Editorial

The Importance of Sex in the Stress–Heart Disease Relationship and the Potential Contribution of Gender to Future Research

Simon L. Bacon

We now have numerous studies that have linked increased levels of negative emotions and stress with the development and progression of cardiovascular disease—a relationship that seems to be sex specific in its pattern of outcomes.[1,2] However, the mechanisms of these relationships are still a source of much debate. One of the strongest potential pathways linking acute psychological stress with worse outcomes is through mental stress-induced myocardial ischemia (MSIMI).[3] Though there is a large overlap (ca. 70%) in individuals who demonstrate both MSIMI and more common (ie, exercise or pharmacological) stress-induced ischemia,[4] these seem to be distinctly different entities. Firstly, it would seem that more individuals are likely to have MSIMI only than exercise/pharmacological stress-induced ischemia only (20% versus 10%).[5] Furthermore, the profiles and potential mechanistic factors of those at risk for MSIMI compared with exercise/pharmacological stress-induced ischemia are different. For example, those individuals who exhibit MSIMI are more likely to be women, have greater microvascular disease, have poorer left ventricular dysfunction, and display endothelial dysfunction, whereas exercise/pharmacological stress-induced ischemia is generally associated with men and those with larger and more diffuse coronary artery plaque.[4–6] Though there are sex differences in the rates of presentations of both MSIMI and exercise/pharmacological stress-induced ischemia, both men and women do exhibit both of these forms of ischemia. However, we do not know if the mechanistic factors that underlie these stress-induced ischemia differ by sex; for example, does MSIMI in women differ from MSIMI in men? Understanding these processes can ultimately help in the development of better tailored diagnostic procedures and interventions to treat cardiovascular disease.

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The article by Sullivan et al[7] provides some important initial insights into sex differences in the potential mechanisms driving MSIMI. This secondary analysis of 678 (25% women) patients in the MIPS study (Mental Stress Ischemia Mechanisms and Prognosis) evaluated mental stress (public speaking)-induced vascular and hemodynamic responses. The authors found that MSIMI was generally driven by peripheral vasoconstriction in women compared with increased hemodynamic workload in men, results that were independent of exercise/pharmacological stress-induced ischemia. These results suggest that men with MSIMI are effectively cardiac stress reactors, with increased myocardial oxygen demands, and women with MSIMI are more likely to be vascular reactors, with greater endothelial driven increases in vascular resistance (which leads to increased left ventricular afterload and dysfunction).[8] However, the article by Sullivan et al does only provide initial insights, and there is a great deal of further information that we need. For example, building a more complex map of MSIMI, to include additional measures of the autonomic nervous system, the hypothalamic–pituitary–adrenal axis, nitric oxide release and usage, coagulation, and, most importantly, microvascular function, along with a more balanced sample of men and women is needed to adequately disentangle sex differences in MSIMI.

Clinically, the article by Sullivan et al[7] also provides a platform for future studies to build on to improve sex-specific diagnostic procedures[9] and treatments.[10] From a diagnostic perspective, several reviews of myocardial perfusion studies (the method used in the article by Sullivan et al to assess ischemia) using exercise/pharmacological stress have consistently found lower sensitivity and specificity for the prediction of heart disease in women relative to men.[11,12] Historically, one of the primary explanations for this imbalance in imaging techniques in women, compared with men, has been attributed to anatomy.[11,13–15] However, the study by Sullivan et al suggests that these limitations might not be solely anatomic and that there could well be physiological drivers to the poorer capacity of exercise/pharmacological stress perfusion imaging to detect ischemia in women. In contrast, the use of acute psychological stress tasks might actually be more appropriate in women, eliciting a more accurate physiological response,[16,17] which, in turn, may have greater prognostic ability.[3] With regards to the potential MSIMI treatment options, there is little data that has explored this question, let alone any sex-specific aspects. The REMIT study (Responses of Mental Stress-Induced Myocardial Ischemia to Escitalopram Treatment) assessed the efficacy of a selective serotonin reuptake inhibitor (escitalopram) to reduce MSIMI. After 6 weeks, the selective serotonin reuptake inhibitor lead to significant reductions in MSIMI and no statistical impact on exercise-induced ischemia.[10] This improvement seemed to be driven by increased left ventricular function (at rest and after mental stress) and stress-induced decreases in rate pressure product (a measure of myocardial oxygen demand). Unfortunately, these outcomes were not

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broken down to explore sex-specific patterns. From the article by Sullivan et al,[7] one might expect that improved left ventricular function would have been the hallmark of MSIMI reductions in women and improved myocardial oxygen demand in men. The potential sex-specific benefits of selective serotonin reuptake inhibitors, along with the usage of existing additional therapies or the development of new interventions (either on their own or in addition to selective serotonin reuptake inhibitors), need to be assessed. Further focused sex-specific research on both of these issues is certainly needed.

Finally, another important future extension to the study by Sullivan et al[7] would be to explore the independent role that gender may play in the evolution of MSIMI and whether there are specific mechanistic pathways that might relate to certain gender patterns, above and beyond sex. One of the great complexities here is to actually define gender, which is a multifaceted, complex, psychosocial, and cultural construct.[18,19] It includes elements such as gender identify (eg, masculinity or femininity), gender role (eg, child caretaking or being the primary income earner), and institutional gender (eg, access to childcare or pay inequity). This contrasts to the more physiological/anatomical notion of sex. Of note, the difference between sex and gender has been considered akin to that of genotype versus phenotype,[20] meaning that both aspects must be assessed to fully understand their unique and combined impact. Highlighting this is the growing literature that is showing the impact of certain aspects of gender on cardiovascular outcomes, which are independent of sex.[21] These distinctions could also have direct implications for the results of the study by Sullivan et al[7] because there is some suggestion that sex may drive heart disease pathways associated with factors such as abdominal obesity and insulin-resistance, whereas gender my drive heart disease through factors such as psychology distress and acute stress.[22] As such, how much of the sex difference seen could actually be attributable to gender or how much more might gender be able to explain the variability of stress responses? As with the arguments above, answers to these questions should ultimately lead us to better tailored medical care.

Disclosures

None.

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