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RESEARCH LETTER

Structural Coronary Microvascular Dysfunction in Asymptomatic Patients With Apical Hypertrophic Cardiomyopathy

It has been reported that coronary microvascular dysfunction (CMD) exists in patients with hypertrophic cardiomyopathy (HCM).[1] However, it remains unclear whether CMD potentially exists in asymptomatic patients of HCM without angina or symptom of heart failure. Furthermore, data on the presence of CMD are more lacking in the variant of HCM, such as apical hypertrophic cardiomyopathy (APH). In this study, we sought to assess CMD by invasive measurement in asymptomatic patients with APH.

Between October 2021 and September 2022, 14 consecutive patients with APH were prospectively included and analyzed. All patients were referred to us because of giant negative T-wave in precordial leads on electrocardiography without any symptoms. As previously described,[2] APH was defined as hypertrophy predominating in the left ventricular apex, with wall thickness in the apex ≥15 mm and a ratio of maximal apical to posterior wall thickness ≥1.5, based on echocardiography. The cases showing hypertrophy involving basal segment, left ventricular outflow tract obstruction, or apical aneurysm were excluded. The patients with obstructive coronary artery disease defined as >50% diameter stenosis by visual assessment was excluded as well. All patients provided written informed consent. This study was approved by the local ethical committee and was conducted according to the principles of the Declaration of Helsinki.

What is the clinical question being addressed?

Whether coronary microvascular dysfunction exists in patients with apical hypertrophic cardiomyopathy.

What is the main finding?

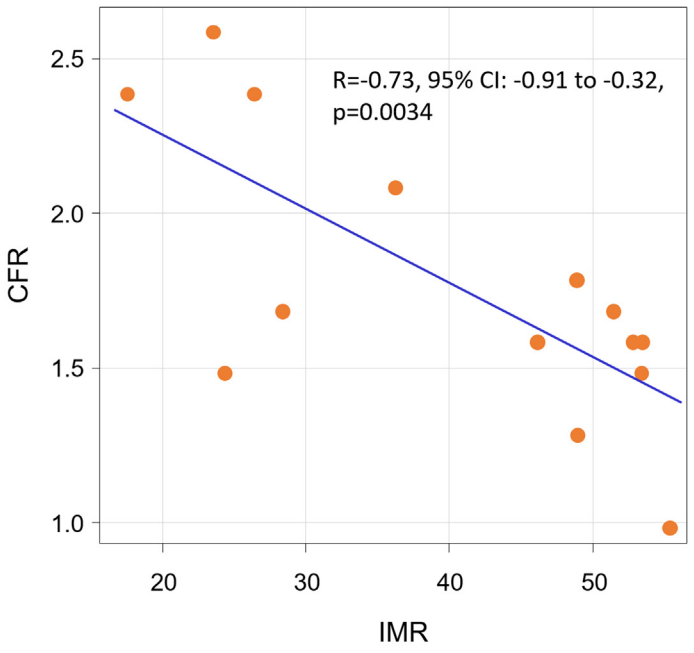
Structural coronary microvascular dysfunction is a predominant mechanism of impaired microcirculation under maximally vasodilated conditions in patients with apical hypertrophic cardiomyopathy.

Following coronary angiography, invasive physiological assessment of the microcirculation was obtained systematically with previously described method[3] using a pressure wire (PressureWire X, Abbott Vascular). Fractional flow reserve (FFR), index of microvascular resistance (IMR), and coronary flow reserve (CFR) were measured. An IMR value of ≥25 and CFR value of <2.0 were considered abnormal, respectively. The correlation between IMR and CFR was analyzed using the Spearman test.

Mean age was 71.1 ± 8.0 years (50% men). Mean systolic and diastolic blood pressure were 127.9 ± 12.4 mmHg and 75.1 ± 9.8 mmHg, respectively. Mean heart rate was 72.1 ± 9.8 bpm (sinus rhythm in all patients). On echocardiography, mean left ventricular ejection fraction was 67.9% ± 3.7%, and mean posterior and apical wall thickness were 11.3 ± 0.9 mm and 18.9 ± 1.8 mm, respectively. Coronary angiography revealed no significant epicardial coronary lesions in any patient. Median physiological values were FFR: 0.90 (IQR: 0.87-0.90), IMR: 42.9 (IQR: 26.6-52.1), and CFR: 1.65 (IQR: 1.53-2.03), respectively. High IMR was observed in 78.6% (11/14) of the cases and low CFR was observed in 71.4% (10/14) of the cases respectively while none of the cases demonstrated low FFR ≤0.80. Importantly, a significant negative linear correlation was observed between IMR and CFR ($R = -0.73$; 95% CI: −0.91 to −0.32; $P = 0.0034$) (**Figure 1**). Correlation between apical wall thickness and physiological values were statistically significant as well: a positive linear correlation to IMR ($R = 0.83$; 95% CI: 0.52-0.94; $P < 0.001$) and a negative linear correlation to CFR ($R = -0.79$; 95% CI: −0.93 to −0.45; $P < 0.001$), respectively.

This cross-sectional study demonstrated the presence of CMD in asymptomatic patients with APH. CMD is increasingly recognized as an increased risk for adverse cardiovascular events.[4] Two distinct endotypes of CMD have been previously documented by evaluating microvascular resistance, termed structural CMD, and functional CMD.[5] Structural CMD is characterized by a reduced CFR in the presence of

FIGURE 1 Structural Coronary Microvascular Dysfunction in Apical Hypertrophic Cardiomyopathy



The **solid blue** line indicates the regression line; the **orange points**, each individual physiological measurement. CFR = coronary flow reserve; IMR = index of microvascular resistance.

an increase in microvascular resistance. This endotype is considered to represent architectural deterioration in the microvasculature which impairs microcirculation under maximally vasodilated conditions. In the present study, the association between microvascular resistance and consequent coronary vasodilation was clearly demonstrated in patients with APH. Continuous compression of the microvasculature by hypertrophic myocardium would result in the impairment of microcirculation. Our findings might illustrate mechanism and pathophysiology of structural CMD in APH.

It is thought that APH may be less benign than previously suspected in comparison with classic HCM.[2] Although perfusion abnormalities assessed by cardiac magnetic resonance have been well described in classic HCM, correlating with severity of late gadolinium enhancement, degree of hypertrophy and myocardial fibrosis,[2] the clinical significance of perfusion abnormalities in APH is unknown. One of the difficulties of quantitative analysis of myocardial perfusion in this variant of HCM is that it would be localized hypertrophy in the left ventricular apex. On the other hand, physiological measurement using a pressure wire could be easily performed in catheter laboratory for the comprehensive assessment of coronary physiology regardless of localization of myocardial hypertrophy. Considering the impact of CMD on increasing risk of cardiovascular events, this Research Letter is hypothesis-generating, suggesting potential benefits of early detection by invasive physiological assessment and early intervention for APH even in patients who are asymptomatic. Further investigation may provide novel insights on the association between physiological values, left ventricular mass, degree of myocardial fibrosis, and clinical outcomes.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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