Time-Varying Spectral Analysis of Heart Rate and Left Ventricular Pressure Variability During Balloon Coronary Occlusion in Humans
A Sympathoexcitatory Response to Myocardial Ischemia
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IMPORTANT:

OBJECTIVES
We assessed time-varying spectral components of heart rate and left ventricular (LV) pressure variability during coronary angioplasty to elucidate dynamic autonomic responses to transient myocardial ischemia.

BACKGROUND
Sympathoexcitatory reflexes elicited by acute coronary occlusion are rarely addressed in the clinical settings because of a lack of technique to monitor transient changes in sympathetic activation.

METHODS
RR interval and LV pressure and volume were serially recorded in 14 patients with effort angina during balloon coronary angioplasty. Wavelet analysis was applied for determination of nonstationary spectral components of RR interval and LV peak pressure variability.

RESULTS
The wavelet analysis revealed that coronary occlusion provoked low-frequency (LF) fluctuations of RR interval (seven patients) and LV peak pressure (six patients) at 0.06 ± 0.01 Hz, but not in the remaining patients. Following the balloon inflation, the LF component of RR interval began to increase after the onset of myocardial ischemia, peaked at about 80 s, and then declined in the late phase of inflation. Consequently, the ratio of low to high frequency component rose to be significantly greater in the LF augmentation group than in the no LF augmentation group in the middle phase of coronary occlusion. The patients with no LF augmentation had little evidence of myocardial ischemia as reflected by changes in ST segment and LV systolic function during coronary occlusion.

CONCLUSIONS
The wavelet analysis of RR interval and LV pressure variability clearly showed a dynamic profile of spectral components in response to transient coronary artery occlusion. The resultant regional myocardial ischemia elicited a profound sympathoexcitatory response followed by a gradual suppression. This method provides a useful tool to gain a new insight into the nonstationary autonomic influence on the cardiovascular system. (J Am Coll Cardiol 1999;34:1924–31) © 1999 by the American College of Cardiology

Experimental coronary occlusion elicits sympathoexcitatory reflexes through activation of sensory endings in the ischemic left ventricle (1–3) whose afferent fibers travel to the spinal cord via the sympathetic afferents (3,4). These reflexes could exaggerate myocardial ischemia further by increasing myocardial oxygen consumption while maintaining cardiac function transiently by enhancing contractility. In the clinical settings, this reflex is supposed to be responsible for hypertension and tachycardia frequently observed in the early stages of acute myocardial infarction (5). The recent introduction of spectral analysis of beat-by-beat heart rate variability has provided quantitative markers of sympathovagal balance and revealed that coronary occlusion elicits variable changes in heart rate variability (6–10). This is likely attributable to complex interaction between excitatory reflexes mediated by sympathetic afferent fibers and inhibitory reflex mediated by vagal afferent fibers (11). A relative contribution of these opposing reflexes on sympathetic efferent activity has been shown to depend on the severity and the site of myocardial ischemia. Therefore, the spectral components and their magnitude of cardiovascular variability could vary as the coronary occlusion time elapsed. To date, the dynamic nature of cardiac sympathetic activity during coronary occlusion has not been studied in clinical
settings because of the lack of a technique to trace the nonstationary level of autonomic function.

The purpose of this study was to reveal the time-varying profile of autonomic balance while myocardial ischemia was progressing during balloon coronary occlusion in humans. We applied wavelet transform for RR interval and left ventricular (LV) pressure variability, which allowed valid and serial evaluation of transient changes in spectral components.

METHODS

Patient population. The study group consisted of 14 patients (9 men and 5 women; mean age, 59 ± 10 years; range, 36 to 74 years). All patients had effort angina and an electrocardiographically positive, symptomatic exercise stress test. Three patients had electrocardiographic evidence of prior myocardial infarction. Elective coronary angioplasty was performed at 15 target lesions (6 left anterior descending coronary arteries, 7 left circumflex coronary arteries and 2 right coronary arteries). All antiarrhythmic agents had been withdrawn 24 h before the procedure. Beta-adrenergic blocking agents which had been given to eight patients were withdrawn more than 48 h before the coronary angioplasty. All patients provided written informed consent and the protocol was approved by our institute’s Committee on Clinical Investigation. All procedures were successfully performed, and no complications were encountered.

Study protocol. An 8F conductance catheter (Sentron, Roden, the Netherlands) together with a 2F micromanometer-tipped catheter (Millar Instruments, Houston, Texas) was inserted from the left femoral artery and placed along the long axis of the left ventricle to the apex (12). The volume catheter was connected to Sigma-5/DF signal conditioner processor (Leycom Cardiodynamics Inc, Zoetermeer, the Netherlands) that used a dual excitation algorithm. Segmental volumes were summed to yield total conductance which was calibrated by actual volume derived from left ventriculogram.

Coronary angioplasty was performed through the right femoral sheath while electrocardiogram (ECG) and LV pressure and volume were serially recorded on digital tape (RD-130TE, TEAC Corp., Tokyo, Japan) for later analyses. Patients were advised to breathe regularly and refrain from talking during balloon coronary occlusion. They were asked to grade the severity of chest pain according to Smokler’s numeral scale after balloon deflation (13): grade 1 was mild, grade 2 was moderate, grade 3 was moderately severe and grade 4 was maximally severe. In 12 patients, coronary collateral recruitment was graded by contralateral or ipsilateral coronary angiography during balloon coronary occlusion using Rentrop criteria (14).

Data acquisition and analysis. We excluded the ECG and LV pressure-volume data obtained during the first balloon inflation from this analysis because myocardial ischemia had already been provoked by the first positioning of balloon catheter through the target lesion (15). Electrocardiogram, micromanometer pressure and conductance catheter volume were played back from the digital tape and digitalized at 1,000 Hz per channel by an analog-to-digital converter (DT31-EZ, Data Translation Inc., Marlboro, Massachusetts) and stored on a hard disk memory system using a computer (Optiplex-GXMT, Dell Computer Corp., Round Rock, Texas). Hemodynamic variables derived from digital pressure and volume data were analyzed with software developed in our laboratory as reported previously (8,16). The time constant of isovolumic LV pressure (Tau) decay was calculated by the derivative method of Raff and Glantz (17). Beat-to-beat RR interval and LV peak pressure were interpolated at 2 Hz to ensure equidistant sampling in each time series (8). The very low-frequency (LF) nonstationarity (<0.01 Hz) and the baseline trend were removed using a moving average function which did not affect the higher frequencies (HFs). The beat-to-beat spectral estimation analysis was based on the discrete wavelet transform using Gabor basis wavelet (18) and 256-event data. Theoretically, applying the basis wavelet to the original signal by dilution operations could result in a decreased time resolution in very LF. Nevertheless, this method has a great advantage over the traditional stationary spectral analysis in that the wavelet distribution enables one to decompose a signal in nonsteady states, into a function of time and frequency (19). The frequency contents were then classified as HF (HF: ≥0.15 Hz) and LF (LF: 0.04–0.14 Hz) components. In this study, the augmentation of power spectra was defined to be present if the peak power of fluctuation was above the level of mean +2 standard deviation of the baseline power (Fig. 1). Additionally, spectral components of the entire time series before and during balloon occlusion were examined using a conventional maximum entropy method (8). Power of the analyzed bands was expressed as absolute values and units normalized to the total power (7,8).

Statistical analysis. Data are expressed as mean ± standard deviation unless otherwise indicated. Differences in time-series data obtained by wavelet analysis were analyzed with analysis of variance for repeated measures and with the Bonferroni’s method for multiple comparisons. Differences between the baseline and coronary occlusion were compared with paired t test, and differences between two groups were
examined with unpaired *t* test. The level of statistical significance was set at *p* < 0.05.

**RESULTS**

**Patient characteristics and time-varying spectral data.** A marked augmentation of LF fluctuation of RR interval variability was provoked with balloon coronary occlusion of eight target arteries in seven patients. In these patients, a concomitant increase in LF component of LV peak pressure variability was observed during coronary occlusion of five target lesions. There were no significant changes in these power spectral components in the remaining seven patients except one patient who showed an increase in LF component of LV peak pressure variability. Prior myocardial infarction was documented in one of seven patients with LF augmentation and in two of seven patients without LF augmentation. No significant differences were found in age (56 ± 13 vs. 63 ± 5 years), Canadian Cardiovascular Society angina class (1.7 ± 0.5 vs. 1.7 ± 1.0) and the distribution of coronary target lesions between LF augmentation and no LF augmentation groups, respectively. There was an insignificant trend for the grade of collateral recruitment to be less in LF augmentation group (1.3 ± 1.1 vs. 2.0 ± 1.0), whereas the magnitude of ST segment deviation (0.18 ± 0.09 vs. 0.04 ± 0.03 mV, *p* < 0.01) and the severity of chest pain (1.9 ± 1.5 vs. 0.6 ± 0.5, *p* < 0.05) during coronary occlusion were significantly greater in LF augmentation group.

The beat-to-beat dynamics of RR interval fluctuations in each patient are shown within the three-dimensional framework of time, frequency and power, where the augmentation of the LF fluctuation is readily defined at 0.06 ± 0.01 Hz (Fig. 2). In contrast, no appreciable changes in LF fluctuation of RR interval were seen in the remaining seven patients during coronary occlusion (Fig. 3). These differences were clearly recognized by serial changes in LF component averaged every 10 s (Fig. 4). In the LF augmentation group, the LF component began to rise at 48 ± 11 s of the balloon inflation after the critical ST deviation; either 0.1 mV elevation or 0.1 mV depression was documented at 30 ± 8 s. The LF power peaked at 81 ± 19 s and then gradually declined in the late phase of coronary occlusion while myocardial ischemia progressed. Following LF augmentation, HF component began to increase in the middle to late phase of coronary occlusion, but the changes did not reach statistical significance (Fig. 4). Consequently, the ratio of LF to HF component in the LF augmentation group rose to be significantly greater than that of the no LF augmentation group in the middle phase of coronary occlusion. Release of the occlusion was followed by prompt return of LF component to the control level. The time sequence of spectral components of LV peak pressure variability was similar to that of RR interval variability (Fig.
The LF power spectra obtained by the maximum entropy method were also increased in LF augmentation group (Table 1). Although a significant correlation \( Y = 2.5X - 0.7, r = 0.92, p < 0.001 \) was found between LF power \( X \) by maximum entropy method and the peak LF power \( Y \) by the wavelet analysis, the changes in spectral power were substantially higher in the wavelet analysis than the maximum entropy method.

**Ventricular hemodynamic changes.** Coronary occlusion resulted in significant differences in LV systolic and diastolic function while the baseline cardiac function was similar between the two groups (Table 1). Left ventricular systolic pressure and heart rate did not change appreciably in either group during coronary occlusion. In the LF augmentation group, coronary occlusion increased LV end-diastolic and end-systolic volumes by 11% \( p < 0.01 \) and 34% \( p < 0.01 \), respectively, resulting in a decline in LV ejection fraction by 12% \( p < 0.05 \). Left ventricular peak \( +\text{dP}/\text{dt} \) fell, and LV end-diastolic pressure rose with a significant prolongation of Tau and a trend to decline for peak \( -\text{dP}/\text{dt} \).

In the no LF augmentation group, most of the hemodynamic variables did not show significant changes during coronary occlusion except Tau \( +24\%, p < 0.01 \), the most sensitive hemodynamic parameter to myocardial ischemia. Consequently, there was an inverse correlation \( r = -0.61, p < 0.02 \) between changes in LV ejection fraction and in LF components during coronary occlusion.

**DISCUSSION**

The wavelet analysis employed in this study revealed a dynamic nature of cardiovascular variability provoked by brief periods of coronary artery occlusion. The major findings obtained by this new method include the following:

1) LF components and the ratio of LF to HF component of RR interval and LV pressure variability began to increase after the onset of a significant ST deviation, peaked at the middle to late phase and then declined in the late phase of coronary occlusion.

2) The magnitude of maximal LF component was related to the severity of regional myocardial ischemia.

3) The maximal LF component detected by the wavelet analysis correlated well with the LF component of entire time series obtained by the maximum entropy method.

**Sympathoexcitation during myocardial ischemia.** The average spectral changes by coronary angioplasty were quite concordant with those obtained from previous experimental
and clinical studies. Rimoldi et al. (20) experimentally documented that regional myocardial ischemia provoked a powerful sympathoexcitatory response with a marked increase of the LF component of RR interval and arterial pressure variability. In clinical settings, ischemia-induced sympathetic overactivity was first described by Webb et al. (5) who found tachycardia and hypertension in the early phase of myocardial infarction. Recently, Lombardi et al. (21) applied autoregressive power spectral analysis of heart rate variability to detect autonomic disturbance within the first few hours of acute myocardial infarction in humans. They found a relative predominance of LF component independently from the infarct localization. The wavelet analysis employed in this study expanded these pioneering clinical findings to time-frequency representations of RR interval and LV peak pressure variability to reveal a dynamic profile of sympathovagal balance as the coronary occlusion time elapsed.

The possible mechanisms for a dome-shaped increase in LF component and a later increasing trend in HF components involve a complex neural, metabolic and mechanical interaction during myocardial ischemia. Generally, acute myocardial ischemia elicits both excitatory reflexes mediated by sympathetic afferent fibers and inhibitory reflexes mediated by vagal afferent fibers (1,3,22,23). The relative magnitude of these opposing reflexes was shown to be related to the site and severity of myocardial ischemia and the grade of ischemia-induced cardiac deterioration (5,11,24). Although the LV endings of all these fibers act as polymodal receptors, the effective stimulus to these receptors seems to differ considerably between sympathetic and vagal afferent fibers. Lombardi et al. (11) showed that global ischemia, by occluding the main left coronary artery, elicited early sympathoexcitatory followed by a predominant vagal inhibitory reflex as the heart failed. These findings could be explained by other experimental observations that the vagal inhibitory receptors respond largely to the attendant increase in heart size with a latency of 20–40 s while ischemia per se seems to be of little or no importance (22). By contrast, myocardial ischemia is known to effectively stimulate sympathetic afferent receptors with a much shorter latency (10 to 20 s) (11). Therefore, localized ischemia without profound cardiac deterioration could elicit predominant sympathoexcitatory reflex rather than reflex vagal inhibition. They confirmed experimentally that regional ischemia, by occluding the distal coronary artery, produced a marked and sustained increase in sympathetic discharge. These previous data suggest that the LF augmentation observed in this study could faithfully reflect sympathoexcitatory excitation provoked by regional ischemia during balloon coronary occlusion. However, the decline of LF augmentation in the late phase of coronary occlusion could attribute to the vagally-mediated sympathoinhibition manifested as ischemia-induced cardiac dysfunction progressed.

Figure 3. Three-dimensional continuous spectral plots (wavelet transform) of RR interval in patients who showed no augmentation of low-frequency component during coronary occlusion. Format and abbreviations are as in Figure 2.
The mean heart rate did not change significantly during coronary occlusion despite a marked increase in LF fluctuation of RR interval. Similar findings were found in the previous experimental study where regional ischemia did not appreciably change mean heart rate while increasing cardiac sympathetic activity (11). Recently, Kawada et al. (25) found that tonic gain of heart rate by sympathetic stimulation was canceled by simultaneous vagal stimulation, whereas phasic gain from sympathetic stimulation was amplified. Our disparate responses of mean heart rate and RR interval variability might be attributable to such interaction between the sympathetic and vagal systems in controlling heart rate.

Clinical implications. Cardiac sympathosympathetic reflex could result in two opposite consequences during coronary occlusion. For a short period following coronary occlusion, reflex-mediated increase in LV contractility might be able to support cardiac function to maintain normal arterial pressure, while potentially aggravating myocardial ischemia through an augmentation of myocardial oxygen consumption. Hereby, this reflex results in an underestimate of actual cardiac depression in the early phase of myocardial ischemia. However, total cardiac function deteriorates progressively as direct cardiodepressive action of myocardial ischemia gradually predominates over the reflex-mediated increase in LV contractility. Under these conditions, activation of afferent vagal receptors would occur and in turn suppress cardiac sympathetic nerve activity, resulting in a manifestation of actual deterioration of cardiac performance. As far as cardiac function is not severely compromised following acute coronary occlusion, early introduction of beta-blockers is rational for effective prevention of progression of myocardial ischemia.

Study limitations. Most of the patients studied had the target lesion in the left anterior descending artery or circumflex artery. Therefore, these data could not determine the relationship between the location of ischemia and the prevalence of hemodynamic fluctuations. Secondly, the nature of the LF component is still controversial despite consistent evidence that the normalized LF component of heart rate variability serves as a marker of sympathetic modulation of the sinus node (6,7). We have also demonstrated that cardiovascular variability at the frequency of 0.06 to 0.07 Hz has a high coherence with corresponding components of muscle sympathetic nerve activity in humans (26). The normalized LF component showed a parallel increase with plasma norepinephrine levels during the course of tachycardia-induced heart failure (8). Finally, the response of hemodynamic variability to coronary occlusion was not uniform in some patients. This seems to be caused by heterogeneity of coronary lesions and extent of ischemia, the presence of prior myocardial infarction or development of coronary collateral vessels. Destruction of nerve endings by myocardial infarction or repetitive ischemic insult could result in a loss of sympathetic reflexes originating from the ischemic area (27). Sympathoexcitation might be modified by another complex interaction with arterial baroreflex modulation accompanying hemodynamic changes or altered central mechanisms related to pain perception and to the stressful situation (28).
Conclusions. The wavelet analysis of RR interval and LV pressure variability clearly showed a dynamic profile of sympathetic-overflowatory response to brief periods of coronary artery occlusion in humans. The regional myocardial ischemia elicited a profound sympathoexcitatory response followed by a gradual suppression which presumably attributed to vagal inhibitory reflex. Thus, the time-frequency analysis of cardiovascular variability provides a useful tool to gain new insight into the nonstationary autonomic influence on the cardiovascular system.

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