Is physiology of coronary blood flow different in men and women?

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The study in this issue of the *Journal* analyzed the blood pressure (BP) and heart rate responses after adenosine infusion in a large group of patients undergoing vasodilators stress testing.[1]. The hypothesis tested is that there is a gender- and age-dependent responses to adenosine that can identify high-risk patients with a worse prognosis especially in young women.

The authors cite several prior studies. Izadnegahdar et al.[2] analyzed sex differences in acute myocardial infarction (AMI) hospitalization and early mortality rates in young adults. They observed that the overall, age-standardized AMI rates as well 30-day mortality rates declined similarly in men and women from 2000 to 2009, although there was an excess 30-day mortality in women less than 55 years of age compared to younger men. Wilmot et al.[3] estimated the annual percentage change in mortality between 1979 and 2011 in patients less than 55 years of age. The estimated annual percentage change in mortality was − 2.8% in men and − 1.9% in women. However, the cardiac deaths were 3.5 times higher in men.

In France Gabet et al.[4] observed that in 2014, more men than women were hospitalized for acute coronary syndromes (ACS) (36,480 women or 32.2% vs. 76,927 men or 67.8%). Mean age at hospital admission was higher in women (73.8 years) than in men (65.8 years). The proportion of patients aged < 65 years was 25.2% among women and 46.7% among men. In-hospital mortality was higher in women than in men (6.4% vs. 3.4%). The age-standardized rate of patients hospitalized for ACS was approximatively three times lower in women compared to men.

Otaki et al.[5] examined the relationship between cardiovascular risk factors, prevalence, and severity of coronary atherosclerosis in a large (1635 individuals), prospective, multinational registry of consecutive young (less than 45 years) individuals undergoing coronary computerized tomographic angiography. They found by multivariable analysis that male sex was the strongest predictor of both calcified and non-calcified plaques and that family history of coronary artery disease (CAD) was the strongest predictor for obstructive CAD. Therefore, it may be questionable the assumption that in CAD patients, female gender represents a negative prognostic risk factor. On the other hand, there is no clear explanation about the mechanisms of the high prevalence of sudden cardiac death in women without obstructive CAD. Endothelial dysfunction or coronary microvascular dysfunction could be suggested as mechanisms that induce ischemia in women with non-obstructive CAD.[6]

The PET prognosis multicenter registry[7] showed that the addition of stress myocardial perfusion Rb-82 PET data provided improvement in risk re-classification in both women (n = 2904) and men (n = 3133). For both men and women, there was a direct proportional relationship between increasingly abnormal stress perfusion score and age. For the oldest group of women with a > 10% perfusion defect, the annual adjusted CAD mortality was comparable to that of the corresponding group of men. Conversely, the event rate was very low in women < 50 years of age and the percentage of abnormal myocardium at vasodilator stress testing (adenosine or dipyridamole) was of borderline significance.

In the paper of Gebhard et al heart rate, systolic and mean BP significantly increased during adenosine infusion and the increase was significantly higher in women compared to men. Patients ≤ 55 years had a higher heart rate reserve (peak heart rate during adenosine infusion minus baseline heart rate/baseline heart rate ×100) as

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compared to patients > 55 years. The increase in heart rate is expected after vasodilator infusion whereas an increase in BP is an unexpected finding.

In the ADVANCE MPI trial, systolic BP decreased by 14 ± 13 mm Hg with adenosine and by 13 ± 14 mm Hg with regadenoson, while diastolic BP decreased by 10 ± 8 mm Hg with both agents.[8]

Adenosine affects the cardiovascular system by different actions mediated by four 4 subtypes of adenosine receptors (A_1, A_{2A}, A_{2B}, A_3). A_1 receptors affect the activity of sinus node and atrioventricular node inducing bradycardia and AV block. Activation of A_{2A} and A_{2B} produces coronary and peripheral vasodilation causing a decrease in BP. Further, a direct A_{2A} receptor-mediated activation of sympathetic afferents in the sinoatrial node level increases heart rate. For this reason, the injection of regadenoson that activates only A_{2A} receptors is systematically associated with a significant increase in heart rate.[9] An increase in BP could be due to increases in cardiac output, heart rate, and cardiac contractility and/or an increase of sympathetic driven peripheral resistance (likely due to anxiety). Therefore, different physiological mechanisms could compensate for the peripheral vasodilation induced by A_{2A} receptors stimulation to prevent a decrease in BP. Women have smaller coronary arteries, higher coronary blood flow and consequently high endothelial shear stress.[10] Reduced global quantitative stress blood flow or coronary flow reserve defined as microvascular dysfunction can be detected by quantitative PET with perfusion tracer in women;[11] however, Gebhard et al. found a significant association between heart rate and systolic BP increase and stress-induced perfusion defects by SPECT (using semiquantitative visual analysis which is not ideal for evaluating microvascular dysfunction). Diffuse epicardial coronary atherosclerosis in the absence of flow-limiting stenosis in association to microvascular dysfunction could induce regional flow maldistribution[12] detectable by SPECT, but likely underestimate the degree of abnormality. A prospective study with quantitative PET in men and women less than 55 years is needed to confirm these preliminary findings.

Disclosure

Raffaele Giubbini and Domenico Albano declare that there is no conflict of interest to disclose.

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