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Sex Differences in Myocardial Infarction and Rupture

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Although myocardial rupture occurs in a relatively low percentage (2–4%) of cases of acute myocardial infarction (MI), it is associated with an extremely high mortality rate due to cardiogenic shock (up to 90% in cases of free wall rupture and 50% of cases involving septal rupture), and it accounts for up to 25% of in-hospital death [1]. Understanding the molecular mechanisms leading to myocardial rupture therefore represents an important challenge for improving the short term prognosis of MI. In the present issue of the *Journal*, Fang and coauthors [2] investigate an intriguing aspect of the pathophysiology of this disease, which relates to the mechanisms underlying the gender differences in the rate of post-MI rupture.

It is well documented that the incidence of acute MI varies according to both gender and age. The Framingham study, for example, has demonstrated that the incidence of acute MI is 2.5-fold higher in males than females before age 45, however, this gender difference disappears after 55 years of age [3]. Clinical studies indicate that the rate of acute mortality, including sudden death, in men is about twice that observed in women [4]. This poorer prognosis in men is also supported by the observation that myocardial rupture after MI is observed twice as often in men than in women [5]. The prognosis of MI is also usually worse in younger patients due to the absence of a history of chronic ischemia and secondary collateral development, and because an early MI is usually due to the accumulation of several risk factors, such as diabetes, smoking, metabolic syndrome and consumption of recreational drugs [6].

These clinical observations of sex differences in the incidence and the prognosis of acute cardiovascular events correlate with several studies conducted in large mammals [7–10]. In a monkey model of aging, gender differences in gene and protein expression can explain several aspects of the characteristic protection of females against cardiovascular disease, including a better preservation with aging of the expression of enzymes of glycolytic and oxidative pathways [10], a better cardiovascular response to β -adrenergic stimulation [9], less apoptosis and myocyte hypertrophy in old female monkeys than in old male monkeys [11], as well as differences in the composition of the extracellular matrix of conductance vessels, such as elastin and collagen isoforms, which correlates with lower vascular stiffness in females compared to males [7,8]. Some of these differences between males and females are already present at a young age, especially for genes expressed on sex chromosomes, suggesting that gender differences in expression of genes and proteins in the cardiovascular system can already be programmed early in life [8].

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Gene expression diverges between males and females in multiple tissues. One of the first descriptions of such divergence relates to the differential expression of cytochrome P450 isoforms in the liver, which directly affects the rate of drug clearance [12]. Although some of these differences can be attributed to sex hormones, other stimuli are involved as well, including the gender difference in the rate and frequency of release of growth hormone, which in turn affects specific transcription factors [13], or hormone-independent transcription factors, such as Rsl [14]. Another example includes the kidney, which is more sensitive to disease and graft rejection in men than women [15]. These clinical observations also relate to a difference in expression of specific gene clusters involved in drug clearance and osmotic control [16]. The brain also shows sex-specific gene divergences at the prenatal stage, whereas most of these differences disappear in the adult, except for genes encoded by sex chromosomes [16]. Interestingly, gender-specific gene expression in the mouse brain is found at an embryonic stage that precedes the production of sex hormones [17]. Other cases of gender divergence in gene expression include the hepatic response to ethanol consumption in rats [18], and the sensitivity of murine hematopoietic stem cells to benzene intoxication [19]. An example of gender difference in the heart includes the genomic response to pressure overload, a condition in which male mice show a more robust over-expression of genes involved in immunity and inflammation than females [20], which is in agreement with the more pronounced inflammatory response found in male mice after MI as described here by Fang et al [2]. In addition, previous studies in rodents have documented a gender difference in cardiac remodeling following MI [21]. These studies are all supportive of a lower rate of cardiac remodeling in females compared to males, including less inflammatory response, lower collagen deposition, reduced infarct expansion and a lower percentage of cardiac rupture [21].

Cardiac rupture after MI results from an imbalance between mechanical stretch and tensile resistance of the necrotic tissue. Several studies have shown that an imbalance between the enzymatic activity of matrix metalloproteases (MMPs) and collagen deposition represents the molecular mechanism underlying the increased risk of rupture [21,22]. Among the multiple forms of MMPs, the gelatinases MMP2 and MMP9 are expressed both in cardiac fibroblasts and in myocytes, and can degrade several types of collagen (including the types 1 and 3) [23]. Disruption of the collagen matrix by increased MMP activity leads to increased stress for the cardiomyocytes, and therefore leads to further hypertrophy and remodeling [24]. In addition, this dissociation of collagen bundles by MMPs stimulates further collagen synthesis through transcriptional activation of the corresponding genes [24]. The role of collagen in the resistance of the ventricular wall against rupture is further supported by the observation that transgenic mice with cardiac over-expression of the β_2 -adrenergic receptor have a lower rate of rupture compared to wild type mice, which correlates with a higher accumulation of interstitial collagen in the transgenic animal [25]. It should be kept in perspective, however, that in the clinical setting, treatment with β -blockers will decrease the risk of rupture by decreasing myocardial wall stress.

In the current study, Fang et al. [2] confirm this gender difference in the risk of cardiac rupture after MI, and further delineate its mechanisms. The novelty brought by the present study relates to the fact that total collagen content does not differ between genders, however males are characterized by a 70% reduction in cross-linked collagen, which indicates more breakdown and therefore more fragility of the collagen network in males. The study also indicates that MMP9 is probably responsible for the increased degradation of collagen bundles, as a consequence of the higher inflammation observed in infarcted myocardium from males compared to females. The therapeutic relevance of the study is highlighted by the observation that an MMP inhibitor significantly reduces the increased risk of rupture in male mice.

As with any provocative study, more questions are raised than answered. Four of these questions are briefly noted here that need to be addressed in the future:

1. What hemodynamic mechanisms may contribute to the incidence of rupture in this model? An important parameter to examine would be LV wall stress. For example, at any given LV pressure, increased LV volume and a thinner wall will increase LV wall stress, which would increase the possibility of rupture.
2. Why are there such striking strain differences in incidence of rupture in mice ranging from 81% in males in this study using the 129svj strain, to 3-4% in males in other strains (such as FVB) reported by this group previously [26]. Examination of the differences in myocardial genes and proteins in these strains might provide further mechanistic insights.
3. Another question raised by the study is whether this gender difference in the risk of cardiac rupture relates to a different genetic or hormonal pattern. It has been shown, for example, that sex hormones can also dictate the expression of extracellular matrix and MMPs in the aorta [8,27]. The fact that the gender difference in the incidence of MI disappears after menopause [3] also supports this notion. In addition, it has been shown that the hormonal pattern directly affects ventricular remodeling after MI. For example, estrogens and testosterone have opposite effects on myocyte size and cardiac function after MI in mice, with estrogen preventing myocyte hypertrophy and preserving ejection fraction, while testosterone has the opposite effects [28]. An additional study from the same authors showed that testosterone is also responsible for a higher rate of cardiac rupture due to higher inflammatory response in the same model of MI [29]. These data correlate with the observations by Fang et al of a higher rate of rupture in males compared to females, associated with higher inflammatory reaction and a more pronounced activation of MMP9 [2].
4. Another question stemming from this study relates to identifying which signaling pathways are involved in this gender difference of MMP activation and collagen deposition. A likely suspect is the transcription factor NF- κ B, which is essential for the transcription of the genes encoding MMPs and collagen isoforms in the heart [30]. NF- κ B is activated upon cardiac stress, such as overload or ischemia, by the proteasomal degradation of its specific inhibitor, I- κ B α , which is constitutively produced and binds NF- κ B, thereby preventing the activation of the transcription factor [31]. Multiple pathways mediating cellular stress can activate I- κ B kinases, which phosphorylate I- κ B α [31]. Upon phosphorylation, I- κ B α is tagged for ubiquitylation and proteasomal degradation, thereby allowing the nuclear translocation of NF- κ B, which becomes transcriptionally active [31]. If NF- κ B is really involved in the mechanisms of cardiac rupture after MI, manipulating proteasome activity after MI might affect the balance between MMP activation and collagen deposition. Protective effects of proteasome inhibitors have already been demonstrated in the context of pressure overload [32], where these inhibitors prevent or reverse cardiac hypertrophy while improving contractile function, and thereby limit the transition into heart failure. A similar mechanism appears to be activated in a setting of post-ischemic volume overload [33]. Future studies will be needed to determine whether proteasome inhibition may improve the short-term and long-term prognosis of MI by reducing the risk of myocardial rupture and slowing the transition into heart failure, respectively.

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