



Atrial fibrillation and cardiac sympathetic reflexes in heart failure

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This editorial refers to 'Atrial fibrillation impairs cardiac sympathetic response to baroreceptor unloading in congestive heart failure' by P.A. Gould *et al.*, doi:10.1093/eurheartj/ehi468

Why do heart failure patients with atrial fibrillation progress more rapidly to pump failure and death than those who remain in sinus rhythm?¹ There are many conceivable mechanisms: adverse ventricular remodelling and synchronization; higher filling pressures, yet loss of atrial contraction and lower stroke volume; atrial remodelling; a greater risk of atrial thrombus and embolic stroke; an increased likelihood of central sleep apnoea, which increases the risk of premature death; loss of vagal and sympathetic modulation of heart rate variability; adrenergic augmentation of atrio-ventricular nodal conduction; adverse effects of rate and rhythm modifying drugs; and altered neural regulation of the heart and circulation by reflexes arising specifically from the atria.

Gould *et al.*,² from Melbourne, take up the latter theme, using a radiotracer method Esler developed to quantify the release rate of norepinephrine into plasma. A series of publications from this laboratory has transformed our understanding of the time course, magnitude, and organ specificity of sympathetic nervous system activation in heart failure. It is now evident that sympathetic activation is first directed at the failing heart in proportion to the increase in filling pressure; that the relative increase in cardiac norepinephrine spillover (CNES) is far greater than that of any other organ;³ that the prognosis of patients with end-stage heart failure can be predicted by their rate of CNES;⁴ and that the mode of death from heart failure can be anticipated from kinetic-based calculations of catecholamine release and storage rates.⁵ Important to the present study is their observation, in nine heart failure patients with secondary pulmonary hypertension, that a simultaneous reduction in both pre-load and systemic blood pressure, caused by an infusion of sodium nitroprusside (SNP), increases total body norepinephrine spillover

(TNES), yet at the same time decreases CNES.⁶ Four of these patients had atrial fibrillation. Azevedo *et al.*⁷ resolved this apparent paradox, instead using non-hypotensive and hypotensive lower body negative pressure (LBNP) as their experimental intervention. All of their patients had sinus rhythm. Reductions in cardiac filling pressure during non-hypotensive LBNP had no effect on CNES in subjects with normal left ventricular systolic function, but lowered CNES in those with heart failure. Hypotensive LBNP increased CNES significantly in control subjects, but had no effect in the group with heart failure. These and related findings led to the proposal that elevated left atrial pressure elicits a sympatho-excitatory reflex, ordinarily quiescent, and with an afferent limb directed specifically to the heart. Such a reflex would account for the early and selective increase in CNES present in patients with mild heart failure.⁸ Does atrial fibrillation perturb this putative reflex?

Gould *et al.*⁹ have previously shown that chronic atrial fibrillation does not influence the magnitude of sympathetic overactivity in patients with heart failure, studied supine. The purpose of the present investigation, involving Classes II and III heart failure patients with an LVEF <40%, was to determine whether the presence of atrial fibrillation was associated with an impaired cardiac sympathetic response to 10 min of 20° and 30° head-up tilt, a manoeuvre that unloads high-pressure baroreceptors, by lowering systolic blood pressure and stroke volume, and in addition, low-pressure mechanoreceptors situated in the atria, ventricles, and pulmonary veins. Anticipating that baroreceptor-induced cardiac adrenergic responses would differ between those in sinus rhythm and atrial fibrillation by 20%, these authors calculated that a sample size of nine for each group would provide an adequate test of this hypothesis.

These authors studied 18 subjects, nine with atrial fibrillation of at least 3 months' duration and nine with sinus rhythm, while on their therapy for heart failure; two-thirds in each group had an ischaemic cardiomyopathy and one-third had dilated cardiomyopathy. Complete data for 30° head-up tilt were only acquired in seven subjects in each group. Tilt caused a significant reduction in cardiac filling pressures in both groups. The transcardiac norepinephrine gradient increased in those with sinus rhythm, but started from a lower baseline, and was essentially absent in subjects with atrial fibrillation.

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Next tested was the hypothesis that attenuation of this reflex response results from increased atrial fibrosis, compromising atrial mechanoreceptor distension in response to alterations in filling pressure. For this purpose, right atrial appendages were collected from a separate group of 23 cardiac surgical patients, 12 in sinus rhythm and 11 in atrial fibrillation. Because the latter exhibited greater collagen density, the authors speculated that the impaired cardiac sympathetic response to baroreceptor unloading in heart failure patients with co-existing atrial fibrillation may be secondary to atrial fibrosis.

The authors are to be congratulated for accomplishing this technically demanding experiment. As they correctly point out, a non-invasive method, such as heart rate variability, could not have addressed their primary hypothesis. However, very few subjects were studied. This sample size may have been sufficient to detect significant attenuation of the cardiac sympathetic response to head-up tilt between the two groups, but there were imbalances in age and blood pressure and transcardiac norepinephrine gradient at baseline. Head-up tilt induced substantial reductions in systemic blood pressure, but these were found not significant statistically. Head-up tilt, which affects simultaneously many reflex systems, is not a clean stimulus, and some mechanistic insights related to the interaction between high and low pressure reflexes¹⁰ in affecting the present neural responses may have been missed because of this small sample size.

Owing to the withdrawal of the Webster thermodilution flow catheter, and the lack of commercially available alternatives, these investigators were unable to quantify coronary sinus plasma flow, an important element of the equation developed by this laboratory to derive cardiac-specific norepinephrine release rates. Thus, in contrast to previous investigations from this laboratory and others,³⁻⁸ in the present study, the estimation of cardiac sympathetic activity was based on the norepinephrine gradient between the radial artery and the coronary sinus, adjusted for the uptake of tritiated norepinephrine by the left ventricle. The authors acknowledge this limitation, inform us that coronary sinus blood flow has not been found to change significantly when cardiac filling pressure is lowered in heart failure, and refer to unpublished data from their laboratory in a handful of patients that would suggest that changes in coronary blood flow in response to unloading may not differ sufficiently between sinus rhythm and atrial fibrillation patients with heart failure to account for the present findings.

The pathological studies examined atrial tissue for collagen density, but did not evaluate mechanoreceptor afferents for arboreal damage or distortion. Decreases in atrial compliance, because of fibrosis, might alter the stimulus to mechanoreceptors, and hence sympathetic activation, but this supposition is unsupported, and the intervention applied in the catheterization laboratory involved mechanoreceptor unloading, rather than stretch. Only right atrial tissue was obtained; however, the contributions of afferents arising from the left atrium and pulmonary veins to any disturbance in neural regulation triggered by high left ventricular filling pressure are likely to be far greater. Whether these patients had heart failure is not stated, and norepinephrine stores were not quantified.

How might the blunted response to head-up tilt in heart failure alter prognosis in heart failure once the atria

fibrillate? Insofar as CNES relates inversely to survival,⁴ rather than inferring increased risk could this impaired reflex be protective, by attenuating the pathological consequences of increased cardiac adrenergic drive when such patients are seated or ambulant? Less sympathetic discharge directed at the AV node would have the additional benefit of attenuating the ventricular response to atrial fibrillation (all patients in the present study were beta-blocked with carvedilol). The authors speculate that this blunted cardiac adrenergic response to head-up tilt might be a manifestation of reduced tissue norepinephrine stores, a marker of greater risk for death from progressive heart failure than from sudden death.⁵ If so, then this finding would be consistent with the relative risks reported in the retrospective analysis of the SOLVD trials, which stimulated the present study.¹ It may also shed light on controversy as to the relative efficacy of beta-adrenoceptor blockade in heart failure patients in atrial fibrillation vs. sinus rhythm. In contrast, if an attenuated CNES response to head-up tilt results from decreased norepinephrine stores, this finding would be a manifestation of the underlying disease process, not atrial fibrillation *per se*.

Curiously, CNES did not fall, as would be anticipated from previous studies,^{6,7} but rather rose, paradoxically, in those with sinus rhythm (*Figure 2*). Consequently, unclear is whether the present findings refute the concept that high filling pressures stimulate a cardiac-specific sympatho-excitatory reflex in heart failure,⁷ or reflect differences in disease progression, and hence cardiac norepinephrine stores, between the two groups of patients selected for the present study. To distinguish between these two possibilities, the investigators are encouraged to study the relationship between cardiac reflex responses and norepinephrine content in future experiments. Replicating this protocol before and after conversion to sinus rhythm would provide additional insight into the functional and prognostic importance of altered cardiac sympathetic reflexes in heart failure.

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