Hypertrophy and inflammation: too much for one heart

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This editorial refers to "Myocarditis in hypertrophic cardiomyopathy patients presenting acute clinical deterioration" by A. Frustaci et al., on page 733

Hypertrophic cardiomyopathy (HCM) is a genetically determined disease characterized by heterogeneous genetic, morphologic, and clinical patterns. Although it is half a century since Teare1 first described the disease, interest in morphologic, and clinical patterns. Although it is half a century since Teare1 first described the disease, interest in HCM is growing as we move from understanding disease pathology towards prognostic assessment and risk stratification.

Microscopic findings of HCM are distinctive and include myocardial hypertrophy and gross disorganization of cardiac fibres. Cellular disarray and disorganization of the myofibrillar architecture within a given cell are standard.2 Patients with HCM often exhibit myocyte necrosis and replacement fibrosis in the left ventricle. A spectrum of severity and distribution is observed, ranging from isolated small scars to extensive transmural fibrosis. These pathological features are considered the consequence of myocardial ischaemia due to coronary microvascular dysfunction.3 Myocardial fibrosis may contribute to the increased ventricular chamber stiffness and impaired relaxation identifiable in most patients with HCM and is the substrate for the genesis of ventricular arrhythmias and sudden death.

The clinical course of HCM varies. Some patients’ symptoms are absent or mild and remain stable. However, most patients develop symptoms of variable degree that progress and worsen over time. A general relationship exists between the extent of hypertrophy and the severity of symptoms, but this relationship is not absolute, and some patients have severe symptoms with only mild and apparently localized hypertrophy. The transition from a hypertrophied and non-dilated state with intact contractility to one of systolic dysfunction may evolve gradually or have a more abrupt presentation and occurs in 3.5–15% of patients.4 It appears to result, at least in part, from wall thinning and scar formation.

Sudden death can occur in previously asymptomatic patients. Nevertheless, the most reliable features used to identify high risk patients include young age (<30 years) at diagnosis, a family history of HCM with sudden death, an abnormal blood pressure response to exercise, presence of ventricular tachyarrhythmias in Holter monitoring, and genetic abnormalities associated with increased prevalence of sudden death.5

HCM evolves differently even among patients who share identical disease-causing mutations. The wide array of disease manifestations has prompted investigators to search for additional factors responsible for the rapid clinical deterioration experienced by some patients with HCM. Frustaci et al.6 provide interesting evidence associating acute myocarditis with the episodes of clinical deterioration observed during the progression of HCM. The authors studied clinical, angiographic, and histological data from 119 consecutive patients with HCM. Forty-two were admitted for a recent acute clinical deterioration, 20 experienced worsening of heart failure symptoms and systolic dysfunction and 22 manifested multiple episodes of sustained ventricular arrhythmias. At the histological level, diagnosis of myocarditis was established by the presence of inflammatory infiltrates, mainly composed of activated T lymphocytes (CD45R0+) associated with focal necrosis of the adjacent myocytes that were often severely hypertrophied and disorganized. The investigators observed these histological findings, consistent with overlapping active myocarditis, in 28 of the 42 unstable patients but in none of the 77 stable HCM patients. Moreover, a viral genome (influenza A, enterovirus, adenovirus, HCV, or EBV) was detected in 14 of the 28 patients with myocarditis and none of the HCM patients without myocarditis.

In many Cardiology textbooks, myocarditis is the first chapter of the myocardial diseases section, followed often by a chapter devoted to dilated cardiomyopathy as a potential aetiological cause. However, myocarditis is never linked with HCM. The results of the Frustaci study suggest a new paradigm for patients with HCM and abrupt clinical decompensation, namely heart failure or arrhythmias. Frustaci’s results suggest that fibrous replacement in HCM is due not only to myocardial ischaemia, as is classically considered, but also to interstitial inflammatory infiltrates, commonly interpreted as a part of the healing process of myocyte necrosis during active myocarditis (Figure 1).

If viral myocarditis is the cause of clinical destabilization and eventual progression to end-stage disease, our prognostic and therapeutic considerations will require modification. As the authors point out in Discussion, a significant proportion of acute viral myocarditis patients experience...
spontaneous resolution due to virus clearance; the clinical impairment is usually transient and without sequelae. However, preventing the evolution towards chronic myocarditis, itself often associated with fulminant heart failure or death, may require immunomodulating and/or immunosuppressing drugs that can impact recovery of cardiac function. These therapies should be considered if histological signs of disease activity continue and the patient’s clinical and haemodynamic condition deteriorates, despite appropriate heart failure therapy. However, a word of caution is needed in the context of HCM. The current treatment strategy for HCM patients at high risk of sudden death with or without heart failure is the prophylactic placement of implantable cardioverter-defibrillators, and only afterwards should we consider additional treatments to reduce myocardial inflammation. Prospective studies are required before we could advise alterations to current practice.

Several questions about this novel aetiopathogenic cause of HCM decompensation remain unanswered. First, are patients with HCM more prone to suffer acute myocarditis than the general population? The answer to this question is complex because myocarditis in the general population is probably rather common, subclinical, and with complete recovery, making it difficult to obtain precise incidence data. Moreover, the clinical diagnosis of myocarditis is challenging owing to the heterogeneous manifestations and the lack of distinctive features. On the other hand, the predisposition of HCM patients to infectious disorders is poorly understood. Endocarditis is a recognized complication of HCM, particularly in patients with the obstructive form of the disease, with a prevalence of ~0.5%. However, the mechanism of infection of viral myocarditis differs from that of bacterial endocarditis.

Second, how much time elapses between myocardial infection in HCM and the development of symptoms? In general, myocarditis begins as a focal process that spreads to involve the myocardium diffusely over a period of several weeks. Knowing whether patient histories included a flu-like syndrome in the weeks or months preceding HCM deterioration would be valuable. Regardless, HCM patients should be counselled on risk-avoidance for viral exposures and encouraged to receive timely vaccinations.

Finally, is identification of a viral genome in the biopsy sample associated with worst prognosis? Unfortunately, sampling error due to the patchiness of myocarditis’ infection pattern can occur, precluding detection of either inflammation or a viral genome. Moreover, immunopathogenetic factors are probably involved. The current hypothesis is that a cardiotoxic viral infection stimulates cross-reactive cytotoxic T lymphocytes and also elicits a humoral response with subsequent immune-mediated persistent myocardial damage. Therefore, identification of a viral genome in biopsy samples is important as a proof of concept but it may not be possible or required in every episode of HCM decompensation. Research directed toward less invasive methods of assessing myocardial inflammation and necrosis, such as cardiac-MRI with gadolinium, myocardial electrical impedance, detection of anti-myosin antibodies by nuclear medicine imaging, or measurement of circulating biomarkers of fibrosis, is warranted.

In sum, myocardial inflammation that causes new areas of focal necrosis during active myocarditis may be the drop that pours the pot in an already vulnerable myocardium afflicted with severe hypertrophy, disarray, and fibrosis.

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References

Clinical vignette
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Early detection of local tumour recurrence and pulmonary metastasis in cardiac angiosarcoma with PET-CT and MRI
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A 62-year-old woman underwent radical tumour resection and surgical reconstruction of both atria and left ventricle, as well as mitral valve replacement due to initially diagnosed cardiac angiosarcoma in November 2004; surgical intervention was followed by adjuvant chemotherapy. Preoperative tumour staging included whole-body positron emission tomography-CT (PET-CT) with 18-fluorine-2-fluoro-2-desoxy-D-glucose demonstrating a 4.1×7.2 cm hypervascular mass (Panel A), which arose from the inferolateral wall of the left atrium, that infiltrated the left ventricle, the mitral valve annulus, and the great coronary vein. Concomitant pericardial effusion was noticed. The mass showed an increased glucose uptake [Panel B; standardized uptake value (SUV), 5.4 vs. liver 1.3]. Lymphogenic and haematogenous tumour spread were excluded by PET-CT; postoperative course was uneventful.

Within the following 20 months, follow-up studies using PET-CT showed a regular postoperative situs (Panel C). Recent PET-CT study revealed a 2.3×3.9 cm mass bulging out the inferolateral left ventricular wall (Panel D) with intensive glucose uptake (SUV 9.5 vs. liver 2.5; Panel E). Cardiac magnetic resonance imaging (MRI) confirmed local tumour recurrence with an infiltration of the left ventricular wall and epicardial layer (Panels F and G). A pulmonary nodule in the left superior lower lobe presenting with an increased glucose uptake (SUV 1.5) was histologically confirmed as pulmonary metastasis from cardiac angiosarcoma following a wedge resection. Further metastasis and lymphogenic tumour spread were excluded by PET-CT.

PET-CT and MRI permit early detection of local recurrence and metastatic tumour spread of cardiac angiosarcoma, and therefore, enable efficient surgical therapy.