Muscle sympathetic nerve activity in women and men following acute myocardial infarction: a meaningful difference?

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This editorial refers to ‘Gender differences in sympathetic neural activation following uncomplicated acute myocardial infarction’, by A.J. Hogarth et al., on page 1764

Awareness of an apparent excess of mortality in women, as compared with men, in the days subsequent to acute myocardial infarction (AMI) prompted Hogarth and colleagues to investigate whether there exist sex-related differences in the magnitude of post-infarct efferent sympathetic nerve discharge.1 In a remarkable technical tour de force, these investigators quantified the frequency of fibular nerve muscle sympathetic single- and multifibre discharge [muscle sympathetic nerve activity (MSNA)] in a cohort of 72 carefully assembled Caucasian subjects, divided equally between women and men suffering an uncomplicated acute infarct, and well-matched healthy non-medicated female and male control subjects. Patients were screened by history and laboratory examination to exclude the potential confounding influence of known stimuli to sympathetic excitation or autonomic neuropathy. In study patients, MSNA and pre-specified haemodynamic and autonomic variables were acquired on four separate occasions: 2–4 days, and 3, 6, and 9 months after their AMI. Remarkably, complete microneurographic data were acquired over this time period from 35 of the 36 patients. Equally noteworthy is the investigators’ success in their efforts to match patients and control subjects for age, body mass index, waist circumference, smoking history, creatinine, and fasting glucose and lipids, to match male and female patients and their respective controls for blood pressure (BP) and heart rate (HR), and to minimize the effect of other potential confounding variables. The influence of endogenous oestrogen was effectively excluded by age, and that of exogenous oestrogen by subject selection.

What did they find? In healthy control subjects, sympathetic burst incidence (quantified as the number of impulses per hundred cardiac cycles) was 37% higher in men than in women with similar systolic arterial pressure (P < 0.001). When studied 2–4 days after their AMI, sympathetic burst incidence was augmented significantly, relative to control subjects, in both males (P < 0.01) and females (P < 0.001), with no difference between sexes with respect to the magnitude of sympathetic nerve discharge attained. In the months following infarction, there was a gradual decline in sympathetic burst incidence in both men and women, to levels similar to those in control subjects. On the basis of these findings, the authors concluded that women develop relatively greater sympathetic excitation immediately following uncomplicated AMI that is sustained for 6–9 months. They proposed that such augmentation contributes to the vulnerability of women to adverse events over this period.

These observations confirm previous reports involving healthy subjects of between-sex differences in muscle sympathetic nerve firing rates. The uniqueness of the present investigation lies in its comparison of healthy subject data with MSNA of men and women studied longitudinally at pre-specified time intervals following an uncomplicated AMI. This study, however, is essentially descriptive. The authors do not offer or investigate mechanisms responsible for this relatively greater sympathetic activation in the post-infarct period in women, or provide evidence for its functional importance.

Continuous pulse synchronous outflow from central sympathetic motoneurons is entrained and inhibited by input from baroreceptor afferents whose discharge is stimulated by stretch of mechanically sensitive nerve endings situated in the aorta, carotid sinus, atria, and ventricles.2 Input from arterial baroreceptors ordinarily ceases when pressure, during diastole, drifts below the threshold for nerve firing. Consequently, sympathetic nerve firing tracks diastolic rather than systolic BP.3 Relative to control subjects of similar sex, patients studied 2–4 days after their AMI exhibited lower diastolic BP (P < 0.01 for both groups). There was no...
discernible male–female difference at this time, but 6–9 months later there emerged a significant increase in diastolic BP in women, but not in men.

Healthy men and women differ with respect to several aspects of left ventricular (LV) structure and function. For example, the LV cavity is smaller in healthy women compared with men, even after indexing for body surface area.\textsuperscript{15} Because stroke volume is less, women require a higher HR to achieve a similar cardiac output.\textsuperscript{6,7} Suppression of this HR response by \( \beta \)-adrenoceptor blockade may have had a greater adverse impact in women on cardiac output and reflexively, upon MSNA; their normalization of MSNA 9 months after AMI coincided temporally with a significant increase in HR in women but not in men.

Systolic and diastolic filling characteristics of the male and female LV also merit consideration. Women of post-menopausal age have higher LV systolic pressure and basal LV elastance.\textsuperscript{6,7} The latter may be a function of the smaller chamber volume, or a consequence of increasing arterial elastance or stiffness with ageing.\textsuperscript{8,9} When the heart is coupled to a stiffer vascular system the LV must develop greater systolic stiffness or elastance to maintain optimal ventricular–vascular coupling. Such changes may be mediated by increased inotropy, progressive fibrosis, or hypertrophy. Increased stiffness would constrain LV filling, resulting in a steeper rise in pressure for any given LV volume. Conversely, in young healthy subjects, the stroke volume and HR responses to an acute reduction in preload differ between women and men.\textsuperscript{10} Hogarth et al.\textsuperscript{1} do not comment on diuretic or nitrate administration in the acute peri-infarct period. If given, the steeper relationship between diastolic filling pressure and volume in women would be anticipated to elicit greater reflex sympatho-excitation.

This complexity in health, compounded by the effects of myocardial injury and pharmacotherapy, mandate some characterization of LV structure or function to inform whether, in either the healthy control subjects or in their patients following infarction, there were sex-related differences in the stimuli to cardiopulmonary baroreceptors known to inhibit MSNA reflexively, e.g. atrial pressures, ventricular end-diastolic and end-systolic pressures and volumes, diastolic function,\textsuperscript{11} and stroke volume. Absent are invasive or non-invasive quantification of such variables or plasma natriuretic peptide concentration data. LV ejection fraction, which was reported, provides no mechanistic information concerning potential stimuli to cardiopulmonary mechanoreceptor nerve firing, or neural silence. Residual myocardial ischaemia, whether due to epicardial or microvascular disease, should be considered as an additional sympatho-excitatory stimulus\textsuperscript{12} that if tested for might have differed between men and women.

The investigators' inference that this relatively greater sympathetic activation in women causes increased cardiovascular mortality or morbidity following AMI presupposes (i) a linear relationship between MSNA and norepinephrine release; (ii) that MSNA elicits post-junctional responses of similar relative magnitude in men and women; and (iii) fidelity of MSNA as a surrogate for cardiac sympathetic activity. Plasma norepinephrine concentrations, which correlate with MSNA in chronic heart failure,\textsuperscript{13} were not reported. Hart et al.\textsuperscript{14} recently identified a significant positive correlation between MSNA and total peripheral resistance only in healthy young men, but not in women, and concluded that neural BP regulation must differ between males and females. A significant positive relationship between sympathetic firing rate and calf vascular resistance has been described in heart failure patients.\textsuperscript{15} In the present series, calf vascular resistance was assessed, but not reported. Demonstration of concordance between MSNA and calf vascular resistance, or MSNA and estimated (by ultrasound) total peripheral resistance would provide some assurance that the differences described by Hogarth et al.\textsuperscript{1} are indeed functionally important.

However, even if present, such relationships would be specific to the peripheral circulation. Sympathetic outflow is highly differentiated, with organ-specific discharge governed by discrete central systems and specific reflexes. In the setting of increased left atrial pressure, \( \beta \)-adrenoceptor blockade, and impairment of ventricular systolic function, as in the present series of post-infarct patients, congruence of cardiac and peripheral sympathetic nerve discharge cannot be assumed.\textsuperscript{16,17} Of note, sex differences in vagal HR modulation, which relates inversely to cardiac norepinephrine spillover,\textsuperscript{18} did not parallel MSNA either in healthy controls (the arterial baroreflex was less rather than more sensitive in women) or in patients recovering from their infarction. Interventions such as \( \beta \)-adrenoceptor blockade do not alter, chronically, muscle sympathetic firing rate,\textsuperscript{17} and do not oppose vascular \( \alpha \)-adrenoceptor-mediated vasoconstriction.

Whether increased MSNA can be considered a risk marker of adverse outcome in the post-infarct patient, as has been established for baroreflex sensitivity,\textsuperscript{19} cannot be established from the present sample of 36 patients with uncomplicated AMI. Unknown is whether men and women at higher risk because of excluded co-morbid conditions manifest similar time courses, magnitudes, and sex differences in MSNA. Even if this were the case, however, the nature of microneurography precludes its widespread clinical application. Importantly, the demonstration, in this landmark study, of differences between men and women with respect to sympathetic outflow does not provide sufficient mechanistic information to permit the design and deployment of novel interventions aimed at improving the post-infarct prognosis of high-risk women by attenuating specifically MSNA.

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