HEART RATE VARIABILITY IN MYOCARDIAL ISCHEMIA DURING DAILY LIFE

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Heart Rate Variability in Myocardial Ischemia During Daily Life

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Abstract: The aim of this investigation was to evaluate the role of autonomic nervous activity before and during transient ischemic events. Forty-one ischemic episodes detected on Holter recordings were analyzed for heart rate and heart rate variability (HRV). A time-dependent index of HRV the windowed median successive difference, which is a continuous measure of respiratory sinus arrhythmia and therefore a marker of vagal efferent activity was used. A small window consisting of five beats, which represented one respiratory cycle, was chosen. This method permitted continuous assessment of short-term alterations of vagal modulation. With two exceptions, all ischemic episodes were preceded by an acute almost complete suppression of respiratory sinus arrhythmia. During the entire ischemic episode, HRV stayed at this reduced level, and preceding the end of the ischemia, it increased again. This suppression of intrinsic heart period variations reflects an almost complete withdrawal of modulated vagal outflow immediately before and during ischemic episodes. In 26 cases (63%), Fast Fourier Transformations were carried out when the heart rate was almost constant in two segments around the onset of ischemia. In the other 15 cases we did not perform Fast Fourier Transformations because there was no stationary stage in the data. High-frequency power always decreased drastically at the onset of ischemia, confirming a significant loss of modulated vagal activity ($P < .01$). The low frequency/high frequency ratio did not increase, indicating that sympathetic activity did not increase significantly at the onset of ischemia in about two-thirds of our cases. The extent to which this suppression of modulated vagal activity reflects a similar suppression of vagal efferent activity is discussed, as well as whether this withdrawal of vagal outflow is cause or consequence of the ischemic event. The results suggest that a vagal depression may influence the onset of myocardial ischemia during daily life. **Key words:** heart rate variability, respiratory sinus arrhythmia, windowed median successive difference, autonomic nervous activity, vagal depression, myocardial ischemia.

The role of autonomic nervous activity in connection with transient myocardial ischemia has not yet been sufficiently clarified in detail. The aim of this investigation was to examine sympathetic and vagal activity before and during transient ischemic events detected on Holter monitor recordings. Therefore, we analyzed 24-hour ambulatory electrocardiographic (ECG) recordings for heart rate and heart rate variability (HRV). Analysis of HRV has been established as a noninvasive method to assess cardiac autonomic nervous activity.

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The published investigations that deal with the relationship between autonomic nervous activity and transient myocardial ischemia seem to be contradictory. Bigger et al. showed a decrease in parasympathetic activity without any detectable increase in sympathetic activity during ischemic episodes (1). These authors analyzed continuous 5-minute segments of 24-hour Holter recordings obtained from patients some months after hospitalization for myocardial infarction or unstable angina. Goseki et al. found a decrease in vagal activity during the last 10 minutes before the onset of ischemia in patients with stable coronary artery disease (2). Yoshio et al. showed that vagal activity increased during the 10 minutes before attacks of nocturnal variant angina, whereas sympathetic activity with vagal modulation increased during the last 5 minutes preceding such attacks (3). Lanza et al. demonstrated an increase in vagal activation at the peak of silent ischemic episodes in patients with stable angina (4). Finally, van Boven et al. recently described a parasympathetic withdrawal during ischemic periods at heart rates below 70 beats/min (5).

In all of these studies, frequency-domain methods were used. It is well known that HRV frequency-domain measures need a stationary stage of data. Ischemic episodes invariably show moderate or marked increases in heart rate just after the onset of ischemia. This lack of a stationary stage in the data implies that frequency-domain measures of ischemic events should be regarded with reservation. Lanza et al. also used time-dependent methods (4). These authors analyzed 2-minute segments, which are indeed rather long periods to detect short-term changes in vagal modulation.

We primarily used a time-dependent method and chose an interval as small as possible to measure short-term respiratory modulation of sinus node activity. We found a mean 24-hour heart rate of 76.9 beats/min in our study. Supposing a mean respiratory rate of 15 breaths/min, we assumed that a segment of five consecutive beats would represent a mean respiratory cycle. Therefore, we computed the absolute values of successive heart period differences and calculated a "windowed median successive difference" (w-MSD) for every five consecutive beats. This windowed median represents a continuous measure of respiratory sinus arrhythmia (RSA). This arrhythmia is mainly although not exclusively mediated by vagal mechanisms. It provides an index of vagal efferent activity (6–9). Thus, we were able to assess continuously short-term vagal modulation for the complete Holter recording.

Materials and Methods

Patients and Recordings

We addressed ourselves to 350 cardiologists in the Federal Republic of Germany with the request to send us 24-hour Holter tapes containing marked ischemic episodes. We received 15 tapes, to which we added 5 of our own plus 7 from the University Hospital of Erlangen.

In view of the large number of artifacts in ambulatory long-term ECG recordings, we defined an ischemic event very rigorously. In order to exclude doubtful cases, we accepted as ischemic episodes only horizontal or downsloping ST-segment depressions at 80 ms after the J point of 0.1 mV or greater lasting for at least 3 minutes and ST-segment elevations of 0.1 mV or greater lasting for more than 60 seconds. Consequently, four tapes were excluded as was another tape that showed signs of ventricular hypertrophy. Finally, 22 24-hour long-term ECGs were accepted for our study. They were taken from 22 different patients and showed a total of 41 transient ischemic episodes, 36 ST-segment depressions, and 5 ST-segment elevations.

Our sample consisted of 12 men and 10 women of average age 61 years. A previous myocardial infarction was documented for four of these patients. For 12 patients, we had access to the results of previous coronary angiograms: in two patients, a one-vessel disease, in three patients, a two-vessel disease, and in seven patients, a three-vessel disease was diagnosed. In the meantime, following our Holter recordings, 7 of the 22 patients had undergone bypass surgery because of the severity of their coronary lesions.

Analysis of ECG Tapes

Tape-recorded ECGs were digitized at 128 Hz with use of a Reynolds Pathfinder 3 analyzer fitted for data processing. Thus, our calculation was based on a time unit of 7.8 ms. The durations of all successive R-R intervals were measured. Simultaneously, an analysis of the ST-segments was made at two points, the J point (ST 1) and 80 ms after it (ST 2). The data obtained were analyzed by an Apple Macintosh Quadra computer.

The many arrhythmias, and especially the amount of artifacts, posed enormous problems. In order to eliminate these interferences, we checked all ischemic episodes in detail. Around the onset of ischemia, no beat-to-beat differences >55 ms (seven time units) could be detected that could be

attributed to RSA. All larger differences were apparently caused by noise, artifacts, or various arrhythmias. For this reason, we eliminated all beat-to-beat differences >55 ms or greater from our calculations of w-MSD. During sleep periods with a higher vagal tone, we extended our eliminative criterion to differences >86 ms (11 time units). This technique did not bias the results toward a decrease of parasympathetic tone around the onset of ischemia. During this period no value attributable to RSA was eliminated. The "jumps" (ie, the differences between successive R-R intervals >50 ms) apparently disappear before the onset of and throughout the ischemia. Apart from the ischemic episodes, our elimination procedure may have led to an underestimation of HRV in the time domain. It is possible that the 24-hour w-MSD did not reflect complete parasympathetic modulation.

We calculated a w-MSD for every five consecutive beats, which represents a continuous measure of RSA. The w-MSD can be described as follows: The entire set of the absolute values of successive heart period differences was cut into segments of five values. Heart rate variability within this window was represented by the median. We preferred w-MSD to r-MSSD, which is a mean value-based method, because the use of a median is more adequate in measuring biologic processes (10).

We matched the course of w-MSD (in time units of 1.0 = 7.8 ms) with the synchronous courses of heart rate (in beats per minute), and ST1 and ST2. By analyzing these diagrams, we determined the ischemic episodes, the details of which could be precisely captured in windows of 10 or 20 minutes. Additionally, each long-term ECG was subjected to visual control in order to detect pathologic shifts of the ST-segment and to compare them with the computer-aided calculation. An ECG printout was made for each ischemic episode. We measured the duration and maximal ST-segment deviation of ischemic episodes and distinguished between shifts of ≥0.1 mV, ≥0.2 mV, and ≥0.3 mV.

We calculated three values of heart rate: the mean heart rate of the period from 240 to 30 seconds preceding the onset of ischemia $HR_{t\text{-}240}$, the heart rate precisely at the onset of ischemia HR_{t0}, and the mean heart rate over 24 hours.

We calculated five parameters of w-MSD, including the mean w-MSD for the periods from 240 to 30 seconds preceding the onset of ischemia ($w\text{-}MSD_{t\text{-}240}$) and from 60 to 240 seconds after the onset of ischemia ($w\text{-}MSD_{t60}$). We also recorded the lowest point in the decline of HRV immediately before the onset of ischemia, and we calculated the mean of w-MSD for the entire ischemic episode and for the entire long-term ECG.

We carried out Fast Fourier Transformation when heart rate did not deviate by more than 5 beats/min from the mean value for at least 2 minutes in two segments around the onset of ischemia—first, before the onset of the acute decline in HRV preceding the onset of ischemia, and second, just after the initial increase in heart rate at the beginning of the ischemic event. For these calculations, we eliminated artifacts, if necessary. We did not eliminate any normal R-R signal. In the HRV spectrum, low-frequency (LF) power (0.04–0.15 Hz) reflects sympathetic and vagal modulation of heart rate and is strongly influenced by baroreflex activity (11–13). High-frequency (HF) power (0.15–0.40 Hz) is a marker of vagal efferent activity (11–13). We calculated LF and HF, using power units in milliseconds, and obtained normalized units by dividing LF and HF by total power. As an indicator of sympathovagal balance (13,14), we calculated the LF/HF ratio. The statistical methods used were the paired *t*-test (two-tailed) and the *Z*-test (two-tailed).

Results

The results are summarized in Table 1. The mean heart rate at 240 to 30 seconds preceding the onset of ischemia ($HR_{t\text{-}240}$) was 81.5 beats/min and the heart rate precisely at the onset of ischemia (HR_{t0}) was 86.4 beats/min on average. These are mean daily heart rate levels. In all long-term ECGs, the levels of $HR_{t\text{-}240}$ and HR_{t0} occurred frequently for 2 minutes or longer without causing ischemia. In those intervals, the mean w-MSD was always significantly ($P < .001$) higher than during the ischemic episodes. No correlations between the values of $HR_{t\text{-}240}$, HR_{t0} and age, sex, or vascular state could be found, nor could any correlation between heart rate and the extent of ischemia (duration of and maximum ST-segment shift) be established.

The mean w-MSD at 240 to 30 seconds preceding the onset of ischemia was 13.2 ms (= 1.69 time units). At the beginning of the episodes, between the first and fourth minute, the mean w-MSD was 7.6 ms (= 0.97 time unit). During the whole ischemic episode, the mean w-MSD was 8.0 ms (= 1.02 time units). Immediately before the onset of ischemia, about 15–60 seconds preceding the onset of ST-segment deviation, a decline of w-MSD to an average of 3.9 ms (= 0.5 time unit) was observed.

In 26 cases (63%), we carried out Fast Fourier Transformation in two segments, before and after

Table 1. Characteristics of 22 Patients Who Suffered 42 Ischemic Episodes

Characteristic	Mean Values
Age	60.9
No. of coronary arteries with one or more significant stenoses	2.6
Duration of ischemia (min)	8.4
Max ST deviation (mV)	0.2
Heart rate (beats/min), 240–30 seconds preceding the onset of ischemia	81.5
Heart rate (beats/min), exactly at the onset of ischemia	86.4
Heart rate (beats/min), over 24 hours	76.9
w-MSD (ms), 240–30 seconds preceding onset of ischemia	13.2
Deepest level of w-MSD (ms) immediately before onset of ischemia	3.9
w-MSD (ms), 60–240 seconds after onset of ischemia	7.6
w-MSD (ms) during whole ischemic episode	8.0
w-MSD (ms) over 24 hours	13.3

the onset of ischemia. High-frequency power always decreased significantly at the onset of ischemia ($P < .01$), indicating a marked loss of vagal modulation. The LF/HF ratio did not change significantly when both segments were compared. This lack of an increase in LF/HF ratio seems to indicate that sympathetic activity did not increase at the onset of ischemia in these cases (Table 2). In the remaining 15 cases (37%), we did not perform Fast Fourier Transformations because there was no stationary stage in the data around the onset of ischemia.

No significant correlations between the parameters of HRV and the characteristics of ischemia or age, sex, and vascular state could be established. With two exceptions, all ischemic episodes were preceded by an acute decline in w-MSD into a critical area of almost complete suppression of HRV. The upper limit of this critical area was about 7–10 ms. During the entire ischemic episode, w-MSD stayed at this reduced level, and preceding the end of the ischemia, it increased again. This reduction of HRV before and during ischemic episodes reflects an almost complete depression of modulated vagal activity.

In Figures 1A and 2A, the acute decline in w-MSD preceding the onset of ischemia can be seen. The typical basin-shaped course of HRV precedes a similarly shaped ST-segment depression and is accompanied by a mirror-image course of heart rate. In Figure 1A, a similar decrease and subsequent increase of w-MSD appears first between the 119th and the 124th minute. This decline in HRV only touches the critical limit of about 7–10 ms and precedes only a transient and insignificant ST-segment depression, as can be seen in the course of ST 2. In Figure 2A, the course of the heart rate shows several humps in the second half of ischemia. The first of these heart rate increases deepens the ischemia.

The Fast Fourier Transformations in Figures 1B and 2B, carried out before the onset of the acute decline in w-MSD and after the initial increase of heart rate, both show a dramatic loss of high-frequency power at the onset of ischemia. This indicates an almost complete withdrawal of vagal modulation. The ratio LF/HF was 0.47 before and 0.38 during the ischemic interval in Figure 1B. In the three consecutive intervals in Figure 2B, the ratio LF/HF was 0.79, 0.75, and 0.92. That means that sympathetic activity did not increase during the entire ischemic episode in Figure 1. In Figure 2, sympathetic discharge did not increase, either, at the beginning but probably did increase at the end of this ischemia. In the last interval, the course of

Table 2. Mean Values of 26 Fast Fourier Transformations

Parameter	Before Onset of Ischemia	After Onset of Ischemia
LF (ms)	18.72 ± 6.36	11.85 ± 4.05*
HF (ms)	31.56 ± 8.06	21.03 ± 3.63*
TF (ms)	64.06 ± 6.63	41.54 ± 4.73*
LF_ν†	0.31 ± 0.02	0.29 ± 0.01
HF_ν†	0.56 ± 0.03	0.52 ± 0.02
Ratio LF/HF	0.59 ± 0.09	0.56 ± 0.10

*Significantly different from the mean value before the onset of ischemia at the $P < .01$ level. †Subscript ν (nu) denotes normalized units. LF, low frequency; HF, high frequency; TF, total frequency.

the heart rate showed no stationary state. For this reason, this Fast Fourier Transformation has to be considered with caution.

These spectral analysis results suggest further that the entire course of the heart rate during the ischemic period in Figure 1 was caused by withdrawal of vagal efferent activity. In Figure 2, the initial increase in heart rate at the beginning of ischemia is associated with a concomitant decrease in w-MSD. At the end of this ischemia, the mirror image course of heart rate and w-MSD has sympathetically induced heart rate increases superimposed.

Every reduction of w-MSD to an extent clearly below the critical limit that lasts longer than 1 minute was succeeded by an ischemia. The upper limit of the critical area varied slightly from patient

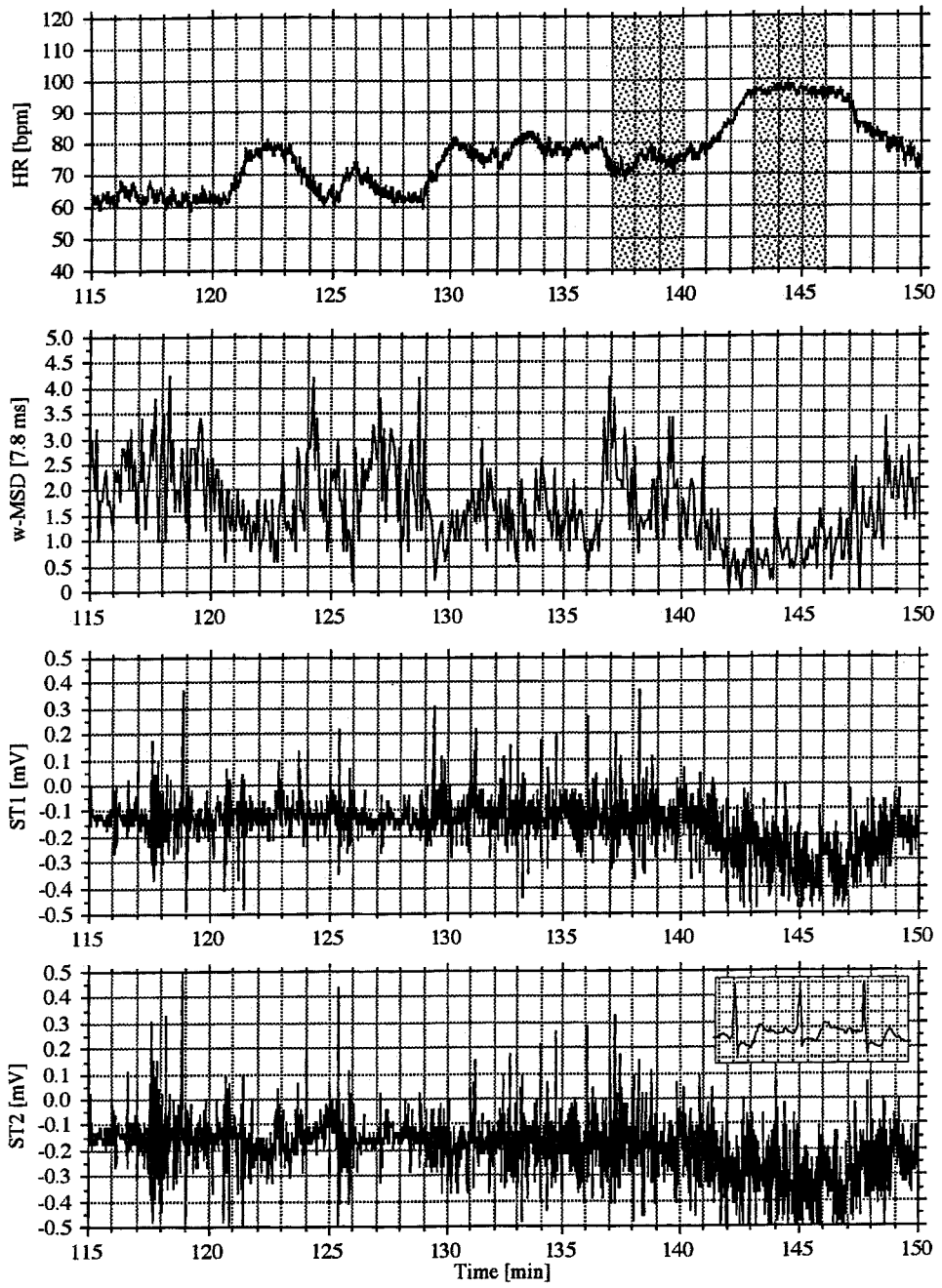
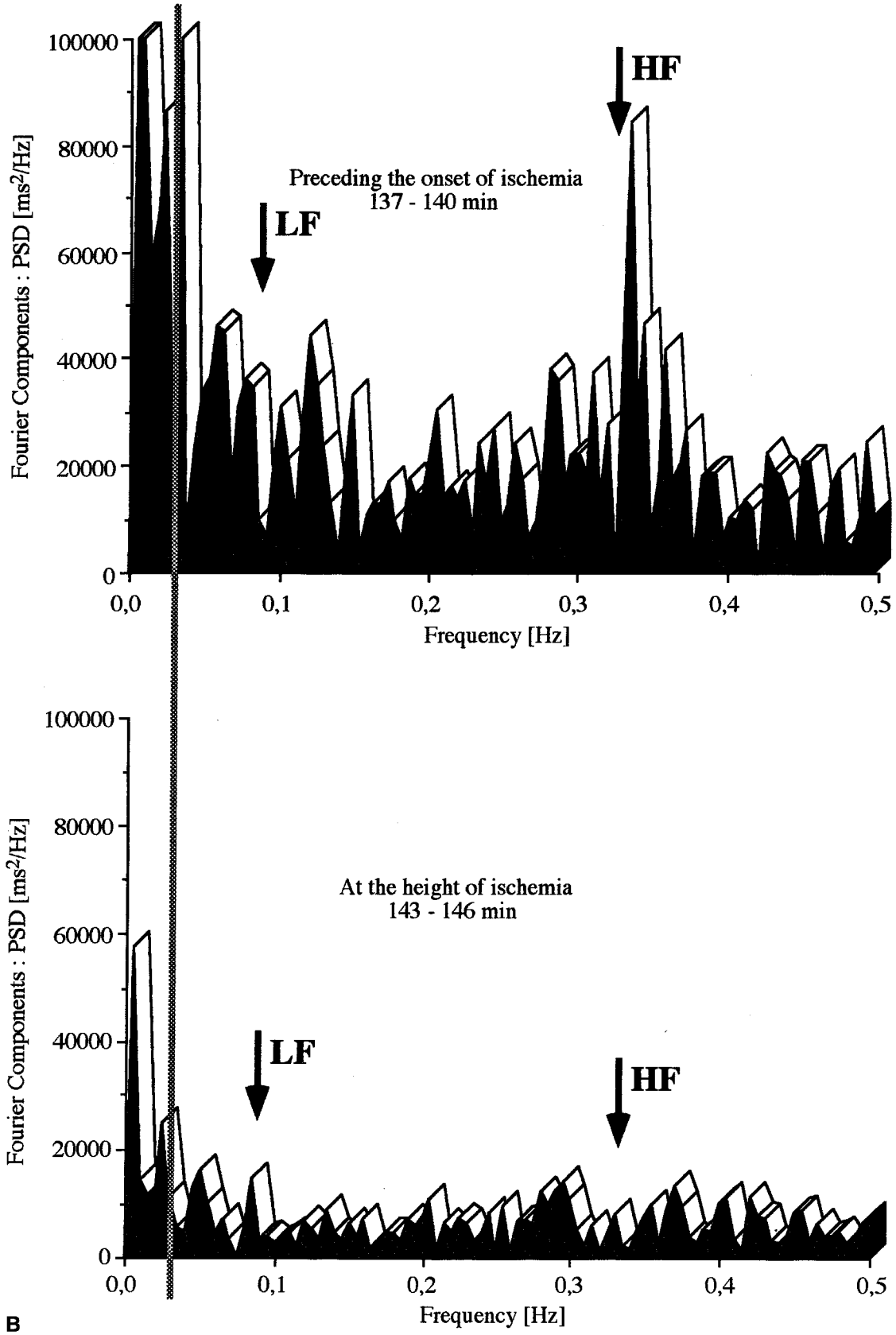


Fig. 1. (A) Diagram of a 35-minute period from a 24-hour ECG showing the course of the heart rate, w-MSD, ST1, and ST2. The decline of w-MSD, which sets in shortly before the 140th minute, shifts deeply below the critical limit of about 1.0 (=7.8 ms). The typical basin-shaped course of w-MSD precedes a similarly shaped ST-segment depression and is accompanied by a mirror-image course of the heart rate. *(Figure Continues)*



B

Fig. 1. *(Continued)* (B) Fast Fourier transformation of two intervals, preceding the onset (top) and at the height (bottom) of ischemia. (Same patient as in A.)

to patient. This limit is certainly influenced by different clinical states of the patients and different medications used by them. To clarify these effects in detail, further investigation will be necessary.

Figure 3 shows an example of so-called variant angina, an ST-segment elevation during sleep. The typical basin-shaped curve of HRV also precedes the course of this type of ischemia. In all five variant angina episodes, we found this same pattern.

Figure 4 illustrates the dynamics of modulated vagal activity in the early morning. Since the patient was still sleeping at the beginning of this interval, w-MSD started at a relatively high level; HRV decreased gradually. Finally, an almost complete suppression of modulated vagal activity preceded an ischemic episode.

Two ischemic episodes (5%) were induced by a tachycardia and terminated by a decline in heart

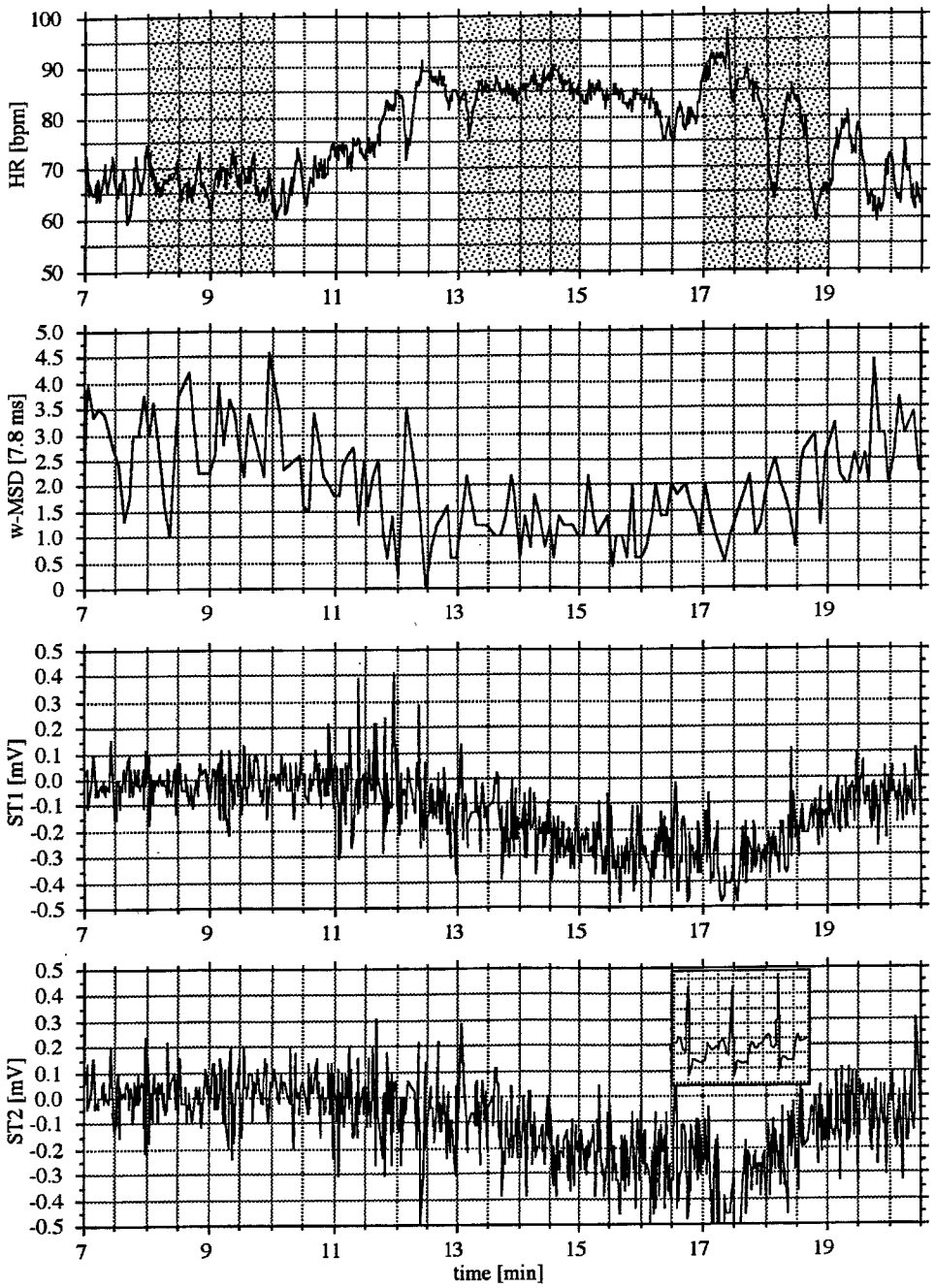


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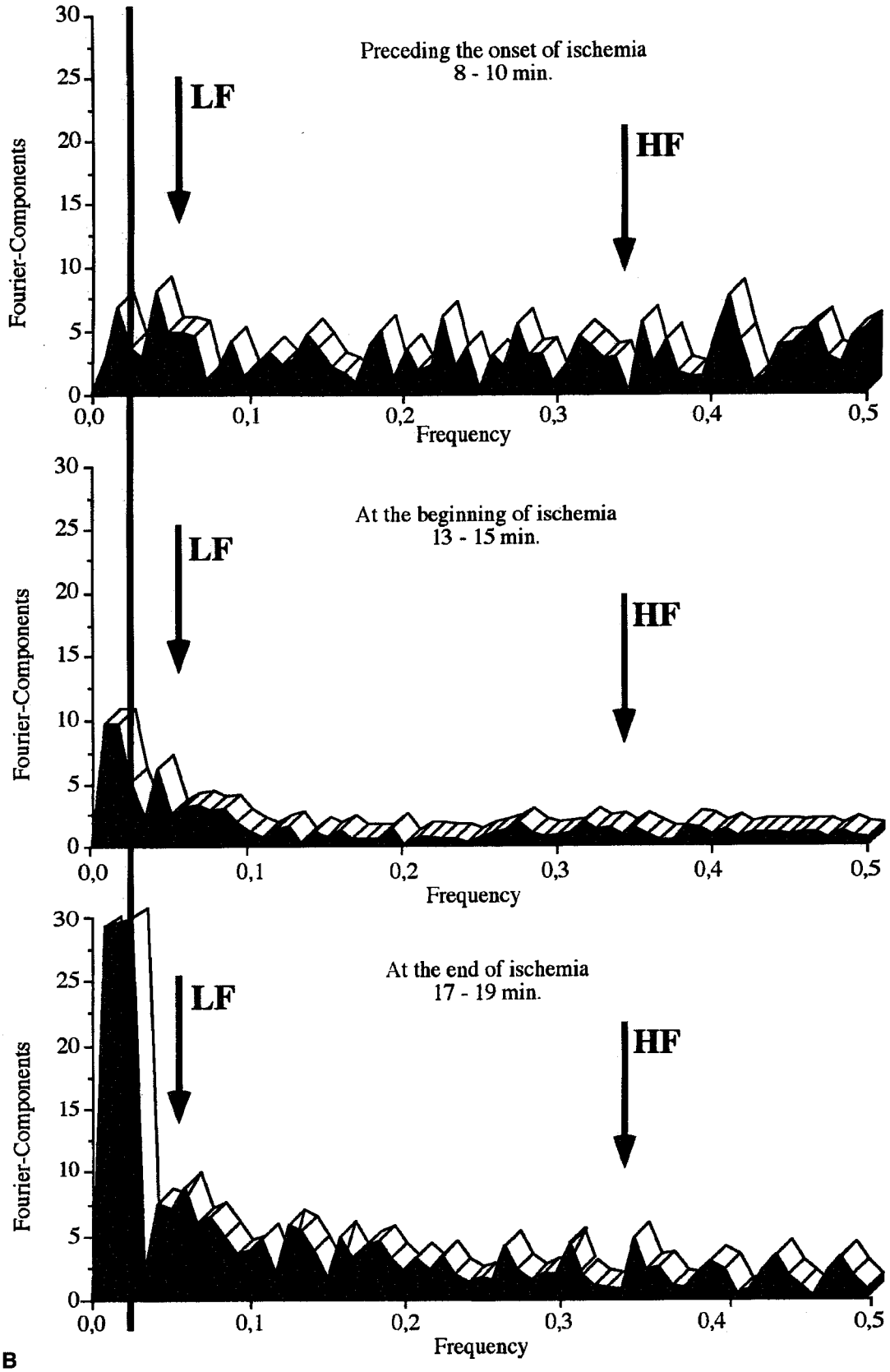
Fig. 2. (A) The basin-shaped course of w-MSD precedes a similarly shaped ST-segment depression and is accompanied by a corresponding increase in heart rate. The rise in heart rate after the 17th minute deepens the ischemia. *(Figure Continues)*



B

Fig. 2. *(Continued)* (B) Fast Fourier Transformation of three intervals, preceding the onset (top), at the beginning (mid), and at the end (bottom) of ischemia. (Same patient as in A.)

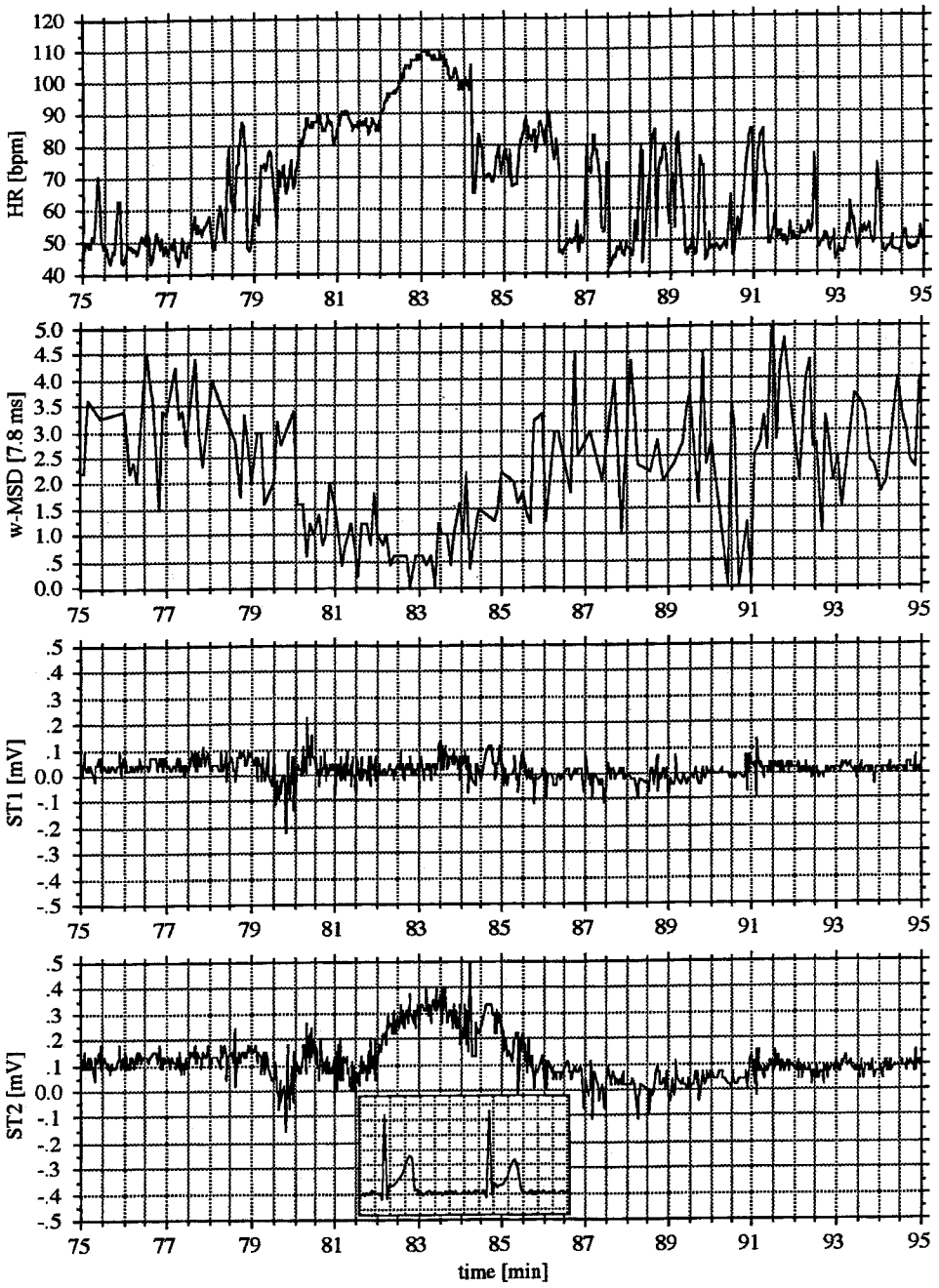


Fig. 3. The basin-shaped pattern of w-MSD precedes an ST-segment elevation (variant angina) and a similar increase in heart rate. w-MSD, windowed median successive difference.

rate. At the same time, w-MSD remained almost unchanged at slightly above the critical limit. In 30 cases (73%), heart rate at 240 to 30 seconds preceding the onset of ischemia increased only modestly (<10 beats/min) during these 210 seconds). In nine cases (22%), moderate or marked increases in heart rate (>10 beats/min) were found during this period. The constant finding preceding the onset of ischemia was an acute decline in w-MSD. This decline in HRV preceded the electrocardiographic onset of ischemia by about 1–2 minutes. In one case, we found a tachycardia that lasted more than 10 minutes with a heart rate of about 150 beats/min without signs of ischemia. The w-MSD was almost constant at about 16 ms during this interval, which is markedly elevated above the critical limit. Later, a pronounced ischemic episode was detected in the same long-term ECG. The

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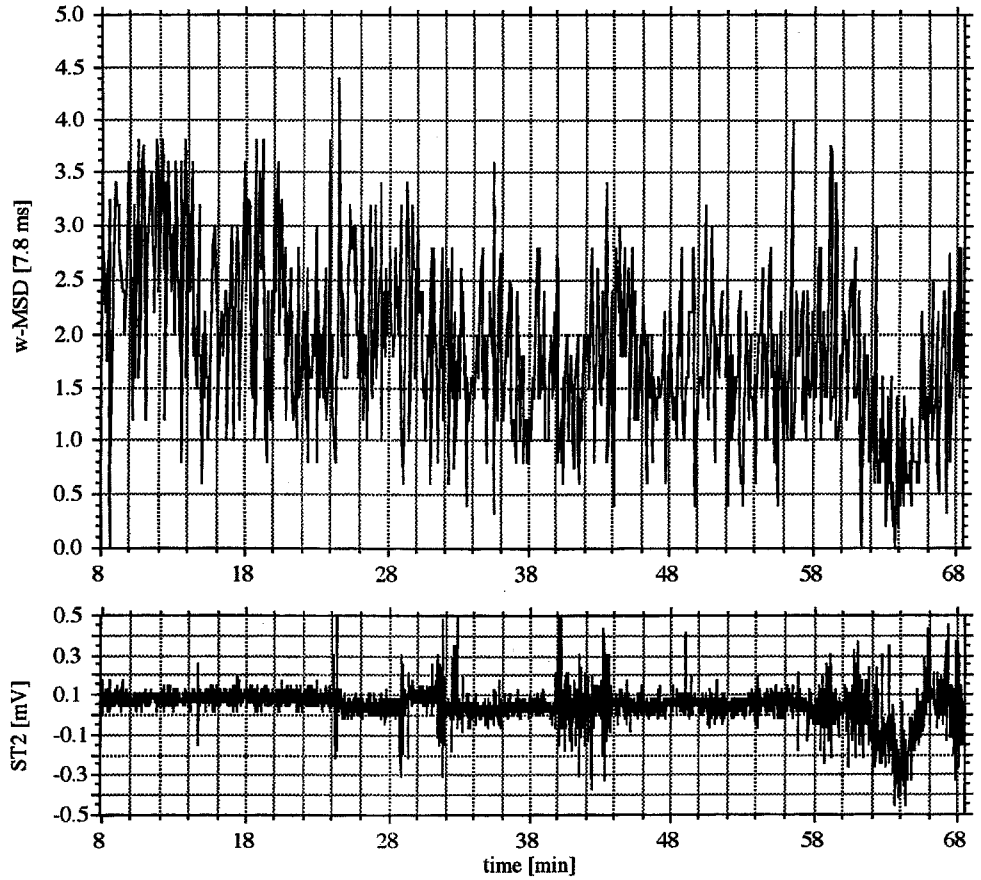

Fig. 4. Diagram of the synchronous courses of w-MSD and ST 2 for a 60-minute period very early in the morning (5:08–6:08 a.m.); w-MSD decreases in a wavelike pattern. The last downswing leads to an almost complete suppression of HRV and precedes a similarly shaped ST deviation. w-MSD, windowed median successive difference. HRV, heart rate variability.

mean heart rate preceding the onset of this episode was 84 beats/min. The w-MSD declined immediately before the onset of ischemia to values near zero (1.6 ms) and remained at an average level of 7.8 ms during the whole episode.

Discussion

The vast majority (95%) of transient myocardial ischemic events in our study is preceded by an almost complete suppression of HRV. Basin-shaped courses of w-MSD precede similarly shaped courses of ST-segment depression, the equivalent of subendocardial ischemia, as well as mirror image-shaped courses of ST elevation, the equivalent of transmural ischemia.

The w-MSD is a continuous measure of RSA, which represents vagal modulation by breathing. For that reason, w-MSD is a marker of vagal efferent discharge. Like the other markers of vagal activity in the time and frequency domains (r-MSSD, pNN50 [the proportion of differences >50 ms in successive R-R-intervals], HF power), w-MSD does not measure vagal tone directly but rather measures modulated vagal activity.

Malik and Camm have pointed out that increased or decreased modulated vagal activity is not necessarily related to an increase or decrease of the tonic stimulus (15). Goldberger et al. showed a dissociation of HRV from vagal tone by increasing blood pressure experimentally with phenylephrine (16). A dissociation of HRV from vagal tone occurs in situations of a saturating influence of high vagal tone on the sinus node. Diseases such as advanced heart failure or complicated myocardial infarction are likely to be accompanied by decreased responsiveness of the sinus node to neural modulation (14). In these cases, decreased HRV cannot be interpreted as a loss of vagal tone.

The Holter recordings of our study were obtained under daily living conditions. Patients with advanced heart failure or complicated myocardial infarction

were excluded from the study. We had no information about the behavior of arterial blood pressure during our Holter recordings. However, it is known that there are no or only slight increases in blood pressure preceding the onset of ischemia during daily living activities (17,18). Therefore, the conditions of our study suggest that w-MSD, by measuring modulated vagal activity, is a correct indicator of vagal efferent discharge.

The question of whether the depression of HRV preceding the onset of ischemia is cause or consequence of the ischemic event will now be considered. Myocardial ischemia triggers several cardiac reflexes (19). Can this reflex activity have induced the suppression of w-MSD and HF components of HRV in our study? Based on our results, the following can be said. First, it has been proposed that myocardial infarction often augments sympathetic afferent traffic and that this, in turn, reduces vagal efferent activity (20,21). Myocardial ischemia of a certain degree may have the same effect. We examined about two thirds of ischemic episodes in our database by Fast Fourier Transformation. In the remaining cases we did not perform power spectral analysis for methodical reasons. The lack of increase of the LF/HF ratio indicates that sympathetic activity did not increase significantly at the onset of ischemia in these cases. This result is in agreement with the study of Bigger et al. (1), who did not find any detectable increase in sympathetic activity during ischemic episodes. Therefore, reduced vagal outflow, as a result of increased sympathetic activity, can be excluded for the great majority of our cases. Second, increased vagal reflex activity induced by myocardial ischemia may result in a saturating overstimulation of the sinus node. This would lead to decreased HRV parameters. In the period before and just after the onset of ischemia, the decrease in w-MSD was always accompanied by an increase in heart rate. There was no dissociation between vagal tone and HRV in our study. Overstimulated vagal reflex activity can be excluded.

Most important in this cause-effect relationship is the time sequence of the events: the onset of the acute decline in HRV precedes the ECG onset of ischemia by about 1–2 minutes. Ischemic events on the ECG tracings are likely to become evident after an appreciable delay from the beginning of myocardial ischemia. It seems, however, unlikely that an ischemic process already has a measurable influence on the sinus node activity 2 minutes before the onset of the ECG changes. In conclusion, our results do not support the view that the ischemia has induced the decline in HRV. It must be considered that, on the contrary, the withdrawal of vagal outflow has influenced the onset of ischemia.

About 10 years ago, Deanfield et al. (22) and Chierchia et al. (23) suggested that increased myocardial demand cannot be the common cause of acute ischemia in patients with coronary heart disease. These authors demonstrated that silent ischemia during unrestricted daily activity occurs at heart rates significantly less than those observed at the onset of ischemia during exercise testing. Furthermore, they showed, as in our study, that there are relatively small changes in heart rate preceding silent ischemic events. Consequently, it has been postulated that silent myocardial ischemia occurs predominantly as a result of a decrease in coronary blood supply. A role of coronary spasm in inducing ischemia during daily activity was ruled out by Chierchia et al. (23). The exact mechanism of a primary impairment of regional myocardial perfusion during the day has not yet been established. Our results suggest that a vagal depression may be involved in inducing myocardial ischemia during activities of daily living.

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