Have Imagers Aptly or Inadvertently Overlooked the Neuronal Myocardial Compartment?

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Imaging of the myocardium has been immensely challenging but equally rewarding. The heart is a constantly moving organ, normally beating 60–100 times a minute and every beat studded with multiphasic physiology. The continuous imaging is pleasing, but quantitative measurements require meticulous gating. Contrast-based imaging requires precise timing to capture contrast transition and a method to preclude contamination from myocardial tracer uptake and to differentiate target uptake from that in the residual blood pool. All the challenges of cardiac imaging have constantly spurred growth in imaging of the cardiovascular system. The contractility of the myocardium is the most prominent trait related to outcomes, and various morphofunctional imaging strategies have focused on muscle mechanics for the assessment of global and regional ejection fraction and of strain and strain rates. Echocardiographic, MR, and radionuclide imaging have performed comparably well. Molecular imaging has targeted muscle ischemia, apoptosis, and necrosis with impressive results. Inducible myocardial ischemia has allowed indirect assessment of significant coronary artery stenosis and has been ably supplemented by CT angiography. The interstitial compartment has predominantly been amenable to MR imaging, which has uniquely addressed the presence of interstitial edema and myocardial fibrosis. The neuronal component of the myocardium, which may directly or indirectly influence the other components or disintegrate because of them, has been sparingly evaluated. This lack of evaluation of the neuronal component may be an inadvertent oversight or an apt omission due to transcending G protein, as mediated by β-adrenergic receptor kinase 1 and β arrestins. The polymorphisms of β₁ receptors (Arg389) and α₁ receptors (del 322–325) in heart failure populations have been described as resulting in increased β-receptor sensitivity and decreased regulatory inhibition of neuronal norepinephrine release. With the supraphysiologic norepinephrine contents of the cleft, in addition to β-receptor desensitization there is gradual downregulation of hNET1 that adds to norepinephrine toxicity and further obtunds hNET1. When explanted hearts from transplant recipients were compared with unused donor (normal) hearts, hNET1 expression by immunoblot analysis was significantly reduced in failing hearts (Fig. 1). In addition, in paired specimens from patients before and after placement of a left ventricular assist device (LVAD), the post-LVAD samples showed a dramatic increase in hNET1 protein levels (Fig. 2). It is therefore expected that an in vivo imaging strategy for the assessment of hNET1 integrity would mirror remodeling and recovery in heart failure.

This concept of hNET1 downregulation has been best exemplified by radiolabeled metaiodobenzylguanidine (MIBG) imaging (3–6). MIBG is a norepinephrine analog with storage, transport, and reuptake characteristics similar to those of norepinephrine in sympathetic neurons. Downregulation of hNET1 and consequently reduced norepinephrine reuptake is reflected by a low MIBG concentration in the neurons. On the other hand, the increased norepinephrine demand in heart failure and accelerated norepinephrine release lead to an exaggerated rate of MIBG washout. In clinical imaging, radioiodinated MIBG uptake in the failing myocardium has been quantified as the heart-to-mediastinum ratio (with mediastinal uptake presumed to be background uptake). A low ratio (and a high washout rate) in heart failure patients is associated with a worse prognosis, and β blockers improve myocardial MIBG retention. Resolution of MIBG uptake correlates with reverse remodeling. A markedly reduced MIBG uptake in end-stage heart failure has also been shown to be reversible by unloading of the LVAD implantation (6).
In comparison with parasympathetic neurons, sympathetic neurons are evolutionarily primitive (1). Parasympathetic neurons have evolved with cholinesterase protection, but sympathetic neurons rely completely on the neuronal hNET1 reuptake mechanism to manage norepinephrine excess and hence are easily overwhelmed. In the absence of a metabolic inhibitor of norepinephrine in the synaptic cleft, the excess norepinephrine causes adrenoceptor modulation, myocyte apoptosis, and myocellular loss, further worsening myocardial function. The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) and ADMIRE-HF extension trials have confirmed the prognostic significance of imaging neuronal dysfunction (2). Although ADMIRE-HF used MIBG imaging, assessment of postsynaptic β receptors and presynaptic neuronal norepinephrine synthesis provides additional information about sympathetic integrity.

The articles in this supplement provide the first comprehensive review of the state of modern imaging of heart failure and neuronal dysfunction. It contains the distilled work of several decades of high-quality laboratory and clinical work.

DISCLOSURE

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REFERENCES

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