) was accompanied by marked increase of both $LFP(t)$ (485%) and $HFP(t)$ (4160%), usually associated with a strong vagal activation. We hypothesize that a slight reduction in vagal activity pulled this system out of a state of saturation, resulting in a small HR increase and a marked increase of HRV power. The opposite phenomenon, termed *shutdown,* occurred at t=3500.