Coronary Microvascular Dysfunction in Patients with Cardiomyopathies

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A nginal symptoms and electrocardiographic changes suggestive of myocardial ischemia, despite angiographically normal coronary arteries, are common in patients with cardiomyopathies and those with left ventricular hypertrophy secondary to pressure overload. Studies using positron-emission tomography (PET) to measure regional myocardial blood flow have demonstrated that maximum myocardial blood flow and coronary flow reserve are severely blunted in patients with hypertrophic as well as dilated cardiomyopathy.1,2 In the absence of epicardial stenoses, blunted maximum myocardial blood flow and coronary flow reserve are suggestive of coronary microvascular dysfunction.3,4 Furthermore, it has been demonstrated that in both hypertrophic and dilated cardiomyopathy, the severity of coronary microvascular dysfunction, assessed by measuring myocardial blood flow with PET, is an independent predictor of prognosis.2,5 In patients with cardiomyopathies, coronary microvascular dysfunction can be sustained by a number of different pathogenetic mechanisms. These include structural and functional abnormalities of the intramural arterioles as well as extravascular mechanisms (eg, increased extramural compression).4

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Anderson-Fabry disease (AFD) is an X-linked deficiency of lysosomal α-galactosidase A.6 This deficiency results in multiorgan damage from glycosphingolipid deposition, leading to renal, cardiac, and cerebrovascular disease and premature death. Patients with AFD complain of angina despite angiographically normal coronary arteries. Recent studies have also shown that there is progressive deterioration in left ventricular systolic function and myocardial scarring in patients with AFD cardiomyopathy. A number of mechanisms may contribute to microvascular dysfunction in these patients. AFD cardiomyopathy is characterized by globotriaosylceramide (Gb3) and related glycosphingolipid deposition in myocytes, conduction tissue, vascular endothelium, and valvular tissue. This is accompanied by secondary changes, such as myocyte hypertrophy and fibrosis, often mimicking hypertrophic cardiomyopathy.7 In the vasculature, Gb3 accumulates in endothelial and smooth muscle cells, possibly causing structural abnormalities that may be responsible for vascular dysfunction. In addition, it has been demonstrated that patients with AFD have increased intima-media thickness in the carotid and brachial arteries and abdominal aorta. These structural changes are accompanied by evidence of abnormal flow-mediated vasodilatation in the brachial artery compared with healthy controls.8

In a recent study, Elliott et al9 used PET to measure regional myocardial blood flow at baseline and during adenosine hyperemia in patients with AFD with angiographically normal coronary arteries. The results of this study showed that both resting (0.99±0.17 versus 1.17±0.25 mL/g per minute; P<0.05) and hyperemic (1.37±0.32 versus 3.44±0.78 mL/g per minute; P=0.0001) myocardial blood flow were severely blunted in patients with AFD compared with a group of gender- and age-matched normal volunteers (Figure, A). The reductions in myocardial blood flow observed in patients with AFD were homogeneous throughout the whole left ventricle, without any significant regional difference. Furthermore, it is worth noting that, in this AFD cohort, the coronary flow reserve (the ratio of hyperemic to resting myocardial blood flow) was blunted in patients both with and without anginal symptoms. In a small subgroup of patients, PET measurements were repeated after replacement therapy with Fabrazyme (Genzyme Corp, Cambridge, Mass) at a dose of 1 or 2 mg/kg every 2 weeks. While patients were on treatment, follow-up PET scans were obtained 17.1±1.9 months after the baseline scan. Both resting (0.99±0.16 versus 0.99±0.16 mL/g per minute; P not significant) and hyperemic (1.56±0.29 versus 1.71±0.3 mL/g per minute; P=not significant) myocardial blood flow before and after 10.1±2.3 months of enzyme-replacement therapy were comparable (Figure, B).

In this issue of the Circulation: Heart Failure, Chimenti et al10 report the results of a study of 46 patients with AFD in whom a number of clinical parameters were correlated with histopathologic findings obtained from endomyocardial biopsies taken during cardiac catheterization. Patients underwent a symptom-limited exercise stress test, stress myocardial perfusion imaging with 99mTc-sestamibi, and left ventricular and coronary angiography with thrombolysis in myocardial infarction frame count. Patients were stratified on the basis of presence (n=13) or absence (n=33) of anginal symptoms. A group of 26 gender- and age-matched patients with mitral stenosis, normal left ventricular function, and coronary angiograms undergoing valve replacement served as controls. All 13 patients with angina received enzyme replacement therapy with Fabrazyme at a dose of 1 mg/kg every 2 weeks. They underwent repeat echocardiography and myocardial
perfusion imaging at 6 and 12 months of follow-up. Repeat angiography with endomyocardial biopsy was performed in 5 patients after 12 months of treatment.

The results of this study showed evidence of elevated troponin I in 6 of 13 patients with anginal symptoms. The exercise stress test showed evidence of myocardial ischemia, and myocardial perfusion scintigraphy showed fixed perfusion defects, stress-induced perfusion defects, or both in all patients with AFD with a history of angina. The epicardial coronaries were structurally normal but showed higher thrombolysis in myocardial infarction frame count (indicative of slow flow) in all patients with anginal symptoms. Furthermore, in 3 of 13 patients with angina, there was evidence of aneurysms in the posterior left ventricular wall at angiography. Histology showed luminal narrowing of the intramural arteries with increased external/lumen ratio due to hypertrophy and proliferation of smooth muscle and endothelial cells that were filled with glycosphingolipids. There was also evidence of replacement fibrosis that exceeded that in patients with AFD without angina and in the control group. No changes in any of the study parameters were noted in the subgroup of patients treated with enzyme-replacement therapy who were re-evaluated at follow-up.

This is an interesting report in which a significant cohort of patients with AFD have been studied extensively using a range of noninvasive and invasive techniques. The results of this investigation provide evidence linking clinical, functional, and structural parameters in the same patients. They also support the hypothesis that structural changes in intramural arterioles, mainly due to deposition of Gb3 in endothelial and smooth muscle cells, are indeed responsible for coronary microvascular dysfunction, which in turn could be the cause of myocardial damage, as evidenced by increased troponin I and fixed perfusion defects observed in the scintigrams.

There are, however, a number of issues that need to be considered. First, patient stratification, based exclusively on the presence or absence of anginal symptoms, limits the inferences that can be derived from the results of the study. Symptoms, including angina, can be elusive, and silent myocardial ischemia is frequent, even in patients with coronary artery disease. The introduction of Holter monitoring brought about the discovery that episodes of painless ST segment depression are common in patients with stable angina and reflect reversible silent myocardial ischemia. In the case of acute myocardial infarction, the incidence of painless events has been estimated at ≈30%. Different from Chimenti et al, other studies have reported evidence of coronary microvascular dysfunction in AFD in patients both with and without a history of chest pain. AFD is a multisystem disorder with widespread structural and functional vascular changes that generally affect different arterial systems. If the presence of angina is a specific indicator of coronary microvascular disease, it would be expected that patients with AFD with a history of angina have significantly more adverse cardiac events at follow-up, similar to patients with dilated or hypertrophic cardiomyopathy in whom the severity of microvascular dysfunction (assessed with PET) predicts major adverse cardiac events. Unfortunately, in the Chimenti et al study, there is no information on the relationship between anginal history and incidence of cardiac events at follow-up.

Second, myocardial perfusion imaging was only performed in patients with a history of angina. Evidence of either reversible or fixed perfusion was present in all 13 patients with angina. Whereas reversible perfusion defects were always observed in the territory of the left coronary artery, fixed defects (ie, scars) were confined to the territory of the right coronary artery. Using cardiovascular magnetic resonance with gadolinium, Moon et al reported on the patterns of late gadolinium enhancement, a marker of myocardial scarring, in 18 patients with AFD. Evidence of late gadolinium enhancement was present in 13 of 18 patients (9 males and 4 females), although a history of chest pain was only present in 6 of 18 patients. The amount of late enhancement ranged from 1.2% to 20.6% of the left ventricle, with more hyperenhancement in males, in whom the percentage of hyperenhancement was related to left ventricular mass. In 12 of 13 patients, hyperenhancement was confined to the basal infero-lateral wall of the left ventricle and, unlike the hyperenhancement associated with myocardial infarction that always involves the subendocardium, in 8 patients with AFD, the hyperenhancement was not subendocardial and primarily involved the mid layers of the ventricle.

Third, in the Chimenti et al study, enzyme replacement therapy with Fabrazyme did not lead to appreciable changes in any of the study parameters. This is at odds with the results of Hughes et al, who, using the same drug at similar doses, reported that after 6 months of active treatment there was a significant reduction (−11.5 g) in left ventricular mass, as measured with cardiovascular magnetic resonance, compared with an increase of 21.8 g in the placebo group (P=0.0041).

Figure. A, Myocardial blood flow at rest and during adenosine-induced hyperemia in patients with AFD and controls. B, Myocardial blood flow at rest and during adenosine-induced hyperemia pre- and post-enzyme replacement therapy (Fabrazyme). MBF indicates myocardial blood flow; Base, myocardial blood flow at rest; ADO, myocardial blood flow during adenosine stress (140 μg/kg per minute, intravenously). *P<0.05 versus controls; **P<0.0001 versus controls. Reproduced with permission from Elliott et al.
In addition, Hughes et al\textsuperscript{15} reported a 20% mean reduction in myocardial Gb\textsubscript{3} content, as assessed by serial transvenous endomyocardial biopsies, in patients receiving Fabrazyme compared with a 10% mean increase in patients receiving placebo. In the Kalliokoski et al study,\textsuperscript{13} plasma Gb\textsubscript{3} concentration decreased significantly, and patients reported symptomatic improvement after treatment with Fabrazyme, although no significant changes in resting or hyperemic blood flow compared with baseline were noted. The latter is consistent with the findings of Elliott et al\textsuperscript{9} who did not find any improvement in resting or hyperemic blood flow in a subgroup of patients with AFD who repeated the PET scan after enzyme replacement therapy.

In summary, different pathogenetic mechanisms are responsible for CMD in patients with cardiomyopathies. CMD can contribute to myocardial ischemia in patients with angiographically normal coronary arteries and can be an aggravating factor in patients with genetic or secondary myocardial diseases in whom the severity of CMD has been shown to predict outcome at follow-up.

**Disclosures**

None.

**References**


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