Studying the neuronal side of the synaptic cleft. A tool for investigating the paradox of sympathetic nervous system and heart failure in dilated cardiomyopathy

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It is widely accepted that heart failure is associated with the activation of the sympathetic nervous system. This results in increased circulating norepinephrine levels and predicts poor prognosis. Data indicate that selective cardiac adrenergic activation precedes systemic activation and predicts the progression of asymptomatic left ventricular dysfunction to heart failure. It has been hypothesized that the chronic increase in adrenergic activity may produce desensitization of signal transmission as well as direct adverse biological effects on myocytes in the failing human heart. The reduced inotropic effect of beta adrenoceptor agonists has been attributed to three major post-synaptic mechanisms: down-regulation of beta2 receptors; increase in the function of or amount of inhibitory Gi protein and up-regulation of receptor kinase proteins (beta adrenoceptor kinase BARK1) leading to the uncoupling of both beta1 and beta2 receptors. Moreover, several studies suggest that catecholamines exert a direct toxic effect on cardiac myocytes and alter energy phosphate levels and cardiac enzymes involved in beta-oxidation.

On the other hand, profound alterations in adrenergic nerve function and integrity have also been described in the failing heart. These include reduced stores of myocardial norepinephrine, a reduced myocardial turnover, defects in catecholamine synthesis, as well as reduced effects of indirectly acting sympathomimetics, such as tyramine. Should these data be interpreted, as evidence of functional denervation of the failing heart, a paradox would rise; why is clinical outcome related to the level of sympathetic activation when the heart is protected against it through functional denervation?

In contrast to agonists, such as isoproterenol, the inotropic effect of norepinephrine is increased in the ex-vivo failing human myocardium. However, cocaine and desipramine shift the concentration-response curves of norepinephrine to the left in normal, but not in failing myocardium. Since cocaine and desipramine inhibit neuronal uptake, this finding suggests that norepinephrine is less inactivated because of an impairment in neuronal (re)uptake in heart failure. In agreement with this interpretation, radioligand binding experiments, using the uptake inhibitor hydrogen-3-mazindol, revealed a significant decrease in norepinephrine uptake-1 carrier density in failing myocardium. It has thus been hypothesized that a sympathetic system might be altered at both sides of the synaptic cleft. In contrast to post-junctional phenomena, sympathetic neuronal integrity can be non-invasively evaluated in the human heart. To this purpose, epinephrine, norepinephrine and dopamine have been labelled with C or F to trace their neuronal uptake, metabolism and vesicular storage. As metabolism of radio-labelled catecholamines by monoamine oxidase (MAO) or catechol-O-methyl-transferase (COMT) give rise to metabolites that clear the myocardium, myocardial retention of radioactivity primarily reflects storage of labelled catecholamines within adrenergic vesicles in sympathetic nerve terminals. In addition, C and F-labelled catecholamine analogs, many of which are false adrenergic transmitters, have been developed as tracers of norepinephrine uptake by sympathetic nerve terminals. These analogs are not metabolized by MAO and COMT, thus allowing the application of tracer kinetic modelling techniques to positron emission tomography data. Among these substances, the most used in the literature are meta-hydroxyephedrine (HED, N-methylmetaraminol) and 123iodo-metiodobenzylguanidine (MIBG). Both HED and MIBG are internalized by the neuronal cells through the uptake-1 system, a transporter and energy demand system. By contrast, the myocardial uptake is mediated by the uptake-2 system, whose activity is very low in the human heart. An important difference between these two tracers is the fact that HED requires the use of positron emission tomography, which MIBG does not require. Thus, the use of HED allows a more precise estimation of disorders in the tracer retention fraction with respect to MIBG, by which only a crude estimation of the heart to mediastinum ratio can be obtained, together with an evaluation of washout rates from the myocardium. Nevertheless, both tracers can delineate the homogeneity of neuronal fibre integrity throughout left ventricular walls.

The use of these techniques has provided a major advancement in our comprehension of the relevance of adrenergic nervous system function in heart failure. In failing myocardium, the retention of HED is

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reduced and this phenomenon is linked to a reduced density or function of uptake-1 carrier protein. Recently, Ungerer and co-workers evaluated a population of patients undergoing heart transplantation because of end-stage cardiomyopathy\cite{10}. They found a reduced density of carrier-1 proteins which was inversely correlated with the expression of BARK-1, while beta receptor density was within the normal range. These data seem to indicate that an abnormal uptake-1 function can be associated with postsynaptic abnormalities, leading to decreased effectiveness of beta\textsubscript{1} stimulation. In partial agreement with this hypothesis, the study published by Bengel and co-workers in the present issue reports a direct correlation between HED retention and global or regional left ventricular function in patients with dilated cardiomyopathy\cite{10}. However, differently from studies in animal models of myocardial sympathetic denervation\cite{11}, abnormalities in neuronal, and in contractile function, were not associated with a decrease in oxygen consumption.

To our knowledge, the reduced function in carrier-1 proteins has not been conclusively proven to be a marker of a loss of neuronal endings. This question remains of crucial relevance since a reduction in neuronal density might imply reduced exposure to norepinephrine, while selective impairment in uptake-1 function would imply increased exposure of cardiomyocytes to this substance. Both mechanisms might theoretically lead to progression of dysfunction, although by completely different pathways.

In the model of heart transplantation, evidence of innervation by HED has been shown to be associated with peculiarities in both myocardial glucose metabolism and blood flow regulation\cite{12}. Altogether, these findings support the concept that the sympathetic nervous system might play a role in several steps of the processes coupling regional myocardial function with metabolism and energy production. Although the pathways of this interaction have not been fully understood, the imaging of myocardial uptake-1 function has been shown to provide information of striking relevance in the clinical setting. In fact, data already indicate that markedly reduced retention of MIBG can predict a very poor prognosis among patients with end-stage heart failure and dilated cardiomyopathy\cite{13}. Moreover, preliminary investigations suggest that this index can be used either to predict\cite{14} or to monitor\cite{15} the effectiveness of therapy with beta-blockers. Thus, the study of the neuronal side of the sympathetic synaptic cleft seems to retain the potential to guide the therapeutic strategy in patients with heart failure due to dilated cardiomyopathy. Future research is needed to define whether a reduced tracer uptake implies reduced density of neuronal fibres, or a reduced expression of carrier-1 protein. This information will surely help in understanding the role of catecholamines in the progression of heart failure and thus the role and indications of beta-blocker therapy.

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