Effect of Repetitive, Transient Coronary Occlusions During Percutaneous Transluminal Angioplasty on Autonomic Cardiac Control: *Influence of the Occlusion Site*

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Background: Previous findings suggest that transient myocardial ischemia and reperfusion may elicit changes in the autonomic balance. In this study, a spectral analysis of heart rate variability was used to assess the modifications of sympathovagal balance induced by coronary angioplasty and their relationship with the occlusion site.

Methods: We studied 23 patients (17M, 6F, age 58 ± 10 years) with left anterior descending and 19 patients (15M, 4F, age 56 ± 9 years) with right coronary artery stenosis. Spectral analysis of heart rate variability was performed, by autoregressive model, in basal conditions and during each balloon inflation. At least two inflations of 90–120 seconds were performed in each patient.

Results: In patients with left anterior descending artery stenosis, the first occlusion induced marked changes in the autonomic balance, which moved toward a sympathetic predominance. The low frequency component of the spectrum and the low-to-high frequency ratio increased from 59 ± 10 normalized units (NU) to 75 ± 10 NU ($P < 0.001$) and from 2.4 ± 1.4 to 7.3 ± 4.7 ($P < 0.001$) respectively, while the high frequency component decreased from 30 ± 11 NU to 14 ± 7 NU ($P < 0.001$). These changes showed a progressive attenuation during repetitive occlusions, and were significantly correlated with the entity of myocardial ischemia assessed by the ST-segment shift measured on the intracoronary electrocardiographic lead. On the contrary, in patients with right coronary artery stenosis the first occlusion was ineffective with regard to the spectral parameters whereas the third occlusion induced a significant increase in the high frequency component (from 31 ± 9 NU to 41 ± 10 NU, $P < 0.01$) and decrease in the low-to-high frequency ratio (from 2.1 ± 0.9 to 1.3 ± 0.5, $P < 0.05$) suggesting a vagal activation. The entity of vagal activation was not correlated with the ST-segment shift.

Conclusions: Our data indicate that repetitive coronary occlusions induce significant changes in the autonomic balance. The direction and the time course of these changes are related to the occlusion site.

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percutaneous transluminal coronary angioplasty; myocardial ischemia; spectrum analysis; autonomic nervous system

Clinical and experimental evidences suggest the occurrence of autonomic disturbances during acute myocardial infarction.[1-5] These autonomic disturbances may contribute to both the development of complex arrhythmias and to sudden death induced by myocardial infarction or abrupt coronary occlu-

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sion.[6-9] On the contrary, little is known about the response in man of the autonomic nervous system either to brief periods of spontaneous myocardial ischemia and reperfusion,[10,11] or during coronary angioplasty, which is known to reproduce a similar physiopathological setting.[12-15]

Analysis of heart rate variability provides a useful noninvasive method of quantifying autonomic control on cardiac rhythm. Although it is now sufficiently clear that low values of heart rate variability are frequently observed after myocardial infarction (and are strongly related to increased mortality, particularly sudden death), only few and inconclusive data are available on the effect of transient myocardial ischemia and reperfusion on heart rate variability.[10,11,16-20]

In this investigation we evaluated, by spectral analysis of heart rate variability, the response of the autonomic nervous system to brief, repetitive coronary occlusions during coronary angioplasty. In particular, the present work was intended first to assess the influence of the occlusion site on the direction and entity of the autonomic changes; second to approach the effect of repeated occlusions on the time course of these changes; and third to investigate the quantitative relationship between the autonomic changes and myocardial ischemia.

METHODS

Subjects

We studied 67 patients referred for coronary angioplasty with major single vessel coronary artery disease causing stable angina. All patients met the following criteria:

(1) Diagnostic coronary arteriography performed on a previous occasion, showing a single stenosis located in the proximal segment of the left anterior descending artery (LAD) or in the mid segment of the right coronary artery (RCA) and determining a 60% to 80% reduction in arterial diameter, measured by the computer program included in the General Electric Advantx DF 6000 system (General Electric Medical Systems, Waukesha, WI, USA).
(2) Inducible myocardial ischemia documented with a positive exercise electrocardiogram or myocardial perfusion scintigraphy.
(3) Echocardiographic evidence of normal left ventricular ejection fraction and no regional wall motion abnormalities at rest.

Patients were excluded from the study if they had: recent unstable angina, previous myocardial infarction, hemodynamically significant valvular disease, heart failure, cardiomyopathies, rhythm disturbances other than sporadic ectopic beats, hypertension, or diabetes. Patients treated with digoxin, ACE inhibitors, or antihypertensive or antiarrhythmic drugs were excluded from the study, while in those taking beta-blockers or calcium antagonists the treatment was gradually withdrawn at least four half-lives before the study. Seven patients were excluded from the protocol because they could not tolerate the withdrawal of beta-blocker or calcium antagonist therapy. All participants gave informed consent to the study.

Study Protocol

Premedication with diazepam (5-10 mg perorally) was given in the catheterization laboratory and isosorbide dinitrate was administered intravenously at a constant infusion rate of 4 mg/hour throughout the study. Atropine was not administered to any patient. Patients were instructed to breathe at a constant rate, to avoid unnecessary talking, and to signal intolerable chest pain by a hand movement. Contrast medium injections were avoided during data acquisition and patients were unaware of the timing of the balloon inflation.

At least two inflations lasting 90-120 sec were performed in each subject, and the total amount of monitored inflations was 100. Deflation of the balloon before 90 seconds due to hemodynamic instability or severe chest pain (9 patients), occurrence of arrhythmias (2 patients), nonstationary sinus rhythm during or immediately after vessel occlusion (4 patients), and unsuccessful angioplasty (3 patients) caused the exclusion of the patient from further analysis. Occurrence of arrhythmias (1 case) or nonstationary sinus rhythm (3 cases) during the third inflation caused the exclusion from the analysis of that particular RR sequence. In all, 42 patients fulfilled the study protocol requirements and were divided according to the site of the stenosis: RCA in 19 patients (15M, 4F, mean age 56 ± 9 years) and LAD in 23 patients (17M, 6F, mean age 58 ± 10 years).

The measurement of the ST-segment shift during

arterial occlusion was performed on the intracoronary electrocardiographic lead.

Spectral Analysis of Heart Rate Variability

The participants were connected to a standard electrocardiogram recorder with chest electrodes. Respiratory activity was monitored by a nose-tip thermistor. Arterial blood pressure was measured directly from the guiding catheter. Electrocardiograms were digitized with an analog-to-digital converter and stored in a microcomputer.

Spectral analysis was performed according to the standards specified by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[21] After reviewing the electrocardiograms on the computer display, sequences of about 250 consecutive respiriatory rate (RR) intervals of stationary sinus rhythm were analyzed. Baseline data were obtained from the region immediately preceding balloon positioning through the stenosis. Since the ischemic time was too short (90-120 sec) to allow a satisfactory evaluation of the power spectrum components, the effect of vessel occlusion on spectral parameters was evaluated on two RR interval series starting, respectively, 20 sec after the beginning of arterial occlusion (period A, including the ischemic and reperfusion phases) and immediately after balloon deflation (period B, including the reperfusion phase only).[21] An autoregressive model was used to estimate the power spectrum of the heart rate variability.[21-23] The autoregressive coefficients were automatically calculated by the computer program, while the model order was chosen as one that minimized Akaike's final prediction error figure of merit.[24] Each spectral component was then identified by the center frequency and quantified by its power. The latter was also expressed as both a natural logarithm of the absolute power and as normalized units (NU). Normalized units were obtained by dividing the absolute power (ms × ms) of the individual component by total variance (after having subtracted from it the DC component), and multiplying this ratio by 100. The use of normalized units facilitates the comparison of spectra with large differences in total variance.[25] Only components with an individual power > 5% of the total power were considered to be significant. Those at 0.04-0.15 Hz were defined as low frequency components and those at 0.15-0.40 Hz as high frequency components. The former have been shown to reflect sympathetic cardiac function with vagal modulation; the latter seem to provide a more specific index of vagal control.[22,25-28] The RR interval variance and the low frequency to high frequency ratio were also calculated. The low frequency to high frequency ratio has been reported to be an index of sympathovagal balance.[22]

Statistical Analysis

Data were expressed as mean ± 1 standard deviation. Two-ways repeated measure analysis of variance (ANOVA) was used to assess the statistical significance of differences between mean values. Linear regression analysis was used to assess the relation of spectral parameters to ST-segment shift. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Baseline and procedural data such as age, sex distribution, percent stenosis, inflation time, chest pain, and ST-segment shift are shown in Table 1. No significant differences were observed between

Table 1. Procedural Data in Patients Subjected to Left Anterior Descending or Right Coronary Artery Angioplasty

	LAD (n = 23)	P	RCA (n = 19)
Age (years)	58 ± 10	NS	56 ± 9
Male sex	17 (74%)	NS	15 (79%)
Stenosis (%)†	72 ± 7	NS	71 ± 8
Inflation time (sec):			
1st inflation	107 ± 11	NS	112 ± 11
2nd inflation	110 ± 12	NS	115 ± 10
3rd inflation	114 ± 9	NS	119 ± 4
Chest pain:			
1st inflation	22 (96%)	NS	17 (89%)
2nd inflation	20 (87%)	NS	15 (79%)
3rd inflation	5 (56%)	NS	4 (57%)
ST shift (mV)‡:			
1st inflation	0.9 ± 0.6	NS	0.8 ± 0.5
2nd inflation	0.4 ± 0.3*	NS	0.5 ± 0.3*
3rd inflation	0.3 ± 0.2*	NS	0.4 ± 0.3*

LAD = left anterior descending group; RCA = right coronary artery group; * = P < 0.05 vs 1st inflation; † = coronary stenosis calculated as the percent reduction in arterial diameter; ‡ = ST-segment shift evaluated from the intracoronary electrocardiographic lead.

LAD and RCA groups with regard to these variables. About 90% of patients of both groups experienced chest pain during the first inflation; this percentage decreased to about 55% during the third inflation. The same trend was observed with regard to the mean values of the ST-segment shift which significantly decreased from the first to the third inflation ($P < 0.05$ in both groups). Table 2 reports the main hemodynamic and spectral parameters measured, i.e. in basal conditions and (during ballon inflation) in the LAD and RCA. In the former group we observed a significant increase in the heart rate, low frequency component power, and low- to high-frequency ratio associated with a decrease in the high frequency component power during the first balloon inflation (Table 2 and Fig. 1). Such modifications showed a progressive attenuation during the subsequent inflations such that no significant changes were observed during the third inflation. We also observed a slight, though significant, increase in heart rate and a decrease in systemic arterial pressure during the first balloon inflation, with progressive attenuation during the subsequent occlusions.

On the contrary, in the RCA group,the first balloon inflation did not induce significant changes in the hemodynamic or spectral parameters due to the wide scatter of the individual responses. Neverthless, during the subsequent inflations we observed a slight but significant increase in the high frequency component power and a decrease in the low frequency to high frequency ratio (Table 2 and Figure 1). The RR interval and the RR interval variance showed a trend towards a progressive increase during the three series of inflation, although it did not reach the statistical significance.

Results obtained from the analysis of period B (including only the reperfusion phase of each balloon inflation) were superimposable to those obtained from period A(Table 3).

Changes in the low- and high-frequency component induced by the balloon inflation were more significant if data were expressed in normalized units as opposed to in absolute power (Tables 2 and 3).

Finally, the changes in the low frequency component, high frequency component and low frequency to high frequency ratio induced by each occlusion were significantly correlated to the entity of the ST-segment shift in the LAD group ($r = 0.706$, $r = -0.574$, $r = 0.610$, respectively; $P <$

Table 2. Spectral Parameters During Left Anterior Descending or Right Coronary Angioplasty

	LAD				RCA			
	Basal (n = 23)	1st Inflation (n = 23)‡	2nd Inflation (n = 23)‡	3rd Inflation (n = 9)‡	Basal (n = 19)	1st Inflation (n = 19)‡	2nd Inflation (n = 19)‡	3rd Inflation (n = 7)‡
HR (bpm):	72 ± 12	77 ± 13*	75 ± 13	73 ± 15	71 ± 12	71 ± 12	70 ± 12	69 ± 10
SAP (mmHg):	127 ± 18	123 ± 17*	124 ± 17	124 ± 19	130 ± 19	128 ± 17	128 ± 18	129 ± 17
DAP (mmHg):	73 ± 11	74 ± 11	73 ± 11	73 ± 13	71 ± 10	70 ± 10	70 ± 11	71 ± 9
Variance:								
($msec^2$)	2041 ± 1706	2085 ± 1370	1750 ± 917	2062 ± 1423	1857 ± 1188	1901 ± 1228	2008 ± 1053	2812 ± 915
(ln $msec^2$)	7.34 ± 0.77	7.42 ± 0.70	7.28 ± 0.72	7.36 ± 0.84	7.29 ± 0.75	7.31 ± 0.78	7.43 ± 0.65	7.88 ± 0.39
LF component:								
($msec^2$)	726 ± 700	919 ± 650*	527 ± 388	546 ± 523	627 ± 508	595 ± 528	594 ± 449	976 ± 469
(ln $msec^2$)	6.09 ± 1.15	6.56 ± 0.77**	5.95 ± 0.94	5.88 ± 1.05	6.10 ± 0.91	5.97 ± 1.04†	6.08 ± 0.84	6.79 ± 0.44†
(NU)	59 ± 10	75 ± 10***	64 ± 9*	59 ± 7	57 ± 9	54 ± 12†††	53 ± 10††	51 ± 7†
HF component:								
($msec^2$)	359 ± 388	210 ± 260*	238 ± 214*	277 ± 244	349 ± 286	405 ± 319†	505 ± 450†	780 ± 347*††
(ln $msec^2$)	5.36 ± 1.09	4.85 ± 0.99**	5.00 ± 1.12*	5.18 ± 1.13	5.45 ± 1.02	5.49 ± 1.29†	5.71 ± 1.21†	6.56 ± 0.50*††
(NU)	30 ± 11	14 ± 7***	25 ± 8*	30 ± 6	31 ± 9	35 ± 11†††	37 ± 12*†††	41 ± 10**†
LF/HF ratio:	2.4 ± 1.6	7.3 ± 4.7***●	2.9 ± 1.5**	2.1 ± 0.7	2.1 ± 0.9	2.0 ± 2.0†††	1.8 ± 1.1††	1.3 ± 0.5*†

DAP = diastolic arterial pressure; HF = high frequency component of the spectrum; HR = heart rate; LAD = left anterior descending coronary artery angioplasty group; LF = low frequency component of the spectrum; Ln = natural logarithm; NU = normalized units; RCA = right coronary artery angioplasty group; SAP = systolic arterial pressure; *, **, and *** = $P < 0.05$, $P < 0.01$ and $P < 0.001$ vs baseline; †, ††, and ††† = $P < 0.05$, $P < 0.01$ and $P < 0.001$ vs LAD group; ‡ = spectral analysis performed on period A (including the ischemia and reperfusion phases).

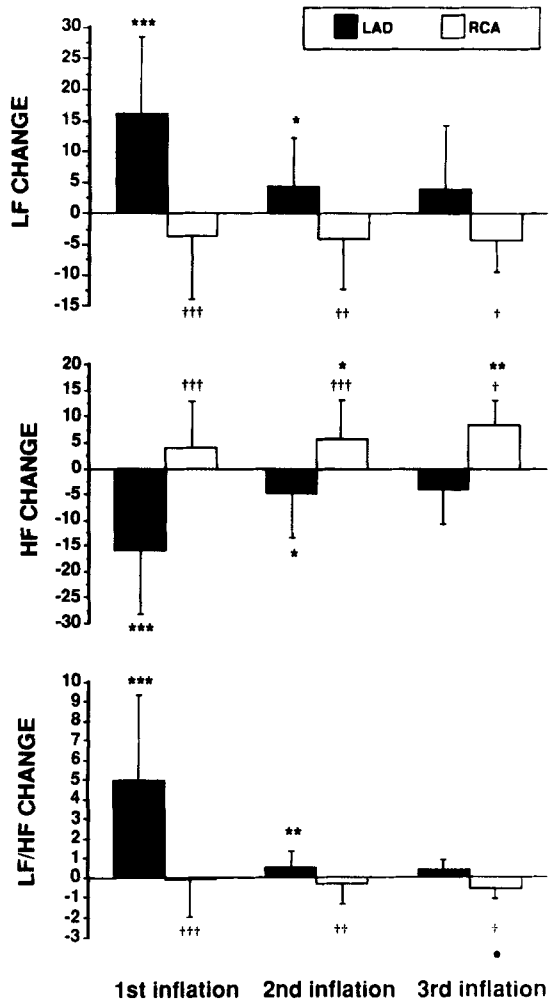

Figure 1. Bar graphs showing the changes from baseline in the low frequency component (LF, upper panel), high frequency component (HF, middle panel) and low frequency to high frequency ratio (LF/HF, lower panel) induced by repetitive balloon inflations in the left anterior descending artery (LAD) or in the right coronary artery (RCA). Spectral parameters were obtained from analysis of period A (see Methods). *, ** and *** = $P < 0.05$, $P < 0.01$, and $P < 0.001$ vs baseline (ANOVA); †, †† and ††† = $P < 0.05$, $P < 0.01$, and $P < 0.001$ vs LAD group (ANOVA).

0.0001 in all cases) but not in the RCA group (Figs. 2, 3 and 4).

DISCUSSION

The main findings of the present study are:

(1) Changes in spectral parameters indicating a vagal withdrawal and a shift of the autonomic balance toward a sympathetic dominance during and immmediately after left anterior descending artery occlusion.

(2) These modifications were more evident during the first inflation and progressively attenuated during the following inflations.

(3) In patients with LAD occlusion the electrocardiographic evidence of myocardial ischemia paralleled the autonomic response so that the ST-segment shift was significantly correlated to the changes in the low frequency component, high frequency component and low frequency to high frequency ratio.

(4) The occlusion of the RCA induced changes in spectral parameters opposite to those observed in the LAD, and which were evident only after repetitive occlusions.

A number of lines of evidence suggest that autonomic disturbances frequently occur during the early hours of acute myocardial infarction.[1-4,29] The direction and/or entity of these autonomic changes varies depending on the infarction site. In fact, signs of sympathetic overactivity may occur during infarction of the anterior left ventricular wall, whereas signs of vagal activation are frequently observed during posteroinferior myocardial infarction.[1,29] More recently, a study performed by spectral analysis in the early hours of an acute myocardial infarction failed to show evidence of a vagal hyperactivity in patients with inferior wall myocardial infarction, although sympathetic hyperactivity was significantly reduced when compared to patients with anterior localizations.[30] However, evidence obtained in the presence of protracted ischemia and acute myocardial infarction should be only cautiously applied to the pathophysiological setting of transient myocardial ischemia. With this regard, Bigger et al. found a withdrawal of parasympathetic neural activity during episodes of asymptomatic ST depression, while autonomic changes also were observed during variant angina.[10,11] The occlusion of the LAD for 1 minute during coronary angioplasty determined an increase in cardiac noradrenaline spillover during the early phase of reperfusion.[12] This sympathetic hyperactivity might be due to the activation of myocardial afferent nerves.[31] The activation of sympathetic afferent cardiac fibers during myocardial ischemia may be triggered by the mechanical distortion of their sensor endings occurring in the setting of regional wall motion abnormalities,

Table 3. Spectral Parameters During Post-Ischemic Reperfusion

	LAD				RCA			
	Basal (n = 23)	1st Inflation (n = 23)‡	2nd Inflation (n = 23)‡	3rd Inflation (n = 9)‡	Basal (n = 19)	1st Inflation (n = 19)‡	2nd Inflation (n = 19)‡	3rd Inflation (n = 7)‡
Variance:								
(msec^2)	2041 ± 1706	1919 ± 1341	1763 ± 975	2101 ± 1501	1857 ± 1188	1941 ± 1392	2105 ± 1099	2686 ± 830
(ln msec^2)	7.34 ± 0.77	7.36 ± 0.75	7.27 ± 0.73	7.39 ± 0.81	7.29 ± 0.75	7.30 ± 0.79	7.49 ± 0.62	7.85 ± 0.36
LF component:								
(msec^2)	726 ± 700	801 ± 558	619 ± 329	668 ± 404	627 ± 508	521 ± 397	614 ± 345	848 ± 299
(ln msec^2)	6.09 ± 1.15	6.47 ± 0.73*	6.24 ± 0.69	6.29 ± 0.75	6.10 ± 0.91	6.01 ± 0.72†	6.24 ± 0.65	6.69 ± 0.34
(NU)	59 ± 10	76 ± 9***	65 ± 10**	59 ± 7	57 ± 9	53 ± 11††	53 ± 10†††	50 ± 8†
HF component:								
(msec^2)	359 ± 388	161 ± 36*	264 ± 200	355 ± 280	349 ± 286	340 ± 230††	434 ± 254†	718 ± 234*†
(ln msec^2)	5.36 ± 1.09	4.71 ± 0.93**	5.25 ± 0.88	5.58 ± 0.83	5.45 ± 1.02	5.51 ± 0.93††	5.84 ± 0.78*†	6.52 ± 0.41*†
(NU)	30 ± 11	14 ± 7***	25 ± 8*	29 ± 6	31 ± 9	34 ± 11†††	36 ± 10*†††	42 ± 8**††
LF/HF ratio:	2.4 ± 1.4	6.7 ± 3.7***	3.0 ± 1.6**	2.1 ± 0.7	2.1 ± 0.9	2.1 ± 2.1†††	1.7 ± 1.0††	1.2 ± 0.4*††

HF = high frequency component of the spectrum; LAD = left anterior descending coronary artery angioplasty group; LF = low frequency component of the spectrum; Ln = natural logarithm; NU = normalized units; RCA = right coronary artery angioplasty group; *, ** and *** = $P < 0.05$, $P < 0.01$ and $P < 0.001$ vs baseline; †, †† and ††† = $P < 0.05$, $P < 0.01$ and $P < 0.001$ vs LAD group; ‡ = spectral analysis performed on period B (only post-ischemic reperfusion phase).

or by the release from the ischemic myocardium of adenosine, which has been shown to increase sympathetic nerve traffic in humans.[31-33] On the other hand, some data indicate that myocardial ischemia in the postero-inferior left ventricular wall may lead to autonomic changes opposite from those observed in the ischemia of the anterior wall. In fact, vagal afferent fibers are preferentially distributed to the infero-posterior wall of the left ventricle, and may be activated during myocardial ischemia, probably through the local release of prostaglandins.[34-36] Moreover, the activation of these vagal fibers may inhibit the noradrenaline release at a presynaptic level.[37] McCance and Forfar failed to demonstrate a net increase in cardiac noradrenaline spillover after right coronary artery occlusion.[12]

The results of our study support the findings mentioned above, showing a shift of the autonomic balance toward a sympathetic dominance during LAD occlusion, and complex changes during RCA occlusion. It is of interest that the autonomic changes induced by LAD angioplasty were more evident during the first inflation and markedly blunted during the following ones. Since the sympathetic activation was significantly related to the entity of myocardial ischemia (Figs. 2 and 4) and the latter progressively decreased from the first to the third occlusion (Table 1), it is conceivable to presume that ischemic "preconditioning" of myocardium might have occurred during repetitive occlusions, blunting the intensity of myocardial ischemia and of the autonomic imbalance at the same time.[38] What is perhaps less clear is the late occurrence of the autonomic changes during repetitive RCA occlusions. These changes were not directly related to the entity of myocardial ischemia (Figs. 2, 3 and 4). Moreover, previous findings suggest that these cardioinhibitory reflexes may be triggered by the local release of prostaglandins, rather than by myocardial ischemia itself.[36] Since complex interaction, including inhibitory and excitatory reflexes arising from the heart, is likely to occur during myocardial ischemia, we can postulate that the stimulation of chemosensitive vagal afferent fibers during the first RCA occlusion might have been masked by the direct, counteracting effect of myocardial ischemia on the autonomic balance.[31,39] Vagal activation would then become evident during the following occlusions once the severity of myocardial ischemia is reduced.

Our data are in contrast with those obtained by

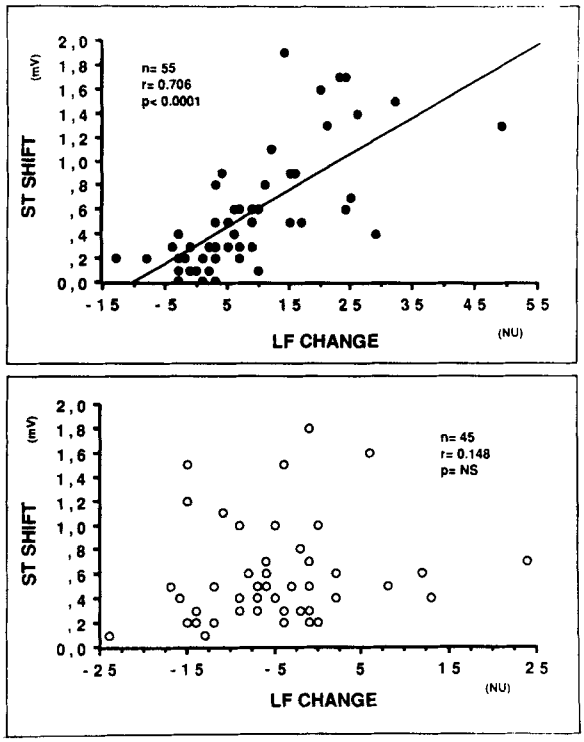

Figure 2. Scattergram of relation between the ST-segment (ST) shift on the intracoronary electrocardiographic lead and the low frequency component (LF) change from baseline values during occlusion of the left anterior descending artery (LAD, upper panel) or right coronary artery (RCA, lower panel). The correlation was significant in the LAD group only. Spectral values were obtained from analysis of period A (see Methods).

Airaksinen et al.[20,40,41] In fact, they found that balloon inflation could elicit divergent individual autonomic reactions without significant changes in the mean values of total variance, whereas a subsequent study demonstrated a significant increase in the absolute values of both components (high frequency and low frequency) of the spectrum.[41] The direction of these changes was unpredictable on the basis of the occlusion site.[20,41]

A major factor contributing to explain the differences between our findings is that the authors used an RR interval sequence which is considered too short (60 seconds, i.e. about 75 RR intervals) to allow a reliable spectral analysis in the frequency domain, especially in the range of the low frequency component.[21] On the contrary, in the present study we used a longer RR interval sequence (about 250 RR intervals) to perform spectral analysis, which allowed a more complete and reliable evaluation of the power spectrum components and of their modifications during coronary angioplasty. Moreover, since period A was longer than the occlusion period, the autonomic changes showed in Table 2 should be attributed more correctly to the ischemia-reperfusion sequence, rather than to ischemia alone. In our opinion, the inclusion of the early reperfusion period in the RR interval sequence might have been helpful in detecting an autonomic imbalance. In fact,there could be a "phase lag" in the autonomic response to transient ischemia and/or reperfusion itself could determine an additional effect on the autonomic balance. This hypothesis seems supported by our data, since the autonomic patterns obtained from the analysis of period B, which included the reperfusion phase only, were very similar to those obtained from

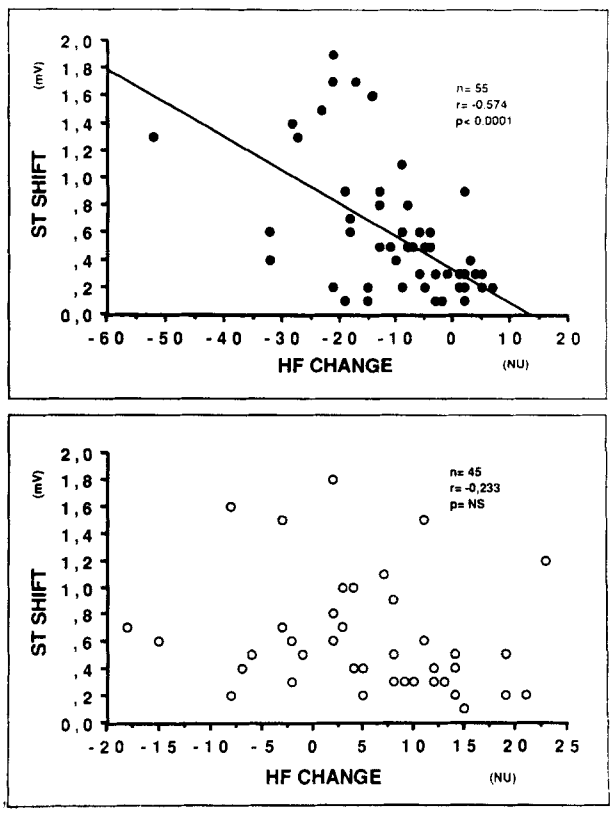

Figure 3. Scattergram of relation between the ST-segment (ST) shift on the intracoronary electrocardiographic lead and the high frequency component (HF) change from baseline values during occlusion of the left anterior descending artery (LAD, upper panel) or right coronary artery (RCA, lower panel). The correlation was significant in the LAD group only. Spectral values were obtained from analysis of period A (see Methods).

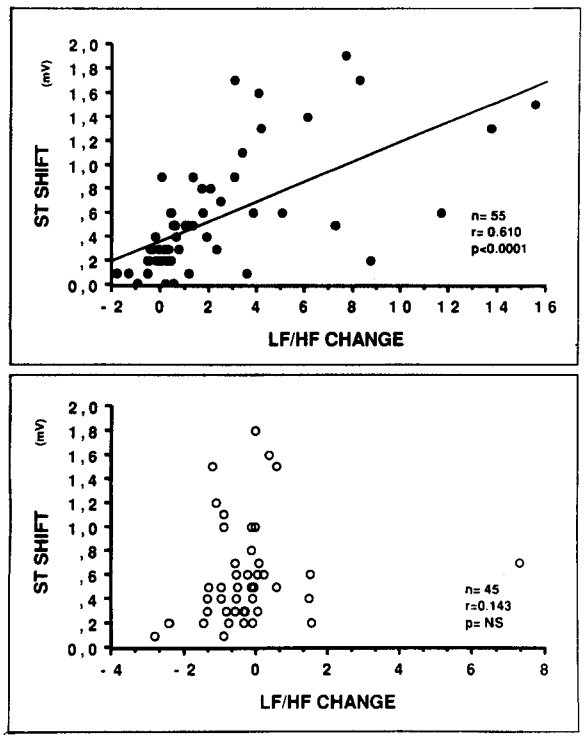

Figure 4. Scattergram of relation between the ST-segment (ST) shift on the intracoronary electrocardiographic lead and the low frequency to high frequency ratio (LF/HF) change from baseline values during occlusion of the left anterior descending artery (LAD, upper panel) or right coronary artery (RCA, lower panel). The correlation was significant in the LAD group only. Spectral values were obtained from analysis of period A (see Methods).

period A. With this regard, previous data concerning the relative effect of ischemia and of postischemic reperfusion on the autonomic balance are contrasting. In fact, although Lombardi et al.[42] found in anesthetized dogs that the periods of occlusion and of reperfusion may elicit different reflex responses, subsequent experiments have demonstrated that the autonomic changes induced by transient coronary occlusion may actually persist during the reperfusion phase.[36] Also, McCance and Forfar found that cardiac noradrenaline spillover during LAD coronary angioplasty increased after the ischemic phase, during the early phase of reperfusion.[12]

Study Limitations

One concern that could be raised about the interpretation of our results is that the sympathetic activation observed during the occlusion of the LAD may be consequent to the induction of chest pain and its associated reaction of anxiety, rather than to the direct activation of an autonomic reflex. Although this possibility cannot be excluded, it must be considered that no signs of sympathetic activation were observed in the RCA group, even if a high percentage of these patients (89%) experienced chest pain.

Transient ischemia and postischemic reperfusion are dynamic phenomenons characterized by rapid progression-regression phases. Therefore, a word of caution must be spent in interpreting data obtained from spectral analysis of heart rate variability requiring stationarity of the level of autonomic heart rate modulation in this pathophysiological setting. However, this potential bias might have only played a secondary role in our study as: first, we excluded the first 20 seconds of ischemia from the analyzed segments; and second, we observed a substantial similarity of the spectral patterns obtained from period A and B, which is consistent with a substantial stationarity of the level of the autonomic modulation of heart rate throughout the period of analysis. Finally, we cannot exclude that the different time course of the autonomic changes observed in left-sided and right-sided angioplasties might be, at least in part, related to side-related differences in the dynamic evolution of the reperfusion phase.

The results obtained during RCA angioplasty may have been biased by the induction of ischemia in the sinus-atrial node. However, proximal stenoses of the RCA were not included in this study, and the direct occlusion of the branch to the sinus-atrial node during balloon inflation was avoided in all cases.

CONCLUSIONS

In summary, our results indicate that transient, repetitive coronary occlusions cause changes in the autonomic balance. The direction and the time course of these changes are related to the occlusion site.

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