Influence of medical intervention on sympathetic activity in heart failure

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Chapter III

Sympathetic activation in heart failure
The sympathetic nervous system

The sympathetic nervous system is activated in patients with heart failure. At the systemic level, plasma norepinephrine (NE) levels are increased, predominantly caused by an increased release from the adrenal medulla and sympathetic nerve endings (especially in the heart) and a decreased plasma clearance through the kidney and reduced re-uptake in the sympathetic nerve endings. In milder forms of heart failure, a correlation has been demonstrated between plasma concentrations of norepinephrine and mortality. However, the activation of the sympathetic nervous system in heart failure does not involve elevated sympathetic nerve outflow to all organs in a homogeneous manner. Rather, regional sympatho-excitation is seen and appears to be preferentially directed to the heart and kidneys.

Cardiac NE is released from the presynaptic neuron into the synaptic cleft (figure 1). In the synaptic cleft, NE binds to $\beta_1$ receptors resulting in a positive inotropic response of the myocyte. NE is mainly removed (and thus inactivated) from the synaptic cleft through re-uptake in the presynaptic nerve endings. At the presynaptic level, two uptake mechanisms are operative, the uptake-1 mechanism, which dominates at relatively low concentrations of NE in the synaptic cleft and is sodium- and ATP-dependent. The uptake-2 mechanism becomes activated at higher levels of NE and is a passive process. In addition, at higher concentrations, NE is removed from the synaptic cleft by spillover to plasma.

Presynaptic NE release is regulated through systemic sympathetic activation and can be reduced.

Figure 1 Schematic representation of the interaction between presynaptic neuron, the synaptic cleft and the myocyte.
by clonidine, a drug known to cause inhibition of central inhibition of sympathetic outflow. However, sympatho-excitatory β2-receptors and angiotensin-II receptors contribute to NE release from the nerve terminals. In addition, recent research has focused on the role of parasympathetic control of cardiac sympathetic activity indicating that the lack of basal parasympathetic inhibition of cardiac sympathetic activity may play a role in the pathogenesis of increased cardiac sympathetic activation in heart failure.

In summary, in the failing human heart, an increased concentration of NE in the synaptic cleft is observed. These elevated levels of NE are considered to be the result of an increased firing rate, a decreased efficiency of NE uptake (probably related to a decreased number of uptake sites) or both. These disturbances in NE metabolism will result in depletion of intraneuronal myocardial NE content and downregulation of the myocardial β-adrenoceptors.

Because sustained sympatho-excitation is maladaptive in heart failure thereby exerting detrimental effects and is correlated to prognosis, assessment of sympathetic nervous activity is valuable to predict clinical outcome and to evaluate the effect of therapeutic strategies in these patients. Several quantitative and qualitative tools are used to assess different parts of regional and systemic sympathetic activity.

Methods to assess cardiac sympathetic activity in vivo

Plasma norepinephrine levels.

Plasma norepinephrine concentrations can be measured. In large cohorts of patients with heart failure, a correlation between mortality and plasma NE levels has been demonstrated. There are however, large inter- and intra-individual fluctuations in measured NE levels. This makes plasma NE levels difficult to use as a prognostic marker of the syndrome of heart failure in an individual patient. Moreover, plasma NE levels are not directly correlated to cardiac sympathetic activity for two reasons. Firstly, plasma levels depend not only on the rate of release of NE but also on the rate of clearance from the plasma pool. In patients with heart failure, it is estimated that approximately 50% of the observed increase in the plasma concentration of NE is due to reduced clearance. Secondly, cardiac contribution to the total plasma pool of NE is relatively small (approximately 3 to 10% in patients with heart failure). Therefore substantial changes in the rate of cardiac NE release may not be detected if only plasma concentration is measured. However, in patients with heart failure, the heart appears the site where sympatho-excitation is the most prominent.

It should be emphasized that lowering of plasma NE levels perse is not related to mortality. This was recently demonstrated for moxonidine (MOXCON study, unpublished data) and some years ago for ibopamine. These two randomized, placebo controlled trials showed a significant reduction in plasma NE levels. However, mortality was increased in the actively treated groups as compared to placebo.
Norepinephrine spillover.
Elevated cardiac norepinephrine spillover as measured by isotope-dilution techniques is a very sensitive and reproducible method to quantify cardiac sympathetic activity in heart failure.\textsuperscript{13,14} Tracer amounts of radioactive norepinephrine are infused to steady state concentrations. Arterial and coronary sinus bloodsamples are taken and coronary sinus plasma flows are derived from thermodilution-determined blood flows and the hematocrit. The rate of norepinephrine spillover is calculated according to the Fick principle, (mostly) corrected for fractional extraction of [\textsuperscript{1}H]NE across the heart\textsuperscript{14,15}. The increase in the rate of NE appearance in the coronary sinus plasma (as reflected by an increase in NE spillover) results from an increase in cardiac sympathetic nerve firing and neuronal release but has also been attributed to a reduced neuronal re-uptake (uptake-1 mechanism) of NE by the cardiac sympathetic nerves. The major drawback of this method is its invasive nature and therefore it is not suitable for routine clinical use.

Cardiac norepinephrine gradient.
The cardiac norepinephrine gradient is assessed by subtracting the plasma norepinephrine concentration in the ascending aorta from that in the coronary sinus. This method is especially used to assess cardiac release of norepinephrine in response to a tyramine challenge\textsuperscript{16} in cardiac transplant recipients. The tyramine-mediated release of norepinephrine in these patients implies that sympathetic reinnervation is possible after orthotopic cardiac transplantation.\textsuperscript{17}

Scintigraphic imaging with $^{123}$I-Metaiodobenzylguanidine ($^{123}$I-MIBG).
MIBG has been shown to be taken up by sympathetic nerves in a manner similar to norepinephrine but it is not metabolized. Neuronal uptake in the myocardium is mainly achieved through the sodium dependent active uptake-1 mechanism. A sodium independent neuronal uptake of MIBG has been reported at higher concentrations of MIBG and is probably the result of passive diffusion. This mechanism is of minor importance in clinical practice because the concentrations at which this mechanism has been described may never occur under physiological circumstances. Thus, the distribution of MIBG in the myocardium depicts the distribution of sympathetic neurons with functioning uptake mechanisms. MIBG uptake can thus be considered a sensitive index of nerve function and viability.

Cardiac MIBG uptake has been related to mortality and severity of disease.\textsuperscript{18-22} Moreover, cardiac MIBG uptake can be influenced by medical interventions like converting enzyme inhibitors\textsuperscript{23} and β-blockers\textsuperscript{24,25}, drugs that are known to favorably influence morbidity and mortality in heart failure. Cardiac uptake of $^{123}$I-MIBG can be visualized non-invasively by scintigraphy, either using planar or tomographic imaging.

It is essential to quantify cardiac MIBG uptake in order to use it in research and clinical practice. Several methods have been used. Regional cardiac $^{123}$I-MIBG uptake can be quantified relative to
the highest uptake in the myocardium in both planar and tomographic images.\textsuperscript{30,31} This relative scaling only provides information on localized cardiac pathology and is not suitable in clinical evaluation of changes in cardiac MIBG uptake due to therapeutic interventions. A slightly different approach correlates myocardial MIBG uptake to thallium distribution.\textsuperscript{32,33} Areas showing reduced MIBG uptake relative to \textsuperscript{201}thallium are considered denervated. Regional uptake in these regions can be quantified. To correct for the nonspecific (nonvesicular) \textsuperscript{123}I-MIBG uptake and differences in attenuation, the mediastinum is frequently used as a reference for the quantification of myocardial MIBG uptake in planar scintigraphy more or less assuming that mediastinum uptake is constant. The use of a reference region has recently been debated.\textsuperscript{14} Changes in heart/mediastinum ratio were attributed to confounding changes in mediastinal uptake. An alternative quantification method was developed and validated in our institution using high quality Single Photon Emission Computerized Tomography (SPECT) imaging.\textsuperscript{35} In this method, the count density (cd) in the left ventricular cavity is used as a reference. Volumes of myocardium and left ventricular cavity are reconstructed from SPECT acquisitions. The left ventricular cavity count density is calibrated by the \textsuperscript{123}I activity in a venous blood sample (BS), drawn at the time of acquisition. Subsequently, cardiac \textsuperscript{123}I-MIBG uptake can be calculated according to the equation:

\[
\text{Cardiac \textsuperscript{123}I-MIBG uptake} = (\text{Myocardial cd/Cavity cd}).\text{BS} \quad (\text{Bq/ml})
\]

Since the left ventricular cavity is contained within the myocardial area the influence of attenuation can be neglected. Myocardial uptake has to be corrected for both the physical decay of the isotope and the dose administered.

**Positron emission tomography with \textsuperscript{C11}-hydroxyephedrine (HED) and \textsuperscript{C13}-epinephrine (EPI).**

Decreased HED retention is related to functional changes of the sympatho-adrenergic system and has been correlated to uptake-1-carrier density and local norepinephrine content with regional variation in idiopathic dilated cardiomyopathy.\textsuperscript{36} In addition, it has been shown that left ventricular areas of reduced HED uptake show markedly reduced perfusion responses to sympathetic stimulation.\textsuperscript{37} The presynaptic uptake-1 mechanism is also responsible for the myocardial accumulation of EPI. Tracer retention of EPI is higher than HED with a longer clearance half-time for EPI than for HED suggesting a more efficient retention mechanism for EPI and is dependent on vesicular storage and metabolism.\textsuperscript{38}

**Indirect measurement of sympathetic activity.**

Heart rate and especially heart rate variability (HRV) are strongly influenced by activation of the sympathetic nervous system. In patients with heart failure, heart rate is higher and HRV is reduced.
Power spectrum analysis is frequently used to analyze the relative contribution of the sympathetic and the parasympathetic nervous system. Low frequency oscillations (0.04-0.15 Hz) are believed to be evoked by sympathetic activity. High frequency oscillations (0.15-0.4 Hz) in the spectrum are influenced by parasympathetic activity. Generally speaking, heart rate variability is reduced in heart failure with a shift to low frequency oscillations.

Muscle sympathetic nerve traffic
Finally, measuring muscle sympathetic nerve traffic (MSNA) can assess sympathetic activity at the effector level. In heart failure, MSNA is increased as measured by microneurographic quantification of the number of bursts in postganglionic sympathetic fibres to skeletal muscle. Moreover, with increasing severity of disease, MSNA increases. Increased MSNA has also been demonstrated in subjects with hypertension.

Mechanisms mediating the toxicity of chronic sympathetic stimulation
Although increased levels of norepinephrine as a result of chronic sympathetic overstimulation are not the sole factor responsible for the process of heart failure, they certainly play an important role. Several mechanisms of action have been attributed at the level of the myocyte to the progressive disease process (Table 1). Firstly, norepinephrine contributes to cardiac cell necrosis and apoptosis. In addition, many other factors have been shown to trigger apoptosis, which also have been implicated in the pathogenesis of heart failure. These factors include tissue necrosis factor, angiotensin II, myocardial stretch and oxidative stress. Secondly, chronic activation of the sympathetic nervous system contributes to the development of dilation of the left ventricle, not only by altering loading conditions (by causing peripheral vasoconstriction and by enhancing intravascular volume by impairment the excretion of salt and water by the kidneys) but possibly also by a direct effect on the myocytes and the extracellular matrix. These effects can lead to increased myocardial oxygen demand. Thirdly, norepinephrine can provoke arrhythmias in patients

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<td>Mechanisms mediating toxicity of catecholamines in failing myocardium</td>
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<tr>
<td>increasing dysfunction of myocytes</td>
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<td>stimulation of apoptosis and necrosis</td>
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<td>stimulation of ventricular remodeling</td>
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<td>peripheral vasoconstriction thus increasing afterload</td>
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<td>salt and water retention by the kidneys</td>
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<td>induction of arrhythmias</td>
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<td>induction of ischemia by an increase of heart rate</td>
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with heart failure by increasing automaticity of cardiac myocytes and by increasing the transport of potassium from the extracellular space to the intracellular compartment. Both these effects are mediated through stimulation of the $\beta_2$-receptors. Stimulation of $\beta_2$ receptors leads to changes in Ca$^{2+}$-influx across the sarcolemma which is critical for the induction of ventricular arrhythmias as higher concentrations of intracellular calcium induce afterdepolarizations especially under conditions that favor Ca$^{2+}$-loading (hypoxia, increased catecholamines, digitalis toxicity).

In addition, stimulation of $\alpha_1$-receptors by norepinephrine may increase delayed afterdepolarizations and triggered activity, especially in the presence of myocardial ischemia. It should be emphasized that NE can also produce arrhythmias by its ability to cause myocardial ischemia, hypertrophy and fibrosis. It was recently demonstrated that abnormal heterogeneous sympathetic innervation of the myocardium exists in dogs with inherited ventricular arrhythmias and sudden death suggesting a relation between sympathetic nerve distribution and arrhythmias.

In addition, in patients with arrhythmogenic right ventricular dysplasia, regional abnormalities of sympathetic activation can be demonstrated by $^{123}$-MIBG scintigraphy. Finally, activation of the sympathetic nervous system has a positive chronotropic effect, thereby adversely affecting the relation between myocardial oxygen demand and supply. In addition, tachycardia may exacerbate the abnormal force frequency relation that is known to exist in the failing heart (i.e. a decrease in contractile force with increasing heart rates).

References

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