Review

Gender, sex hormones and autonomic nervous control of the cardiovascular system

Anthony M. Dart*, Xiao-Jun Du, Bronwyn A. Kingwell

Baker Medical Research Institute and Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

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1. Introduction

The autonomic nervous system is of importance in the natural history and treatment of a number of pathophysiological states involving the cardiovascular system. These include hypertension and diseases of the vasculature as well as myocardial ischaemia and cardiac arrhythmias. Gender differences in the incidence and clinical course of a range of cardiovascular states are also well recognised. Both short and long term prognosis after myocardial infarction are worse for women than men [1–4], whereas women with non-ischaemic cardiomyopathy have improved survival [5,6]. In addition to the well known difference in age of presentation of coronary heart disease, women are more likely to suffer from Raynaud’s phenomenon, and to experience pre-syncope or syncopal episodes. An appreciation of gender differences in the structure and function of the autonomic nervous system is therefore important to a full understanding of a number of common and important clinical presentations [7].

Gender differences in the autonomic nervous system may be present because of developmental differences or due to the effects of prevailing levels of male and/or female sex hormones. Such prevailing hormone levels may also produce differences between pre- and post-menopausal women and amongst pre-menopausal women at different phases of the menstrual cycle, which is characterized by oestrogen secretion in the late follicular (pre-ovulatory) phase followed by a secondary phase of secretion in the luteal (post-ovulatory) phase. Progesterone secretion occurs during the luteal phase.

Differences in the autonomic system may be due to differences in afferent receptor stimulation, in central reflex transmission, in the efferent nervous system and in post synaptic signaling. At each of these potential sites of difference, there may be effects due to different size or number of neurons, variations in receptors, differences in neurotransmitter content or metabolism as well as functional differences in the various components of the reflex arc.

2. Methods of assessment of autonomic nervous activity

As indicated in the Introduction there are multiple potential sites in the autonomic nervous system which may be subject to gender related differences. Consequently the examination of gender differences may require use of a wide range of experimental and clinical methodologies. In this section brief mention will be made of techniques specifically related to this question.

Neurotransmitter release from efferent terminals may be estimated from plasma levels, particularly for the sympathetic nervous system by measuring plasma noradrenaline (NA) and adrenaline levels or their urinary excretion. Such methods, which are available for both animal and human studies, do not account for clearance or regional changes that may however be estimated from determination of transmitter spillover [8]. It is also possible to measure extracellular concentrations regionally from microdialysis. Estimation of cholinergic neurotransmission by assay of acetylcholine is more problematic due to the activity of cholinesterase leading to rapid hydrolysis.

Neural firing patterns and frequency can be determined

*Corresponding author. Tel.: +61-3-9276-2071; fax: +61-3-9276-2495.
E-mail address: a.dart@alfred.org.au (A.M. Dart).

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by direct recording in animals and from accessible sites in man. In animal studies these may include both afferent and efferent fibre recording of both divisions of the autonomic system. In human studies they have been restricted to efferent fibre recording of accessible sympathetic nerve fibres.

The efficacy of neurotransmitter release can be determined by measuring physiological and/or biochemical post-synaptic responses known to be mediated, at least in part, by the autonomic nervous system. Pharmacological blockade with agents administered either centrally or systematically may allow physiological responses to be attributed to sympathetic or vagal activity. Certain physiological changes, such as the pattern of variation in heart rate and blood pressure, may allow conclusions about overall balance of sympathetic/parasympathetic responsiveness. Such measures are particularly useful in humans as they may be obtained non-invasively and provide an integrated assessment of autonomic function incorporating both pre and post synaptic aspects of control. Thus a relative preponderance of high (respiratory) frequency (HF) over low (0.1 Hz) frequency (LF) spectral power of heart rate analysed in the frequency domain is indicative of a parasympathetic preponderance [9,10]. Changes in LF power per se are less specific indicators of sympathetic autonomic modulation [8–10]. Analysis of the baroreflex provides information on the integrated reflexes of sympathetic and vagal nerves in controlling heart rate and blood pressure. The baroreflex can be assessed by frequency domain analysis of the relationship between heart rate and blood pressure variability or by perturbing pressure receptor afferent activity and measuring reflex heart rate and blood pressure responses.

3. Physiology

3.1. Basal state

In humans, resting plasma concentrations and urinary excretion of NA and adrenaline are generally not different between males and females [11–13] however, males have been found to have higher resting sympathetic nerve activity to muscles, as determined by micro-neurography [13,14] particularly below the age of 50 in most [15,16] but not all studies [17]. Variations in the plasma concentration of NA have been found during the menstrual cycle [18,19] and muscle sympathetic nerve activity was also higher in the mid-luteal than the early follicular phase [19].

Numerous human studies have examined heart rate variability and related indices of sympathetic/parasympathetic balance. The majority of studies have found women to have a lower LF/HF power ratio than men, suggesting a preponderance of vagal over sympathetic responsiveness [20–23]. Higher LF power in men has been found in several studies [22–26]. These data suggest that males have a preponderance of sympathetic over vagal control of cardiac function compared with females.

3.2. Sympathoadrenergically mediated vasoconstriction

Finger blood flow was reduced in response to infused adrenergic agonists in men but not women [27]. Forearm vasoconstrictor responses to intra-arterial NA were also significantly less in women than in men [28]. A subsequent study [29] indicated that an enhanced response to β-AR stimulation in premenopausal women accounts for the reduced vasoconstrictive response seen when NA is infused alone.

In line with the enhanced responses seen in men, tail arteries from male rats show greater vasoconstriction to perivascular stimulation than do female rats [30]. The reactivity of isolated aortic rings to catecholamines is greater for male than for female rats [31]. However male responses are similar to those of ovariectomised females suggesting an inhibitory effect of oestrogen on vasoconstrictory responses [32]. Systemic responses to NA but not electrical stimulation are reduced in males with orchidectomy. Treatment with testosterone, but not with oestrogen, in castrated rats enhanced the vasopressor action of NA [33]. Vasoconstrictive effect of neuropeptide Y (NPY), a sympathetic co-transmitter, is more pronounced in male than that in female rats and NPY release and actions can be upregulated by testosterone but down-regulated by oestrogen [34,35].

In contrast to tail arteries and aorta, responses to electrical field stimulation in mesenteric resistance vessels are greater in young female rats compared with males whereas there is no difference in older animals [36]. Other studies have shown that α-AR affinity and vascular catecholamine sensitivity increase in small mesenteric arteries of female and oestrogen treated male rats compared with native male rats [37]. However testosterone did not affect α-AR density or affinity in female rats [37].

3.3. Responses to stressors

3.3.1. Posture, valsalva manoeuvre and deep breathing

A number of studies have reported that men show a greater response in systolic blood pressure to a number of cardiovascular stressors [38,39]. Some but not all studies have however found gender differences in the response to valsalva and deep breathing [40–42]. Interpretation of the results of human responses to stressors requires consideration that women apparently perceive the relative strength of stressors differently to men [43].

The increase in plasma NA in response to head up tilt was significantly greater in older males than older females [44]. Heart rate variability analysis demonstrated that in response to tilt young females yielded lower power at LF and lower LF to HF ratio than the younger men.
3.3.2. Exercise

In a study of healthy young men and women, rise in systolic blood pressure was more marked for men after a range of different activities including treadmill walking, rowing and cycling [12]. Women have a blunted adrenaline rise in response to posture and moderate physical activity in some studies [45,46] but an enhanced adrenaline response in others [47]. Urinary excretion of NA and adrenaline, however, were not different between males and females following exercise [12] whilst NA spillover in response to exercise was greater in men than women [48].

As discussed, neuroendocrine responses to exercise have produced variable responses with some studies showing reduced or similar catecholamine responses in women relative to men [47,49,50]. Some of these inconsistencies may have arisen because of variation in plasma glucose and insulin levels. To prevent this in the studies of Davis et al. [51] subjects were infused with dextrose to maintain plasma glucose at euglycaemic levels during exercise. With such conditions systolic blood pressure and plasma levels of NA, adrenaline and pancreatic polypeptide all increased substantially more with exercise in males than females.

Gender differences are also a result of differences in metabolic stimulation. In the study of Ettinger et al. [52] microneurography and metabolic measurements were performed at rest and after repetitive hand grip exercise performed under non-ischaemic and ischaemic conditions. This design permitted study of the role of metaboreceptor activated autonomic reflexes associated with ischaemic metabolite accumulation. In these studies, it was shown that the smaller rise in nerve firing rate in response to exercise in women was probably the result of a smaller change in intracellular pH and other metabolites, and not as the result of differences in muscle mass, leading to reduced mechanoreceptor mediated afferent stimulation.

3.3.3. Hypoglycemia

Activation of neuroendocrine responses are an important counter regulation to hypoglycaemia. Responses to hypoglycaemia have been compared in healthy young male and female volunteers [53]. The threshold levels for neurohumoral responses were similar in men and women. However, increases in sympathetic nerve activity once threshold hypoglycaemic levels have been reached, were greater in men than women. Similarly there were greater increases in plasma adrenaline levels. The differences in neurohumoral response without difference in hypoglycaemic threshold was interpreted as a difference in central or effector sympathetic mechanisms. Healthy control women and women with type 1 diabetes have a significantly reduced sympathetic nervous response to hypoglycaemia than men. Interestingly, however, hypoglycaemia is not more prevalent in women with type 1 diabetes than in men [54]. In an attempt to resolve this paradox, Davis et al. [17] studied the effects of antecedent hypoglycaemia which is known to blunt subsequent neuroendocrine responses to a further hypoglycaemic episode. Such blunting was much less marked for women and only occurred after more severe antecedent hypoglycaemia. Differences in blunting were also evident for pancreatic polypeptide, a marker of vagal activity.

3.3.4. Hypoxia and hyperoxia

In a clinical study measuring muscle sympathetic nerve activity [14], the latency for achieving peak response to isocapnic hypoxaemia was significantly shorter in women compared with men. Recovery from hypoxaemia was also more rapid in women than men. Conversely in response to hyperoxaemia sympathetic nerve activity decreased significantly only in men. In keeping with the more rapid responses seen in women, female rats show enhanced dopamine and NA turnover in carotid body and brainstem NA cell groups in response to hypoxia compared with males [55].

3.3.5. Cold temperature and mental stress

Responses to direct cooling may result from a number of mechanisms including direct effects on cutaneous, venous α-AR [56]. Responses to cooling a contralateral limb are believed to arise by thermoreceptor stimulation leading to increased sympathetic neural activity which is more marked in premenopausal women than men and in premenopausal than postmenopausal women [57,58].

In response to mental arithmetic and deep inspiration hand and skin blood flow was reduced in men but, paradoxically increased in women. In a series of ingenious experiments involving whole body heating or cooling to increase or reduce central sympathetic outflow to the hand, Cooke at al. [59] showed the responses to mental arithmetic depended on the prevailing level of sympathetic tone to resistance vasculature. Thus, the differences in resting blood flow between men and women, which probably account for differences in Raynaud’s phenomenon, are not due to local structural changes which limit maximum flow but to the basal differences in central sympathetic tone. Similarly evidence against structural factors limiting flow is that forearm hyperaemic flow is actually greater in women than men [60]. Also in keeping with these findings is that female patients with Raynaud’s syndrome show a paradoxical vasodilatation with mental stress [61].

3.3.6. Neuronal reflexes controlling cardiovascular function

Huihuri et al. [62] found women to have reduced baroreflex sensitivity, measured during the valsalva manoeuvre. In post menopausal women, those on hormone replacement therapy (HRT) had higher baroreflex sensitivity than those not on HRT. Changes in baroreflex sensitivity during the menstrual cycle and with the use of the oral contraceptive have also been examined [19,63]. Sympathetic but not vagal cardiac baroreflex sensitivity was greater during the early follicular than the mid-luteal phase.
and both were greater in the low hormone (placebo) compared with the high hormone phase of oral contraceptive use.

Compared with intact female animals, ovariectomized animals showed enhanced sympathetic activation and attenuated baroreflex sensitivity or vagal tone and such differences were minimized by oestrogen treatment [64,65]. The inhibition in lumbar sympathetic activity induced by cardiopulmonary receptor stimulation in rats with sino-aortic baroreceptor denervation was significantly greater in female than male animals [66].

3.4. Summary

Human and animal data indicates significant differences exist between males and females in basal function of the autonomic nervous system. There is consistent data to suggest males have higher sympathetic, and females higher parasympathetic, cardiac autonomic activity. Sympathetic nerve firing rates, at least to leg muscles, are more pronounced in men than women. However, sympathetic outflow to the forearm seems to be greater in women. In the majority of vascular beds, basal sympathetically mediated vasoconstriction is greater in men than women. However, animal data suggests that the converse may be true in the mesenteric circulation. Furthermore, there are clear gender differences in the autonomic response to stressors which vary according to the nature of the stress.

4. Aging and pathophysiology

4.1. Aging

Cardiac responses to isoprenaline were similar in older males and females but greater in younger males than females indicating a greater age-dependent decline in function in males than females [67]. Below the age of 50 muscle sympathetic nerve activity was significantly greater in men than the women but no differences between genders were noted for older subjects [15]. In the study of Kuo et al. [24], the percentage LF power was significantly higher in the younger males than the younger females whilst the percentage HF power was significantly higher in the younger females than the younger males. The gender differences were largely lost after 55 years of age. Yamasaki et al. [22] also found a decline with age for both HF and LF power. The decline with age was more marked for men than for women.

4.2. Obesity

In obese men and women subjected to severe weight restriction, plasma adrenaline increased more in men than women [68]. In a study of healthy older men and women [69], NA spillover was found to be significantly higher in men than in women. NA spillover was positively related to waist circumference again suggesting that distribution of body fat is an important determinant of sex differences in sympathetic activity. In the study by Jones et al. [16], increased muscle sympathetic nerve activity was also found in young males compared with young females. There was significant correlation for both males and females between muscle nerve activity and percentage body fat. However, for any given percentage body fat, nerve activity was greater in the males. Muscle sympathetic nerve activity also was strongly correlated with the waist to thigh ratio. An adjustment for waist-to-thigh ratio eliminated gender difference in sympathetic nerve activity [16]. Thus, this study suggests that at least part of the sex difference in sympathetic neural activity is associated with the different pattern of fat distribution between the genders.

4.3. Myocardial ischaemia and arrhythmias

Myocardial ischaemia may activate both vagal and sympathetic afferent fibres within the heart. A predominance of vagal activation following myocardial ischaemia may have both beneficial and harmful effects and experimental studies have shown that augmented vagal activity is antifibrillatory during myocardial ischaemia [70]. However, there are also data to suggest that extreme vagal activation results in asystole or haemodynamic instability [71]. There seems to be a female preponderance of unexplained syncope amongst middle-aged patients with myocardial infarction [72]. Furthermore, women had a higher risk of hypotensive and bradycardia reactions following admission with myocardial infarction [73] and a higher risk of acute haemodynamic complications following an acute angioplasty [74].

Airaksinen et al. [75] analysed changes in heart rate, heart rate variability, blood pressure and ventricular ectopy in 114 men and 65 women undergoing single vessel coronary artery angioplasty with a short episode of ischaemia. Although there were no significant differences at baseline, heart rate variability during coronary artery occlusion was higher in women than men. Significant severe bradycardia and hypotension was much more common in women than men. These findings are in agreement with an experimental study in rats showing a significant early fall in heart rate and mean arterial pressure in female rats after coronary artery ligation [7]. Post infarction arrhythmias induced by sympathetic activation were more severe in male than female rats [76,77].

4.4. Summary

The relative preponderance of sympathetic versus parasympathetic responsiveness in males, indicated in the previous section, seems to be lost with age. Male–female differences in sympathetic activity are related to body fat distribution with elevated sympathetic activity found with...
‘male’ type obesity. The female preponderance of parasympathetic activity may underlie female resistance to ischaemic tachyarrhythmias but at the expense of increased susceptibility to bradycardia-related events.

5. Mechanisms for the sex differences in the autonomic nervous system

Studies of the mechanisms accounting for gender and hormonal effects on the autonomic nervous system have generally required animal or tissue studies.

Some sex differences in the autonomic nervous activity are already present pre-natally. For instance, the distribution of neuropeptides in the brain differs between the brains of premature male and female rats [78], female rats have fewer ganglionic neurones [79] and acetylcholinesterase (AChE) activity is higher in newborn males than females [80].

Although information is limited accumulating evidence suggests that gonadal hormones, especially ovarian hormones, have significant effects on the brain, peripheral efferent nerves and signaling pathways of effector organ/cells that respond to neurotransmitters.

5.1. Central effects of gonadal hormones

Gonadal hormone signals are mediated through binding of steroids to cytoplasmic/nuclear receptors (genomic actions) and membrane receptors (non-genomic actions). Cytoplasmic hormone/receptor complexes then bind to DNA and modulate gene transcription. Binding of the hormones with membrane receptors leads to rapid onset of non-transcriptional actions with changes in neuronal excitability due to alterations in properties of lipid membrane, ion-channels and signal transduction systems. Neurons containing nuclear oestrogen receptor (ER) have been identified in brain centers involved in the regulation of cardiovascular function [81,82]. Membrane binding sites for oestrogen, progesterone and testosterone are also present in these regions [83].

It has been shown that sex hormones affect multiple aspects of central neuronal function. Intravenous or intracerebral administration of oestrogen increased vagal tone and suppressed sympathetic efferent activity in ovariec tomized female and male rats and these actions were blunted by intracerebral injection with selective oestrogen receptor antagonists indicating a central effect of oestrogen [65,84]. Oestrogen increased the density and affinity of muscarinic receptors [85,86].

The synthesis and clearance of neurotransmitters are regulated by sex hormones. Testosterone activates the catecholamine synthetase tyrosine hydroxylase, TH [87–89]. Vathy et al. [90] observed that male rats had a significantly fewer NA uptake-1 transporters than females in hypothalamus, preoptic area and frontal cortex measured by 3H-nisoxetine binding. Neuropeptide-Y mRNA levels are higher in male than female rats, reduced after castration and restored by testosterone replacement [91]. For cholinergic neurons, the activity of choline acetyltransferase (ChAT) and high-affinity choline uptake (HACU) are higher in female than male rats [80]. Ovariectomy reduces the activities of ChAT and HACU and reduced neuronal acetylcholine content in cerebral cortex and these changes were reversed by administration of oestrogen [92,93].

5.2. Peripheral effects of gonadal hormones

As in centrally localized neurons, the synthesis and metabolism of catecholamines and ACh in peripheral neurons are also modulated by gonadal steroids [94]. Mouse hearts from females contain more ACh than those from males [95]. Treatment of ovariectomized rats with oestrogen and progesterone increases the density of β-AR and muscarinic receptors in the heart [96]. Testosterone activates ChAT and TH in peripheral nerves [97,98].

Electrical stimulation of efferent vagal nerves induced more pronounced bradycardia in female than in male rats, but the bradycardic response to methylcholine did not differ between the sexes, indicating a larger quantity of ACh release by nerve activation in female hearts [99]. There were however no differences in bradycardic response to efferent vagal nerve stimulation between intact and ovariectomized female rats [64].

Neurotransmitter release is regulated by heterogenous inhibitory (e.g. α1-AR, muscarinic receptor M2) and facilitatory (e.g. β2-AR) receptors localized on the presynaptic membrane. α-AR density and activity in a number of tissues are higher in women [37,100,101]. Whilst direct quantitation of presynaptic receptor density is difficult, some studies revealed higher levels of α3-AR density or sensitivity in platelets in women than men [102–104] and platelet α3-AR density correlated significantly with variations in circulating oestrogen levels [105]. However, such differences were not observed by others [106–109]. We previously showed a more pronounced presynaptic inhibition of neuronal NA release in perfused rat heart apparently due to a higher α3-AR density and/or activity in females [110]. Such difference disappeared after ovariec tommy. There may also be a role for nitric oxide which is produced in response to oestrogen and is known to inhibit NA release presynaptically [111–116].

Inactivation of catecholamines after release depends on neuronal and extra-neuronal uptake by specific transporters. It is not clear whether there are gender differences in this process although some previous studies indicated a more efficient clearance of exogenous adrenaline in females than males [117,118]. Oestrogen may also upregulate the catalytic activity of catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) [119].

Recently described novel effects of oestrogens may also
contribute to hormonal modulation of the autonomic nervous system. In mice with disruption of ERα gene, sympathetic density in uterus increased by 1.9–3.5-fold [120]. Nerve growth factor (NGF) promotes nerve growth and phenotype development and sex differences in peripheral levels of NGF have been reported [121]. Oestrogen possesses a profound anti-apoptotic effect in cardiomyocytes and the vascular endothelium. Recently, Gollapudi and Oblinger [122] have shown that in NGF-supported PC12 cells expressing ERα by transfection, oestrogen protects cells from apoptosis. In male rats, aging is associated with reduced content and exocytotic release of NA and this is not present in aged females [123–125]. Further studies are warranted to examine the significance of this action of oestrogen and its role in sex-difference in autonomic function especially under senescent and pathological conditions.

5.3. Summary

Experimental data indicates the presence of receptors for gonadal hormones in the CNS, including in regions relevant for the functioning of the autonomic nervous system. Central administration of oestrogen enhances parasympathetic activity. In addition, there is evidence that testosterone enhances NA and NPY synthesis as well as reducing activity of NA clearance. Conversely, oestrogen enhances the activity of choline uptake and acetylcholine synthesis. Studies with peripheral tissues also indicate that oestrogen is associated with increased synthesis and release of acetylcholine. All these observations are consistent with the previously discussed observations that, in general, parasympathetic responsiveness is greater in females and sympathetic responsiveness greater in males. Recent developments indicate that oestrogen may also modulate nerve density and survival via effects on nerve growth factor. In addition, the anti-apoptotic effects of oestrogen may explain why age related decline in autonomic activity is more evident in males than females.

6. Conclusions

The autonomic nervous system plays a major role in the regulation of the cardiovascular system under both physiological and pathophysiological conditions. There is substantial evidence of gender difference in the functioning of the autonomic system, including specific effects of both male and female sex hormones, as summarised in Table 1. As a generalisation, at least in humans, there is a preponderance of sympathetic mediated responses in males and of parasympathetic in females — perhaps related to divergent gender roles pertaining during human evolution. These phylogenetic influences play a major role in modulating the course of many current and widely prevalent diseases.

Table 1
Summary of sex-related differences under physiological and pathophysiological conditions and the contribution by autonomic nervous system

<table>
<thead>
<tr>
<th>Physiologic and/or disease state</th>
<th>Gender difference</th>
<th>Autonomic nerve involvement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease state</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of Raynaud’s syndrome</td>
<td>F&gt;M</td>
<td>+ +</td>
<td>[59]</td>
</tr>
<tr>
<td>Prevalence of presyncope/syncope</td>
<td>F&gt;M</td>
<td>+ +</td>
<td>[72–74]</td>
</tr>
<tr>
<td>Survival of non-CAD heart failure</td>
<td>F&gt;M</td>
<td></td>
<td>[5.6]</td>
</tr>
<tr>
<td>Survival after myocardial infarction</td>
<td>M&gt;F</td>
<td>±</td>
<td>[1–4,126]</td>
</tr>
<tr>
<td>Risk of ventricular arrhythmias</td>
<td>M&gt;F</td>
<td>+</td>
<td>[76,77,127]</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Present</td>
<td>±</td>
<td>[128–130]</td>
</tr>
<tr>
<td>Central obesity</td>
<td>M&gt;F</td>
<td>+</td>
<td>[16,68,69]</td>
</tr>
<tr>
<td><strong>Physiological state</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure rise on aerobic exercise</td>
<td>M&gt;F</td>
<td>±</td>
<td>[12,46,131]</td>
</tr>
<tr>
<td>Haemodynamic response to isometric exercise</td>
<td>M&gt;F</td>
<td>+</td>
<td>[52]</td>
</tr>
<tr>
<td>Morphology of ECG ‘T’ wave</td>
<td>Present</td>
<td>±</td>
<td>[132–134]</td>
</tr>
<tr>
<td>Tolerance to cold temperature</td>
<td>M&gt;F</td>
<td>+</td>
<td>[57–59]</td>
</tr>
<tr>
<td>Tolerance to repeated hypoglycaemia</td>
<td>M&gt;F</td>
<td>+</td>
<td>[17,53]</td>
</tr>
</tbody>
</table>

ANS, autonomic nervous system; CAD, coronary artery disease. (+ +) Strong evidence, (+) good evidence, (±) conflicting data. M, males; F, females.

References

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