The expanding cardiovascular phenotype of Marfan syndrome

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In this issue of the journal, Kiotsekoglou et al. report on right ventricular systolic dysfunction in patients with Marfan syndrome (MFS). Over the past years, several studies have demonstrated mild, though significant, left ventricular systolic and diastolic dysfunction in patients with MFS.1–5 This is the first study indicating impaired right ventricular function.

Marfan syndrome is an autosomal dominant connective-tissue disorder caused by mutations in the fibrillin-1 gene (FBN1). Cardiovascular manifestations are mainly characterized by progressive dilatation of the aortic root, leading to aneurysm formation which may—when left untreated—lead to aortic dissection or rupture. Other established cardiovascular manifestations include mitral valve prolapse, dilatation of the pulmonary artery, and dilatation or dissection of the descending thoracic or abdominal aorta.

Although not commonly related to MFS, dilated cardiomyopathy, beyond that explained by aortic or mitral valve regurgitation, seems to occur with higher prevalence in patients with MFS, implicating involvement of the extracellular matrix protein fibrillin-1 in ventricular structure and/or function.6 Whether left ventricular dysfunction is a rare but severe complication of MFS or rather a widespread and general asymptomatic finding was unclear until recently. Several studies have now demonstrated that both systolic and diastolic left ventricular functions are impaired in patients with MFS. These alterations may already be present in childhood.1–4

This study by Kiotsekoglou et al. is the first one to demonstrate that right ventricular function is also impaired. This is conceivable when keeping in mind the underlying structural and functional role of the fibrillin-1 protein.

Fibrillin-1 is one of the major constituents of the 10–12 nm microfibrils composing the extracellular matrix. These are located primarily around the periphery of the amorphous elastin component of the elastic fibres. Elastin plays an important role in mediating elastic recoil.7 Microfibrils appear to subserve several global functions including scaffolding for tropoelastin deposition and elastic fibre formation and anchoring endothelial and epithelial cells to elastic fibres. Microfibrils are extensible themselves and may contribute to the mechanical properties of mature elastic tissues by means of load redistribution between individual elastic fibres.8

Immunohistochemical studies of the myocardium with antibodies directed to fibrillin-1 demonstrated that microfibrils form myofiber-collagen fibre linkages at sites where the power of myocardial contraction is being transmitted to the extracellular connective tissue framework in the myocardium.9 Mutations in the FBN1 gene may cause structural and/or functional abnormalities in the microfibrils, leading to impairment of myocardial contraction. Another pathway through which fibrillin-1 probably interferes with myocardial function is through the complex transforming growth factor-β (TGF-β) signalling process. TGF-β’s are multipotential cytokines that regulate cell performance and tissue morphogenesis. Recent studies have shown that the amount of fibrillin-1 in the matrix may be one determinant of the reservoir for TGF-β.10

Sakai and co-workers demonstrated that fibrillin was homologous with the family of latent TGF-β-binding proteins (LTBPs), which serve to hold TGF-β in an inactive complex in various tissues, including the extracellular matrix. Researchers showed that fibrillin can bind TGF-β and LTBPs.11–14

Dietz and co-workers hypothesized that abnormal fibrillin, or reduced levels of fibrillin, in connective tissue might result in an excess of active TGF-β.15 The current hypothesis is that fibrillin-1 participates in the regulation of TGF-β signalling through direct interaction between the large latent complex and the matrix. Since the large latent complex binds TGF-β, abnormal fibrillin-1 fibres will lead to failed matrix sequestration of the latent TGF-β complex and hence to increased amounts of active TGF-β, which is in turn at the basis of the pleiotropic manifestations in MFS.15 The involvement of the TGF-β pathway in cardiovascular abnormalities such as mitral valve prolapse and aortic root aneurysm has been confirmed in mouse models of MFS.
In essence, these data document that fibrillin-1 and microfibrils are not needed for elastic fibre formation, as originally inferred, but rather contribute to elastic fibre homeostasis in postnatal life.16–19

Although the exact role of the TGF-β pathway in the myocardium has not been elucidated so far, some evidence for involvement is suggested. Elevated TGF-β1 gene expression has been measured in ventricular biopsies from hypertrophic and dilated cardiomyopathy patients;20,21 the Leu10→Pro polymorphism in the TGF-β1 gene is associated with end-stage heart failure in dilated cardiomyopathy patients.22

Of interest with regards to this particular study is that mutations in the 3′ untranslated region of the TGF-β3 gene have been identified in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC)—a disease primarily affecting the right ventricle.23 This may indicate a common pathophysiological mechanism underlying the observed right ventricular dysfunction in MFS and ARVC through the TGF-β pathway.

Inherent to the new paradigm regarding the pathophysiology of MFS is the recently recognized opportunity for productive therapeutic intervention. Indeed, numerous studies have clearly demonstrated the ability of angiotensin inhibition, and occur independently of the haemodynamic consequences of the drug.24–26

Compelling evidence for a positive effect—not related to haemodynamic changes—of ARB’s on aortic root growth has been provided in a mouse model of MFS and in a small human study in children with severe MFS.27–29 Ongoing large scale trials in MFS patients are underway—these trials will also be assessing ventricular function as a secondary endpoint.30

All these exciting new data regarding pathophysiology and treatment in MFS are examples of how (rare) monogenetic disorders may also become better understood through our knowledge of MFS.

One may have some methodological concerns with the study reported in this journal, but these are inherent to the study of the right ventricle which has a much more complicated geometry and function when compared with the left ventricle. The main message of this study is that fibrillin-1 and microfibrils in myocardial scars: application of antibody to fibrillin. J Mol Cell Cardiol 1990;22:749–75.


