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The Bezold-Jarisch Reflex in Acute Inferior Myocardial Infarction: Clinical and Sympathovagal Spectral Correlates

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Summary

Background: The cardiodepressor Bezold-Jarisch reflex (BJR) in acute inferior myocardial infarction (AMI) is traditionally considered as an indicator of successful thrombolysis.

Hypothesis: The study aim was to elucidate the role of the autonomic nervous system in the pathogenesis of a BJR response in patients with AMI by tracing spectral profiles of heart rate variability (HRV).

Methods: We studied 32 patients who presented with BJR after starting intravenous thrombolysis for an inferior AMI. Spectral components of HRV were analyzed over the three specific 5-min periods preceding and following reflex activation. Clinically, the occurrence of BJR was correlated with the outcome of thrombolysis to achieve timely reperfusion and sustained coronary artery patency.

Results: The BJR was associated with early reperfusion in 94% of the patients, and with benign transient bradyarrhythmias and patent Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow right coronary arteries in 89% of the patients. Spectral analysis revealed a characteristic pattern of a sympathetic predominance with an impending gradual vagal withdrawal up to the onset of BJR, as reflected by progressive increases in low-frequency and reciprocal changes in high-frequency powers.

Conclusions: The BJR in inferior AMI represents a reliable prognosticator of timely reperfusion and sustained coronary patency. Stimulation of vagal afferents in response to sympathetic overactivity may be the underlying pathogenetic mechanism promoting a BJR response.

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Introduction

The cardiodepressor Bezold-Jarisch reflex (BJR) is characterized by sudden bradycardia associated with hypotension, decreased inotropy, and coronary vasodilation.[1–3] Both experimental and early clinical reports with intracoronary thrombolysis demonstrated a similar sympathoinhibitory reflex response after occlusion and recanalization of the right coronary artery.[4–7] Although there are only a few clinical studies relative to BJR after intravenous thrombolysis in acute myocardial infarction (MI), this reflex response has earned a reputation as indicator of successful thrombolysis, particularly in the setting of an inferior MI.[7–9] However, the pathophysiologic neural mechanisms underlying this phenomenon remain largely unknown. Spectral analysis of heart rate variability (HRV) may offer a unique opportunity to provide new insight into the cardiac sympathovagal interactions modulating reflex excitation.

The primary aim of the present study was to analyze the autonomic neural changes accompanying BJR by evaluating power spectral analysis of HRV in the periods preceding and following reflex activation. We also determined characteristics and clinical relevance of BJR as a noninvasive predictor of early reperfusion and sustained infarct-related coronary artery patency in patients with an inferior MI.

Methods

Study Population and Treatments

Over a 2.5-year period, 124 patients presenting to our institution with an inferior MI were entered into a prospective registry of arrhythmia monitoring during the first 24 h. Thirty-two of these patients who manifested the BJR constituted the present study group. Upon admission to the cardiac care unit, all patients had a 24-h Holter monitor placed prior to receiving thrombolysis. Patients were treated within 6 h from the onset of symptoms with intravenous thrombolysis (accelerated tissue-type plasminogen activator [rt-PA] 100 mg, over 90 min).

Unless contraindicated, conjunctive therapy included intravenous nitrates, aspirin, oral beta-adrenergic blockers, and angiotensin-converting-enzyme inhibitors, and heparin adjusted to keep the activated partial thromboplastin time at twice the upper normal limit. Specifically, metoprolol was started routinely early in 30 patients prior to receiving thrombolysis. Beta-blocker therapy was continued in two patients who had taken it chronically after an old MI. The infusion of heparin was continued for 3 to 4 days after MI. Patients were excluded if they were in cardiogenic shock, had bundle-branch block, sick sinus syndrome, atrial fibrillation, pacemaker dependence, received chronic antiarrhythmic drug therapy, or were treated with lidocaine, other antiarrhythmic drugs, or opiate medication.

Clinical signs of congestive heart failure on admission were categorized according to Killip classification.[10] Patients with a BJR response were advised to undergo coronary angiography and ventriculography 4–6 days after MI to verify their infarct-related coronary patency. Patients with > 70% narrowing of the luminal diameter of a major epicardial artery were judged to have significant single-, double-, or triple-vessel coronary artery disease. The infarct-related artery was identified on the basis of the location of the infarction as determined by 12-lead standard electrocardiogram (ECG) and/or by the pattern of regional dysfunction. Left ventricular ejection function was evaluated angiographically or by echocardiography prior to hospital discharge.

A control group of 12 patients of similar age and gender distribution (9 men and 3 women, mean age 61 ± 13 years) with inferior MI and same electrocardiographic criteria of early reperfusion but without a BJR response was also included to assess sustained coronary patency.

Electrocardiogram and 24-Hour Holter Recordings

Standard 12-lead ECGs were acquired serially before and 2 h after the beginning of thrombolysis on a daily basis through hospital discharge, and whenever any change in the patient's clinical status was observed. The lead showing the greatest ST-segment elevation on admission before thrombolysis was used for ST-segment analysis 80 ms after the end of the QRS complex. A 24-h Holter ECG recording was started in all patients prior to the onset of thrombolysis. The three-channel Galix MA-3C Holter recorder (Galix Biomedical Instrumentation, Inc., Miami Beach, Fla., USA) was used for ST-segment and HRV analysis utilizing 3.0 software.

Frequency-Domain Measures of Heart Rate Variability

For spectral analysis of HRV, the Galix system computed all normal R-R intervals by fast Fourier transformation in 5-min blocks of data after the signal went through a Hanning window. All beat annotations were visually reviewed and verified manually. Average heart rate and power spectral density of R-R interval variability was then automatically calculated for each of the three specific 5-min time intervals over the 15-min period just before the onset (−15, −10, −5) and after the end (5, 10, 15) of each BJR episode, and for the two 5-min time intervals after administration of atropine (A_5, A_{10}). The HRV spectral bands used were total power (TP, 0.000–0.500 Hz), very low-frequency power (VLF, 0.003–0.040 Hz), low-frequency power (LF, 0.040–0.150 Hz), and high-frequency power (HF, 0.150–0.398 Hz).[11] We used the LF/HF power ratio as an index of sympathovagal balance.[12, 13] The TP and the VLF, the LF and the HF oscillatory components were computed in absolute units (ms^2). In addition, the LF and HF components were obtained in normalized units by dividing the power of each component by the total power minus the VLF component and multiplying by 100. Technically inadequate ECG recordings with significant amounts of artifact or heart block were excluded from analysis. A minimum of three 5-min analyzable data before and after the BJR and a minimum of 85% successive normal sinus QRS complexes for each 5-min interval were required for a tape to be accepted as valid. Intraobserver variability as assessed by a second count of spectral HRV indices on all tapes was < 10%.

Control spectral measurements were obtained after a 10-min rest period in the supine position from a population represented by 10 healthy nonsmoker volunteers (mean age 47.6 ± 14.2 years) without a history of cardiopulmonary disease, and normal laboratory findings, echocardiogram, and exercise test.

Definitions

An inferior MI was indicated by ST-segment elevation of ≥ 1mV in at least two of the leads II, III, and aVF, and was confirmed by elevation of total creatine kinase and its MB isoenzyme (> 2 times the upper normal limit) and the development of new Q waves.

The BJR was defined as a sudden and transient episode of bradycardia and hypotension after the initiation of thrombolysis that was not drug-induced, and was followed by ST-segment elevation resolution. The onset of the BJR was indicated by a drastic reduction of mean heart rate to > 30% of the value preceding the onset of bradycardia. The end of BJR was indicated by a sustained increase of mean heart rate of > 30% of the value during the BJR.

Resolution of the ST-segment elevation was defined as a decrease in ST-segment elevation > 70% of the peak value in the lead showing maximum ST-segment elevation before the onset of BJR in the 12-lead ECG and the Holter ST-trend.[14, 15] Patients with BJR were characterized as successfully early reperfused if there was a progressive and/or rapid resolution of the initial ST-segment elevation and of chest pain within the first 2 h after initiation of thrombolysis as estimated by clinical and ECG criteria. The infarct-related artery was judged patent if angiography revealed complete antegrade Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow reperfusion.[16]

Statistics

Data are presented as the mean ± standard deviation (SD). Results of frequency-domain measures were transformed to their natural logarithms to achieve normal distribution. Bon-

TABLE I Characteristics of the study population

Patients (no.)	32
Age (years)	56 ± 12
Male, gender (%)	28 (87.5)
Prior MI (%)	4 (12.5)
Killip class I–II (%)	32 (100)
Time from symptom onset to rt-PA (h)	2.6 ± 1.4
Peak creatine kinase (IU/L)	1760 ± 904
Time from rt-PA onset to BJR (min)	49 ± 34
Duration of BJR (min)	7.3 ± 5.2
Time after BJR to ST resolution (min)	22 ± 18
Ejection fraction (%)	49 ± 10
Coronary angiography (no.)	27
Single-/double-/triple-vessel disease (no.)	10 / 10 / 7

Values are expressed as mean ± standard deviation or number (%).
Abbreviations: BJR = Bezold-Jarisch reflex, MI = myocardial infarction, rt-PA = accelerated tissue-type plasminogen activator.

feroni's multiple-comparison test was applied to test the significance of the transformed variables among the 5-min periods. A two-tailed p value of < 0.05 was considered statistically significant.

Results

Clinical Data

Of the 124 patients with inferior MI, 32 (26%) demonstrated the BJR. The demographic and clinical characteristics of the study group patients (28 men and 4 women, 34–82 years old) are listed in Table I. Mean time from onset of chest pain to beginning of thrombolysis was 2.6 ± 1.4 h. Concomitant ST-segment elevation in right precordial leads was found in six patients (19%). In all patients the BJR was characterized as reperfusion induced, as assessed by the ST-segment elevation recovery (Fig. 1). Thirty patients (94%) had early resolution of the ST-segment elevation within the 2-h "cutoff-point" of initiating thrombolysis. As summarized in Table I, mean time from onset of thrombolysis to BJR was 49 ± 34 min, mean duration of the BJR was 7.3 ± 5.2 min, and the median time to ST resolution after the end of the reflex event was 22 min. No patient had a new elevation of cardiac enzymes after the initial peak up to the angiographic verification of coronary patency. Transient bradyarrhythmias incident to BJR comprised profound sinus bradycardia in 13 patients, nodal rhythm in 13 patients, and complete heart block in 6 patients. In each case there was a simultaneous decrease in systolic blood pressure causing hemodynamic compromise which responded to conservative measures, such as resuming a Trendelenburg position and receiving intravenous fluids (15 patients) and/or administering intravenous atropine 0.5–1.5 mg (17 patients). Ventricular arrhythmias during the thrombolytic period were only seen after the BJR, manifesting as sustained episodes of accelerated idioventricular rhythm in three patients, and sporadic nonsustained runs of accelerated idioventricular rhythm in another patient.

All patients preserved left ventricular ejection fraction > 40%. Twenty-seven patients consented to coronary angiography, which was performed 5.1 ± 0.6 days after MI. Of these patients, 37% had single-vessel disease, 37% had double-vessel disease, and 26% had triple-vessel disease. Angiography identified the right coronary artery as the infarct-related coronary artery in all patients. Patent vessels with TIMI grade 3 flow were documented in 24 patients (89%), and occluded right coronary arteries in 3 patients (11%). Ten of the control group patients (83%) with inferior MI who did not experience a BJR were found to have TIMI grade 3 flow at coronary angiography performed at a similar timing after thrombolysis.

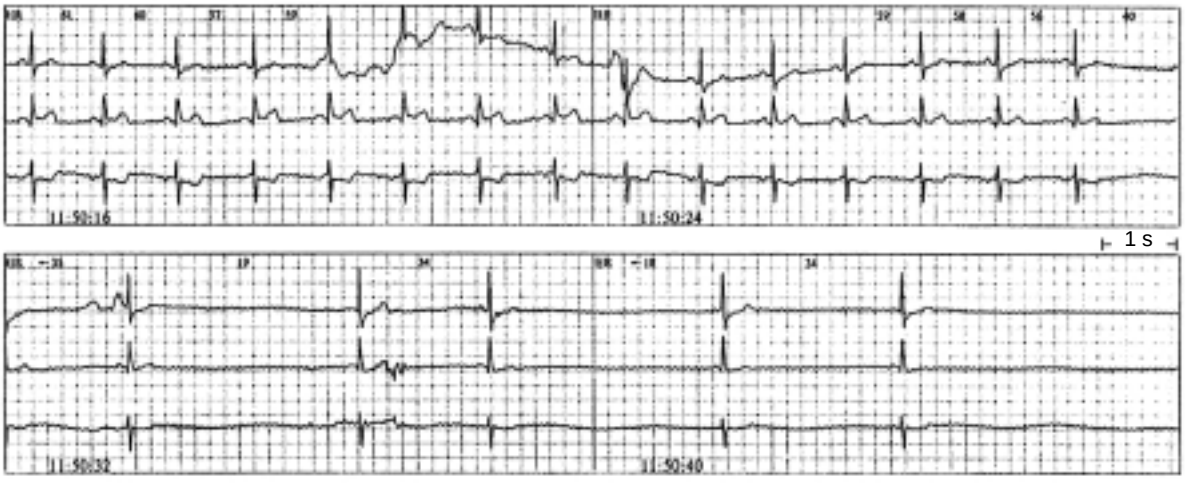

FIG. 1 Representative example of a Bezold-Jarisch reflex episode associated with reperfusion during thrombolytic therapy. The continuous three-channel Holter recording (HR) (16 s strips) reveals successful reperfusion, almost coincident with the beginning of marked bradycardia, as indicated by the resolution of the ST-segment elevation in the second channel and the recovery of the ST-segment depression in the third channel.

TABLE II Spectral profiles of heart rate variability preceding and following Bezold-Jarisch reflex

	Time	HR (beats/min)	TP [ln (ms^2)]	VLF [ln (ms^2)]	LF [ln (ms^2)]	HF [ln (ms^2)]	LF-NU	HF-NU
Controls (n = 10)		72 ± 11	9.6 ± 0.5	7.4 ± 0.61	6.4 ± 0.7	5.1 ± 0.74	58.8 ± 12.51	38.18 ± 11.28
Before BJR (n = 19)	−15	67 ± 9.4 [a,b]	8.2 ± 0.7 [d,b]	7.6 ± 0.7 [a,b]	6.9 ± 1.0 [b]	5.7 ± 1.1 [c,b]	73.7 ± 12.6 [e,f]	24.4 ± 11.5 [a,e]
	−10	67 ± 9.6 [a,b]	8.2 ± 0.6 [d,b]	7.5 ± 0.6 [a,b]	7.1 ± 0.7 [a]	5.9 ± 1.1 [c,b]	75.2 ± 12.1 [e]	22.3 ± 10.5 [g,h]
	−5	65 ± 9.1 [c,b]	8.5 ± 0.3 [c,b]	7.9 ± 0.4 [c,b]	7.2 ± 0.7 [d,b]	5.8 ± 0.7 [c,b]	80.6 ± 6.7	17.7 ± 5.9 [g]
After BJR (n = 12)	5	57 ± 7.9 [c,b]	8.2 ± 0.7 [d,b]	8.0 ± 0.7 [c,b]	7.3 ± 0.9 [d,b]	4.8 ± 0.6 [b]	83.1 ± 5.5	15.2 ± 4.3
	10	60 ± 9.3 [c,b]	8.5 ± 0.7 [c,b]	8.1 ± 0.8 [c,b]	7.4 ± 0.8 [d,b]	4.9 ± 0.8 [b]	88.5 ± 4.2	10.5 ± 4.0
	15	60 ± 9.2 [c,b]	8.2 ± 0.9 [a,b]	8.0 ± 0.8 [c,b]	7.2 ± 1.0 [d,b]	4.7 ± 1.0 [b]	82.7 ± 7.2	15.1 ± 5.1
Atropine (n = 7)	A_5	82 ± 11.2	7.0 ± 1.1	6.4 ± 1.0	5.7 ± 1.2	3.6 ± 1.8	85.4 ± 10.4	12.3 ± 9.1
	A_{10}	89 ± 10.9	6.3 ± 0.4	6.1 ± 0.4	4.4 ± 0.4	1.9 ± 0.8	87.2 ± 8.5	8.92 ± 6.9

Significant differences were found within the HR group and each frequency-domain variable.
Time = 5 min recordings of HRV before the onset (−15, −10, −5) and after the end of BJR (5, 10, 15), and after atropine (A_5, A_{10}).
Values are mean ± standard deviation.
[a] $p < 0.05$ vs. A_5.
[b] $p < 0.001$ vs. A_{10}.
[c] $p < 0.001$ vs. A_5.
[d] $p < 0.01$ vs. A_5.
[e] $p < 0.001$ vs. 10
[f] $p < 0.05$ vs. A_{10}.
[g] $p < 0.01$ vs. A_{10}.
[h] $p < 0.01$ vs. 10.
Abbreviations: BJR = Bezold-Jarisch reflex, Controls = control subects, HR = heart rate, HRV = heart rate variability, HF = high-frequency power, LF = low-frequency power, NU = normalized units, TP = total power, VLF = very low-frequency power.

Fluctuations of Heart Rate Variability Preceding and Following the Bezold-Jarisch Reflex

Indices of HRV could be analyzed in 19 patients preceding the onset of BJR, and following the end of BJR in 12 patients who recovered with use of the Trendelenburg position and in 7 patients in whom intravenous atropine was administered (Table II).

The average heart rates did not differ significantly during the 5-min periods preceding and following the BJR, but showed a notable decreasing trend after the end of the reflex. Atropine administration was followed by a significant increase in heart rate of both A_5 and A_{10} compared with every 5-min interval before and after the end of BJR.

There were no significant changes in TP, VLF, LF, and HF, expressed in absolute units, among the 5-min periods preceding and following the BJR. However, measures significantly decreased following atropine administration.

Low frequency, in absolute units, had an increasing trend before the onset and after the end of BJR. The value 10 min after the end of the reflex was found significantly increased compared with the −15 and −10 periods, and the −15 value was found decreased compared with A_{10} ($p < 0.05$).

High frequency, in absolute units, declined prior to onset of BJR, and this trend continued for 10 min following the end of the reflex. The value 10 min after the end of the reflex was found significantly decreased compared with the −10 and −15 periods, the −15 period was found increased compared with A_5 ($p < 0.05$), and the −5 and −10 periods were found significantly increased compared with A_{10} ($p < 0.01$).

Changes in the LF/HF ratio appeared in parallel with LF prior to reflex activation, and showed a further progressive increase for 10 min after the end of BJR (Fig. 2). All periods before reflex activation, and the first and the third period after reflex termination were found significantly decreased compared with A_5 or A_{10} ($p < 0.05$).

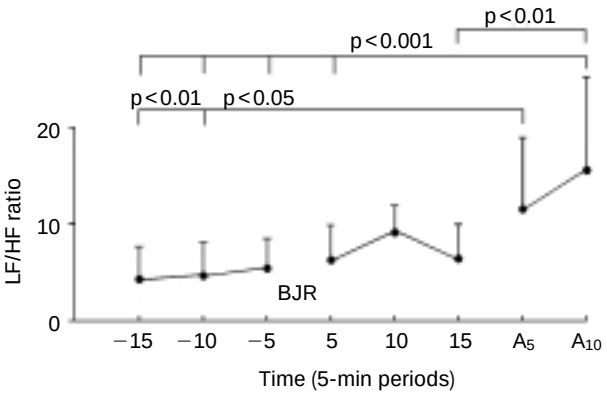

FIG. 2 Time course of cardiac sympathovagal modulation (LF/HF ratio) toward sympathetic predominance as assessed in 5-min heart rate variability time periods before the onset (−15, −10, −5) and after the end (5, 10, 15) of Bezold-Jarisch reflex (BJR), and following atropine administration (A_5, A_{10}). HF = high-frequency component, LF = low-frequency component.

Discussion

Background

As early as 1867, von Bezold and Hirt pioneered the far-reaching discovery that the injection of intravenous veratrum alkaloids induced apnea, bradycardia, and hypotension.[1] Besides Jarisch and Zotterman,[2] who confirmed these results, a host of other investigators contributed greatly to increase our knowledge about the coronary BJR, involving receptors, couched in different terminologies, as ventricular mechanosensitive or chemosensitive neuroreceptors, mostly located in the inferioposterior left ventricular wall, which discharge irregularly and sporadically into small nonmyelinated afferent C-fibers in the vagi.[2–5] Although these receptors have not been described anatomically or histologically, and the precise mechanisms and the natural stimulus to the cardioinhibitory reflex response are insufficiently understood, stimulation by stretch, distension of an infarcted area, or chemical substances are thought to modulate the arterial baroreflex mediating efferent vagal activation.[17] Fundamental experimental evidence suggests that locally released mediators that occur within minutes after the onset of ischemia, and particularly during reperfusion, such as prostaglandins, serotonin, and oxygen-derived free radicals, may activate the cardiac vagal afferent pathways.[3, 4, 17] Reflex bradycardia and hypotension has been observed to occur in animal models after prolonged coronary occlusion and reperfusion, and in humans, in the laboratory, after intracoronary injection of contrast material.[3, 4, 18] In clinical practice, BJR responses are observed in patients with inferior ischemia in association with coronary spasm and might account for most of the bradyarrhythmias in up to 61%, occurring within the first hour of posterior MI.[19, 20]

Clinical Relevance of Reperfusion-Induced Bezold-Jarisch Reflex

The first clinical descriptions of BJR are to be found in early studies of intracoronary thrombolysis in inferior MI, linking a 65–100% BJR response to the time of recanalization of the right coronary artery.[5–7] Koren *et al.* studied in depth the transient bradycardia and hypotension phenomenon following intravenous thrombolysis with streptokinase, indicating a 42% occurrence in patients with inferior AMI.[8] More recent convergent data of Shah *et al.* and Hohnloser *et al.* demonstrated a 23–50% appearance of sudden sinus bradycardia in thrombolyzed patients with inferior MI using prourokinase or rt-PA, associated with angiographically patent right coronary arteries within the first 24 h.[21, 22] Rarely, in the above referenced studies, has a reflex bradycardia also been described after anterior descending or circumflex artery reopening.[6, 7, 15]

The present study constitutes the largest patients series of the occurrence of the BJR phenomenon reported to date. We showed a similar incidence of BJR after treatment with rt-pA in approximately 30% of patients, and the same relatively well-tolerated transient nonmenacing bradyarrhythmias amenable to volume expansion or atropine alone. We confirmed that a BJR response indicative of successful reperfusion occurs early after initiation of thrombolytic therapy, and within the 2-h time window of successful thrombolysis, which is considered the most critical period of clinical significance.[23] Moreover, using the same ECG criterion of > 70% reduction in the ST-segment elevation after initiation of thrombolysis to assess early reperfusion, compared with published data of 45–55% early reperfusion rates,[21, 22] our study suggests that the appearance of the BJR enhances the probability of early reperfusion in up to 94%.

Furthermore, the issue of preservation of coronary patency following complete ST-segment elevation resolution in MI has been examined in only one prior study.[15] Consistent with the results reported by Dissmann *et al.*[15] of an 87% coronary patency at late angiography (7 ± 5 days), our control-group patients and the patients exhibiting a BJR response showed similar rates of patent vessels (88 and 83%, respectively). Although conjectural, the fact that in our study a BJR response was associated with higher early reperfusion rates implies that there is an added beneficial effect of this phenomenon in preserving sustained coronary patency.

Thus, by today's practical difficulties in noninvasively clarifying timely successful thrombolysis, the simple BJR response provides promising prognostic information for the decision-making physician judging optimal reperfusion.

Dynamics of Sympathovagal Balance Preceding and Following the Bezold-Jarisch Reflex

To our knowledge, this is the first clinical study using spectral analysis of HRV to investigate yet unknown sympathovagal interactions modulating reperfusion-induced BJR response in MI. Although we failed to detect any significant differences in spectral indices of HRV, one could speculate that the relative sympathetic predominance and simultaneous vagal inhibition before the onset of BJR may lead to activation of vagal receptors resulting in reflex bradycardia and hypotension (Fig. 2). However, the absence of a specific autonomic pattern suggests that additional factors such as extent of AMI, time from acute event, residual left ventricular function, and relative distribution of sympathetic and vagal afferents may all contribute to the complex phenomenon of a BJR response.

Our investigation leads to several additional new observations. First, cardiac neural modulatory changes leading to BJR do not develop abruptly, but a long duration of subtle but gradually increased sympathovagal interactions is required to evoke a BJR response. Second, after the end of the reflex, there is a further increasing reciprocal link between the LF and HF components, suggesting a persistent predominance of the sympathetic drive to the cardiodepressor event. These compensatory response-kinetics would have remained hidden as there was no significant change or even a slight slowing of the sinus rate, assuming vagal overactivity. Third, intravenous atropine administration leading to significant increases in heart rate was accompanied by diminished total power and a notable increasing shift of the sympathovagal balance in favor of sympathetic activity, which was mainly attributed to the decreased

vagal activity. In addition, we observed that the fluctuations of the autonomic tone did not trigger severe ventricular tachyarrhyhmias. Rather, it could be argued that the increased vagal drive after the end of BJR might have acted protectively in reducing ventricular vulnerability, as suggested by the presence of the benign accelerated idioventricular rhythm episodes after the end of the reflex. Perhaps this relative parasympathetic dominance resulting in a concomitant, albeit not significant, reduction in heart rate increases the ventricular fibrillation threshold while facilitating nonmenacing rhythm disturbances based on abnormal automaticity.[24]

Study Limitations

Our study design for a noninvasive assessment of early reperfusion could be challenged by the lack of early angiographic information. However, the validity of rapid ST-segment elevation resolution in a range of > 50% as a marker of early coronary patency has been confirmed by several previous angiographic studies.[21, 22] Thus, we defined "complete" resolution of ST-segment elevation by the cut-off point of > 70%, for which there is consensus that it is a specific noninvasive marker of early reperfusion.[14, 15] Furthermore, we defined early reperfusion at 2 h after initiation of the 90-min thrombolysis to avoid possible erroneous judgment because of the known frequent fluctuations in the ST segment before final stabilization.[21, 22] Finally, our results are based on HRV analysis in 5-min time periods, which might have failed to identify more subtle changes of the sympathetic and the vagal activity.

Conclusion

The BJR in inferior AMI represents a reliable prognosticator of timely reperfusion and sustained coronary patency. The results of this study support the hypothesis that stimulation of vagal afferents in response to sympathetic overactivity may be the underlying pathogenetic mechanism promoting a BJR response.

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