One explanation for why females have more optimal cardiac blood flow compared to males

The myogenic response is defined as that the muscle layer of small blood vessels, called resistance vessels, responds to changing blood pressure (within a certain range) by constricting (smaller vessel diameter) when intraluminal pressure is increased and dilating (larger vessel diameter) when the pressure decreases. This mechanism is also called pressure-induced myogenic constriction, and this action by resistance vessels allows for proper maintenance of blood flow to tissues. Furthermore, dilatory substances/factors released from the endothelium, cells that make up the inner layer of blood vessels, can diffuse to adjoining muscle cells to cause vasodilation that modulates the level of myogenic constriction. One of the most prominent dilators derived from the endothelium is nitric oxide (NO). Some pathological conditions, such as hypertension (high blood pressure), cause a reduction in NO and lead to an enhanced myogenic constriction resulting in reduced tissue blood supply. Thus, attenuating the myogenic response by promoting production of the endothelium-derived relaxing factors (EDRF) is important for maintaining optimum blood supply to tissues.

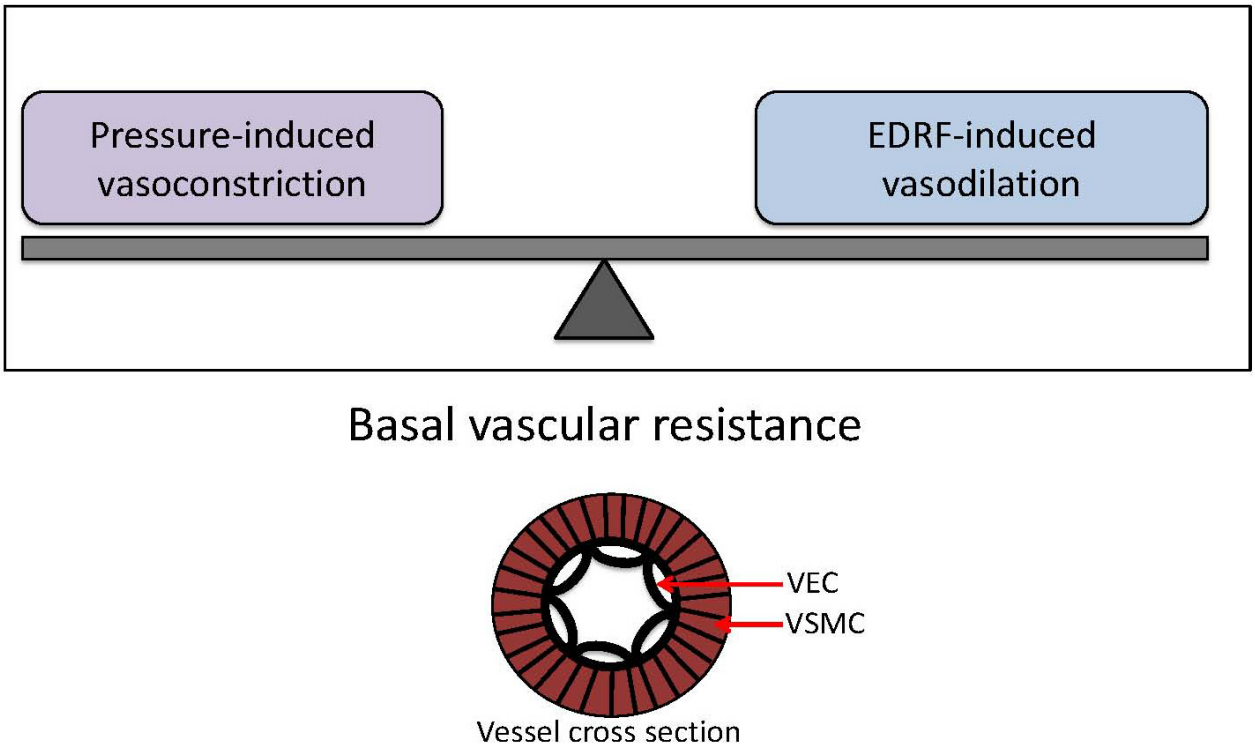

Fig. 1. Basal vascular resistance, as a function of balance between the pressure-induced vasoconstriction and EDRF-induced vasodilation. EDRF: endothelium-derived relaxing factors; VEC: vascular endothelial cells; VSMC: vascular smooth muscle cells.

Recently, another EDRF, epoxyeicosatrienoic acids (EETs), has been demonstrated to be able to modify the myogenic response. After being synthesized in endothelial cells, the vasodilatory EETs are broken down by an enzyme called soluble epoxide hydrolase (sEH) into non-vasoactive by-products. We have previously demonstrated that increases in tissue EET levels, either through deletion of the sEH gene and/or inhibition of sEH function, promote vessel dilation. Therefore, therapeutic interventions that compromise sEH can elevate EET tissue content and potentially improve heart function in patients with ischemic (deficient blood supply) heart diseases. Interestingly, enzyme content of sEH is lower (downregulated) in the female gender, thereby accompanied with elevated EET levels compared to males, whereas the sequential function of this phenomenon in the regulation of myogenic constriction in coronary blood vessels remains unknown.

In this study we hypothesized that increasing endothelial production of EETs, due to reduction of their degradation by sEH, lessens the myogenic constriction of coronary blood vessels and creates better blood supply to the heart. Since sEH is downregulated leading to increased EETs in females, it is plausible to believe that better cardiac blood flow is innately present in the female gender. To test this, we conducted experiments on male and female mice that were either normal or had the gene for the sEH removed. We measured heart EET levels, and also isolated coronary arteries from these mice to test the intensity of myogenic constriction. Additionally, we used drugs that could counteract the dilation effects of both EETs and NO in the vessels to determine whether the gender difference we observed was indeed due to changes in the actions of sEH.

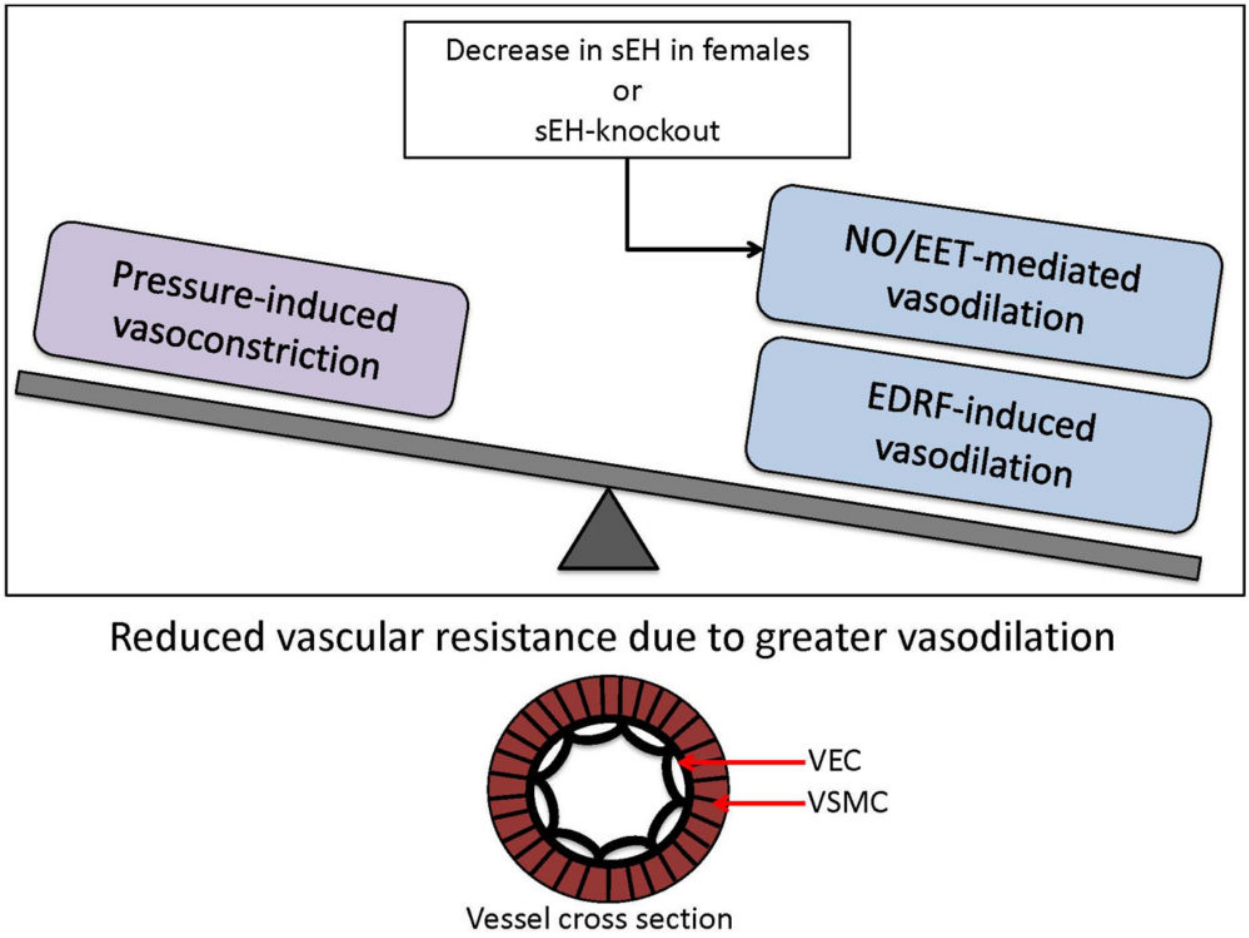

Fig. 2. Reduced basal vascular resistance, as a function of deficient sEH gene and/or female-dependent downregulation of sEH to increase EDRF-induced dilator responses that counteract the pressure-induced myogenic constriction. sEH: soluble epoxide hydrolase; EET: epoxyeicosatrienoic acid; NO: nitric oxide.

Our results show that compared to normal males, normal female mice have higher cardiac EET levels, which are similar to those in male and female mice with the sEH gene genetically removed. This elevation in EETs resulted in reduced myogenic constriction in their coronary vessels. When actions of EETs were blocked, the previously observed reduction in myogenic constriction was eliminated, providing evidence that either deficiency or downregulation of sEH evokes an EET-driven decrease in myogenic constriction. Sequential blocking the action of NO, the difference in myogenic constriction between male and female mice was abolished. Thus the greater inhibition of myogenic constriction in the female gender seems to involve both EETs and NO, but the function of NO is only seen when the actions of EETs are blocked. These findings point to the important roles of endothelial EETs and NO in moderating coronary myogenic response in a gender specific manner.

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Publication

Female-favorable attenuation of coronary myogenic constriction via reciprocal activations of epoxyeicosatrienoic acids and nitric oxide.
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