Sex and gender differences in symptoms of myocardial ischaemia

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Online publish-ahead-of-print 14 September 2011

This editorial refers to ‘Gender differences in symptoms of myocardial ischaemia’, by M.H. Mackay et al., on page 3107

Women with acute coronary syndromes (ACS) or myocardial infarction (MI) still undergo treatment significantly later than men. The reasons for this are unclear, but so-called ‘atypical symptoms’ in women have been under suspicion.1 Women are assumed to complain of anginal symptoms that differ from the classical picture of those of men, making diagnosis more difficult and delaying effective therapy. This phenomenon is of great relevance for healthcare in women and therefore has been investigated in numerous studies.2 It has been discussed whether sex or gender is the crucial factor for different presentation—whether differences exist between women and men in the biological mechanisms of pain, i.e. sex, or whether socio-cultural mechanisms, such as lack of awareness of risk or reporting behaviour, mainly contribute to the differences, i.e. gender. Do women have a different form of angina from men, do they interpret pain differently, or do they report it differently?

A significant number of studies analysing sex and gender differences in the presentation of MI and angina pectoris agree that women differ from men in their reported symptoms, even though the differences may be small. Most of these studies necessarily had a retrospective design, inquiring of patients after the event concerning the related symptoms. Only studies that focus on a first MI avoid the recall effect—that patients learn from events concerning the related symptoms.3 It has not yet been established whether vallinoid receptors start with the stimulation of afferent nerve endings in the heart. Pain generation in the heart is a complex process (Figure 1). It starts with the stimulation of afferent nerve endings in the heart. Nerve growth factor (NGF) is one of the substances involved in cardiac pain sensation.4 NGF leads to vallinoid receptor activation and stimulation of afferent nerves in the heart. Regarding this first step, it has not yet been established whether vallinoid receptors and NGF are differently expressed in female and male hearts. Both are reduced in diabetic hearts, and this may contribute to the occurrence of silent ischaemia in patients with diabetes. Their manipulation modulates pain sensation in an ischaemic transgenic mouse model. In addition, activation of the RAGE (receptor for advanced glycation end-products)–NF-kB (nuclear factor-kB) axis prevents pain sensation in diabetic hearts.5 Neuropathy is particularly frequent in diabetic patients, the elderly, and...
smokers, and may be mediated by RAGE and the NF-κB pathway. Diabetic neuropathy is also related to reduced synthesis of NGF, and depletion of calcitonin gene-related peptide (a marker for nociceptive nerves)-containing neurons. In addition to female gender, diabetes and old age are associated with atypical presentation of myocardial ischaemia, and their effects as modulating factors should be discussed.

Transmission of pain occurs by activation of sympathetic and vagal nerves. Sympathetic nerves predominate on the anterior surface of the heart where perfusion mainly comes from the left anterior coronary artery, whereas parasympathetic nerves arise from the posterior and inferior surfaces, mainly perfused by the right coronary artery or left circumflex artery. Thus, activation of the parasympathetic nervous system, which is more related to nausea and emesis, may characterize pain in patients with right dominant systems. This may also give rise to sex differences since right dominant coronary systems have been reported to be more frequent in women.11

Cardiac afferents then converge in the spinal cord with input from other somatic organs. Sympathetic afferents converge with somatic input on spinothalamic tract cells and vagal afferents in the nucleus tractus solitarius. The latter may stimulate efferent impulses in the autonomic nervous system, leading to nausea and emesis.

Angina perception in the central nervous system requires activation of specific brain areas that differ from those responsible for the perception of somatic pain. Patients with silent ischaemia exhibit the same degree of thalamic activation but less cortical activation, in the periaqueductal grey and hypothalamus, than those with clinical ischaemia, i.e. silent ischaemia is characterized by disturbed central processing of pain.12 Endorphins may also contribute to different pain sensation in women and men. Endorphins rise in ischaemia, are affected by sex hormones, and modulate central pain perception.13

Cerebral perception and reporting of pain are probably closely related, but not identical. Women and men may report pain differently because of different socialization and training of verbal responses. Reporting is related not only to pain perception, but also to self-perception and perception of the environment. Gender roles of patient and of the investigator, the format of questions, and linguistic phenomena, which include the socio-cultural dimension of gender, may all play a role. A number of studies have agreed that men and women may report pain differently even though their sensitivity to pain may be the same.2,14

In summary, sex and gender contribute to differences in the reporting of symptoms caused by myocardial ischaemia in women and men. There may be differences in the biological processes at synaptic and nerve levels and there may be gender differences due to women’s and men’s habits in perceiving and reporting a sensation. Thus, if we want to understand the reasons for different presentation of women and men with ischaemia, we have to consider the whole picture, including sex and gender issues.

The recent study by Mackay et al.15 focuses on the investigation of ‘Sex differences in the symptoms of myocardial ischaemia’. It
uses a novel approach: the study of pain reporting during well-defined objective ischaemic periods. For the first time ischaemia during percutaneous coronary intervention (PCI) is used for this purpose. It bans the gender dimension from the title, assuming that answering the questionnaire is not influenced by gender issues. The authors are investigating patients who undergo planned PCI and determine the nature of symptoms during the procedure by using a standardized questionnaire which is answered twice, the first time before PCI and related to previous symptoms and the second time during PCI, inquiring about the current symptoms. This selection of patients undergoing PCI eliminates patients with acute first MI and patients with non-obstructive CAD and may reduce the number of patients with atypical symptoms or complicated or multivessel lesions that are less suitable for PCI. Symptoms during PCI and symptoms of angina before PCI are determined with the same questionnaire. By doing this the authors accept a possibly strong recall effect. Patients undergoing PCI are now experienced in describing their symptoms! In this aspect, they may differ significantly from patients who are naive to such an experience.

Another issue is also noteworthy: in the selected patient cohort 20% had diabetes. Indeed, diabetic patients frequently exhibit silent ischaemia because of diabetic neuropathy. Thus in the part of the analysis that searches for factors decreasing the odds ratio of the reporting of chest or typical symptoms irrespective of sex, we would expect a strong effect of diabetes. Surprisingly, an effect of diabetes is not detected. However, unexpected and unexplained, current clopidogrel therapy had surprisingly an effect of diabetes is not detected. However, unexpected and unexplained, current clopidogrel therapy had an effect.

In conclusion, the study by Mackay and co-workers has great merits in that it measures sex-specific symptoms in a setting of objective myocardial ischaemia. However, because of unexplained findings and exclusion of the gender dimension, extrapolation of the findings beyond the well-defined setting of investigator-induced ischaemia should be avoided.

Acknowledgement

I thank Anne Gale for editorial assistance and Stefanie Schmidt for editing the literature and excellent secretarial support.

Conflict of interest: none declared.

References