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Circulating Lp-PLA2 is associated with high valvuloarterial impedance and low arterial compliance in patients with aortic valve bioprostheses

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ABSTRACT

Background: We previously reported that plasma Lp-PLA2 was associated with aortic valve disease progression and degeneration of bioprostheses. Low systemic arterial compliance and high valvuloarterial impedance (Z_{va}) are predictors of poor survival in patients with aortic valve disease. However, the prevalence of high Z_{va} after AVR is largely unknown and whether Lp-PLA2 could predict Z_{va} has not been documented. We investigated the relationships between plasma lipoprotein-associated phospholipase A2 (Lp-PLA2) mass and activity and valvuloarterial impedance (Z_{va}), an index of global LV hemodynamic load, in patients that underwent aortic valve replacement (AVR).
Methods: A total of 195 patients with aortic bioprostheses underwent echocardiographic assessment of the prosthetic aortic valve function 8 ± 3.4 years after AVR. Lp-PLA2 mass and activity were measured.
Results: In this group of patients, the mean Z_{va} was elevated (5.73 ± 1.21 mm Hg·ml^{-1}·m^2). In univariate analyses, Lp-PLA2 mass ($p = 0.003$) and Lp-PLA2 activity ($p = 0.046$) were associated with Z_{va}. After adjustment for covariates including age, gender, clinical risk factors, anti-hypertensive medications, body mass index and prosthesis size, Lp-PLA2 mass was associated with high Z_{va} (≥4.5 mm Hg·ml^{-1}·m^2) (OR: 1.29, 95%CI: 1.10–1.53; $p = 0.005$) and was inversely related with the systemic arterial compliance ($\beta = -0.01$, SEM = 0.003; $p = 0.003$).
Conclusions: An increased Z_{va}, an index of excessive hemodynamic load, was highly prevalent 8-year post-AVR and was independently related to circulating Lp-PLA2.

1. Introduction

Elderly patients with calcific aortic valve stenosis (CAVS) may also have arterial atherosclerosis as well as medial elastocalcinosis. Young subjects with a bicuspid aortic valve also commonly have reduced aortic elasticity as a result of structural abnormalities of the aortic wall and/or aortic dilation. Hence, it is not surprising that patients with (CAVS) often have reduced compliance in the large arterial circulation and thereby ensuing systolic hypertension. Hence, in patients with CAVS the LV often faces a double (valvular plus arterial) load and in these patients the occurrence of LV dysfunction, symptoms and adverse events should logically be related to the global hemodynamic burden faced by the ventricle. We previously proposed to calculate the valvulo-arterial impedance (Z_{va}) to assess the global (valvular + arterial) LV hemodynamic load in CAVS patients [1]. This parameter provides an estimate of the cost in mm Hg for each systemic mL of blood indexed for body size pumped by the left ventricle. Values of $Z_{va} > 4.5$ mm Hg·ml^{-1}·m^{-2} indicate increased global LV hemodynamic load [1]. The Z_{va} has been shown to be superior to the standard parameters of AS severity (i.e., gradients and EOA) in predicting LV dysfunction and patient clinical outcomes [1].

Recently, we have documented that lipoprotein-associated phospholipase A2 (Lp-PLA2) was highly expressed in the aortic valves of patients with CAVS as well as in aortic bioprostheses explanted for a dysfunction [2,3]. Lp-PLA2 is transported by lipoproteins in circulation and is also produced by macrophages in atherosclerotic plaques, mineralized aortic valves and explanted aortic bioprostheses [2–4]. Lp-PLA2 produces lysophosphatidylcholine (LysoPC), which promotes inflammation and mineralization of the aortic valve and aorta [2,5,6]. In addition, circulating Lp-PLA2 is an independent predictor of the hemodynamic deterioration of aortic bioprostheses [3]. Also, we showed that blood plasma Lp-PLA2 was independently associated with a faster progression of CAVS [7]. Recently, a small study has also highlighted that circulating Lp-PLA2 was independently associated with an elevated pulse wave velocity, a marker of aortic rigidity, in a group of patients with prehypertension [8]. Hence, we hypothesized that Lp-PLA2 mass

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and/or activity could be associated with a reduced arterial compliance and an increased valvuloarterial impedance in patients that have undergone aortic valve replacement (AVR).

2. Methods

2.1. Study patients

From June 2008 to June 2010, 203 consecutive patients with a bioprosthesis in the aortic position were prospectively recruited for this cross-sectional study that included a Doppler-echocardiography and a blood sample. The protocol was approved by the Institut Universitaire de Cardiologie et de Pneumologie de Québec ethical committee and written informed consent was obtained from the subjects. For this study, 8 patients had incomplete echo data to calculate Z_{va} and were excluded leaving 195 patients for the analyses. The baseline characteristics of this cohort were previously reported in [2,3] and summarized in Table 1. All patients underwent isolated AVR procedure at the Quebec Heart & Lung Institute. Exclusion criteria were as follows: (1) Presence of >mild paravalvular regurgitation; (2) significant concomitant mitral valve disease, defined by >mild mitral regurgitation or mitral valve effective orifice area (EOA) <1.5 cm^2; (3) subvalvular flow acceleration precluding measurement of blood pressure valve EOA; (4) LV systolic dysfunction defined by a LV ejection fraction <50%; and (5) congestive heart failure with New York Heart Association (NYHA) Class III or IV. All patients recruited in the study had a clinical examination, a complete plasma glycemic and lipid profile, and a complete Doppler echocardiographic examination.

2.2. Echocardiographic measurements

All patients underwent a complete comprehensive echocardiography with assessment of prosthesis hemodynamic. Peak transprosthetic flow velocity was determined by continuous-wave Doppler. Mean transprosthetic gradient was calculated using the modified Bernoulli equation. Bioprosthetic valve EOA was calculated using the standard continuity equation. The absolute and annualized changes in mean gradient and EOA were calculated as follows: absolute change = (value at last follow-up echo − value at 1-year postop echo) annualized change = (value at last follow-up echo − value at 1-year postop echo) / time between 1 year and last follow-up echocardiographic exams. Patient-prosthesis mismatch (PPM) was defined as not clinically significant (i.e mild or no PPM) if the indexed EOA was >0.85 cm^2/m^2, moderate if it was >0.65 cm^2/m^2 and ≤0.85 cm^2/m^2, and severe if it was ≤0.65 cm^2/m^2. LV minor axis internal dimension (LVID), posterior wall thickness (PWT), and inter-ventricular septal thickness (IVST) were measured at end-diastole according to the recommendations of the American Society of Echocardiography [9]. The relative wall thickness (RWT) was calculated by dividing the sum of the LV posterior wall and inter-ventricular septal thicknesses by the LV internal dimension (RWT = [PWT + IVST] / LVID). Left ventricular mass was calculated with the corrected formula of the American Society of Echocardiography and was indexed to a 2.7 power of height [9]. As a measure of global LV hemodynamic load, we calculated the valvulo-arterial impedance: $Z_{va} = (SBP + \Delta P_{mean}) / SVi$ where SBP is the systolic blood pressure, ΔP_{mean} the mean transvalvular gradient, and SVi is the stroke volume indexed to a 2.04 power of height [1]. The systemic arterial compliance was calculated by using the ratio of stroke volume index to pulse pressure. Energy loss index was measured as (aortic area × prosthetic valve area) / [aortic area − prosthetic aortic valve area] × body surface area [10]. The aortic area was measured at the sinotubular junction. Structural valve failure was defined as previously described [3].

Table 1
Clinical characteristics of patients.

Variables	Total (n = 195)	Low Z_{va} < 4.5 (n = 29)	High Z_{va} ≥ 4.5 (n = 166)	p
Age (y)	76 ± 8	77 ± 8	75 ± 8	NS
Male gender	138 (71)	20 (69)	118 (71)	NS
Body mass index (kg/m^2)	28.2 ± 5	30.0 ± 6	27.9 ± 5	0.04
Waist circumference (cm)	99 ± 14	102 ± 22	98 ± 12	NS
Follow-up time (yrs)	8.0 ± 3.4	8.7 ± 3.3	7.9 ± 3.4	NS
Risk factors				
Hypertension	138 (71)	22 (76)	116 (70)	NS
Diabetes	42 (22)	6 (21)	36 (22)	NS
Obesity (BMI ≥ 30)	51 (26)	13 (45)	38 (23)	0.02
History of hypercholesterolemia	152 (78)	22 (76)	130 (78)	NS
History of smoking	121 (62)	17 (59)	104 (63)	NS
Coronary artery disease	93 (47)	15 (52)	78 (47)	NS
Medications				
Statin	43 (22)	6 (21)	37 (22)	NS
ACEi	62 (32)	11 (38)	51 (31)	NS
ARB	52 (27)	10 (35)	42 (25)	NS
Calcium channel blocker	58 (30)	12 (41)	46 (28)	NS
β-Blocker	91 (47)	11 (38)	80 (48)	NS
Diuretics	82 (42)	7 (24)	75 (45)	0.03
Operative data				
Stented bioprosthesis	138 (71)	19 (66)	119 (72)	NS
Porcine bioprosthesis	133 (68)	23 (79)	110 (66)	NS

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; Values are expressed as means ± SD or n (%).

2.3. Clinical and operative data

Previous and current medical history included history of smoking, documented diagnoses of hypertension (patients receiving antihypertensive medications or having known but untreated hypertension [blood pressure ≥140/90 mm Hg]), diabetes (fasting glucose ≥7 mmol/l), hypercholesterolemia (patients receiving cholesterol-lowering medication or, in the absence of such medication, having a total plasma cholesterol level >6.2 mmol/L) coronary heart disease (history of myocardial infarction or coronary artery stenosis on coronary angiography), renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.73 m^2), and detailed information on current medication were collected. Body weight, height and waist circumference were measured following standardized procedures. Blood pressure, heart rate and NYHA class were also assessed. Operative data including model and size of bioprosthetic valves were also recorded.

2.4. Laboratory data

Overnight fasting plasma was collected and immediately processed by the laboratory for the measurement of glucose, total cholesterol, low density-cholesterol (LDL), high density-cholesterol (HDL), and triglyceride (TG) levels. LDL-cholesterol (LDL-C) was calculated with the Friedewald formula when triglyceride levels ≤5.0 mmol/l. No patient had triglyceride levels ≥5.0 mmol/l. Apolipoprotein A-I (Apo A-I) and Apolipoprotein B (ApoB) concentrations were measured by a nephelometric method using polyclonal antibodies on the Behring BN-ProsPect (Dade–Behring). Plasma ox-LDL was measured by sandwich ELISA with the monoclonal antibody 4E6 (Mercodia) directed against the modified apoB-100 of ox-LDL. The test was conducted according to the manufacturer instructions and optical density was read at 450 nm. Results were expressed as units per liter (U/l). Plasma Lp-PLA2 activity was measured by a colorimetric activity method (Cayman). The level of Lp-PLA2 activity in nmol/min/ml was calculated from the absorption curve (410 nm). The assay was carried out in duplicate. Plasma Lp-PLA2 mass was determined by ELISA kit R&D systems according to manufacturer instructions.

2.5. Statistical analyses

Results are expressed as mean ± SD and compared using unpaired Student's tests. Categorical data were expressed as a percentage