Original Paper

Systolic Heart Function, Kidney Filtration and the Number of Coronary Atherosclerotic Plaques in Lean and Overweight Patients

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Key Words

Cardiorenal syndrome • Atherosclerosis • Hypertension

Abstract

The objective of this study was to quantify the number of vessels with stenotic points in the coronary circulation of lean and overweight individuals submitted to coronary angiography and ventriculography to verify the possible associations with glomerular filtration and the systolic ventricular function. Eighty-six patients with a previous history of myocardial ischemia were studied. Two groups were formed: non-elderly (G1), $n = 38$, 52.8 ± 1.2 years old, and elderly (G2), $n = 48$, 70.1 ± 1.2 years old. Both groups were divided into 2 subgroups according to the estimated glomerular filtration rate (eGFR): ≥ 60 and < 60 ml/min/m². The results showed that G1 had 0.36 ± 0.11 versus 1.25 ± 0.45 stenoses/patient (≥ 60 vs. < 60 ml/min/m²; $p < 0.05$, respectively) and G2 had 0.91 ± 0.28 versus 1.83 ± 0.33 stenoses/patient (≥ 60 vs. < 60 ml/min/m², respectively). The other variables, such as central and brachial arterial blood pressures, did not manifest significant differences in relation to the eGFR. The following significant correlations were observed: between the quantity of coronary stenotic points and the eGFR ($R^2 = 11.2\%$; $r = -0.33$; $p < 0.001$), and between eGFR and the ventricular ejection fraction ($R^2 = 5.1\%$; $r = 0.57$; $p < 0.0001$). The ejection fraction correlated significantly with the number of vessels with stenoses in the coronary bed ($R^2 = 13.4\%$; $r = -0.36$; $p < 0.008$). In conclusion, although the correlations are considered weak, interrelationships between heart and kidney were demonstrated in this study.

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Introduction

The interactions between the cardiac and renal systems in acute and chronic pathological situations have been grouped together in the so-called cardiorenal syndrome (CRS). The CRS was divided into five types according to the organ initially affected and to the acute or chronic nature of the disease affecting it: type 1, presence of an acute cardiac dysfunction and, consequently, acute renal damage; type 2, chronic cardiac insufficiency leading to chronic renal dysfunction; type 3, acute renal disease promoting acute cardiac dysfunction; type 4, chronic renal disease leading to chronic cardiac dysfunction; and type 5, systemic conditions causing cardiac and renal dysfunction [1].

Regarding type 4 CRS, it has been demonstrated that even moderate reductions in glomerular filtration rate (GFR) correlate with high mortality percentages mostly caused by coronary ischemic events [2]. When compared to the public in general, patients with chronic kidney disease (CKD) are considered to be at high risk for the emergence of myocardial ischemic events, cardiac insufficiency and death from cardiovascular diseases (CVD) [3–5]. The prevalence of fatal events stemming from CVD reaches high levels in patients with terminal renal disease [6–8].

Thus, GFR is currently considered an independent risk factor predictive of CVD [9, 10]. On the other hand, risk factors considered to be traditional indicators of CVD, such as systemic arterial hypertension [11, 12], left ventricle hypertrophy, coronary diseases [13], and increases in LDL cholesterol are present during the progression of CKD [14, 15]. Renal disease and CVD share the same etiopathogenic risk factors, making it difficult to quantify the contribution of each factor to these interactions.

Systemic atherosclerosis could play an important role in the link between the kidney and cardiac dysfunction. A reduction in the GFR could worsen the cardiovascular ischemic events due to the presence of atherosclerotic plaques in the coronary circulation. The presence of these obstructions in the coronary vascular bed and their correlations with glomerular filtrations and cardiac systolic function have not yet been firmly established. The objective of this study was to quantify the number of vessels with stenoses bigger than 60% present in coronary circulation and to verify their possible association with the ventricular systolic function and glomerular filtration in patients who were submitted to coronary arteriography due to a previous history of myocardial ischemia.

Patients and Methods

This is a cross-sectional study of an initial population of 186 patients with or without a diagnosis of systemic arterial hypertension clinically suspected of having myocardial ischemia. These patients were being attended at medical clinics and were sent from there to the hemodynamic hospital sector to be submitted to a coronary angiography exam. All these patients had previous symptoms that were interpreted by doctors as being related to myocardial ischemia. For this study, they were also submitted to ventriculography. All the patients signed the statement of consent, and the protocol was approved by the Medical Ethics Committee of the Federal University of Uberlândia, Brazil. The diagnosis of high blood pressure levels was confirmed when the systolic arterial pressure (SBP) was ≥ 140 mm Hg and/or the diastolic pressure (DBP) was ≥ 90 mm Hg in at least 3 medical registers during the 3 months prior the beginning of this study. This was also the case when during this same period the patients had normal levels of systemic arterial pressure due to the use of antihypertensive drugs. The MDRD formula with 4 components [16], was used to determine the estimated GFR (eGFR). These values were obtained from the results of at least one serum creatinine exam registered on the patient's chart during the 3 months preceding the hemodynamic exam. Exclusion criteria were as follows: contraindications for the use of iodine contrast ($n = 32$); incomplete registers ($n = 4$); hospitalization during the previous 3 months for other comorbidities such as neoplasias and infectious diseases ($n = 2$); technical errors detected in coronary angiography and/or ven-

triculographic exams ($n = 1$), and hemodynamic instability ($n = 3$). Patients were also excluded when their body mass index (BMI) was >30 ($n = 50$) and when they had an eGFR >130 ml/min/m² ($n = 8$). After the exclusion criteria, 86 patients remained and they were divided into two groups: G1, under 60 years old, i.e. the non-elderly group ($n = 38$) and G2, 60 years old and upwards, i.e. the elderly group ($n = 48$). Each of these groups was divided according to eGFR: <60 ml/min/m² (G1: $n = 8$; G2: $n = 24$) or ≥ 60 ml/min/m² (G1: $n = 30$; G2: $n = 24$).

Before the exam, the patients answered a questionnaire about their habits, clinical symptoms, pre-existing illnesses and the medicines they were taking. Brachial measurements of arterial SBP and DBP were performed using an oscillometric device, (HEM 431-C; Omron, Kyoto, Japan), connected to the left or right upper arm. The brachial arterial blood pressures in this study were registered at the same moment as the central SBP and DBP were obtained at the root of the aorta during the hemodynamic study. The SBP index was calculated by multiplying the brachial SBP values by the number of antihypertensive drugs used by patients. The abdominal waist was measured with a measuring tape.

For the coronary angiography study, radioscopy was used to place a catheter at the root of the aorta (Hicor Coroskop; Siemens, Germany). After the coronary angiography study, ventriculography was performed to determine the left ventricular ejection fraction (LVEF) using an infusion pump (Liebel Flarsheim, Germany). A 60-ml average of contrast (Pielograf 76%; Shering®, SP, Brazil) was injected into the ventricle. The LVEF was considered to be the difference in the size of the area determined by the contrast before and after ventricular ejection. In this study, stenosis was considered to be an obstruction of $\geq 60\%$ in the coronary lumen. During the exam, the number of coronary vessels with stenotic points in accordance with this criterion was quantified. The angiograms were performed by three independent physicians who visually rated the stenotic area. In case of disagreement, the software Quantcor CSF Coroscop (Siemens Medical Systems) was used. All physicians were blinded to the values of the eGFR of the patients. We considered the following vessels: left main coronary artery, anterior interventricular artery, circumflex artery and right coronary artery with their branches. The absence of stenotic coronary vessels was considered to be 0 points, one vessel = 1 point, two vessels = 2 points, three vessel = 3 points and four vessels = 4 points.

Statistical Analysis

Tests were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, Calif., USA; available at www.graphpad.com). The normality of the data was verified using the D'Agostino test, Student's *t* test was used for the groups with parametric distribution, and the Mann-Whitney test was used for nonparametric groups. The H1 hypothesis was that the number of vessels with stenotic points in patients with eGFR <60 ml/min/m² was greater than in groups with eGFR ≥ 60 ml/min/m². All these tests were performed one-tailed. Values of $p < 0.025$ were considered significant for comparisons between the groups (Bonferroni correction). The multiple regression tests (progressive stepwise regression) were performed to compare the influence between the variables. For these calculations, the BioEstat 5.0 was used and alpha error = 0.05 was determined as a decision level. The values are presented as means $\pm$ standard error.

Results

The clinical characteristics of the groups are shown in table 1. Table 2 shows the results of coronary angiography and ventriculography. When the number of stenosed vessels was considered as the dependent variable, we obtained for eGFR: $R^2 = 11.3\%$; ($r = 0.33$; $F = 10.6$; $p < 0.002$), and for age: $R^2 = 3\%$; ($r = 0.37$, $F = 6.9$; $p < 0.002$). When LVEF was the dependent variable, we obtained in relation to the number of stenosed vessels: $R^2 = 13.4\%$ ($r = 0.36$; $F = 13.0$; $p < 0.008$), and for age: $R^2 = 1.9\%$ ($r = 0.41$, $F = 5.6$; $p < 0.002$) (table 3). The number of vessels with stenotic points is represented in figures 1 and 2. G1 and G2 were quite homogeneous in their composition because no significant differences were noted regarding the number of male and female participants, smokers, or those using lipid-lowering drugs (table 1), nor in the systolic pressure index (table 2). The values of brachial and central SBP, DBP, and pulse pressure did not manifest any differences in the groups that were examined, nor was

Table 1. Clinical characteristics of patients (n = 86)

	G1			G2		
	<60 ml/min/m ²	≥60 ml/min/m ²	p value	<60 ml/min/m ²	≥60 ml/min/m ²	p value
Number	8	30		24	24	
Age, years	53.8 ± 1.5	51.8 ± 0.9	ns	70.4 ± 1.5	69.7 ± 1.3	ns
Females/males, n	3/5	14/16		9/15	10/14	
eGFR, ml/min/m ²	56 ± 2.5	92 ± 3.1*	<0.0001	53 ± 1.6	76 ± 1.6*	<0.0001
BMI	24.7 ± 1.0	25.3 ± 0.4	ns	25.1 ± 0.6	25.4 ± 0.6	ns
Abdominal waist F/M, cm	88.3 ± 3.3/95.2 ± 3.5	87.3 ± 3.2/89.0 ± 2.9	ns/ns	90.3 ± 3.2/91.0 ± 3.1	90.6 ± 2.9/86.6 ± 3.4	ns/ns
Smoker yes/no, n (%)	3/8 (37)	8/30 (26)	ns	2/24 (8)	3/24 (12)	ns
Diabetes yes/no, n (%)	2/8 (25)	6/30 (20)	ns	8/24 (33)	7/24 (29)	ns
Lipid-lowering drugs users, n (%)	4/8 (50)	17/30 (56)	ns	11/24 (45)	8/24 (33)	ns
Antihypertensive drugs, n	1.6 ± 0.3	1.6 ± 0.4	ns	1.5 ± 0.4	1.7 ± 0.3	ns

Values are presented as means ± SEM. ns = Not significant. * p < 0.025.

Table 2. Assessment of systemic hemodynamics and renal function (n = 86)

	G1			G2		
	<60 ml/min/m ²	≥60 ml/min/m ²	p value	<60 ml/min/m ²	≥60 ml/min/m ²	p value
Number	8	30		24	24	
Stenosis/patients	1.25 ± 0.45	0.36 ± 0.11*	0.004	1.83 ± 0.33	0.91 ± 0.28*	0.017
SBPb, mm Hg	140 ± 8.7	134 ± 3.8	0.23	142 ± 4.8	147 ± 4.2	0.25
DBPb, mm Hg	82 ± 3.2	80 ± 2.1	0.028	79 ± 3.3	88 ± 2.7	0.26
PPb, mm Hg	57 ± 6.2	53 ± 3.5	0.25	63 ± 4.6	59 ± 3.2	0.33
SBPc, mm Hg	155 ± 11.2	148 ± 4.6	0.26	157 ± 4.7	155 ± 5.9	0.42
DBPc, mm Hg	83 ± 1.8	85 ± 2.8	0.37	82 ± 2.0	80 ± 2.6	0.25
PPc, mm Hg	71 ± 10.2	63 ± 4.5	0.21	74 ± 4.1	75 ± 4.9	0.45
SBPIx	372 ± 50	357 ± 34	0.42	363 ± 27	403 ± 39	0.21
EF, %	62.5 ± 4.9	75.9 ± 2.3*	0.004	65.8 ± 4.0	74.0 ± 2.3	0.09

Values are presented as means ± SEM. SBPb = Brachial SBP; DBPb = brachial DBP; SBPc = central SBP; DBPc = central DBP; PPb = brachial pulse pressure; PPc = central pulse pressure; SBPIx = SBP index; EF = ejection fraction. * p < 0.025.

Table 3. Intensity of predictor variables (%) on the dependent variable

Variables	Independent			
	stenoses	eGFR	LVEF	age
Dependent				
Stenoses	n	11.3% (r = 0.33; F = 10.6; p < 0.002)	n	3.0% (r = 0.33; F = 10.6; p < 0.002)
eGFR	n	n	5.1% (r = 0.57; F = 15.7; p < 0.0000)	22.5% (r = 0.47; F = 24.2; p < 0.0000)
LVEF	13.4% (r = 0.36; F = 13.0; p < 0.0008)	n	n	1.9% (r = 0.41; F = 5.63; p < 0.0018)

n = Not performed; % = R².

Fig. 1. Number of vessels with stenotic points in non-elderly patients (G1).

Fig. 2. Number of vessels with stenotic points in elderly patients (G2).

there either a significant difference in the number of diabetic patients in the evaluated groups or a significant correlation between abdominal waist and the number of stenotic points ($p > 0.05$).

Discussion

In our study, after classifying the patients according to their GFR, we observed that patients with $\text{eGFR} < 60 \text{ ml/min/m}^2$ had a greater quantity of vessels with stenotic points in the coronary circulation both in older and younger patients (fig. 1 and 2). In multivariate analysis, the number of stenosed vessels was weakly influenced by glomerular filtration and by the patients' ages. However, the influence of eGFR on the number of stenosed vessels was almost 4 times greater than the influence of age in our sample; $R^2 = 11.3$ and 3.0% , respectively ($p < 0.001$).

The presence of a greater number of vessels with arteriosclerotic plaques in patients with reduced renal function accompanies the chronic loss of renal function. This fact is much more evident in patients in the final stages of CKD [23, 24]. Our data demonstrates, however, that this could also be a fact in the initial stages of CKD in hypertensive patients (fig. 1 and 2). From the physiopathological point of view, the metabolic syndrome with the activation of the sympathetic systems and of renin-angiotensin is also capable of promoting inflammatory vascular alterations which affect both the heart and the kidneys [25]. There is

ever greater evidence that inflammation plays a very important role in starting the atherosclerotic process and arteriosclerosis itself is currently described as an inflammatory disease [26]. A high percentage of patients with CKD manifest serological evidence of the presence of an activated inflammatory response [27]. Thus, patients with moderate reductions in the GFR would have an increase in the production of inflammatory cytokines above and beyond the accumulation of advanced products of glucose degradation [28].

The interactions between heart and kidney are indicated by the renal perfusion flow which is intimately connected with ventricular systolic function [17]. However, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) did not find any correlation between the base renal function and the cardiac index, although all their patients had acute heart failure [18]. Other studies also failed to establish such a correlation [19, 20]. Our study, on the contrary, found a positive but weakly significant correlation between LVEF and eGFR (fig. 2). Our patients were hemodynamically stable, had normal LVEF (table 2) and did not have acute heart failure. This correlation between LVEF and eGFR found in our patients was probably due to the accuracy of the LVFE measurement obtained by ventriculography, which is considered the gold standard for such evaluation and which was not utilized in the other studies. Another possibility that was excluded from our study was the possible influence of obesity on renal function such as glomerular hyperfiltration [21, 22].

The mere number of these vessels with stenotic points in the coronary bed could not effectively reflect the severity of the ischemic episode and the consequent damage to the ventricular function. This happens because the size of the myocardial area affected by ischemia depends on the location of the obstruction and on the collateral circulation developed after the obstruction of the blood flow. We could assume that a greater number of vessels with stenotic points greater than 60% would reflect a larger area damaged by the myocardial ischemia. For example, a recent or former myocardium infarct could be a mechanism by which left ventricular dysfunction may occur; hibernation of myocardium is another and both could produce regional wall motion abnormalities. In our study, however, we were able to verify that the number of points had a weak but significant influence on LVEF and that the greater their number, the less was the LVEF of the patients (table 3). This correlation, although considered weak, favors the idea that ischemic episodes reported by patients before coronary angiographic studies may have promoted motility dysfunction of the ventricular wall.

Another link between cardiovascular and renal systems to be considered is the presence of arterial hypertension in the sample that was studied. The rise in blood pressure is an independent factor in the initiation of the atherosclerotic process, and it is present from the beginning of renal dysfunction. However, all the patients had similar blood-pressure levels both in the brachial and in the central measures (table 2). If we compare the number of antihypertensive drugs and the quantity of these drugs used for the reduction of systolic pressure values, G1 and G2 do not manifest significant differences. Thus, it is possible that the reduction of eGFR was one of the reasons for the increase in the quantity of obstructions detected in the coronary bed.

This paper has the methodological limitations of a cross-sectional study. The nature of the studied population limited our ability to test the strength of the association between the reduction of the renal function and the number of stenoses in the coronary bed. This was due to a lack of more detailed information about laboratorial data such as the glycemic and lipid profiles. Moreover, these patients were not tested for the presence of proteinuria. In the ambulatory, specific laboratorial setting, testing for the presence of albumin and proteinuria is normally performed only on diabetic patients.

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