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ORIGINAL ARTICLE

Observational Study

Association of arterial stiffness with coronary flow reserve in revascularized coronary artery disease patients

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Abstract

AIM: To investigate the association of arterial wave reflection with coronary flow reserve (CFR) in coronary artery disease (CAD) patients after successful revascularization.

METHODS: We assessed 70 patients with angiographically documented CAD who had undergone recent successful revascularization. We measured (1) reactive hyperemia index (RHI) using fingertip peripheral arterial tonometry (RH-PAT Endo-PAT); (2) carotid to femoral pulse wave velocity (PWVc-Complior); (3) augmentation index (AIx), the diastolic area (DAI%) and diastolic reflection area (DRA) of the central aortic pulse wave (Arteriograph); (4) CFR using Doppler echocardiography; and (5) blood levels of lipoprotein-phospholipase A_2 (Lp-PLA_2).

RESULTS: After adjustment for age, sex, blood pressure parameter, lipidemic, diabetic and smoking status, we found that coronary flow reserve was independently related to AIx (b = -0.38, r = 0.009), DAI (b = 0.36, P = 0.014), DRA (b = 0.39, P = 0.005) and RT (b = -0.29,

P = 0.026). Additionally, patients with CFR < 2.5 had higher PWVc (11.6 ± 2.3 *vs* 10.2 ± 1.4 m/s, *P* = 0.019), SBPc (139.1 ± 17.8 *vs* 125.2 ± 19.1 mmHg, *P* = 0.026), AIx (38.2% ± 14.8% *vs* 29.4% ± 15.1%, *P* = 0.011) and lower RHI (1.26 ± 0.28 *vs* 1.50 ± 0.46, *P* = 0.012), DAI (44.3% ± 7.9% *vs* 53.9% ± 6.7%, *P* = 0.008), DRA (42.2 ± 9.6 *vs* 51.6 ± 11.4, *P* = 0.012) and LpPLA2 (268.1 ± 91.9 *vs* 199.5 ± 78.4 ng/mL, *P* = 0.002) compared with those with CFR ⩾ 2.5. Elevated LpPLA2 was related with reduced CFR (*r* = -0.33, *P* = 0.001), RHI (*r* = -0.37, *P* < 0.001) and DRA (*r* = -0.35, *P* = 0.001) as well as increased PWVc (*r* = 0.34, *P* = 0.012) and AIx (*r* = 0.34, *P* = 0.001).

CONCLUSION: Abnormal arterial wave reflections are related with impaired coronary flow reserve despite successful revascularization in CAD patients. There is a common inflammatory link between impaired aortic wall properties, endothelial dysfunction and coronary flow impairment in CAD.

Key words: LpPLA2; Coronary artery disease; Arterial stiffness; Coronary flow reserve; Reactive hyperemia index

Core tip: The present study is a contribution to investigate the association between the abnormalities in arterial wave reflections and coronary flow reserve. We demonstrated that augmentation of the systolic component of the central aortic pulse wave instead of diastolic is related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Furthermore, endothelial dysfunction as assessed by reactive hyperemia index and an inflammatory process as assessed by increased levels of lipoprotein-associated Phospholipase A_2 are related with increased arterial stiffness and abnormal wave reflections in coronary artery disease patients.

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INTRODUCTION

Atherosclerosis is a complex process with many faces which include impaired coronary microcirculatory function, endothelial dysfunction, increased arterial stiffness and discrete plaque formation within epicardial coronary tree.

The measurement of peripheral vasodilator response using fingertip peripheral arterial tonometry (PAT) provides a useful method for assessing arterial endothelial function[1-3]. Previous studies have shown an independent association of reactive hyperemia (RH-PAT) index with coronary endothelial function[3] and cardiovascular risk in patients with coronary artery disease (CAD)[4].

Coronary flow reserve assessed by Doppler echocardiography (CFR) is a reliable, non-invasive method to identify epicardial coronary patency as well as coronary microcirculatory integrity[5-8]. The scaling values of decreasing CFR constitute a comprehensive indicator of cardiovascular risk even in the presence of critical epicardial coronary stenosis[6].

Pulse wave velocity (PWV)[9] a valid marker of arterial stiffness, is independently related with the impairment of coronary microcirculation as assessed by CFR in patients with CAD[10,11]. Increased arterial stiffness causes an early arrival of wave reflection in systole instead of diastole and thus reduces coronary perfusion. Augmentation index (AIx), aortic diastolic reflection area (DRA) and index (DAI), derived by pulse wave analysis, are non-invasive markers of wave reflections[9,11-13]. However, the association between the abnormalities in wave reflections and coronary flow reserve in CAD patients after successful revascularization has not been fully investigated.

Lipoprotein-associated Phospholipase A_2 (Lp-PLA_2) is an inflammatory biomarker related with endothelial dysfunction, carotid atherosclerosis, impaired coronary flow reserve and increased arterial stiffness in CAD patients[14]. However its association with abnormal wave reflections has not been clarified.

In the present study we hypothesized that abnormal arterial wave reflections may determine coronary flow reserve. Thus, we examined the association of abnormal wave reflections, as assessed by AIx, DRA and DAI with coronary flow reserve using Doppler echocardiography after successful revascularization in CAD patients. Finally we examined the association of wave reflection with endothelial dysfunction as assessed by RHI and with inflammatory process assessed by circulating levels of LpPLA2.

MATERIALS AND METHODS

Study population

We enrolled 70 patients (84.3% men, mean age 60.2 ± 9.8 years) with (1) exercise- and/or stress-related angina (2) evidence of reversible ischemia during stress echocardiography or thallium scintigraphy (3) stenosis of ⩾ 50% in the left main coronary artery and or ⩾ 70% in one or several of the major coronary arteries before inclusion in the study as defined in the ESC guidelines[15] (Table 1). All the patients had undergone successful revascularization (PCI, *n* = 64 or CABG, *n* = 6) into their LAD within a year before inclusion in the study. PCI was considered successful when there was remained reduction in the caliber of the stenotic artery to < 20%

Table 1 Clinical, biochemical and vascular markers of the study population

Variables	Values (n = 70)
Clinical	
Age (yr)	60.2 ± 9.8
Gender (males), *n* (%)	59 (84.3)
Hypertension, *n* (%)	38 (54.2)
DM, *n* (%)	23 (32.8)
Dyslipidemia, *n* (%)	57 (81.4)
Smoking, *n* (%)	43 (61.5)
FH of CAD, *n* (%)	25 (35.7)
SBP (mmHg)	128 ± 18
DBP (mmHg)	77 ± 10
Medications	
ASA *n* (%)	70 (100)
Nitrates *n* (%)	38 (54.3)
ACEIs/ARBS *n* (%)	59 (84.2)
CCBs *n* (%)	12 (17.1)
Statins *n* (%)	65 (92.8)
β-blockers *n* (%)	60 (85.5)
Biochemical	
Chol (mg/dL)	198.8 ± 40.8
TG (mg/dL)	148.2 ± 79.9
HDL (mg/dL)	40.9 ± 11.4
LDL (mg/dL)	134.5 ± 35.9
Glu (mg/dL)	106.5 ± 32.5
CRP (mg/L)	2.44 ± 1.66
Lp-PLA$_2$ (ng/mL)	231.9 ± 90.9
Vascular markers	
CFR	2.65 ± 0.94
RHI-PAT	1.37 ± 0.43
PWVc (m/s)	10.32 ± 2.39
AIx (%)	35.8 ± 15.4
SAI (%)	50.6 ± 8.7
DAI (%)	49.4 ± 8.7
DRA	45.4 ± 12.6
RT (ms)	115.1 ± 22.5
SBPc (mm Hg)	133.2 ± 19.6
DBPc (mmHg)	83.3 ± 12.4

FH: Family history; CAD: Coronary artery disease; DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ASA: Acetylsalycilic acid; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptors blockers; CCBs: Calcium channel blockers; Chol: Total cholesterol; TG: Triglycerides; LDL: Low density; HDL: High density lipoprotein; FPG: Fasting plasma glucose; CRP: C-reactive protein; Lp-PLA$_2$: Lipoprotein-phospholipase A$_2$ patients with multivessel coronary artery disease before revascularisation; CFR: Coronary flow reserve; PWVc: Pulse wave velocity as measured with complior apparatus; AIx: Augmentation index; SAI: Systolic area index; DAI: Diastolic area index; DRA: Diastolic reflection area; RT: Return time; SBPc: Central systolic blood pressure.

with a final TIMI flow grade 3 without side branch loss, flow-limiting dissection, or angiographic thrombus (as visually assessed by angiography[16]). All participants attended our preventive medicine laboratory. Using valid questionnaire, we recorded pharmaceutical regimens and other cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, family history of CAD).

Exclusion criteria were: The presence of acute infection, malignancy, chronic heart failure (class NYHA Ⅲ and Ⅳ), chronic obstructive pulmonary disease, recent major surgery, and severe chronic auto-immune diseases, liver and renal impairment. We also excluded patients with recent (within 6 mo) acute cardiovascular events.

Blood sampling for measurement of Lp-PLA$_2$ was performed on the morning before we performed echocardiography and vascular tests in all patients.

The study protocol was approved by the Local Ethics Committee, conducted in compliance with the Declaration of Helsinki and written informed consent was obtained from all patients before study entrance.

Peripheral arterial tonometry

Measurement of peripheral vasodilator response with fingertip peripheral arterial tonometry (PAT) technology (EndoPAT; Itamar Medical Ltd, Caesarea, Israel) is increasingly being used as an alternative measure of endothelium-dependent dilation in response to reactive hyperemia[3]. The EndoPAT device records digital pulse wave amplitude (PWA) using fingertip plethysmography and consists of two finger-mounted probes, which include a system of inflatable latex air-cushions within a rigid external case. A blood pressure cuff is placed on one upper arm (study arm), while the contralateral arm serves as a control (control arm)[2]. PWA is measured continuously during three phases: A quiet baseline period, 5-min forearm occlusion (with inflation of the arterial pressure cuff to supra-systemic pressure), and reactive hyperemia following cuff release.

The reactive hyperaemia index (RHI) is calculated as follows: The ratio of the average amplitude of the PAT signal over a 1-min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of a 3.5 min time period before cuff inflation (baseline)[3]. The result is further divided by the same ratio from the control arm, which allows the device to account for potential effects of systemic changes in vascular tone during testing. The final ratio is then multiplied by a proprietary baseline correction factor.

The reactive hyperemia index (RHI) measures nitric-oxide dependent changes in vascular tone[17]. An RHI < 1.35 has been related with impaired coronary endothelial function[3]. All studies were stored digitally and were analyzed by personnel blinded to clinical and laboratory data, using a computerized station.

Pulse waveform analysis

Assessment of arterial wave reflections was performed non-invasively with the commercially available Arteriograph apparatus (TensioMed Budapest Hungary, Ltd) by analysis of the oscillometric pressure curves registered on the upper arm with a single pressure cuff. The principle of the oscillometric method is based on plethysmography and registers oscillometric pulsatile pressure changes in the brachial artery[18]. An upper arm cuff was applied to the patient and after a first simple BP measurement, the cuff was over-inflated with 35-40 mmHg beyond the systolic BP. During systole, the blood volume having been ejected into the aorta generates pulse wave (early systolic peak, P1). This pulse wave runs down and reflects from the bifurcation of aorta, creating a second wave (late systolic peak, P2). Both early and late systolic peak were

obtained and recorded on the computer as pulse waves. The software of Arteriograph decomposes the early, late systolic and diastolic waves and also determines the onset and peaks of the waves, measuring noninvasively and other hemodynamic parameters as central systolic and diastolic blood pressure (SBPc, DBPc mmHg), augmentation index (AIx%), return time (RT in sec.) of the wave reflection, systolic area index (SAI%), diastolic area index (DAI %) and diastolic reflection area (DRA)[18].

The AIx is defined as the ratio of the difference between the second (P_2, appearing because of the reflection of the first pulse wave) and first systolic peaks (P_1 induced by the heart systole) to pulse pressure (PP), and it is expressed as a percentage of the ratio [Aix = 100 × (P_2-P_1)/PP]. DRA is derived by duration of the diastole and the area between the expected (theoretical) diastolic pressure curve without reflection and the truly measured diastolic curve with reflection and reflects the quality of the coronary arterial diastolic filling. SAI and DAI are the areas of systolic and diastolic portions under the pulse wave curve of a complete cardiac cycle, respectively. Thus, the higher the DAI and DRA are, the better the coronary perfusion is. Furthermore, RT is the time of the pulse wave travelling from the aortic root to the bifurcation and back, so this value is smaller as the aortic wall is stiffer[18].

All studies were stored digitally and were analyzed by personnel blinded to clinical and laboratory data, using a computerized station.

Echocardiography

Studies were conducted using a Vivid 7 (GE Medical Systems, Horten Norway) phased array ultrasound system using second harmonic imaging. Dr Ignatios Ikonomidis, counting more than 5500 CFR echo studies the last 10 years, has performed the echocardiographic examinations and the CFR measurements for this study[5,8,14]. All studies were stored digitally and were analyzed by two observers blinded to clinical and laboratory data, using a computerized station (Echopac GE, Horten Norway). All patients had adequate quality of images for analysis.

Coronary flow reserve

We assessed transthoracic Doppler Echocardiographic-derived coronary flow reserve by obtaining the color-guided pulse-wave Doppler signals. In the long axis apical projections using a 7 MHz transducer, we recorded the maximal velocity and velocity-time integral in the distal LAD at baseline and during hyperaemic conditions after the intravenous administration of adenosine (0.14 mg/kg per minute)[5-8] for 3 min. Measurements of three cardiac cycles were averaged. CFR was calculated as the ratio of hyperemic to resting maximal diastolic velocity. The feasibility of the method was greater than 98% for all indices in our study cohort (initially 71 patients were recruited, but one patient was excluded due to unfeasible CFR study).

The mean CFR value of our cohort (< 2.5) was used for subgroup analysis after previously published cutoff values for impaired CFR in CAD patients[6,19].

PWV measurement

The carotid-femoral PWV (PWVc) was assessed by measuring the pulse transit time and the distance travelled between the two recording sites. For pulse wave recording we used a validated noninvasive device (Complior SP®, Alam Medical, France) with capability of online wave recording. A simultaneous recording was performed by two pressure-sensitive transducers of two different pulse waves based over the right common carotid artery and the right femoral artery, respectively. Measurement of the distance between the transducers over the body surface allowed obtaining PWVc. Measurements were performed by a single observer, blinded to clinical and laboratory data, and the whole procedure has been internally validated in our laboratory[8,20].

Lp-PLA$_2$ levels

Serum levels of Lp-PLA$_2$ were measured in our biochemistry laboratory with a commercially available enzyme-linked immunoassay (ELISA) (PLAC test, diaDexus, Inc, San Francisco, CA) with minimum detection limit of 0.34 ng/mL[14]. The inter- and intra assay variations were < 5% and 8%. An Lp-PLA$_2$ concentration of 235 ng/mL has been suggested to use as a clinical decision threshold[21]. Analyses were performed by personnel blinded to clinical and laboratory data.

Statistical analysis

All variables are expressed as mean ± SD. Statistical analysis was performed using SPSS 21.0 statistical software package (SPSS Inc, Illinois, United States). Categorical data were analysed using the standard chi-square test. Variables were tested by the Kolmogorov-Smirnov test to assess the normality of distribution. Parameters without normal distribution were transformed into ranks for further analysis. Patients were categorised into equal subgroups, according to the median value of CFR in our study cohort. Mean values of continuous variables were compared between groups using unpaired Student's *t*-test or the Mann-Whitney *U*-test, where applicable.

Simple linear regression was used to investigate relations between variables. Multiple linear relations were checked by multiple linear regression analysis using forward or backward procedure. Associations are presented by means of standardized regression coefficient (b). All covariates included in the final models were tested for interactions. Tolerance values for each covariate was > 0.5 in the multivariate models.

RESULTS

Study population characteristics

Clinical and biochemical characteristics of our study

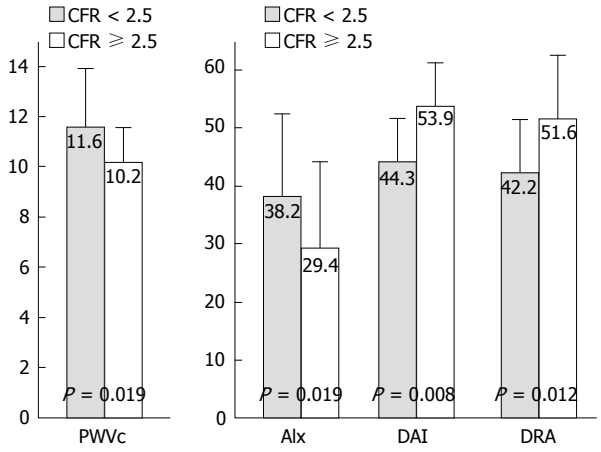

Figure 1 Graphic representation of the differences in pulse wave velocity (m/s), augmentation index (%), diastolic area (%) and diastolic reflection area (%) between patients with reduced coronary flow reserve (< 2.5) and patients with preserved coronary flow reserve (⩾ 2.5). CFR: Coronary flow reserve; PWV: Pulse wave velocity; Aix: Augmentation index; DRA: Diastolic reflection area; DAI: Diastolic area.

population are presented in Table 1. The mean values of the vascular parameters and the pharmaceutical regimen of the study cohort are shown in Table 1.

Determinants of coronary flow reserve.

In univariate analysis, a decreasing CFR was related with increasing PWVc (r = -0.38, P = 0.015), SBPc (r = -0.34, P = 0.022), AIx (r = -0.50, P = 0.003), SAI (r = -0.49, P = 0.006) as well as decreasing RT (r = 0.45, P = 0.009), DAI (r = 0.49, P = 0.006) DRA (r = 0.55, P < 0.001) and RHI (r = 0.47, P = 0.002). Furthermore, RHI was related to AIx (r = 0.48, P < 0.001), RT (r = -0.29, P = 0.024) and SBPc (r = 0.40, P = 0.001).

In multivariate analysis, after adjustment of age, sex, blood pressure parameter, lipidemic, diabetic and smoking status, we found that coronary flow reserve was independently related to AIx (b = -0.38, r = 0.009), DAI (b = 0.36, P = 0.014), DRA (b = 0.39, P = 0.005) and RT (b = -0.29, P = 0.026).

Patients with high vs patients with low coronary flow reserve

Patients were categorised in high and low CFR according to the median value of CFR. Patients with CFR < 2.5 had similar clinical characteristics with those with CFR ⩾ 2.5 with the exception of higher cholesterol level, (Table 2, P < 0.05). However, patients with CFR < 2.5 had higher PWVc, SBPc, AIx, SAI and lower RT, DAI and DRA compared with those with CFR ⩾ 2.5 after adjustment for cholesterol levels (Table 2, P < 0.05 and Figure 1).

Furthermore, these patients with CFR < 2.5 had higher $LpPLA_2$ compared with those with CFR ⩾ 2.5 (Table 2, P = 0.002).

Relation of vascular markers with Lp-PLA$_2$

Elevated $LpPLA_2$ was related with reduced CFR (r = -0.331, P = 0.001), RHI (r = -0.371, P < 0.001) and DRA (r = -0.35, P = 0.001) as well as increased PWVc (r = 0.34, P = 0.012) and AIx (r = 0.34, P = 0.001).

DISCUSSION

In the present study, we found a close association between arterial wave reflection markers, as assessed by AIx, DRA and DAI, and decreasing CFR in CAD patients after successful revascularization. Furthermore, we demonstrated that diastolic component of central aortic pulse wave as expressed with DRA and DAI is an independent determinant of impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Finally we have shown that endothelial dysfunction as assessed by RHI and the inflammatory process as assessed by $LpPLA_2$ are associated with abnormal wave reflection and increased arterial stiffness.

Association between aortic stiffness and coronary flow reserve

Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands and can be expressed by the difference between the hyperemic flow and the resting flow curve. Impaired CFR constitutes a marker of coronary microcirculatory dysfunction and reflects the impairment of the epicardial coronary artery flow in the presence of significant coronary stenosis[6], as well as coronary microcirculatory dysfunction[11,14]. CFR entails strong prognostic significance in stable patients with known or suspected ischemic heart disease, independently of other risk factors[22-26]. Thus, the scaling values of decreasing CFR constitute a comprehensive indicator of cardiovascular risk even in the presence of critical epicardial coronary stenosis[6].

The association of increased PWV with the presence and prognosis of angiographic CAD has been extensively demonstrated[11,27,28]. Experimental studies have shown that low aortic compliance is associated with a reduction in coronary blood flow[29], particularly subendocardial flow[30,31]. In a human study, Leung *et al*[32] have shown that a compliant aorta, as measured by PWV, is associated with a greater improvement in hyperemic coronary blood flow from successful PCI than a stiff aorta and this relationship persisted for PWV even after accounting for stenosis severity. Furthermore, exercise-induced rise in coronary blood flow, related to ischemic threshold, could be determined by aortic stiffness. This is supported by the findings of Kingwell *et al*[33] who found indexes of arterial stiffness were stronger independent predictors of the exercise-induced ischemic threshold than maximum coronary stenosis assessed angiographically.

In the present study, we confirm the above mentioned close relation of PWV with CFR. PWV is a marker of aortic stiffness, whereas AIx, which is largely determined by wave reflections, represents much more the vasomotor

Table 2 Clinical and biochemical parameters of the study population divided by the median value of coronary flow reserve

	CFR < 2.5 (*n* = 34)	CFR ⩾ 2.5 (*n* = 36)	*P*
Clinical			
Age (yr)	62.1 ± 9.2	58.4 ± 10.5	0.265
Males, *n* (%)	29 (85.2)	30 (83.3)	0.869
Hypertension, *n* (%)	20 (58.8)	18 (50)	0.368
Diabetes, *n* (%)	13 (38.2)	10 (27.7)	0.631
Dyslipidemia, *n* (%)	28 (82.3)	29 (80.5)	0.307
Smoking, *n* (%)	23 (67.6)	20 (55.5)	0.449
FH of CAD	14 (41.1)	11 (30.5)	0.334
SBP (mmHg)	130.9 ± 20.3	120.4 ± 14.8	0.011
DBP (mmHg)	77.4 ± 10.4	74.8 ± 8.8	0.058
Medications			
ASA, *n* (%)	33 (97)	34 (94.4)	0.942
Nitrates, *n* (%)	23 (67.6)	27 (75)	0.131
ACEIs/ARBS, *n* (%)	33 (97)	34 (94.4)	0.956
CCBs, *n* (%)	5 (14.7)	7 (19.4)	0.597
Statins, *n* (%)	32 (94.1)	33 (91.6)	0.547
β-blockers, *n* (%)	29 (85.2)	31 (86.1)	0.765
Biochemical			
Chol (mg/dL)	206.7 ± 44.1	190.6 ± 38.9	0.078
TG (mg/dL)	147.0 ± 57.1	143.9 ± 69.7	0.824
HDL (mg/dL)	39.6 ± 8.6	40.9 ± 12.8	0.567
LDL (mg/dL)	141.6 ± 37.8	126.6 ± 32.9	0.055
Glu (mg/dL)	100.9 ± 2 2.7	112.4 ± 39.9	0.126
CRP (mg/L)	2.5 ± 1.8	2.4 ± 1.5	0.279
Lp-PLA2 (ng/mL)	268.1 ± 91.9	199.5 ± 78.4	0.002
Vascular markers			
RHI-PAT	1.26 ± 0.28	1.50 ± 0.46	0.012
PWVc (m/s)	11.6 ± 2.3	10.2 ± 1.4	0.019
AIx (%)	38.2 ± 14.8	29.4 ± 15.1	0.011
SAI (%)	55.7 ± 7.9	46.1 ± 6.7	0.008
DAI (%)	44.3 ± 7.9	53.9 ± 6.7	0.008
DRA	42.2 ± 9.6	51.6 ± 11.4	0.012
RT (ms)	106.1 ± 20.8	123.0 ± 22.1	0.015
SBPc (mm Hg)	139.1 ± 17.8	125.2 ± 19.1	0.026
DBPc (mmHg)	84.7 ± 12.1	80.0 ± 11.0	0.118

FH: Family history; CAD: Coronary artery disease; DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ASA: Acetylsalycilic acid; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptors blockers; CCBs: Calcium channel blockers; Chol: Total cholesterol; TG: Triglycerides; LDL: Low density; HDL: High density lipoprotein; FPG: Fasting plasma glucose; CRP: C-reactive protein; Lp-PLA2: Lipoprotein-phospholipase A2 patients with multivessel coronary artery disease before revascularisation; CFR: Coronary flow reserve; PWVc: Pulse wave velocity as measured with complior apparatus; AIx: Augmentation index; SAI: Systolic area index; DAI: Diastolic area index; DRA: Diastolic reflection area; RT: Return time; SBPc: Central systolic blood pressure; DBPc: Central diastolic blood pressure.

tone in the small medium-sized muscular vessels downstream in the circulation[9,12]. In our study, we demonstrated for the first time that AIx is related to CFR, indicating that not only stiffness of the large elastic arteries impairs CFR, but stiffening of the smaller muscular arteries contributes as well. However, the net effect of increased systemic arterial stiffness on coronary vasodilatory reserve is thought to be mediated by reduced coronary perfusion during diastole.

Increased arterial stiffness increases the velocity of both forward and reflected pulse wave[9]. This increase in velocity of wave of pulse causes arrival of reflected waves at the aorta during systole and not during diastole as it occurs under conditions of normal aortic elastic properties. The early arrival of the reflected waves (1) augments the systolic aortic pressure and thus increase of LV afterload, wall stress and cardiac workload leading to increased myocardial oxygen demands; (2) reduces the diastolic aortic pressure resulting in reduced myocardial perfusion[9,34]. Thus, arterial stiffness causes a mismatch between myocardial oxygen demands and myocardial perfusion resulting in reduction of coronary flow reserve after hyperemia[10,19,22]. Additionally, stiffening of the large arteries, results in reduction of their capacity to function as an elastic reservoir resulting in a greater peripheral runoff of stroke volume during systole[13,29,31]. Together with the reduced elastic recoil, the diastolic blood pressure and hence coronary blood flow is decreased.

Indeed, in our study, we found that DAI and DRA, two markers that reflect the contribution of reflected waves to perfusion of the coronary circulation, were closely associated with CFR, even after adjustment for other factors influencing CFR. This finding supports the above mentioned pathophysiological mechanism.

Role of endothelial dysfunction for the relationship between coronary flow reserve and arterial stiffness

Besides the above mentioned arterio-coronary coupling that may explain the lower coronary flow reserve associated with a stiff arterial tree, arterial stiffness may be a marker of a more generalized vascular disease process which among others, includes endothelial dysfunction. Previous studies have shown that large artery stiffness itself is influenced by endothelial function via basal release of nitric oxide[35] as well as that aortic stiffness is associated with brachial artery endothelial dysfunction[36]. On the other side, adenosine-induced CFR is also thought to be at least partly endothelium dependent[8]. Thus, endothelial function through NO production is an important determinant of coronary flow response to physiological or pharmacological stimuli[10,19].

Reactive hyperaemia peripheral arterial tonometry (RHI-PAT) is a method to assess peripheral microvascular endothelial function and is linked to coronary microvascular endothelial dysfunction[3], as this parameter is predominantly determined by the bioavailability of NO[16]. Both impaired CFR and reduced RHI-PAT have proven prognostic value in CAD patients[4,6,7]. In the present study we document an independent association of peripheral endothelial dysfunction, assessed by RH-PAT, with coronary endothelial dysfunction, assessed by CFR after successful revascularization in patients with CAD. It is possible that coronary endothelial dysfunction may coexist with aortic stiffness and may contribute to abnormal coronary microcirculatory response to hyperemia, as well as impaired aortic wall properties. Furthermore, the association of RHI-PAT with AIx and RT indicates that peripheral endothelial dysfunction contribute to impaired aortic wall properties, as well as that determines at least partly, stiffening of both large

elastic arteries and smaller muscular arteries.

Role of vascular inflammation

On the other hand increased PWV is associated with enhanced vascular inflammation and injury[20,27]. Indeed, in our study we measured LpPLA$_2$ as a marker of vascular inflammation and we found that patients with high LpPLA$_2$ levels had higher PWVc, AIx, and reduced DRA, DAI, CFR and RHI. These findings indicate a common effect of LpPLA$_2$ in all vascular territories, indicating a generalized vascular disease process which causes reduced CFR directly and/or indirectly through arterial stiffness and impaired endothelial function as we mentioned above.

Study limitations

Our results establish a close relation between increasing PWVc, AIx, DAI, DRA, RHI-PAT and CFR in CAD patients. However, this study was not designed to verify whether this relation is causative or secondary to endothelial dysfunction and interstitial fibrosis within aortic and coronary wall in CAD patients. It is possible that the generalized vascular damage was the link between PWVc, AIx and CFR in our study.

In summary, in the present study, we demonstrated that augmentation of the systolic component of the central aortic pulse wave, as expressed by augmentation index and reduced diastolic component of central aortic pulse wave as expressed by diastolic reflection area and index are related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Furthermore, endothelial dysfunction as assessed by RHI and an inflammatory process as assessed by increased levels of Lp-PLA$_2$ are related with increased arterial stiffness and abnormal wave reflections in CAD patients. These findings underscore the need to assess arterial wall properties in CAD patients to better stratify the risk of future events after successful revascularization.

COMMENTS

Background

Atherosclerosis is a complex process with many faces which include impaired coronary microcirculatory function, endothelial dysfunction, increased arterial stiffness and discrete plaque formation within epicardial coronary tree.

Research frontiers

Pulse wave velocity (PWV) a valid marker of arterial stiffness, is independently related with the impairment of coronary microcirculation as assessed by coronary flow reserve in patients with coronary artery disease (CAD).

Innovations and breakthroughs

The authors demonstrated that augmentation of the systolic component of the central aortic pulse wave, as expressed by augmentation index and reduced diastolic component of central aortic pulse wave as expressed by diastolic reflection area and index are related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function.

Applications

These findings underscore the need to assess arterial wall properties in CAD patients to better stratify the risk of future events after successful revascularization.

Terminology

The authors measured (1) reactive hyperemia index (RHI) using fingertip peripheral arterial tonometry (RH-PAT Endo-PAT); (2) carotid to femoral pulse wave velocity (PWVc-Complior); (3) augmentation index (AIx), the diastolic area (DAI%) and diastolic reflection area (DRA) of the central aortic pulse wave (Arteriograph); (4) CFR using Doppler echocardiography and 5) blood levels of Lipoprotein-phospholipase A$_2$ (Lp-PLA$_2$).

Peer-review

The authors studied a group of 70 patients with CAD by means of coronary flow reserve and several indexes related to arteriosclerosis (peripheral arterial tonometry, pulse waveform analysis, carotid to femoral pulse wave velocity) and to inflamation (Lp-PLA$_2$). As expected these indexes were impaired in patients with lower coronary flow reserve.

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