Original Research

Lack of Correlation Between Coronary Flow Reserve and Vascular Remodelling in Hypertensive Patients Without Left Ventricular Hypertrophy: An Optical Coherence Tomography Study

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Introduction: This study aimed to evaluate the relationships between coronary flow reserve (CFR), coronary intima thickness (IT), and intima–media thickness (IMT) in hypertensive patients.

Methods: Thirteen consecutive, never-treated hypertensives (mean age 59.7 years, 6 men), without left ventricular hypertrophy and with angiographically normal coronary arteries, underwent CFR measurement in the left anterior descending artery in response to a bolus intracoronary administration of adenosine, together with an optical coherence tomography (OCT) study for the estimation of IT and IMT.

Results: Hypertensive patients with a low CFR (≤2.5, n=5) compared to those with a normal CFR (>2.5, n=8) exhibited significantly greater aortic pulse pressure (79.2 vs. 59.4 mmHg, p=0.01), while there was no difference with respect to age, sex, or left ventricular mass index (p=NS). Moreover, no difference was found between patients with low and normal CFR as regards maximal IT and IMT, or mean IT and IMT (p=NS for all). In the entire population, CFR exhibited no relationship with IT and IMT (p=NS). Finally, hypertensives with a low CFR compared to those with a normal CFR exhibited a trend towards a smaller left anterior descending area (7.8 vs. 9.5 mm^2, p=0.24).

Conclusions: In hypertensive patients without left ventricular hypertrophy, adverse functional microcirculatory changes assessed by CFR are not accompanied by OCT-estimated alterations in coronary IT and IMT.

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In essential hypertension, remodelling of the small arteries (100-300 μm diameter) is the most prevalent and earliest form of target organ damage, causing increased vascular reactivity and a reduction in coronary flow reserve (CFR) at maximal vasodilation.[1-3] Microvascular function can be accurately assessed by CFR[4] and its impairment has been correlated with carotid atherosclerosis, expressed as the intima–media thickness (IMT), in hypertensive patients without coronary artery disease.[5] Notably, abnormal CFR often accompanies hypertension, even in the absence of left ventricular hypertrophy (LVH).[6,7] The observed reduction in CFR in hypertension is attributed to remodelling of the coronary small arteries and arterioles, as well as to interstitial fibrosis.[8]

Hypertensive patients with LVH show a correlation between CFR functional abnormalities and coronary IMT structural changes measured by intravascular ultrasound.[9] Contrariwise, in hypertensives without LVH, CFR is reduced, independently of structural changes in the coronary artery wall, and there is no significant correlation between maximal plaque thickness and CFR.[9] Currently, in addi-

tion to intravascular ultrasound measurement, intimal thickness (IT) can be more accurately evaluated by optical coherence tomography (OCT), which correlates well with the histological examination.[10,11]

Based on the above, the aim of the present study was to evaluate the possible correlations of CFR with coronary IT and IMT and to investigate, using the more sensitive imaging method of OCT, whether functional changes in the coronary arteries occur independently, and at an earlier stage than structural changes, in essential hypertensives without LVH.

Methods

Study population

The study population consisted of 13 consecutive, never-treated, non-diabetic patients with essential hypertension (age 59.7 years, 6 men, all Caucasian) who underwent diagnostic coronary angiography because of inducible ischaemia during an exercise treadmill test, confirmed with either thallium scintigraphy or dobutamine stress echocardiography, and had no significant stenoses (<30% diameter) in their coronary arteries. Hypertension was diagnosed according to current guidelines.[12]

Exclusion criteria included the presence of more than moderate valvular heart disease, fasting glucose >125 mg/dL, familial dyslipidaemia, increased serum creatinine concentration (≥1.3 mg/dl for women and ≥1.5 mg/dl for men), contraindications for adenosine (asthma, active chronic obstructive pulmonary disease, use of xanthine, bradyarrhythmias), and any other clinically significant systemic disease. We also excluded subjects with left or right bundle brunch block, pre-excitation syndromes, pacing rhythm or atrial fibrillation.

The study protocol, which included a full transthoracic echocardiographic examination and cardiac catheterisation with concurrent CFR and OCT studies, complied with the Declaration of Helsinki and was approved by our institutional Ethics Committee. All participants provided written informed consent after a detailed description of the procedure.

Cardiac echocardiography

A standard transthoracic echocardiographic examination was performed by the same operator in each case, in a dimly lit room, using a Vivid 3 PRO ultrasound imager (General Electric, Milwaukee WI, USA) equipped with a 2.5 to 5 MHz (harmonics) phased-array transducer, according to current recommendations.[13] LV mass was calculated[14] and normalised for body surface area to obtain LV mass index.

CFR measurements

Diagnostic coronary angiography was performed via a standard femoral percutaneous approach using nonionic contrast material. Once the diagnostic coronary angiography had been completed, a 6 F Judkins guiding catheter without side holes was inserted into the left coronary artery ostium without damping of the aortic pressure signal. All patients received 0.2 mg intracoronary nitroglycerine and intravenous heparin (40-70 IU/kg) with a target activated clotting time of >200s.

A 0.014" Doppler guidewire (FloWire, Cardiometrics) was advanced into the proximal part of the left anterior descending artery. ECG, coronary ostial pressure, instantaneous spectral peak velocity, and time-averaged spectral peak flow velocity were recorded continuously and simultaneously.[4] An intracoronary bolus of 60 μg adenosine was then administered into the left coronary artery and further measurements were obtained under peak hyperaemic conditions. CFR was calculated as the ratio of hyperaemic to baseline time-averaged spectral peak flow velocity (Figure 1A).[4] All measurements were performed twice and mean values were calculated.

OCT coronary wall measurements

Following the CFR study, the coronary wall was imaged by means of OCT. An intravascular LightLab OCT catheter (M3 LightLab system, ImageWire, Westford MA, USA) was positioned in the proximal part of the LAD.

We used the continuous flushing technique, which can acquire images of similar quality to the balloon occlusion technique.[10,11] The image wire was automatically pulled back at 3 mm/s for 3 to 6 s, with simultaneous manual infusion of contrast medium (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) from the guiding catheter, with an infusion rate of approximately 2 to 3 ml/s, allowing for displacement of the blood from the artery during the acquisition period. Images at 150 μm intervals from the distal end of the vessel were acquired for at least 3 mm along the vessel length (20 frames per patient). The study was repeated until at least 90% of the image cross-sections were of good quality. Using appro-

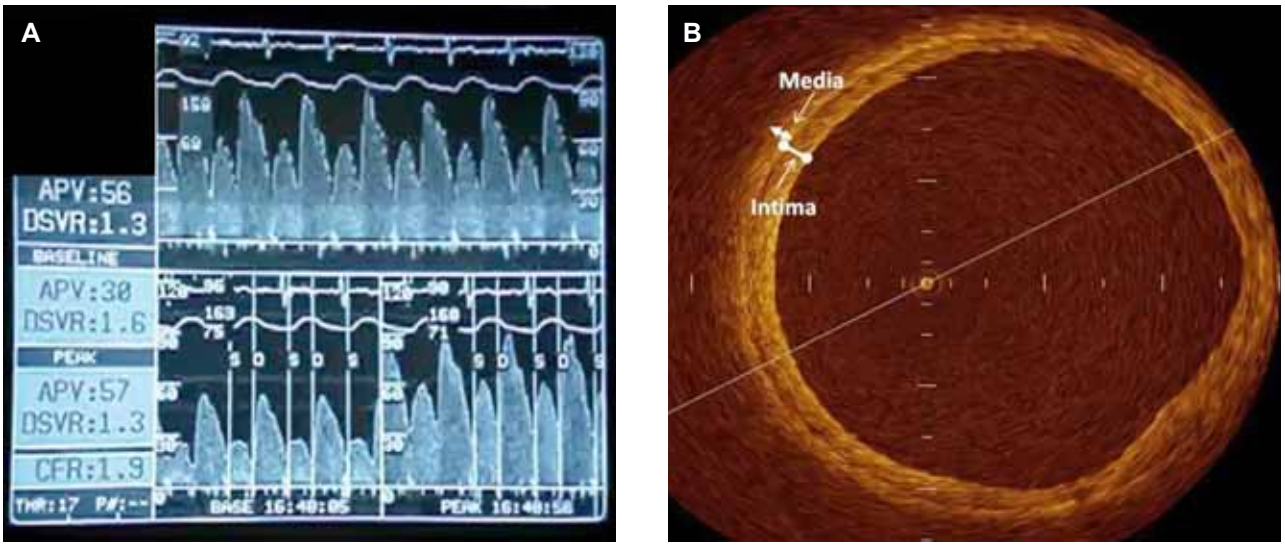

Figure 1. Measurement of coronary flow reserve using a flowire (A) and coronary intima–media and intima thickness using optical coherence tomography (B) in the first part of the left anterior descending artery.

priate software (LightLab Imaging, Inc.) the images were stored and analysed off line by two independent observers on two separate occasions.

The coronary artery wall is imaged by OCT as a three-layer structure (Figure 1B).[10,15] The media is seen as a dark band delimited by the internal elastic lamina and external elastic lamina. Despite its minimal thickness, the internal elastic lamina generates a signal-rich band, while the external elastic lamina is comprised of a few layers of elastic fibres 3-6 mm in size that cause a signal-rich band between the media and adventitia. The adventitia is a signal-rich, heterogeneously textured outer layer. Through visualisation of the internal lamina, OCT can distinguish the atherosclerotic plaque from the muscular media.[11]

IT was identified as the signal-rich layer nearest the lumen and IMT as the distance from the internal border of this layer to the outer border of the signal-poor middle layer. Accordingly, the average values of maximum and minimum IT and IMT were measured for all frames. In the same manner, the lumen area (delimited by the endothelium) was measured.

Statistical analysis

All tests were carried out using the SPSS 15.0 software package. Continuous variables were expressed as mean ± SD. Differences between hypertensives with normal and low CFR were evaluated using the independent-sample Student t-test for continuous variables and the chi-square test for categorical variables. Pearson correlations were calculated to examine any univariate relations between clinical, echocardiographic and CFR parameters and the OCT data.

Results

According to the CFR cut-off value of 2.5, hypertensives were classified into those with a normal CFR (CFR>2.5, n=8) and a low CFR (CFR≤2.5, n=5). Compared to those with a normal CFR, hypertensive patients with a low CFR exhibited significantly greater aortic pulse pressure measured during catheterisation (79.2 vs. 59.4 mmHg, p=0.01). No difference was observed between hypertensives with low and those with normal CFR with respect to age, sex, or left ventricular mass index (p=NS for all) (Table 1).

Regarding the invasively measured morphological indices, no difference was found between patients with low and normal CFR in the average values of maximal IT (246.5 vs. 278.0 μm, p=0.57) and IMT (380.3 vs. 431.7 μm, p=0.40), or in the average values of mean IT (163.6 vs. 200.7 μm, p=0.32) and IMT (286.8 vs. 355.0 μm, p=0.16).

In the entire study population, there was no correlation between CFR and average maximal IT or IMT (r=0.101, p=0.742; Figure 2, upper panel; and r=0.124, p=0.686; Figure 2, lower panel; respectively). Additionally, neither average maximal IT nor IMT were correlated with the vessel area (r=-0.109, p=0.723, and r=-0.075, p=0.807, respectively).

As expected, OCT-derived average maximal IT was correlated with the IMT values (r=0.969, p<0.001). Patients with a normal CFR had a tenden-

Table 1. Demographic and clinical data for hypertensives with low and normal CFR.

Parameters	Hypertensives with low CFR (n=5)	Hypertensives with normal CFR (n=8)	p
Age (years)	63.2 ± 6	57.5 ± 6.3	0.23
Males (%)	20	50	0.35
LVMI (g/m^2)*	92.7 ± 19	82.4 ± 13	0.52
Aortic systolic BP (mmHg)	159.2 ± 21	141.6 ± 16	0.45
Aortic diastolic BP (mmHg)	80.0 ± 7.9	81.0 ± 12.1	0.59
Aortic pulse pressure (mmHg)	79.2 ± 14.6	59.4 ± 8.9	0.01
Average max IMT (μm)†	380.3 ± 103.8	431. 7 ± 104.5	0.40
Average IMT (μm)†	286.8 ± 67.9	355.0 ± 84.8	0.16
Average max IT (μm)†	246.5 ± 84.1	278.0 ± 102.5	0.57
Average IT (μm)†	163.6 ± 48.0	200.7 ± 70.2	0.32
Proximal LAD diameter (mm^2)†	7.88 ± 0.92	9.46 ± 3.32	0.24

*Echocardiography-derived values; †OCT-derived values.
BP – blood pressure; CFR – coronary flow reserve; IT – intimal thickness; IMT – intima–media thickness; LAD – left anterior descending artery; OCT – optical coherence tomography; LVMI – left ventricular mass index

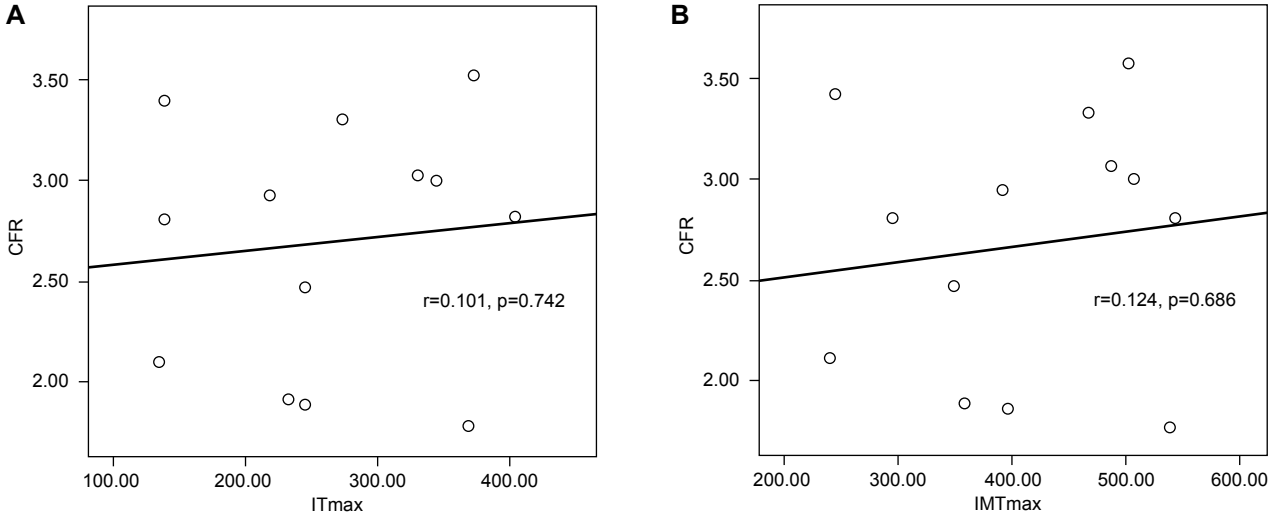

Figure 2. A. Lack of association between coronary flow reserve (CFR) and maximal intima thickness (ITmax, μm) (r=0.101, p=0.742). B. Lack of association between CFR and maximal intima–media thickness (IMTmax, μm) (r=0.124, p=0.686).

cy to have a larger proximal left anterior descending diameter compared to those with low CFR (9.46 ± 3.32 mm^2 vs. 7.88 ± 0.92 mm^2), although the difference did not reach statistical significance (p=0.24).

Discussion

The main finding of the present study is that, in hypertensive patients without LVH, CFR values are not correlated with early IT or IMT adaptations of the coronary vessel wall detected by OCT. Therefore, adverse functional microcirculatory changes occur independently from, and possibly precede vascular remodelling in hypertension.

Coronary remodelling in the form of media thickening is one of the earliest manifestations of hypertension and is mainly caused by complex haemodynamic and neurohumoral interactions.[1,3] The dimensions of the epicardial coronary arteries remain constant,[16,17] resulting in an elevated coronary flow velocity. This may increase longitudinal shear stress at the endothelial surface, causing premature atherosclerosis and/or coronary syndromes. Consistently, we found that hypertensive patients with abnormal microvascular function, as expressed by a CFR≤2.5, had a tendency towards smaller vessel area compared to those with normal CFR. It should be noted that changes in the microcirculation maintain the increase

in vascular resistance that is common in hypertension.[18] However, whether these microcirculatory abnormalities are the cause or the effect in the hypertensive setting still remains under investigation.[19]

CFR is a method of assessing the functional severity of a coronary stenosis.[4] The exact cut-off value that divides "normal" from "abnormal" CFR – i.e. microcirculation dysfunction – is rather vague. The recent CFR consensus[4] considers a value of <2.0 as proof of ischaemia and of haemodynamically significant stenosis, and thus an indication for intervention. Values 2.0-2.5 are the so-called grey zone, and only values >2.5 are considered completely normal. On this basis, we used a CFR cut-off value of 2.5 to divide our study group of hypertensives into those with normal (>2.5) and low (≤2.5) CFR.

In hypertensive patients, several studies have reported that CFR was reduced, despite the absence of a flow-limiting lesion.[7,9,20,21] This pathological alteration has been suggested to cause angina-like chest pain in patients who have no coronary artery disease with[7] or without hypertension,[22,23] and is regarded as a microvascular disturbance. End-organ damage in the form of LVH makes a strong contribution to the attenuation of CFR.[9,21] Carotid IMT has been shown to correlate with traditional risk factors for atherosclerosis and the presence and severity of coronary artery disease,[24,25] as well as with left ventricular mass in patients with hypertension.[26,27] Interestingly, carotid atherosclerosis, measured by IMT, not only reflects coronary morphological changes (coronary IMT measured by intravascular ultrasound)[28] but also coronary functional changes (reduced CFR).[29]

Using the more sensitive method of OCT, our results confirm the previous findings of an intravascular ultrasound study in which reduced CFR was not related to increased coronary IMT in the absence of echocardiographically evident LVH.[9] Moreover, we found no significant difference between patients with low and normal CFR with respect to OCT-measured IMT and IT, with the values of the latter being in agreement with previous reports.[10,11]

Clinical perspectives

The presence of an attenuated CFR, even in hypertensives without LVH, identifies a subgroup at greater risk, because the adverse functional microcirculatory changes could cause insufficient coronary perfusion and impaired wall function during stress. Moreover, repeated stress and regional ischaemia lead to fibrosis, which also impairs cardiac function, leading to heart failure in the absence of obstructive coronary disease. Interestingly, we showed that CFR attenuation is not related to atherosclerotic vascular remodelling in this setting and might constitute the earliest phase of the hypertensive insult to the arterial coronary tree. Finally, from a therapeutic point of view, in selected patients with blunted CFR, apart from blood pressure reduction *per se,* the use of specific drugs that have favourable effects on the microcirculation (e.g. candesartan, nebivolol)[30,31] might attenuate target organ progression and ameliorate the overall prognosis. This strengthens the already established uses of OCT.[32]

Limitations

The current study was cross-sectional, therefore causation cannot be determined for any of the observed relationships. There was also no testing of the endothelium-dependent CFR with the use of acetylcholine. Moreover, a larger number of patients would strengthen these negative results, while the lack of a control normotensive group, as used in previous studies,[9] is another limitation of our work. Nevertheless, an invasive approach (angiography, CFR and OCT estimation) in such healthy subjects remains ethically questionable. Finally, the rather strict cut-off point of CFR >2.5 to define normal microvascular function might misclassify patients as "abnormal", but on the other hand strengthens the true negative conclusions of our study.

Conclusions

In hypertensive patients without LVH, adverse functional microcirculatory changes assessed by CFR are not accompanied by OCT-estimated alterations in coronary IT and IMT. Moreover, these results lend further support to the view that an unfavourable CFR may precede vascular structural remodelling in the early stages of hypertensive disease.

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