

## Hypertrophic Cardiomyopathy, Fibrosis, and Aortic Stiffness

### An Unidentified Association Unraveled by Magnetic Resonance Imaging\*

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Aortic stiffness has been identified as an important predictor of cardiovascular outcome independent of and additive to traditional cardiovascular risk factors in different patient populations including patients with hypertension (1), diabetes (2), and end-stage renal disease (3), and in elderly hospitalized subjects (4). More recently, the prognostic significance of increased aortic stiffness has also been demonstrated in the general population (5). The adverse effects of elevated aortic stiffness are thought to be caused by a premature return of reflected pressure waves in late systole, which increases central pressure and thus systolic blood pressure. Increased systolic blood pressure, in turn, increases the load on the left ventricle, inducing left ventricular hypertrophy, increasing myocardial oxygen demand, and causing subendocardial ischemia. In addition to the effects on the heart, increased aortic stiffness has been associated with an increase in the risk of stroke. Elevated aortic stiffness is not confined to aging or atherosclerotic diseases but has also been reported in noncardiovascular disorders such as generalized inflammatory diseases like rheumatoid arthritis (6) or genetic disorders such as the Marfan syndrome (7). Interestingly, there have been no reports so far investigating aortic stiffness in patients with hypertrophic cardiomyopathy (HCM).

See page 255

The report of Boonyasirinant et al. (8) in this issue of the *Journal* is an important contribution to fill this gap in knowledge. Aortic stiffness was determined in 100 HCM patients and compared with that in 35 control subjects measuring aortic pulse wave velocity (PWV) with velocity-encoded cardiac magnetic resonance (CMR). Remarkably, the authors observed an increased aortic stiffness in patients

with HCM compared with healthy control subjects. There were no differences in age, sex, body surface area, or blood pressure between patients and control subjects, factors known to affect PWV measurements. In addition, aortic dimensions were similar in both groups. Yet, PWV was  $8.72 \pm 5.83$  m/s in patients and  $3.74 \pm 0.86$  m/s in control subjects, a highly significant difference ( $p < 0.001$ ). Furthermore, the authors made another intriguing observation: in the group of patients with HCM, those demonstrating myocardial fibrosis at late gadolinium-enhanced CMR revealed increased PWV compared with HCM patients without myocardial fibrosis ( $9.66 \pm 6.43$  m/s vs.  $6.51 \pm 3.25$  m/s, respectively;  $p = 0.005$ ). Regrettably, no data are presented on the relationship between the extent of myocardial fibrosis and PWV.

What is the link between HCM, myocardial fibrosis, and increased stiffness of the aorta? The paper by Boonyasirinant et al. (8) fails to give a definite answer to this question. Since increased aortic stiffness has been associated with structural changes of the arterial wall with rearrangement of its 3-dimensional architecture (9) and HCM is a disorder characterized by the disorganization of myocardial fiber architecture, it is tempting to speculate that the structural changes in the myocardium and the aortic wall may have a common pathway reflecting different phenotypic characteristics of the same disease. What is more, arterial stiffness may have a genetic component that is largely independent of the influence of traditional cardiovascular risk factors (9). Similarly, HCM is a genetic disorder, which may strengthen the argument for a common pathophysiology of the myocardial and the aortic disease. Another potential explanation is that increased aortic stiffness is the sequel of an atherosclerotic process, which is not infrequently found in patients with HCM. These are interesting questions that await further clarification.

In HCM, stiffening of the aorta may impose an additional burden on an already stiff ventricle. This may have important implications for ventricular-arterial coupling, which is the central determinant of left ventricular performance and cardiac energetics. Modulation of cardiac per-

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formance by the arterial system may affect stroke work and energy efficiency (i.e., the energy consumed by the heart to achieve the required stroke work, at rest and during exercise). It is likely that aortic stiffening may adversely affect cardiac performance in HCM patients especially during exercise. Thus, focusing exclusively on the heart may not be sufficient to completely understand the complex pathophysiology of HCM.

An important question that will have to be addressed in the future is whether the finding of an increased aortic stiffness in HCM patients is a marker of a worse prognosis akin to subjects with hypertension, atherosclerosis, diabetes mellitus, or end-stage renal disease. Since in HCM patients the finding of myocardial fibrosis at delayed enhanced CMR has been suggested as a marker of sudden cardiac death (10), it is tempting to speculate that excessive aortic stiffness may also be associated with worse prognosis in these patients. Yet, the relative contribution of myocardial fibrosis and aortic stiffness to outcome in HCM patients needs to be elucidated in larger studies.

Increased aortic stiffness has been shown to be amenable to pharmacological treatment. For example, in Marfan patients, treatment with angiotensin-converting enzyme inhibitors has been reported to reverse increased aortic stiffness as well as aortic diameter (7). Likewise, in patients with rheumatoid arthritis, statin therapy has been shown to reduce elevated aortic stiffness (6). In HCM patients the effects of angiotensin-converting enzyme inhibition on cardiac performance and coronary flow have been discussed controversially (11). Notwithstanding, it will be important to investigate whether aortic stiffness can be influenced by pharmacological treatment or nonpharmacological interventions (i.e., septal ablation, myectomy) in HCM patients and whether such treatment may result in improved prognosis.

The second important aspect of this article relates to the methodology used for assessing aortic stiffness. Although carotid femoral PWV is considered the "gold standard" for assessing arterial stiffness, measuring the exact distance between the flow-probe position at the carotid and femoral level may be difficult especially in obese men or women with large chest size. In contrast, CMR provides the advantage of allowing exact distance measurements in the 3-dimensional space. Thus, PWV measured from the time delay of aortic flow between the ascending to the descending aorta can be assessed very precisely using CMR. In addition, the method is highly reproducible as elegantly shown by Boonyasirinant et al. (8). Although in HCM patients CMR has proven superior to echocardiography in the accurate characterization of the distribution of left ventricular hypertrophy (12), the most significant advantage of CMR over other imaging modalities may be attributed to the fact that it allows assessment of different morphological and functional parameters in 1 single imaging session including cine imaging, perfusion, and delayed enhancement imaging as well as flow measurements. Thus, CMR may currently be the only imaging technique providing a fully comprehensive nonin-

vasive evaluation of cardiovascular pathophysiology in HCM patients in one single step. In addition, CMR provides unique information on tissue characteristics not obtainable by any other imaging modality. This highlights the outstanding importance of CMR imaging for the complete characterization of complex cardiovascular disease.

In summary, the paper by Boonyasirinant et al. (8) is important because it gives us new insights into the complex pathophysiology of HCM that, apart from being a cardiac disease, may also affect the vascular system. This paper reminds us to broaden our view, which may sometimes be too focused on the heart. We should learn from this paper that in order to better understand cardiac disease we need to look at both the heart and vasculature. CMR is an exceptional and unique imaging modality to support us in this regard.

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