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Articles

Heart Rate Variability Assessment Early After Acute Myocardial Infarction

Pathophysiological and Prognostic Correlates

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Abstract

Background Diminished heart rate variability is associated with less favorable prognosis after myocardial infarction. However, the prognostic value of early (first 48 hours) measurement and the influence of thrombolytic strategies, myocardial infarction location, left ventricular function, ST-segment shift, and infarct-related artery patency on heart rate variability have not been examined comprehensively.

Methods and Results Heart rate variability and ST-segment analysis of 48-hour Holter tapes were performed with the use of a commercial system in 204 patients who were part of an ST-monitoring substudy of the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO-I) trial. Both time-domain measures (SD of the average normal RR interval for all 5-minute segments of a 24-hour ECG recording [SDANN] and percent difference between adjacent normal RR intervals >50 ms computed over the entire 24-hour ECG recording [pNN50]) and frequency-domain measures (low frequency [LF], high frequency [HF], and LF/HF ratio) were assessed on days 1 and 2 after acute myocardial infarction. Coronary angiography performed within the first 24 hours was also available in 75% of the patients. All heart rate variability measures decreased between day 1 and day 2 ($P=.001$) except the LF/HF ratio. There was no difference in heart rate variability among groups assigned to one of four different thrombolytic treatment strategies (streptokinase/subcutaneous heparin, streptokinase/intravenous heparin, accelerated tissue plasminogen activator, and combination streptokinase/tissue plasminogen activator). Heart rate variability measures were lower in anterior versus nonanterior infarcts (SDANN, 53 ± 21 versus 63 ± 24 ms; $P<.005$) and increased with TIMI grade 3 flow (LF, 5.3 ± 1.0 versus 4.8 ± 1.2 ms^2; $P<.01$) and better ejection fraction ($r=.2$, $P<.03$). An inverse correlation between the duration of ST shift and frequency domain measures was observed (LF, $r=-.2$, $P<.009$; HF, $r=-2$, $P<.03$). Lower LF/HF ratio by 24 hours after myocardial infarction was seen in those who ultimately died at 30 days (1.0 ± 0.2 versus 1.3 ± 0.2, $P<.001$) or at 1 year (1.17 ± 0.14 versus 1.26 ± 0.19, $P=.05$).

Conclusions Changes in heart rate variability occurred early after thrombolysis and may be of prognostic value. Heart rate variability measures were improved in patients with better ejection fraction and greater angiographic patency. This suggests a possible mechanism for the enhanced survival observed with TIMI grade 3 flow in the GUSTO angiographic substudy. These data indicate that early heart rate variability assessment after myocardial infarction may be useful in noninvasive risk stratification.

Key Words:
electrocardiography
myocardial infarction
heart rate
prognosis

Diminished heart rate variability is a useful prognostic indicator after myocardial

infarction,[1] with independent predictive value over conventional noninvasive risk-stratification tools such as exercise testing, ejection fraction assessment, detection of ventricular ectopy, and assessment of late potentials.[2 3 4] In addition, heart rate variability parameters correlate well with the angiographic extent of coronary artery disease.[5] Both time- and frequency-domain analyses of heart rate variability are useful for prognostic assessment after myocardial infarction.[6 7]

Previous studies of heart rate variability were performed in the later stages of myocardial infarction and mostly predate the general use of thrombolytic therapy. Hence, the relations between heart rate variability and ventricular function, coronary patency, and prognosis in the setting of thrombolytic therapy remain unclear.

The primary purpose of the current study was to assess whether early (first 48 hours after myocardial infarction) detection of reduced heart rate variability is associated with 30-day and 1-year mortality in patients receiving thrombolytic therapy as part of the GUSTO-I study.[8] In addition, the influences of different thrombolytic strategies, infarct location, left ventricular function, infarct-related artery patency, and ST-segment shift were examined to better evaluate the pathophysiology of abnormalities in heart rate variability.

Methods

Patient Selection

The recently reported GUSTO study[8] included an ECG monitoring substudy designed to assess the speed and stability of reperfusion through noninvasive measures of ST-segment monitoring.[9 10] The details of ST-segment monitoring have been published previously.[9 10] ST-segment monitoring was started preferably within 30 minutes of thrombolytic treatment and administration continued for at least an 18-hour period and up to 24 hours. ST-segment analysis and heart rate data analysis were performed with all personnel in the core laboratory blinded to treatment assignment. ECG editing and interpretation were performed by an experienced operator using a computer-assisted device. Excluded from analysis were patients with <18 hours of effective monitoring time or a data gap of >50% of monitoring time. Comparison of baseline characteristics and in-hospital mortality of patients included in the ECG monitoring study compared with those who were not included did not show significant differences.[10] Patients who underwent Holter monitoring as part of the ECG substudy were included in this assessment of heart rate variability.

Heart Rate Variability Analysis

Heart rate variability parameters were analyzed by use of a commercial software program (Marquette Electronics, version 5.8v002A). All QRS labeling was manually edited by an experienced observer blinded to clinical outcomes. Spectral indexes of heart rate variability were computed by fast-Fourier transformation on each 2-minute segment of the recording, with application of a Hanning window to minimize spectral leakage. Power spectra from sequential prespecified segments were averaged hourly and for the entire 24-hour time period. The following frequency-domain measures were assessed: (1) LF (0.04 to 0.15 Hz), (2) HF (0.15 to 0.40 Hz), and (3) LF/HF ratio. The LF and HF measures were reported as their natural logs (ln). The data were also analyzed by correcting the LF and HF components for total power (0.0 to 1.0 Hz); however, since the results were not significantly different from the uncorrected measures, these data were not reported. Frequency-domain measures were examined during the first hour and then for 1-hour recording intervals at hours 12, 24, 36, and 48 to examine the evolution of changes in heart rate variability over the first 48 hours; overall frequency-domain measures for day 1 and 2 were also obtained.

Two time-domain measures were derived for each 24-hour period: (1) SDANN (SD of the average normal RR interval for all 5-minute segments of a 24-hour ECG recording) and (2) pNN50 (percent difference between adjacent normal RR intervals >50 ms computed over the entire 24-hour ECG recording).

Holter Monitoring

Marquette series 8000 recording units were used to measure the frequency and duration of ST-segment shifts. All recordings were done with modified bipolar

leads aVF, V_2, and V_5 for 48 hours beginning within 1 hour of thrombolysis.

Tapes with excess artifact, significant arrhythmias, bundle-branch block, and marked repolarization abnormalities were excluded from analysis.

Significant ST-segment shift was defined as either ≥1 mm=0.1 mV ST elevation or ≥1 mm horizontal or downsloping ST-segment depression (60 to 80 ms from J-point) lasting ≥1 minute and separated from other episodes by ≥1 minute. All episodes were verified by visual reading by an experienced observer blinded to clinical information.

Coronary Angiography

Coronary angiography was performed as part of the GUSTO angiographic substudy.[11] On the basis of the prespecified protocol, flow in the infarct-related artery was graded at 90 or 180 minutes or 24 hours according to the TIMI criteria,[12] and ejection fraction was calculated from digitally acquired ventricular silhouettes by use of the area-length method.[13]

Statistical Analysis

All data are shown as mean±SD unless otherwise stated. Patients receiving different thrombolytic strategies were grouped together after the initial analysis (Table 2⇓) showed no difference in heart rate variability measures between the four groups.

Student's t test was used for continuous variables and the χ^2 test for dichotomous data to compare heart rate variability measures between groups and between day 1 and day 2. Changes in heart rate variability over time between groups based on hourly measurements were analyzed by use of two-way ANOVA with repeated measures. If significant difference was determined overall, comparison at prespecified time intervals was done by use of unpaired t test with Bonferroni correction.

Linear regression analysis was used to assess association between heart rate variability parameters and measures of ST-segment shift and ejection fraction. Cox proportional hazards model was used to study the independent effect of heart rate variability on mortality.

Results

A total of 288 patients underwent Holter monitoring as part of the GUSTO ECG substudy. Technical failure, excess artifact, bundle-branch block, atrial fibrillation, and frequent arrhythmias resulted in the exclusion of 84 patients from analysis, including 10 patients who died. Of the remaining 204 patients, 26 had insufficient hours of monitoring (<18 hours) on day 2 and therefore were not included in the comparison of day 1 and day 2 heart rate variabilities.

Although patients enrolled in the present study represented only a small subset of the overall GUSTO study population, the clinical and laboratory characteristics of these substudy patients were remarkably similar (Table 1⇓).

Table 1.

Patient Characteristics

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There were 178 patients for whom paired analysis of day 1 and day 2 measures was available. There were significant declines in heart rate variability measures in both the time- and frequency-domain analyses. SDANN declined from 76±33 to 59±23 ms (P=.001) and pNN50 declined from 7±10% to 5±8% (P=.001). The LF spectral component decreased from 5.3±1.2 to 4.9±1.2 ms^2 (P=.001), whereas HF decreased from 4.4±1.1 to 3.9±1.1 ms^2 (P=.001). The LF/HF ratio, however, remained at 1.3±0.2. Heart rate increased slightly during this time period from 72±11 to 75±13 beats per minute (P=.002).

Thrombolytic Strategy

Patients were analyzed according to the four assigned thrombolytic treatment

strategies (streptokinase/subcutaneous heparin, streptokinase/intravenous heparin, accelerated tissue plasminogen activator, and combination streptokinase/tissue plasminogen activator). No significant differences were observed among the four thrombolytic groups in SDANN (78±33, 73±30, 75±38, and 78±31 ms, respectively; P=.9), pNN50 (8±10%, 7±9%, 7±10%, and 7±9%, respectively; P=.9), LF (5.3±1.1, 5.3±1.2, 5.4±1.2, and 5.4±1.4 ms^2, respectively; P=.8), HF (4.4±1.1, 4.2±1.2, 4.3±1.1, and 4.4±1.1 ms^2, respectively; P=.9), or LF/HF ratio (1.2±0.2, 1.3±0.2, 1.3±0.2, and 1.3±0.2, respectively; P=.4). Therefore, for all subsequent analyses, the treatment groups were combined.

Anterior Versus Nonanterior Infarction

There were 78 patients (38%) with an anterior infarction and 126 patients with nonanterior infarction (Table 2⇓). Comparison revealed a higher heart rate but lower heart rate variability measures (SDANN, LF, and HF) in anterior infarcts on day 1 and day 2.

Table 2.

Anterior (n=78) vs Nonanterior (n=126) Myocardial Infarction

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When the change in LF/HF ratio between day 1 and day 2 was examined, patients with anterior infarcts had a decrease in the ratio between day 1 and day 2, whereas nonanterior infarction patients had an increase over the same time period (Fig 1⇓).

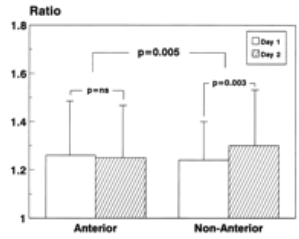

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Figure 1.

Change in mean LF/HF ratio (vertical axis) from day 1 (open bars) to day 2 (hatched bars) by location of infarction.

Left Ventricular Function

There were 138 patients (68%) in whom left ventricular ejection fraction was obtained. Of the two time-domain measures, SDANN did not show any correlation with ejection fraction (r=.02, P=.9), whereas pNN50 had a weak but significant correlation (r=.2, P=.02) on day 2. The LF component of the power spectrum increased with better ejection fraction (r=.2, P=.03), and the HF component showed a similar trend (r=.15, P=.09) by day 2. The LF/HF ratio, however, did not show a correlation with ejection fraction (r=.03, P=.7). Similarly, heart rate did not correlate with ejection fraction (r=.12, P=.1).

ST-Segment Shift

There were 126 patients (62%) with at least one episode of ST-segment shift. The majority (75%) of patients with ST shift had ST elevation, whereas 15% had ST depression and only 10% of patients had both. The mean number of ST-shift episodes per day was 2.1±3.2. The mean duration of these episodes was 80±210 minutes. Compared with those without any ST-segment shift (n=76), no significant differences in time-domain measures (SDANN, 60±25 versus 58±20 ms, P=.6; pNN50, 5±10% versus 4±6%, P=.9) or frequency-domain measures (LF, 4.9±1.2 versus 5.0±1.0 ms^2, P=.4; HF, 3.9±1.1 versus 4.0±1.0 ms^2, P=.7; LF/HF ratio, 1.27±0.23 versus 1.29±0.22, P=.7) were observed over the first 48 hours. When the data were analyzed separately for ST elevation and depression and when the hourly data were examined, the results remained unchanged (data not shown).

Duration of ST-segment shift had a significant but modest inverse correlation with LF (r=−.2, P=.009) and HF (r=−.2, P=.03) on day 2. No correlation was seen between the LF/HF ratio and duration of ST-segment shift (r=−.06, P=.4) on day 2.

Patency of Infarct-Related Artery

A total of 154 patients (75%) underwent a substudy[10] protocol cardiac catheterization within the first 24 hours. Heart rate variability studied during the same time period (ie, first 24 hours) was greater in patients with TIMI grade 3 flow (Table 3⇓). Analysis of the hourly data showed that separation of heart rate variability measures occurred as early as hour 12 and remained significantly separated for the balance of the monitoring period (data not shown).

Table 3.

Heart Rate Variability According to Patency

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Mortality

Heart rate variability analysis with respect to 30-day mortality is shown in Table 4⇓; patients who died had a significantly lower LF/HF ratio on day 2. The relation between heart rate variability and mortality continued to 1 year with reduced LF/HF ratio in those who did not survive (1.17±0.14 versus 1.26±0.19, P=.05). When the Cox proportional hazards model was used, the LF/HF ratio had independent prognostic value (Table 5⇓).

Table 4.

30-Day Status

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Table 5.

Prediction of 30-Day Mortality

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Both LF and the LF/HF ratio examined hourly exhibited a difference that became apparent as early as 12 hours after the infarct and remained separated for the rest of the monitoring period (Fig 2⇓).

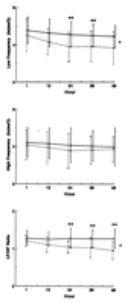

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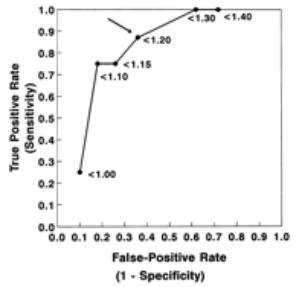
Figure 2.

Mean hourly measures of heart rate variability (LF, HF, LF/HR ratio) during the first 48 hours in patients surviving (solid line) and not surviving (dashed line) at 30 days. *P=.02 for two-way ANOVA with repeated measures for LF and P=.002 for LF/HF ratio. **P<.01 for Student's t test with Bonferroni correction (based on five comparisons).

A receiver-operator curve was subsequently constructed, which revealed that an LF/HF ratio of ≤1.2 had optimal sensitivity of 88%, a specificity of 64%, and a negative predictive value of 99% for 30-day mortality (Fig 3⇓).

Figure 3.

Receiver-operator curve for LF/HF ratio; optimal sensitivity and specificity was seen with a value of 1.2 (arrow).



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Discussion

The primary finding of the present study is that early after acute myocardial infarction, heart rate variability assessment based on Holter monitoring is feasible and prognostically useful in the thrombolytic era. Furthermore, a single hour of heart rate variability measurements taken as early as 24 hours after myocardial infarction may have prognostic value.

The prognostic value of heart rate variability was first reported in a cohort of patients after myocardial infarction in the early 1980s.[1] Over a 31-month follow-up, the relative risk for mortality was 5.3× higher in patients with lower heart rate variability on time-domain measures (SDNN <50 ms). SDNN and SDANN, used in the current study, have been shown to have an excellent (r=.98) correlation.[6] Subsequent analysis[6] of the same patient population showed that frequency-domain measures had similar prognostic value and that there was strong correlation between frequency- and time-domain measures of heart rate variability.

Most analyses have focused on heart rate variability on days 7 through 14 after myocardial infarction; however, more recent data suggest that significant differences are seen earlier[14] and are prognostically useful.[15] The unique features of the present study were that heart rate variability parameters were assessed during the first 48 hours after an acute myocardial infarction. Furthermore, all patients in the present study received thrombolysis. Simultaneous ST-segment analysis was performed in these patients, and early angiographic correlation for infarct-related artery patency and left ventricular function was obtained in 75% of the patients. This allowed a detailed assessment of factors that could influence heart rate variability.

Thrombolytic Strategies

Despite mortality differences shown in the main GUSTO trial,[8] heart rate variability did not appear to be influenced by different thrombolytic strategies, although the sample size was small for this comparison. These results in conjunction with the infarct-related artery patency data do, however, support the open-artery paradigm[16,17] by indicating that patency rather than any drug-specific effect is the desired goal of therapy.

Anterior Versus Nonanterior Infarcts

There were marked differences in heart rate variability measures between anterior and nonanterior infarctions, in both the time and frequency domains. Furthermore, these changes occurred within the first 24 hours. Previously reported studies suggested that anterior myocardial infarctions have greater impairment of heart rate variability than inferior myocardial infarctions[15,18] and that these changes occur earlier[14] ; however, such observations have not been consistent.[19,20] Given that anterior myocardial infarctions were generally larger infarcts, the lower heart rate variability may be a manifestation of greater perturbation of the adrenosympathetic and renin-angiotensin systems. Greater mortality, including sudden death, observed in patients with anterior myocardial infarction may be related, at least in part, to diminished heart rate variability. The current study did not control for adjunctive therapy such as β-blockers, antiarrhythmic agents, and angiotensin-converting enzyme inhibitors, each of which could influence heart

rate variability[21 22 23 24] and may have been administered preferentially to patients with anterior infarction. Lack of information on various medications used is an important limitation of our analysis.

Ejection Fraction

Only two heart rate variability measures correlated with ejection fraction: pNN50 and the LF power-spectrum component. Similarly, previous findings showed that the correlation between ejection fraction and heart rate variability as measured by SDANN[4] and frequency-domain measures[6] is weak, albeit statistically significant. The lack of a strong correlation may explain the independent prognostic value of heart rate variability measures in assessment of ejection fraction, as reported previously.[4]

ST-Segment Shift

There are limited data with respect to heart rate variability in the setting of symptomatic or silent ischemia. We did not observe differences in heart rate variability between patients with or without ST-segment shift. There was, however, a relation between decreased LF and HF values and duration of ST-segment shift. This suggests that prolonged episodes of ischemia may be associated with reduced heart rate variabilitv. possibly on the basis of ischemic left ventricular dysfunction. Recent work[25 26] suggests that after myocardial infarction, heart rate variability measures are similar in patients with and without silent ischemia on Holter monitoring or treadmill testing. Conflicting information exists as to whether heart rate variability increases or decreases in patients with Holter-detected silent myocardial ischemia.[26 27] Bigger et al[28] found that LF and HF components decreased during ST-segment depression; however, the ratio remained unchanged in patients who had an old infarction or unstable angina. Recently, analyses in patients with stable angina showed an increase in the LF/HF ratio during ischemia with a return toward baseline on resolution of the ischemic episode. In one study, this was attributed to a withdrawal in parasvmpathetic activity,[29] whereas sympathetic activation was implicated in the other.[30]

When measured early, ST-segment shifts have been shown to be of prognostic value after myocardial infarction[31 32] ; however, later measurements in a lower-risk patient population have not demonstrated the value of Holter monitoring or other noninvasive techniques.[33] The small number of events in the present study, however, precluded an analysis of whether ST-segment shift and heart rate variability measures obtained from the same Holter recording may have independent value in predicting clinical outcome.

Infarct-Related Artery Patency

Heart rate variability measures were highest in patients with patent arteries (TIMI grade 3). Intermediate flow (TIMI grade 2) was associated with heart rate variability measures closer to those in patients with occluded arteries (TIMI grade 0 or 1). Hermosillo et al[34] performed coronary angiography and heart rate variability analysis 2 weeks after myocardial infarction in 175 patients and found that patients with a patent artery, defined as TIMI grade 2 or 3 flow, had greater heart rate variability. Furthermore, patients who had a patent infarct-related artery had fewer late potentials, a marker for increased ventricular arrhythmia. Recent work[35] in 51 patients receiving thrombolysis showed that patients with reduced heart rate variability, as measured by SDNN, had a higher frequency of inducible ventricular tachycardia and a greater 2-year arrhythmic event rate.

The GUSTO angiographic study confirmed the survival benefit of a better-reperfused artery as a consequence of improved global and regional left ventricular wall motion.[11] Our frequency-domain heart rate variability measures parallel these mortality findings, thereby providing support for the hypothesis that improved infarct-related artery patency may also lead to improved heart rate variability, which, in turn, reduces the risk of sudden cardiac death.

Although 75% of the patients underwent protocol-driven coronary angiography within the first 24 hours, the timing of the angiograms was not uniform and varied between 90 minutes and 24 hours. Thus, closed arteries in a small number of patients may have opened subsequently, whereas others could have reoccluded; therefore, this represents a limitation of our analysis.

Mortality

Although the number of events was low, there was sufficient power to demonstrate a difference in heart rate variability parameters with respect to 30-day mortality. The LF/HF ratio on day 2 was significantly lower in patients who died. Analysis of heart rate variability parameters for 1-hour time periods appeared to be a better discriminator than the combined 24-hour analysis during the first day. This may be explained, at least in part, by changing clinical status during the first 48 hours after a myocardial infarction, such as resolution of the chest pain, opening of the infarct-related artery, administration of adjuvant pharmacotherapy, and early ventricular remodeling. All of these factors can affect heart rate variability, and therefore analysis of all 24-hour data together can hide differences because of averaging.

Historically, the HF component of heart rate variability has correlated best with respiratory rhythm and has generally been interpreted as a measure of parasympathetic tone, whereas the LF components correlated best with peripheral vasomotor activity and thermoregulation, representing both parasympathetic and sympathetic influences.[36] Assessment of LF and HF values in isolation may, however, be too simplistic, resulting in inaccurate interpretation of changes in autonomic tone.[37 38] It may be more appropriate to interpret changes in heart rate variability as affecting the physiological, periodic fluctuations of the autonomic nervous system rather than autonomic activity directly.[37] Thus, the LF/HF ratio appears to be a more accurate marker of shifts in sympathovagal balance.[38] Indeed, we found the LF/HF ratio to be predictive of mortality. We also hypothesized that various factors such as infarct location, ejection fraction, and coronary patency may have differential effects on specific components of the heart rate variability power spectrum, and the net effect in any given individual may be best reflected in the LF/HF ratio. The sensitivity and specificity of an LF/HF ratio of ≤1.2 is comparable to other noninvasive risk-stratification modalities. Although this post hoc-determined value for LF/HF ratio is of prognostic value in this data set, it requires further validity in other myocardial infarction patient populations. The independent prognostic value of the LF/HF ratio over conventional risk-stratification measures, such as infarct-related artery patency and ejection fraction, further supports the value of this type of analysis.

Ten (53%) of the patients who died early were not included in the analysis because of technically inadequate tapes. Since eight (80%) of these patients died within the first 24 hours, it is unlikely that heart rate variability analysis would have served any useful prognostic purpose. This study was likely underpowered to demonstrate significant differences in all five of the heart rate variability parameters assessed.

In conclusion, early identification of high-risk patients by use of heart rate variability assessment could result in interventions that would alter their adverse prognosis. Although specific interventions have yet to be proven beneficial, preliminary work with scopolamine suggests that autonomic tone can be safely and successfully altered.[39 40] Further manipulation of heart rate variability and the related risk of sudden cardiac death could be achieved through the use of common pharmacological agents such as β-blockers and angiotensin-converting enzyme inhibitors or possibly through mechanical revascularization of occluded infarct-related arteries.

Selected Abbreviations and Acronyms

GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries
HF = high frequency
LF = low frequency
pNN50 = percent difference between adjacent normal RR intervals >50 ms computed over a 24-hour ECG recording
SDANN = SD of the average normal RR interval for all 5-minute segments of a 24-hour ECG recording
TIMI = Thrombolysis in Myocardial

Infarction

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