Original Article

Spectral Analysis Related to Bare-Metal and Drug-Eluting Coronary Stent Implantation

Rose Mary Ferreira Lisboa da Silva[1], Carlos Augusto Bueno Silva[1,2], Otaviano José Greco[2], Maria da Consolação Vieira Moreira[1]

Faculdade de Medicina da UFMG[1], Belo Horizonte; Hospital São João de Deus[2], Divinópolis, MG - Brazil

Abstract

Background: **The autonomic nervous system plays a central role in cardiovascular regulation; sympathetic activation occurs during myocardial ischemia.**

Objective: **To assess the spectral analysis of heart rate variability during stent implantation, comparing the types of stent.**

Methods: **This study assessed 61 patients (mean age, 64.0 years; 35 men) with ischemic heart disease and indication for stenting. Stent implantation was performed under Holter monitoring to record the spectral analysis of heart rate variability (Fourier transform), measuring the low-frequency (LF) and high-frequency (HF) components, and the LF/HF ratio before and during the procedure.**

Results: **Bare-metal stent was implanted in 34 patients, while the others received drug-eluting stents. The right coronary artery was approached in 21 patients, the left anterior descending, in 28, and the circumflex, in 9. As compared with the pre-stenting period, all patients showed an increase in LF and HF during stent implantation (658 versus 185 ms^2, p = 0.00; 322 versus 121, p = 0.00, respectively), with no change in LF/HF. During stent implantation, LF was 864 ms^2 in patients with bare-metal stents, and 398 ms^2 in those with drug-eluting stents (p = 0.00). The spectral analysis of heart rate variability showed no association with diabetes mellitus, family history, clinical presentation, beta-blockers, age, and vessel or its segment.**

Conclusions: **Stent implantation resulted in concomitant sympathetic and vagal activations. Diabetes mellitus, use of beta-blockers, and the vessel approached showed no influence on the spectral analysis of heart rate variability. Sympathetic activation was lower during the implantation of drug-eluting stents. (Arq Bras Cardiol. 2014; 103(2):138-145)**

Keywords: **Spectrum Analysis; Myocardial Ischemia; Heart Rate; Stents; Drug-Eluting Stents.**

Introduction

Percutaneous coronary intervention (PCI) is used for patients with coronary artery disease (CAD) and critical obstructive lesion to improve symptoms and increase survival[1,2]. Two types of stent can be implanted: bare-metal stents and the drug-eluting stents. The later have a lower stenosis rate, but are more expensive[3]. They were used in 75% of the PCI procedures in the United States in 2010[4].

Sympathetic activation occurs during myocardial ischemia, which, along with coronary reperfusion, also cause excitation of cardiac vagal nerve endings and activation of the Bezold-Jarisch reflex, resulting in bradycardia and hypotension[5]. Studies have been performed to assess the hypothesis that balloon-catheter coronary angioplasty and its associated transient myocardial ischemia cause changes in neural circulatory control. In a study with 23 patients with angina, coronary artery balloon occlusion caused sympathetic activation, which was attenuated by cardiac sympathetic denervation[6]. Other studies have shown that, in 70 patients exposed to a mean 110-second coronary occlusion, 41% showed no change in heart rate, while 24% showed a decrease in vagal tone[7-9]. There was an association of heart rate variability (HRV) with the incidence of ventricular tachycardia during coronary angioplasty[10], as well as with the increase in sympathetic tone and vagal sympathetic balance in half of the patients, 80 seconds after coronary balloon inflation[11]. Indicators of sympathetic activation and vagal depression identify restenosis after PCI, showing differences in autonomic cardiovascular regulation after the procedure[12]. In patients undergoing drug-eluting stent implantation, vasomotor dysfunction has been reported two weeks after acute myocardial infarction[13], attributed to possible inflammatory reaction, although its lower restenosis rate has been well established[3]. In stable patients with CAD, a HRV reduction has been associated with an increase in systemic inflammation[14]. There are no studies assessing the autonomic nervous system (ANS) of patients undergoing coronary stent implantation and comparing the types of stents implanted. Those are the objectives of the present study.

Mailing Address: Rose Mary Ferreira Lisboa da Silva •
Faculdade de Medicina da UFMG - Av. Alfredo Balena, 190, sala 246, Santa Efigênia, Postal Code 30130-100, Belo Horizonte, MG - Brazil
E-mail: roselisboa@cardiol.br; roselisboa@uol.com.br
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Methods

This is a prospective, longitudinal, observational study including 61 patients aged 18 years and older, of both sexes, and diagnosed with CAD. Those patients received indication for coronary stent implantation and originated from the Cardiac Catheterization Service of the Hospital São João de Deus, in the city of Divinópolis, Minas Gerais state. Patients with the following characteristics were excluded: pregnant women; coexisting conditions that could affect the spectral analysis of HRV, such as atrial fibrillation, pacemaker rhythm, use of antiarrhythmic drugs (except beta-blocker), and heart failure; and previous cardiac transplantation. The indication for either coronary stent implantation or clinical treatment was determined by the attending physicians and according to established guidelines[1,2].

The research project was approved by the Committees on Ethics and Research of the Federal University of Minas Gerais and of the Hospital São João de Deus. The patients were invited to participate in the study at the time of their medical care, and their inclusion was performed consecutively, from February 2009 to June 2011. After accepting the invitation and providing written informed consent, the patients underwent clinical assessment, electrocardiography and PCI, which was performed by the same professional, and consisted of stent implantation under digital Holter monitoring. Three-channel DMS 300-7 Holter recorder (modified V1 and V5, and D3 leads), version 1.0, was used for the spectral analysis of HRV. That spectral analysis was based on the mathematical model of Fourier transformation, after strict manual edition of the recordings, with elimination of artifacts and correction of arrhythmias. The following measurements were taken: low-frequency (LF) components, representing mainly the sympathetic system; high-frequency (HF) components, representing the parasympathetic system; and LF/HF ratio[15]. The spectral analysis of HRV was performed with the patient in the supine position, 5-10 minutes before PCI (baseline) and during stent implantation; the time considered was that from coronary artery occlusion, during endoprosthesis implantation, added up to five minutes, because the analysis was determined with that minimum recording time by the program. In addition, another spectral analysis of HRV was obtained five minutes after the procedure ended. The results of the analysis were expressed in absolute units (ms^2)[15].

Regarding the PCI technique, femoral arterial access was preferred, and, when not available, radial arterial access was used. Patients were sedated with benzodiazepines one hour before the procedure. Multiple projections of radiographic images of the major epicardial vessels to be approached were acquired. A 0.014'' guidewire was advanced and positioned distal to the target lesion. The size and diameter of the balloon and stent were visually estimated based on the subjective analysis of the catheterization lab physician, using the diameter of the guidewire as reference or quantitative angiography. The balloon catheter, in the pre-dilatation technique, or directly the stent, in the technique of direct endoprosthesis implantation, was positioned at the level of the target lesion, under fluoroscopy. Coronary occlusion had a mean duration of 60 seconds, and was performed according to the high-pressure implantation technique (> 12 atm). Additional inflations, called post-dilatation, were performed in some cases, aiming at optimizing the initial results. The procedures were performed under invasive blood pressure monitoring, electrocardiographic recording, and oxygen saturation monitoring. Precordial pain was assessed based on its severity, according to Smokler's numerical scale, being classified as mild, moderate, moderately severe and maximally severe[16].

The SPSS (Statistical Package for the Social Sciences) software, version 14.0, was used for statistical analysis. The results of categorical variables were expressed as numbers and proportions, and those of continuous variables, as measures of central tendency (mean and median) and dispersion. The Mann-Whitney and chi-square or Fisher tests, when appropriate, were used to compare the differences between quantitative continuous variables and qualitative or categorical variables (nominal or ordinal), respectively. The Wilcoxon test was used to compare the periods (before, during and after coronary occlusion) of the spectral analysis components. For comparing more than two groups, Kruskal-Wallis test was used. To assess the correlation between continuous variables, Pearson coefficient was used. The 0.05-level was established for rejecting the null hypothesis.

Results

General characteristics of the case series

The mean age of the patients was 64.0 ± 10.6 years, and 35 (57.4%) were men. Regarding the clinical presentation, 21 patients (34.4%) had stable angina, while 32 (52.5%) had unstable angina, eight of whom (13.1%) one week after acute myocardial infarction, and none of them had any ischemia episode for at least seven days. Table 1 shows the clinical variables.

The distribution of risk factors was as follows: systemic arterial hypertension, 56 patients (91.8%); diabetes mellitus, 13 (21.3%); smoking, 20 (32.8%); positive family history of CAD, 21 (34.4%); and dyslipidemia, 27 (44.3%).

The medications used were as follows: acetylsalicylic acid and clopidogrel, all patients; beta-blockers, 44 (72.1%); calcium channel blockers, 12 (19.7%); angiotensin-converting-enzyme inhibitor, 27 (44.2%); and angiotensin receptor blocker, 21 (34.4%). Of the diabetic patients studied (21.3%), only six used intermediate-acting insulin.

All patients had sinus rhythm before the procedure. The mean heart rate was 71 ± 13.3 bpm (range, 49-120 bpm). Six patients (9.8%) had right bundle-branch block; five (8.2%), left bundle-branch block; and one (1.6%), left anterior hemiblock. Three patients (4.9%) had arrhythmias, as follows: two patients had atrial fibrillation with spontaneous reversion; one patient had transient Mobitz type 2 second-degree atrioventricular block.

Patients' variables related to the procedure

Thirty-four patients (55.7%) underwent bare-metal stent implantation, and the others, sirolimus-eluting stent implantation. Pre-dilatation was performed in 39 patients (63.9%), and post-dilatation in 33 (54.1%). The coronary

Table 1 – Patients' clinical characteristics

Variables	Mean	Standard deviation	Minimum value	Maximum value
Age (years)	64.0	10.6	40	84
SBP (mm Hg)	138.1	20.6	90	190
DBP (mm Hg)	84.6	10.4	60	100
HR (bpm)	71.2	13.3	49	120
RR (bpm)	18.3	1.6	16	24
BMI (kg/m²)	25.9	3.2	18.4	34

HR: heart rate; RR: respiratory rate; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

arteries approached were as follows: right, 21 patients (34.4%); anterior descending, 28 (45.9%); circumflex, 9 (14.8%); and left main coronary artery, 3 (4.9%). In 40 patients (65.6%), the proximal segment of the vessel was the target of the procedure. Precordial pain during stent implantation was reported as follows: no pain, 29 patients (47.5%); mild pain, 17 (27.9%); moderate pain, 7 (11.5%); moderately severe pain, 2; maximally severe pain, 1 patient. Four patients required a second vessel to be approached. Table 2 shows the hemodynamic variables and those of the procedure.

Spectral analysis of heart rate variability related to the procedure

The values shown in Tables 3, 4 and 5 were obtained by use of spectral analysis. Non-parametric Wilcoxon test was used to compare the values of the spectral analysis components before, during and after stent implantation, considering the first stent and the vessel. As shown in those tables, there was an increase in the LF and HF components during stent implantation, and a reduction after that. The logarithmic transformation of those components was performed, and the same *p* value was obtained.

Analysis of the association and correlation between variables

The spectral analysis of HRV before stent implantation showed no association with the following: presence of diabetes mellitus; family history; CAD presentation; beta-blocker use; age; vessel approached or its segment. That analysis used the Mann-Whitney and Kruskal-Wallis tests, and the results are shown in Table 6.

Regarding the type of stent (bare-metal or drug-eluting), no association with the following was observed: sex; diabetes mellitus; positive family history; CAD presentation; pain scale; and vessel approached. The chi-square test was used. The proportions of patients undergoing bare-metal and drug-eluting stent implantation with diabetes mellitus and on beta-blockers were 15% and 29%, and 68% and 78%, respectively. By using the Mann-Whitney test, no influence of age was observed on the following: blood pressure levels; heart rate, body mass index; and stent type.

Comparing the spectral analysis of HRV according to the type of stent, the differential of the magnitude of the alteration in the LF and HF components, during and before stent implantation, was similar between the groups of patients undergoing bare-metal and drug-eluting stenting. However, when using univariate analysis (Mann-Whitney test), the LF component during stent implantation was significantly greater in the group of patients undergoing bare-metal stenting (Table 7).

Pearson coefficient between age and spectral analysis of HRV during stent implantation was 0.07 ($p = 0.55$) for the LF component, 0.13 ($p = 0.29$) for the HF component, and −0.10 ($p = 0.40$) for the LF/HF ratio. In addition, when applying the Pearson coefficient, the spectral analysis of HRV during the procedure showed no correlation with the following: blood pressure levels; heart rate; respiratory rate; duration of occlusion; characteristics of the balloon and of the stent; and the hemodynamic variables of PCI.

Discussion

Recent studies, assessing the ANS of patients after acute myocardial infarction or with acute ischemic chest pain by use of HRV, have identified, in addition to T-wave *alternans* and heart rate turbulence, those at high risk for fatal arrhythmic events and other complications; in addition, they have reported that the autonomic dysfunction or inadequate recovery of HRV after acute ischemia is an important predictor of adverse events[17-19]. The importance of HRV analysis during coronary artery stent implantation has not been investigated, but this study showed sympathetic and parasympathetic activation of different magnitudes during that endoprosthesis implantation. In addition, and avoiding biases, no influence of the variables reported in the literature as capable of altering HRV, such as age, sex, respiratory cycle, blood pressure levels, use of medications and conditions resulting in autonomic dysfunction, was observed[20-22]. Such finding can be explained by the fact that the reduction in HRV, mainly of the parasympathetic nervous system, occurs after the age of 50 years and with no difference between the sexes after the age of 60 years. The patients in the present study had a mean age of 64 years and an almost equal distribution of sexes. The general characteristics of this case series, such as mean age, proportion of male patients and risk factors for CAD, are in accordance with those in the literature, except for the higher proportion of systemic arterial hypertension[4,23].

Table 2 – Hemodynamic variables and of the percutaneous coronary intervention procedure

Variables	Mean	Standard deviation	Minimum value	Maximum value
Occlusion time (min)	1.03	3.2	0.5	3
Balloon diameter (mm)	2.44	0.23	2	3
Balloon length (mm)	17.7	4.03	10	25
ATM	12.4	2.6	8	16
Stent diameter (mm)	3.02	0.36	2.25	4
Stent length (mm)	23.6	6.21	13	39
Stent occlusion time (min)	1.11	0.3	1	2
ATM of the stent	16.0	1.8	12	20
Number of stents	1.5	0.8	1	5
Occlusion time in post-dilatation	1.0	0.5	0	2

ATM: pressure during balloon inflation in atmospheres; ATM of the stent: pressure during stent implantation in atmospheres; min: minutes; mm: millimeters; occlusion time: duration of coronary occlusion in pre-dilatation; stent occlusion time: duration of coronary occlusion during stent implantation; occlusion time in post-dilatation: duration of coronary occlusion in post-dilatation with balloon.

Table 3 – Spectral analysis of heart rate variability before and during stent implantation

Variables	Before (mean)	During (mean)	p value
LF (ms²)	185.7	658.4	0.000
HF (ms²)	121.8	322.8	0.000
LF/HF	9.6	12.2	0.098

HF: high-frequency component of HRV; LF: low-frequency component of HRV; HRV: heart rate variability.

Table 4 – Spectral analysis of heart rate variability before and after stent implantation

Variables	Before	After	p value
LF (ms²)	185.7	220.1	0.771
HF (ms²)	121.8	114.0	0.504
LF/HF (ms²)	9.6	14.9	0.165

HF: high-frequency component of HRV; LF: low-frequency component of HRV; HRV: heart rate variability.

Table 5 – Spectral analysis of heart rate variability during and after stent implantation

Variables	During	After	p value
LF (ms²)	658.4	220.1	0.000
HF (ms²)	322.8	114 .0	0.000
LF/HF (ms²)	12.2	14.9	0.675

HF: high-frequency component of HRV; LF: low-frequency component of HRV; HRV: heart rate variability.

To avoid other interpretation biases, patients using antiarrhythmic drugs were excluded from the present study. However, because of their need to use beta-blockers[1,2] and the prevalence of diabetes mellitus in that population with ischemic heart disease, those conditions were not excluded, and statistical treatment was performed, demonstrating no influence of those variables in the ANS behavior. In addition to the fact that most patients were on beta-blockers and 21.3% of them had diabetes mellitus, a similar proportion of patients with those conditions was observed in the groups undergoing bare-metal and drug-eluting stent implantation.

The studies on spectral analysis of HRV and acute coronary occlusion have not assessed the relationship between the ANS and the atherosclerotic disease location in coronary arteries[7-12]. Hayano et al[24] have reported an

Table 6 – Association between the variables and spectral analysis related to stent implantation

Variables	LF (ms²)	HF (ms²)	LF/HF
DM present	231.7	129.1	6.4
DM absent	173.2	119.9	10.5
p value	0.43	0.66	0.14
FH present	214.7	127.8	9.5
FH absent	170.5	118.7	9.7
p value	0.43	0.81	0.95
CAD clinical presentation			
Stable angina	206.7	127.6	9.2
Unstable angina	166.3	116.6	10
Post-AMI	211.1	127.7	9.6
p value	0.21	0.53	0.71
Use of BB			
Present	653.8	369.4	17.4
Absent	670.0	202.0	10.2
p value	0.49	0.97	0.24
Vessel approached			
Left coronary artery	201	120	9.8
Right coronary artery	158	123	9.7
p value	0.84	0.46	0.86
Proximal segment of the vessel	152	117.2	10.5
Medial segment of the vessel	253.5	128.4	8.2
p value	0.32	0.53	0.31

BB: beta-blocker; CAD: coronary artery disease; DM: diabetes mellitus; FH: family history; AMI: acute myocardial infarction; HF: high-frequency component of HRV; LF: low-frequency component of HRV.

Table 7 – Spectral analysis of heart rate variability according to the type of stent

Variables / stent type	Bare-metal	Drug-eluting	p value
Δ LF (ms²)	6.4	2.6	0.061
Δ HF (ms²)	3.0	0.6	0.257
LF during stent implantation (ms²)	864.5	398.7	0.002

Δ: difference in the values of HRV components between 'during' and 'before' stent implantation; HF: high-frequency component of HRV; LF: low-frequency component of HRV.

association between the reduction in cardiac vagal function and the angiographic severity of the coronary lesion, but no relationship with previous myocardial infarction, atherosclerotic disease location and ventricular function. Moore et al[5], however, have demonstrated that decreasing LF spectral power, measured in ms²/Hz, was independently associated with proximal right coronary artery stenosis greater than 75%, explaining that finding by the fact that such coronary artery is responsible for the sinus node supply, which would influence HRV. The present study showed no association between the vessel affected or its segment and spectral analysis, but a similar proportion of coronary impairment, as in the previously cited study[25], and no heart failure findings among patients.

Regarding the spectral analysis of HRV during myocardial ischemia, Manfrini et al[26] have reported sympathetic activation during spontaneous episodes of myocardial ischemia, with an increase in the LF/HF ratio; the opposite occurred during balloon-induced coronary occlusion, with a decrease in that ratio, in 14 patients with indication for coronary angioplasty. The severity of chest pain, the magnitude of the ST-T segment change and the coronary location were comparable between the spontaneous and balloon-induced forms of ischemia. The opposite response during balloon occlusion is attributed to baroreflex activity. Thus, spontaneous ischemia was accompanied by mechanisms that ignore vagal reaction or was secondary to them, which has not occurred during balloon occlusion.

Coronary artery occlusion can trigger several neural responses. Some are secondary to coronary mechanoreceptors, and others are due to stimulation of ventricular mechanoreceptors and chemoreceptors. The stimulation of mechanoreceptors can result from both an increase in coronary perfusion pressure and the stretch stimulus of the vessel wall, and can induce a decrease in the sympathetic reflex impulse. Conversely, the myocardial blood flow reduction and the ischemia resulting from coronary occlusion can stimulate those receptors and chemoreceptors, and increase activity in sympathetic efferent axons that excite the heart. The vagal fibers seem to exert a small action or none at all. Thus, in balloon-induced coronary occlusion, there is vagal predominance, which can represent a beneficial adaptive mechanism to increase coronary blood flow during myocardial ischemia. Conversely, when coronary perfusion is deficient, an increase in sympathetic activity occurs[27-29]. In the present study, an increase in the LF and HF components was observed, with no significant change in the LF/HF ratio, during stent implantation, as compared with the values of those variables before and after the procedure. Thus, we infer that coronary occlusion with stent implantation caused a predominance of parasympathetic activity via coronary baroreceptor stimuli in response to the stretch stimulus that follows balloon dilatation and endoprosthesis implantation. The reduction in myocardial perfusion related to the procedure-induced occlusion led to sympathetic activation.

The literature lacks studies assessing the spectral analysis of HRV in patients undergoing coronary stent implantation and studies comparing between the types of stent. Some studies assessing the autonomic alterations related to stent implantation for the treatment of carotid atherosclerotic disease[30-31] have detected an increase in the HF component and a decrease in the LF component of systolic blood pressure variability.

Thus, our results cannot be compared with those of studies on heart rate variability of patients undegoing coronary stenting, but only with those whose patients underwent coronary angioplasty[7-11,26]. Those studies have also demonstrated the dynamic pattern of HRV. However, the results are not homogeneous, showing an increase in the LF component during balloon inflation in half of the patients[11], an increase in the HF component in 34% of the patients[9], and a decrease in the LF/HF ratio[26]. In addition to different case series, with patients with spontaneous angina and/or submitted to coronary angioplasty, and different numbers of patients (14, 70 and 14, respectively), the methodology is also different, and not all HRV components have been always measured. The greater sympathetic activation during bare-metal stent implantation cannot be attributed to the anatomical characteristics of the stent or of the balloon, or even to the hemodynamic variables, because no statistical difference was observed. The endothelium-dependent vasomotor response, occurring hours after stent implantation[32] and mainly related to first-generation stents, was not assessed to explain that sympathetic response. Stent implantation triggers several biological responses, such as prosthesis-induced lesion, thrombus formation, inflammation and smooth-muscle cell proliferation, resulting in vasomotor dysfunction[13,33]. However, those responses are observed within 15-28 days, and the precise mechanisms of endothelial dysfunction remain unknown. The findings can have implications for the development of more appropriate prostheses, minimizing smooth-muscle cell proliferation[34]. In the present study, HRV analysis was performed concomitantly with stent implantation, when those biological responses would not have been triggered. Experimental and clinical studies are required to clarify the vascular changes, which cannot be attributed only to acute stent-induced lesion.

The study limitations are related to the small number of patients in each group, according to the type of stent and the vessel approached. In addition, the influence of ventricular function and of inflammation biomarkers was not assessed.

Conclusions

Coronary occlusion due to stent implantation resulted in sympathetic activation and concomitant vagal activation. The following variables showed no influence on HRV spectral analysis: sex; age; diabetes mellitus; blood pressure levels; respiratory rate; use of beta-blockers; and vessel approached or its segment. A higher increase in the LF component was observed during bare-metal stent implantation.

Author contributions

Conception and design of the research e Statistical analysis: Silva RMFL; Acquisition of data: Silva CAB, Greco OJ; Analysis and interpretation of the data: Silva RMFL, Silva CAB, Greco OJ, Moreira MCV; Writing of the manuscript: Silva RMFL, Silva CAB, Greco OJ; Critical revision of the manuscript for intellectual content: Silva RMFL, Moreira MCV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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