JACC: HEART FAILURE
VOL. 2, NO. 4, 2014

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.03.009

CLINICAL RESEARCH

Coronary Microvascular Dysfunction Is Related to Abnormalities in Myocardial Structure and Function in Cardiac Amyloidosis

Sharmila Dorbala, MD,*†‡ Divya Vangala, MA,† John Bruyere Jr, MA,† Christina Quarta, MD,‡ Jenna Kruger, BS,‡ Robert Padera, MD,§ Courtney Foster, MSc, CNMT,† Michael Hanley, MD,* Marcelo F. Di Carli, MD,*†‡ Rodney Falk, MD‡

ABSTRACT

OBJECTIVES The purpose of this study was to test the hypothesis that coronary microvascular function is impaired in subjects with cardiac amyloidosis.

BACKGROUND Effort angina is common in subjects with cardiac amyloidosis, even in the absence of epicardial coronary artery disease (CAD).

METHODS Thirty-one subjects were prospectively enrolled in this study, including 21 subjects with definite cardiac amyloidosis without epicardial CAD and 10 subjects with hypertensive left ventricular hypertrophy (LVH). All subjects underwent rest and vasodilator stress N-13 ammonia positron emission tomography and 2-dimensional echocardiography. Global left ventricular myocardial blood flow (MBF) was quantified at rest and during peak hyperemia, and coronary flow reserve (CFR) was computed (peak stress MBF/rest MBF) adjusting for rest rate pressure product.

RESULTS Compared with the LVH group, the amyloid group showed lower rest MBF (0.59 ± 0.15 ml/g/min vs. 0.88 ± 0.23 ml/g/min; $p = 0.004$), stress MBF (0.85 ± 0.29 ml/g/min vs. 1.85 ± 0.45 ml/g/min; $p < 0.0001$), and CFR (1.19 ± 0.38 vs. 2.23 ± 0.88; $p < 0.0001$) and higher minimal coronary vascular resistance (111 ± 40 ml/g/min/mm Hg vs. 70 ± 19 ml/g/min/mm Hg; $p = 0.004$). Of note, almost all subjects with amyloidosis (>95%) had significantly reduced peak stress MBF (<1.3 ml/g/min). In multivariable linear regression analyses, a diagnosis of amyloidosis, increased left ventricular mass, and age were the only independent predictors of impaired coronary vasodilator function.

CONCLUSIONS Coronary microvascular dysfunction is highly prevalent in subjects with cardiac amyloidosis, even in the absence of epicardial CAD, and may explain their anginal symptoms. Further study is required to understand whether specific therapy directed at amyloidosis may improve coronary vasomotion in amyloidosis. (J Am Coll Cardiol HF 2014;2:358–67) © 2014 by the American College of Cardiology Foundation.

From the *Noninvasive Cardiovascular Imaging Program, Heart and Vascular Center, Departments of Radiology and Medicine (Cardiology), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Cardiovascular Division and Cardiac Amyloidosis Program, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the §Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This study was supported by the Amyloid Foundation, American Society of Nuclear Cardiology Foundation, National Institutes of Health (National Heart, Lung, and Blood Institute grant K23HL092299), and in part by the Demarest Lloyd, Jr. Foundation (Dr. Falk). Dr. Dorbala has received a research grant from Astellas Global Pharma Development.

Amyloidosis is a rare systemic disorder characterized by the extracellular deposition of misfolded protein in various organ systems, including the heart (1,2). Among the several types of amyloid fibrils, the light chain and transthyretin amyloid proteins most commonly affect the heart. Cardiac amyloid deposits result in increased ventricular wall thickness and produce a restrictive cardiomyopathy presenting primarily as biventricular congestive heart failure. Anginal symptoms and signs of ischemia have been reported in some patients with cardiac amyloidosis without obstructive epicardial coronary artery disease (CAD) (3–6). Autopsy studies have shown amyloid deposits around and between cardiac myocytes in the interstitium (7), the perivascular regions (8), and the media of intramyocardial coronary vessels (9,10). Amyloidosis is thus a prime example of a disorder with the potential to cause coronary microvascular dysfunction via 3 major mechanisms: structural (amyloid deposition in the vessel wall causing wall thickening and luminal stenosis), extravascular (extrinsic compression of the microvasculature from perivascular and interstitial amyloid deposits and decreased diastolic perfusion), and functional (autonomic and endothelial dysfunction). Accordingly, we sought to test the hypothesis that coronary flow reserve (CFR), a measure of microvascular function, is reduced in subjects with cardiac amyloidosis without evidence of epicardial CAD. Next, we sought to explore the hypothesis that reduced CFR is a function of increased myocardial mass and increased left ventricular (LV) filling pressures and is associated with subclinical abnormalities in LV systolic dysfunction (strain). Therefore, our primary aim was to study coronary microvascular function in subjects with cardiac amyloidosis compared with subjects with hypertensive left ventricular hypertrophy (LVH). Our secondary aim was to study the morphological and functional correlates of coronary microvascular dysfunction in subjects with cardiac amyloidosis.

ABBREVIATIONS AND ACRONYMS

AL = amyloid light chain
CAD = coronary artery disease
CFR = coronary flow reserve
CT = computed tomography
LV = left ventricular
LVH = left ventricular hypertrophy
MBF = myocardial blood flow
PET = positron emission tomography
2D = 2-dimensional

METHODS

PATIENT COHORT. We prospectively enrolled 31 subjects into 2 study groups. The amyloid group consisted of 21 subjects with confirmed light chain (n = 15) or transthyretin (n = 6) amyloidosis using pre-defined inclusion and exclusion criteria (Online Table 1). Ten subjects with hypertensive LVH on 2-dimensional (2D) echocardiography (LV wall thickness >11 mm) served as controls. Hypertensive subjects with LVH did not have documented kidney disease, peripheral vascular disease, cerebrovascular disease, or CAD (no history of chest pain, myocardial infarction, angiographic CAD, or coronary revascularization). Amyloidosis was diagnosed by endomyocardial biopsy (n = 10) or by a positive extracardiac biopsy specimen with typical features of cardiac involvement on 2D transthoracic echocardiography (n = 11) (e.g., wall thickness measurements >11 mm, bright echogenic myocardium, and echocardiographic evidence of diastolic dysfunction). All biopsy specimens stained positive for amyloid with either sulfated alcian blue or congo red stain, and amyloid typing was determined by a battery of stains, including immunoperoxidase stain for transthyretin and immunofluorescence stain for immunoglobulins G, M, A, kappa, lambda, protein A, and transthyretin. In equivocal cases, biopsy specimens underwent proteomics evaluation.

This study was approved by the Partners Human Research Committee. All study subjects were prospectively enrolled, provided written informed consent, and underwent evaluation of coronary microvascular function by a research test and vasodilator stress N-13 ammonia positron emission tomography/computed tomography (PET/CT) (except for 3 subjects with LVH who underwent clinical N-13 ammonia PET/CT). Obstructive epicardial CAD was carefully excluded in all subjects with amyloidosis by coronary angiography, as described in the following text. All subjects also underwent 2D transthoracic echocardiography with strain analysis to study cardiac morphology and function. Detailed characterization of the amyloid subtype was available for all subjects with amyloidosis, including staining of biopsy specimens.

PET. Rest and vasodilator stress N-13 ammonia PET/CT was performed by using standard protocols and standard preparation (see the Online Appendix). Imaging of all subjects was performed with a whole body PET/CT scanner (Discovery Lightspeed VCT 64; GE Healthcare, Milwaukee, Wisconsin) after an overnight fast. Rest N-13 ammonia images were obtained for 20 min in 2D list mode after intravenous injection of N-13 ammonia (~20 mCi). One hour after rest

Dr. Di Carli has received a research grant from Gilead Sciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Ms. Vangala and Mr. Bruyere contributed equally to this work.

Manuscript received January 14, 2014; revised manuscript received February 24, 2014, accepted March 7, 2014.