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Myocardial Fatigue at a Glance

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Abstract
Expanding on the modern lexicon of heart failure (HF), the novel mechano-energetic concept of myocardial fatigue describes a transiently energy-depleted myocardium with impaired contractility and relaxation in the face of adverse haemodynamic load. It encompasses established concepts of ventricular-arterial decoupling, deranged cardiac energetics and impaired myocardial efficiency, offering an alternative explanation for functional causes of HF.

Definition of Myocardial Fatigue

Expanding on the modern lexicon of heart failure (HF), the novel mechano-energetic concept of myocardial fatigue describes a transiently energy-depleted myocardium with impaired contractility and relaxation in the face of adverse haemodynamic load [1]. It encompasses established concepts of ventricular-arterial decoupling, deranged cardiac energetics and impaired myocardial efficiency, offering an alternative explanation for functional causes of HF (Fig. 1).

Proposed Mechanisms

Since cardiac myocytes share the same β-myosin heavy chain (MHC) isoforms as slow-twitch skeletal muscle (SkM), both of which are considered fatigue-resistant, it is reasonable to assume that the myocardium may also reach a state of fatigue when its energetic buffers become overwhelmed at a threshold of high workload [2, 3]. This will disrupt ATP-dependent processes of cross-bridge cycling and calcium homeostasis, crucial for adequate sarcomeric shortening and relaxation [4, 5]. Failing human hearts have also been associated with an increased isoform switch from α- to β-MHC, which may be more energetically favourable but have been found to have lower contractile reserve and cardiac power output at high levels of cardiac stress, e.g. during exercise [6].

Unlike SkM fatigue where the mechanical activity can be consciously halted to allow recovery, ventricles continue to receive preload and contract against varying degrees of afterload, even when severely impaired. As its name suggests, the fatigued myocardium is largely structurally intact and has the potential to recover, as long as its myocytes are promptly mechanically unloaded (e.g. with arterial vasodilators, aortic valve replacement or left ventricular assist device (LVAD), where applicable). If left untreated, a vicious cycle of rising ventricular end-diastolic pressure, wall stress and ischaemia can arise, which may transition into irreversible myocardial damage.

Clinical Implications

Cardiac fatigue from intensive exercise has been well described [7], but not widely recognized in HF. To date, only anecdotes of myocardial recovery after reversal of afterload mismatch have been reported in cases of presumed end-stage hypertensive heart disease or valvular cardiomyopathy from severe aortic stenosis [8]. Indeed, the prevailing dogma that end-stage HF indicates irreversible disease has been challenged by observations of unexpected myocardial recovery post-LVAD in some patients with HF of idiopathic aetiology, offering support to the notion of a mechanically 'exhausted' myocardium [9]. Myocardial fatigue, injury and damage thus sit on a continuum, aligning with the innumerable phenotypes of HF across the spectrum of ejection fraction.

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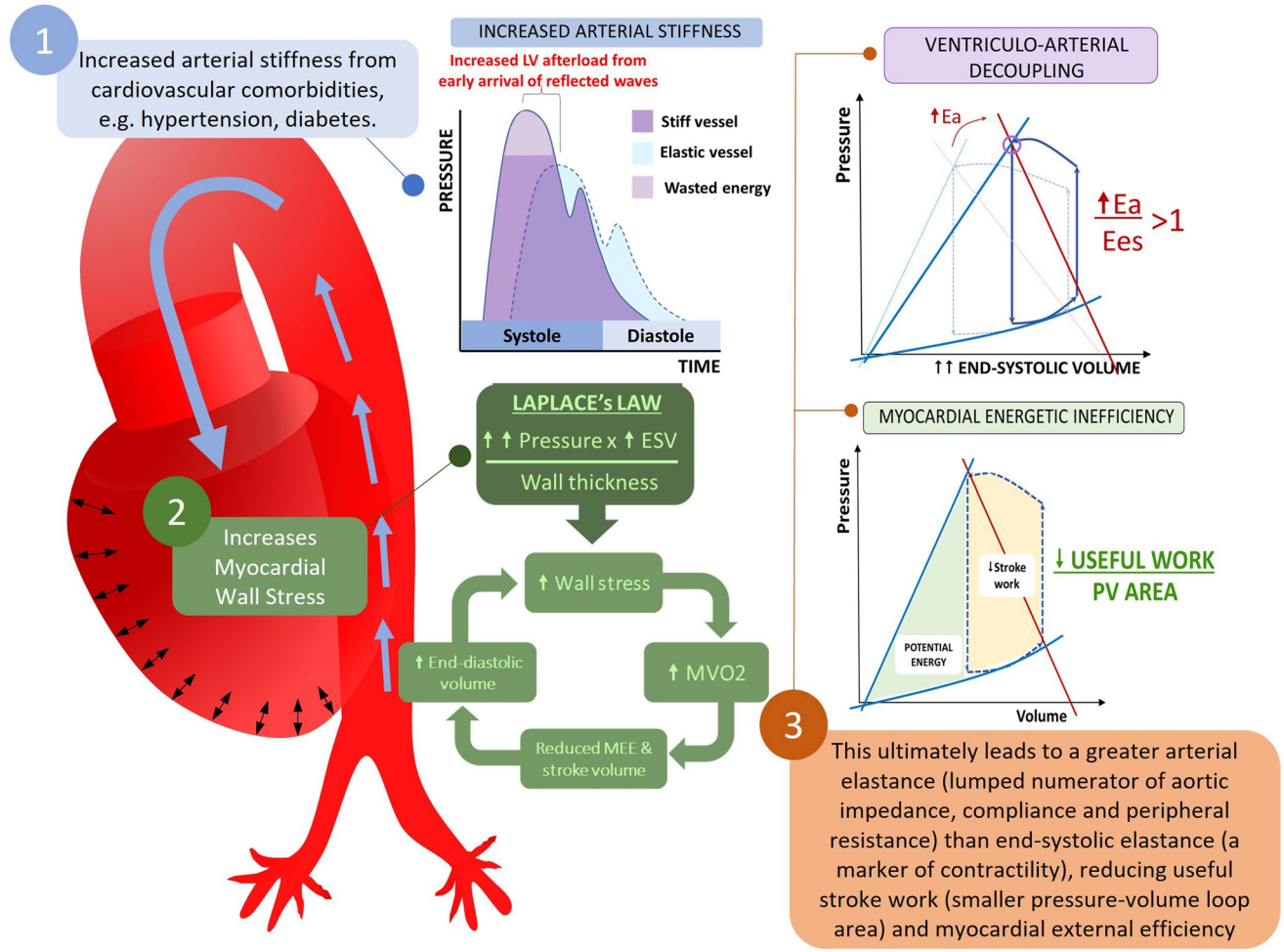

Fig. 1 Mechanistic insights of myocardial fatigue. Abbreviations: Ea, effective arterial elastance (ratio of end-systolic pressure and stroke volume); Ees, end-systolic elastance (mmHg/mL); ESV, end-systolic volume; MEE, myocardial energetic efficiency; MVO2, myocardial oxygen consumption per unit time; PV, pressure–volume loop

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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