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Coronary flow reserve is impaired in patients with aortic valve calcification

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Abstract

Background: Calcific aortic valve disease is an active and progressive condition. Data indicate that aortic valve calcification (AVC) is associated with endothelial dysfunction and accepted as a manifestation of atherosclerosis. Coronary flow reserve (CFR) determined by transthorasic echocardiography has been introduced as a reliable indicator for coronary microvascular function. In this study we aimed to evaluate CFR in patients with AVC.

Methods: Eighty patients, aged more than 60 years, without coronary heart disease or diabetes mellitus were included: 40 had AVC without significant stenosis (peak gradient across the valve <25 mm Hg) and 40 had normal aortic valves (controls). Using transthoracic Doppler echocardiography, we measured coronary diastolic peak flow velocities (PFV) at baseline and after dipyridamole infusion. CFR was calculated as the ratio of hyperemic to baseline diastolic PFV and was compared between groups.

Results: Mean ages for patients with AVC and controls were 68.9 ± 6.2 and 67.6 ± 5.9 years ($P = .3$). There were no significant differences regarding clinical characteristics, laboratory findings, ejection fraction, or peak aortic valve gradients. Mean diastolic PFV at baseline and during hyperemia were 28.4 ± 4.2 and 59.2 ± 7.8 cm/s for AVC and 27.7 ± 3.9 and 68.5 ± 10.5 cm/s for controls. Compared with controls, patients with AVC had significantly lower CFR values (2.12 ± 0.41 versus 2.51 ± 0.51; $P < .0001$).

Conclusion: CFR is impaired in patients with AVC before valve stenosis develops, suggesting that microvascular-endothelial dysfunction is present during the early stages of the calcific aortic valve disease.

Keywords: Aortic valve calcification; Coronary flow reserve; Atherosclerosis

1. Introduction

Calcific aortic valve disease, an active and progressive condition, is common in the elderly. By definition, calcific aortic valve disease comprises a spectrum of clinical conditions ranging from mild valvular thickening (aortic sclerosis or aortic valve calcification (AVC)) to severe calcific valvular stenosis.

AVC is the most common cause of acquired aortic valve stenosis in adults. Despite the common opinion that patients with asymptomatic aortic stenosis (AS) have good prognosis, it has been shown that risk for cardiovascular events is increased in persons with AVC. One study by Otto et al. [1] showed a 50% increase in cardiovascular events (myocardial infarction and cardiovascular death) in patients with AVC without a significant valve obstruction.

Atherosclerotic cardiovascular disease and AVC have many similarities in terms of etiologic factors and clinical characteristics. Histopathologically, AVC is characterized by areas of subendothelial thickening with lipoprotein deposition, inflammation, leaflet calcification, and disruption

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of the basement membrane [2]. Transesophageal echocardiographic studies have shown an independent association between AVC and aortic atherosclerosis [3]. A correlation between the severity of coronary artery lesions and AVC also has been reported [1,3,4]. Based on these data, it is a common belief that atherosclerotic mechanisms are involved in the pathogenesis of calcific aortic valve disease, and AVC is accepted as a manifestation of atherosclerosis.

Coronary flow reserve (CFR), determined by pharmacological stress transthoracic Doppler echocardiography (TTDE), is a reliable and reproducible indicator of coronary microvascular function. A recent trial has demonstrated that CFR obtained by TTDE has a very good correlation with CFR obtained by positron emission tomography, which is accepted as the gold standard for this purpose [5]. A decrease in CFR has been proved to be an early manifestation of atherosclerosis and coronary heart disease (CHD) [6].

With the preceding data in mind, we hypothesized that CFR, an indicator of microvascular function, might be impaired in patients with AVC. Therefore, we used TTDE to evaluate CFR in patients with AVC.

2. Materials and methods

2.1. Study population

Eighty patients (aged >60 years) were enrolled in the study: 40 patients with AVC without significant AS (peak gradient across the aortic valve <25 mm Hg) were assigned to the experimental condition, and 40 age- and sex-matched persons with normal aortic valve morphology and function on two-dimensional and Doppler echocardiographic examinations were used as controls. The study complies with the Helsinki Declaration of 1975, as revised in 2000. The research protocol was approved by the institutional review board and informed consent was obtained from each patient.

Demographic and clinical characteristics, including age, sex, and traditional risk factors for atherosclerosis (hypertension, smoking, dyslipidemia, and family history of premature coronary artery disease) were noted. Patients were defined as hypertensive, if they had a diastolic pressure >90 mm Hg or a systolic pressure >140 mm Hg or if they were being treated with an antihypertensive medication; and as dyslipidemic if they had a total cholesterol level >200 mg/dL, an LDL cholesterol level >130 mg/dL, or a triglyceride level >150 mg/dL or were on a lipid-lowering agent.

CHD was defined as the presence of one of the following: typical angina, ST-segment or T-wave changes specific for myocardial ischemia, Q-waves or incidental left bundle-branch block on ECG, wall motion abnormality on echocardiography, a noninvasive stress test revealing ischemia or any perfusion abnormality, or history of a myocardial infarction or revascularization. Patients having unequivocal symptoms underwent a noninvasive stress test; treadmill exercise or myocardial perfusion scintigraphy, and those demonstrating positive results were excluded.

Patients with CHD, diabetes mellitus, more than mild aortic or mitral regurgitation (grade >1 of 4), rheumatic involvement of the aortic or another heart valve, hypertrophic cardiomyopathy, uncontrolled hypertension prior to the study (systolic blood pressure $\geq$160 mm Hg and diastolic blood pressure $\geq$90 mm Hg), renal dysfunction, asthma, poor echocardiographic image quality or those who were being treated with vasoactive drugs were excluded.

2.2. Echocardiographic examination

Transthoracic echocardiographic examinations were performed with a commercially available system (Acuson Sequoia C256, Acuson Siemens, Mountain View, CA, USA). Aortic valve morphology was assessed in multiple parasternal and apical views. AVC was defined as focal areas of leaflet thickening and calcification-sparing commissures with adequate leaflet motion and a peak flow velocity <2.5 m/s [7]. Patients with thickened leaflets that had a reduced systolic opening and an increased anterograde velocity (>2.5 m/s as shown by continuous-wave Doppler studies) were considered to have AS and were excluded from the study. Two-dimensional, M-mode, and Doppler echocardiographic measurements were performed. Tissue Doppler imaging of the mitral annulus at the septal and lateral sides was performed as well. All echocardiographic measurements were recorded on VHS videotape and analyzed by an experienced single observer who was blinded to the study protocol.

2.3. CFR determination

The mid-distal part of left anterior descending (LAD) coronary artery was visualized using a modified, foreshortened, two-chamber view to reach optimal alignment with the interventricular sulcus. Color-coded two-dimensional and pulsed Doppler recordings of the mid to distal LAD were obtained for each subject. To optimize color-flow imaging, frame rate and flow velocity cut-off were minimized. Wall motion signals were rejected, the Doppler sampler was adjusted to incorporate LAD data alone, and flow was analyzed. Spectral Doppler of the LAD displayed the characteristic biphasic flow pattern, with larger diastolic and smaller systolic components (Fig. 1). Coronary diastolic peak velocities (DPV) were measured at baseline and after dipyridamole infusion (0.56 mg/kg over 4 min). The three highest Doppler recordings were averaged for each measurement. CFR was calculated as the ratio of hyperemic to baseline DPV [8,9]. A CFR value of $\geq$2 was accepted as normal [10].

2.4. Statistical analyses

Statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc., Chicago, IL, USA). The sample sizes for the study