JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 12, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.01.013

Coronary Microvascular Dysfunction as a Mechanism of Angina in Severe AS

Prospective Adenosine-Stress CMR Study

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ABSTRACT

BACKGROUND Although a common symptom in patients with severe aortic stenosis (AS) without obstructive coronary artery disease (CAD), little is known about the pathogenesis of exertional angina.

OBJECTIVES This study sought to prove that microvascular dysfunction is responsible for chest pain in patients with severe AS and normal epicardial coronary arteries using adenosine-stress cardiac magnetic resonance (CMR) imaging.

METHODS Between June 2012 and April 2015, 117 patients with severe AS without obstructive CAD and 20 normal controls were enrolled prospectively. After exclusions, study patients were divided into 2 groups according to presence of exertional chest pain: an angina group ($n = 43$) and an asymptomatic group ($n = 41$), and the semiquantitative myocardial perfusion reserve index (MPRI) was calculated.

RESULTS MPRI values were significantly lower in severe AS patients than in normal controls (0.90 ± 0.31 vs. 1.25 ± 0.21; $p < 0.001$), and were much lower in the angina group than the asymptomatic group (0.74 ± 0.25 vs. 1.08 ± 0.28; $p < 0.001$). In logistic regression analysis, the only independent predictor for angina was MPRI (odds ratio: 0.003; $p < 0.001$). Univariate associations with MPRI were identified for diastolic blood pressure, E/e′ ratio, left ventricular volume and ejection fraction, cardiac index, presence of late gadolinium enhancement, and left ventricular mass index (LVMI). In multivariate analysis, LVMI was the strongest contributing factor to MPRI (standardization coefficient: -0.428; $p < 0.001$).

CONCLUSIONS Our results suggest that, in patients with severe AS without obstructive CAD, angina is related to impaired coronary microvascular function along with LV hypertrophy detectable by semiquantitative MPRI using adenosine-stress CMR. Clinical Trial Registration: NCT02575768 (J Am Coll Cardiol 2016;67:1412–22)

The onset of symptoms marks a dramatic decline in the prognosis of aortic stenosis (AS) (1); thus, it is the most important indication for aortic valve replacement (AVR) (2). Among its symptoms, angina is 1 of the 3 most common and occurs frequently in the absence of epicardial coronary artery disease (CAD) (3–5). Previous studies have demonstrated that angina in patients with normal

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Manuscript received October 22, 2015; revised manuscript received January 6, 2016, accepted January 12, 2016.

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coronary arteries can be attributed to left ventricular (LV) hypertrophy (LVH), which can cause coronary ischemia due to increased LV oxygen demand and impaired myocardial perfusion reserve (MPR) (4,6). This phenomenon has been revealed by invasive coronary catheterization (7) and imaging modalities, such as positron emission tomography (8) and cardiac magnetic resonance (CMR) (9,10). In the absence of significant coronary stenosis, coronary ischemia is indicative of microvascular dysfunction, but it remains unsettled whether the reduced MPR seen in severe AS without obstructive CAD leads to chest pain in response to stress stimuli.

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Adenosine-stress CMR can detect stress-induced abnormal hypoperfusion with signs and symptoms of ischemia without CAD (11,12), and is a reliable noninvasive imaging method that allows assessment of the transmyocardial distribution of coronary blood flow and the MPR index (MPRI). We hypothesized that microvascular dysfunction is responsible for chest pain in patients with severe AS and nonobstructive epicardial coronary arteries. Therefore, adenosine-stress CMR was performed in patients with severe AS and normal epicardial coronary arteries to compare semiquantitative MPRI between patients with and without chest pain. Additionally, MPRI of patients with severe AS was compared with that of normal controls.

METHODS

Patients with severe AS were enrolled prospectively from a single tertiary care center, Samsung Medical Center in South Korea, between June 2012 and April 2015. Subjects who had severe AS and preserved LV ejection fraction (LVEF), defined as ≥50% when assessed by transthoracic echocardiography, were included in this study (**Figure 1**). Severe AS was defined as an indexed aortic valve area (AVA) of <0.6 cm^2/m^2 per guidelines (13). Patients with any of the following criteria were excluded: age <18 years; other concomitant valvular disease of at least moderate severity; previous AVR; obstructive epicardial CAD (>30% luminal stenosis in at least 1 coronary artery on coronary angiography); history of myocardial infarction or acute coronary syndrome; contraindication to adenosine; any absolute contraindication to CMR; or estimated glomerular filtration rate of <30 ml/min/1.73 m^2. In total, 117 severe AS patients without obstructive CAD and with preserved LVEF were screened. We excluded 33 patients with predominant symptoms other than exertional chest pain, such as dyspnea on exertion, syncope, or mixed symptoms. The remaining 84 patients became the subjects of this study and were divided into an asymptomatic group and an angina group based on their predominant presenting symptom at baseline. Twenty healthy asymptomatic subjects with no history of cardiovascular disease, diabetes, or hypertension (mean age: 65.3 years; males: 40%) were recruited to serve as normal controls. The Institutional Review Board of Samsung Medical Center approved this study and all subjects gave written informed consent before the investigation.

Dyspnea on exertion was defined as greater than New York Heart Association functional class II. Angina was defined as exertional chest pain. Those with chest heaviness or chest discomfort were included in the angina group. Those with dizziness or presyncope were included in the syncope group. To classify patient symptoms, all initial symptoms assessed by the primary physician in the medical records were carefully reviewed by 1 cardiologist (S.J.P).

IMAGING. Coronary angiograms were analyzed quantitatively at the angiographic core laboratory (Heart Center, Samsung Medical Center, Seoul, South Korea) with an automated edge-detection system (Centricity CA 1000; GE, Waukesha, Wisconsin) using standard definitions (14). An independent interventional cardiologist interpreted all coronary angiograms. We included only patients without obstructive CAD (<30% reduction in 3 major epicardial arteries and the largest first order branches of each major epicardial artery).

Comprehensive transthoracic echocardiography (M-mode, 2-dimensional, and Doppler) was performed with a dedicated unit (Vivid 7; GE Healthcare, Port Washington, New York). All measurements were performed in accordance with the current American Society of Echocardiography and European Association of Echocardiography guidelines (15,16). The mean transaortic pressure gradient and peak transaortic velocity (V_{max} of AV) were measured in all available views and the highest values were used for analysis. The time-velocity integral at the aortic valve and LV outflow tract levels were acquired through continuous wave and pulse wave Doppler echocardiography, respectively, and the AVA was calculated with the continuity equation (17). The average of 3 consecutive Doppler signals was used.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CAD = coronary artery disease

CMR = cardiac magnetic resonance

LGE = late gadolinium enhancement

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVH = left ventricular hypertrophy

LVMI = left ventricular mass index

MPR = myocardial perfusion reserve

MPRI = myocardial perfusion reserve index

RVEDV = right ventricular end-diastolic volume

RVEF = right ventricular ejection fraction

RVESV = right ventricular end-systolic volume

SV = stroke volume

V_{max} = peak transaortic velocity