MINIREVIEW

Gender Differences in Cardiac Ischemic Injury and Protection—Experimental Aspects

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This review summarizes some available information on gender differences of myocardial injury with particular attention to experimental approach. It has been observed that significant gender differences exist already in normal heart. They involve among others cardiac growth, contractile function, calcium metabolism and function of mitochondria. Differences, characteristic of the normal myocardium, generate the logical presumption of the different reaction of the male and female heart to various pathogenic factors. Most of the experimental studies confirm the clinical observations: increased resistance of the female heart to ischemia/reperfusion injury was shown in dogs, rats, mice and rabbits. Furthermore, gender differences in the ischemic tolerance of the adult myocardium can be influenced by interventions (e.g. hypoxia) imposed during the early phases of ontogenetic development. The already high tolerance of the adult female heart can be increased by adaptation to chronic hypoxia and ischemic preconditioning. It seems that the protective effect depends on age: it was absent in young, highly tolerant heart but it appeared with the decrease of natural resistance during aging. Both experimental and clinical studies have indicated that female gender influences favorably also the remodeling and the adaptive response to myocardial infarction. It follows from the data available that male and female heart differs significantly in many parameters under both physiological and pathological conditions. Detailed molecular and cellular mechanisms of these differences are still unknown; they involve genomic and non-genomic effects of sex steroid hormones, particularly the most frequently studied estrogens. The cardiovascular system is, however, influenced not only by estrogens but also by other sex hormones, e.g. androgens. Moreover, steroid hormone receptors do not act alone but interact with a broad array of co-regulatory proteins to alter transcription. The differences are so important that they deserve serious consideration in clinical practice in search for proper diagnostic and therapeutic procedures. Exp Biol Med 234:1011–1019, 2009

Key words: gender differences; ischemia/reperfusion injury; cardioprotection; adaptive response

General Background

It is well known that numerous health problems are affected by gender. Women are more susceptible than men to depression, osteoporosis, asthma, lung cancer due to smoking, and autoimmune disease (1). However, not all medical problems show gender dimorphism; for example, males do not differ from females in terms of their response to infection. And what is the role of gender in cardiovascular diseases? It is first of all necessary to emphasize that the number of clinical and experimental papers dealing with this topic significantly increased during the last 20 years: according to the data from the Web of Science their amount was negligible still in 1989 (Fig. 1). This trend is obviously the result of at least two facts: the number of examples of different behavior of the male and female heart under physiological and pathological conditions is steadily increasing and there are controversial reports on the beneficial or adverse effects of hormonal replacement therapy (HRT) in women during menopause.

Both clinical and experimental observations support the view that cardiovascular diseases belong to the health

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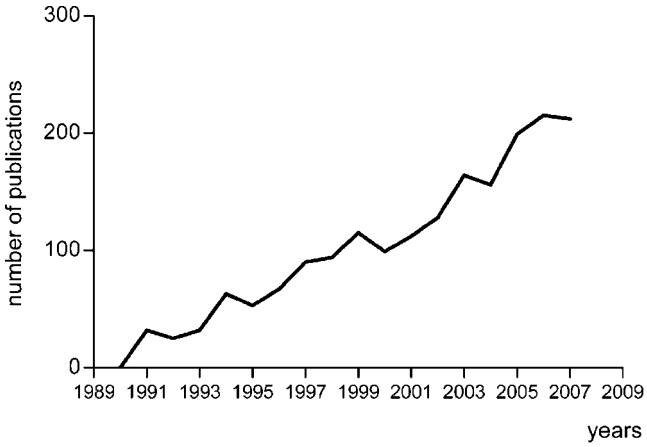

Figure 1. Number of clinical and experimental papers dealing with "gender and heart AND female heart" from 1989 to 2007. Source: Web of Science.

problems where gender differences play an important role (2). Men are generally at greater risk than are age-matched premenopausal women; this concerns not only ischemic heart disease but also other cardiovascular disorders, such as hypertension, arrhythmias, and heart failure. After menopause, however, the incidence of cardiovascular diseases increases in women as well; this observation led to the idea that increase in the incidence of cardiovascular diseases is associated with the decreasing levels of estrogens during menopause. For these reasons HRT and the benefits of administering supplemental estrogen to post-menopausal women have become popular research topics. However, the few large-scale human-subject studies have shown that estrogen replacement in postmenopausal women actually increased the ischemic heart disease (3, 4). Potential reasons for the lack of protection in the clinical trials likely include differences in the pharmacology between conjugated equine estrogen and 17β-estradiol and the age of women at the start of treatment (5).

The decisive role in the search for elucidation of the mechanisms involved in the gender differences should be played by experimental studies on laboratory animals. There is, however, a major limiting factor: the vast majority of experiments have been carried out on males only (1). The reason is first of all the fact that the pathogenetic mechanisms in males are, contrary to females, not influenced by fluctuation of the hormonal activity. Furthermore, the often repeated argument is the complicated comparison of age-matched males and females: the body weight of females is always lower. Despite the growing number of reports in the literature identifying sex-related differences in cardiac function in both rodents and humans, the underlying mechanisms have yet to be determined.

Ischemic heart disease is the leading cause of morbidity and mortality in both men and women and according to the World Health Organization will be the major global cause of death by the year 2020. This review attempts to summarize, therefore, some available information on gender differences of myocardial ischemic injury and protection with particular attention to experimental approach.

Normal Heart

One of the basic cardiac characteristics is, without doubt, its growth. It has been found that in human left ventricular (LV) mass was not significantly different in boys and girls during infancy and childhood (6). Increased absolute and relative heart weight in males becomes evident at puberty when sex-specific hormonal influences are imposed on the original anatomical pattern; this gender difference in absolute values attains in adulthood 15–30%. Since the initial number of cardiac myocytes is likely to be similar in both sexes, their hypertrophic growth in males is significantly more expressed. Aging is associated with a preservation of cardiac muscle mass in women and a reduction in the left and right ventricular weights in men (7). These data are supported by the findings of Zhang *et al*. (8) in the aging monkey heart: LV weight/body weight ratio decreased in old males but did not change in old females; however, despite the decrease in LV weight, the mean myocyte cross-section area in old males increased by 51% as compared with only an 8% increase in old female monkeys. A significant gender difference was also observed in the number of myocytes during development (7). The aging process did not alter the number, size, shape and proportion of myocytes of the female heart in the age range from 20 to 95 years. In contrast, the male heart lost from age 17 to 89 years 45 million myocytes/year in the left and 19 million myocytes/year in the right ventricle. Myocyte cell loss was accompanied by a progressive increase in average myocyte cell volume and this reactive hypertrophic response was capable of compensating, at least in part, for reduction in muscle mass. Mallat *et al*. (9) studied whether gender differences can influence cardiomyocyte apoptosis in normal human heart. Surprisingly, they found that the incidence of this type of cell death is three times higher in men than in women, with no correlation with age. Similar gender differences were found in the human coronary arterial wall (10).

As far as the gender differences of the normal cardiac function are concerned, as early as in 1920 Bazett (11) observed that women had a higher resting heart rate than men. In a large population-based study the average heart rate for women was found to be 3–5 beats faster per minute than that of men (12). Sexual dimorphism appears also in arterial blood pressure in humans during adolescence and persists through adulthood. In men less than 60 years old the average systolic and diastolic pressure is higher than in age-matched women by 6–7 and 3–5 mm Hg, respectively. After menopause, blood pressure (particularly systolic) in women increases so that hypertension becomes more prevalent than or at least as prevalent as in men (13). Echocardiography has demonstrated a better diastolic function in young women

than in age-matched men, and with aging, men have a decrease in systolic function that is not observed in women (14).

Experimental studies are controversial and not concise. Whereas Capasso *et al.* (15) observed in papillary muscles from 6-month-old rats that males had significantly lower rates of contraction and relaxation than females, Curi *et al.* (16) demonstrated that rat male papillary muscle developed higher contractile force than female papillary muscle. Furthermore, Schaible and Scheuer (17), using isolated working rat heart preparation, observed increased cardiac output in males. And, finally, Leblanc *et al.* (18) using papillary muscles found no difference between the sexes until rats were 6 months old. Another view arises from the recent study by Petre *et al.* (19). Despite virtually identical contractile performance of the feline heart under basal conditions, significant sex differences were found at higher stimulation frequencies: the male heart exhibited a higher contractile reserve. These results may provide clues to the mechanisms of sex differences in response to pathological stimuli; nevertheless, we are still waiting for further reliable experiments. Similarly as in humans, gender differences in blood pressure occur in animals: in spontaneously hypertensive rats (SHR), Dahl salt-sensitive rats as well as in New Zealand genetically hypertensive rat the blood pressure in males is significantly higher than in females (20).

The number of studies demonstrating the gender differences at the molecular level increased significantly during the recent years. The extent of the present review allows, however, mentioning only a few differences that can markedly influence the cardiac function under physiological and pathological conditions. To the most important belong undoubtedly the differences in myocardial calcium metabolism. Chu *et al.* (21) studied the expression of the key proteins, regulating Ca^{2+} handling in ventricular cardiomyocytes. They found that the rat female ventricle has significantly higher levels of the L-type calcium channel, ryanodine calcium-release channels (responsible for Ca^{2+} release from the sarcoplasmic reticulum) and Na^{+}/Ca^{2+} exchange protein (responsible for removal of Ca^{2+} from the cardiac cell). Regulation of the expression of these proteins occurs at the transcriptional and posttranscriptional level. Intuitively, it makes sense if more Ca^{2+} enters female myocytes on a beat-to beat basis (as is consistent with more Ca^{2+} channel protein), then—to maintain Ca^{2+} homeostasis—there must be a mechanism to provide higher Ca^{2+} efflux from the cells. No sex differences were found in sarcoplasmic reticular Ca^{2+} ATPase (responsible for Ca^{2+} uptake by sarcoplasmic reticulum) and phospholamban. Significant sex differences in the expression of key ventricular Ca^{2+}-handling proteins were associated with only small differences in the cardiac contractile function. This study is, however, limited because it addresses only differences in protein abundance and not potential sex differences in the function of these proteins.

Significant gender differences were found also in the uptake of Ca^{2+} by cardiac mitochondria (22). Mitochondria from female rat heart have lower Ca^{2+} uptake rates in physiological substrate solutions and are able to maintain mitochondrial membrane potential even at high concentrations of Ca^{2+}. This may be one of the possible explanations why female myocardium suffers less injury with ischemia/reperfusion. Colom *et al.* (23) demonstrated another significant gender difference in the function of cardiac mitochondria. Female rats exhibited lower cardiac mitochondria content; they were more efficient and generated less H_2O_2 than the males. This finding could help to understand the mechanism by which females exhibit lower incidence of different aging-related disorders, including cardiovascular disease. On the other hand, male myocytes have a higher density of β-adrenergic receptors and thus also an increased inotropic response to β-adrenergic stimulation. This leads to the increased influx of Ca^{2+} into the cardiac cell; male myocytes are therefore more threatened by a calcium overload.

The above-mentioned gender differences, characteristic of the normal myocardium (their enumeration is far from complete), create the logical presumption of the different reaction of the cardiac muscle to various pathogenic factors, including ischemia/reperfusion injury.

Ischemic Injury of the Cardiac Muscle

Epidemiological studies have clearly shown that in women before menopause the onset of ischemic heart disease occurs on the average 10 years later than in men, with myocardial infarction occurring 20 years later. Menopause thus plays a decisive role in the increase in cardiovascular risk: there was a 10-fold increase in ischemic heart disease after menopause compared to only a 4.6-fold increase in the same age groups in men (24). This is due probably to the gender differences in the development of atherosclerosis, corresponding to the above-mentioned 10 years, as shown already by Fejfar (25). These facts are supported by the lower levels of LDL and higher levels of HDL in women until menopause.

Most of the experimental studies confirm the clinical observations. We have observed already in 1980s that the isolated right ventricle of female rats is significantly more tolerant to acute oxygen deficiency than that of the male heart (26, 27) (Fig. 2). Intensive investigation of this question started, however, only in recent years. Increased resistance of the female myocardium to ischemia/reperfusion injury (Fig. 3) was shown in dogs, rats, mice and rabbits (28). In this connection it is interesting to emphasize that even in SHR gender differences exist in the sensitivity to ischemia reperfusion. We have shown (29) that cardiac tolerance to ischemia/reperfusion injury, as judged from the degree of postischemic contractile dysfunction, was sex-dependent: recovery of female SHR hearts was significantly better than in SHR males, despite the fact that the degree of hypertension was comparable. Estrogen deficiency in-

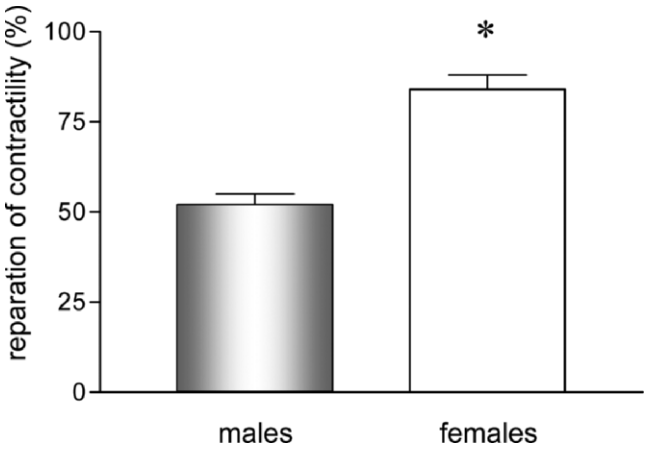

Figure 2. Gender difference in the cardiac tolerance to acute oxygen deprivation in rats (expressed as % of the reparation of contractility of the isolated right ventricle after acute anoxia). * $P < 0.01$; data from Ostadal *et al.* (26).

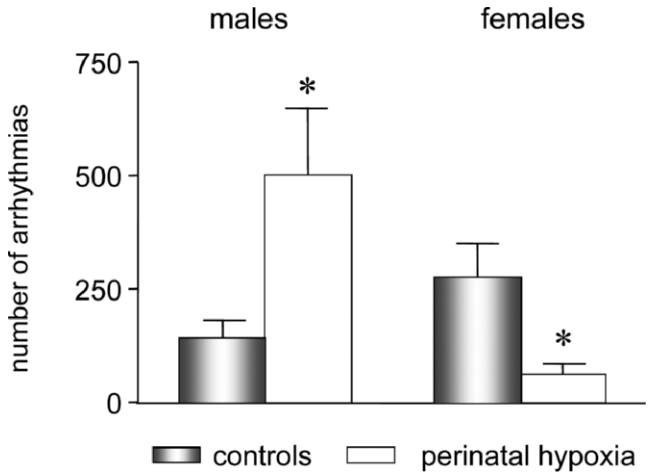

Figure 4. Effect of perinatal hypoxia on the number of ischemic arrhythmias in adult rat males and females. * $P < 0.01$; data from Netuka *et al.* (31)

creased in rat males the sensitivity to ischemia/reperfusion injury; on the other hand, a higher level of this hormone had the opposite effect (30). It is interesting to note that the ischemic tolerance of the adult myocardium can be significantly influenced by interventions imposed during the early phases of the ontogenetic development. We have observed (31) that perinatal exposure to chronic hypoxia significantly increased cardiac tolerance to ischemic injury in adult females as evidenced by the lower incidence and severity of ischemic ventricular arrhythmias as compared with the normoxic group (Fig. 4). The effect of perinatal hypoxia on ischemic arrhythmias in males was quite the opposite. These results support the hypothesis that perinatal hypoxia is a primary programming stimulus in the heart that may lead to sex-dependent changes in cardiac tolerance to ischemia in later adult life. This would have important implications for patients who have experienced prolonged hypoxemia in early life.

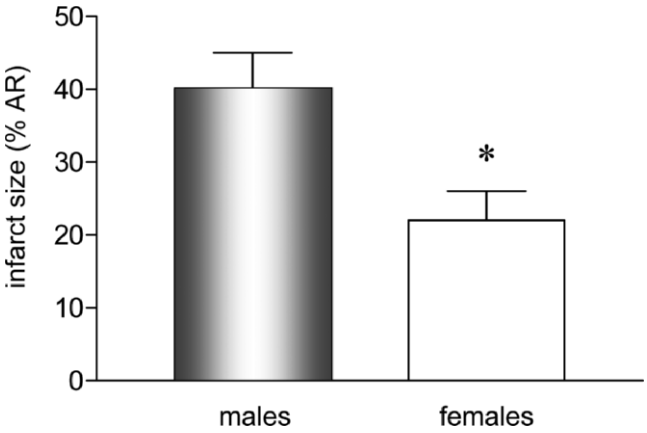

Figure 3. Gender differences in the infarct size in rats. * $P < 0.01$; data from Johnson *et al.* (28).

Possible Role of Hormones

The question remains what is the cause of the gender difference in cardiac sensitivity to ischemia. Even though the role of sexual hormones is far from unambiguous, a large body of evidence indicates that estrogen is involved in gender-related mechanisms of ischemia tolerance. Most of the action of estrogen has been attributed to estrogen binding to either estrogen receptor (ER)-α or ER-β, two nuclear hormone receptors that act as ligand-activated transcription factors binding to DNA response elements (32). Besides the well established cytosolic/nuclear localization, estrogen receptors have also been detected at the level of plasma membrane and mitochondria (33). It is important to note that both ER subtypes are widely expressed within cardiovascular tissues in a broad variety of species ranging from mice to humans. In particular, cardiac myocytes, cardiac fibroblasts, vascular smooth muscle cells, and endothelial cells express relevant amounts of functional ER-α and ER-β proteins (34). A number of studies have examined whether the protection afforded by estrogen is mediated by ER-α or ER-β (32). These studies have been carried out using either genetically altered mice that lack ER-α or ER-β or by addition of an ER-α or ER-β agonist. Unfortunately, there is no consensus regarding which estrogen receptor mediates the protection against ischemia/reperfusion injury: there are data suggesting a role for both ER-α (35–38) and ER-β (39, 40). For the explanation of this obvious discrepancy, different models of ischemia/reperfusion, different end-points, the dose and timing of the addition of agonist should be taken into consideration (32).

The activated estrogen-receptor complex triggers the synthesis of specific mRNAs and the production of a number of proteins that are responsible for the various effects elicited in the different cell types. Along with these genomic effects, additional processes termed nongenomic occur rapidly and

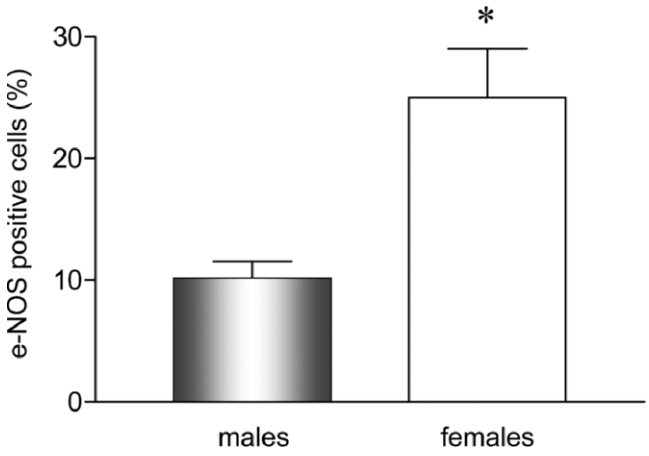

Figure 5. Expression of eNOS in the rabbit heart. * $P < 0.01$; data from Wang *et al.* (44).

independently of protein synthesis (41). Among the many pathways that can modify the susceptibility to ischemic injury in female hearts is the molecule of nitric oxide (42). It has been shown that the expression of endothelial NO synthase (eNOS) is significantly higher in the female heart (Fig. 5); blockade of this enzyme (L-NAME) abolished the gender differences in cardiac sensitivity to ischemia/reperfusion (43, 44). Moreover, it was shown that higher content of eNOS in female heart reduced the activity of L-type calcium channels and thus prevented calcium overload, one of the main causes of ischemia/reperfusion injury (43). It is, however, apparent that the above mechanism is not the only pathway responsible for sex differences in the susceptibility of the heart to ischemia and that this effect is quite complex. It has been observed that the cardioprotection associated with female sex was accompanied by a greater protein expression of the sarcolemmal (28) and mitochondrial (45) K_{ATP} channels; their blockade increased the degree of injury in the female heart. Bae and Zhang (46) hypothesized that the gender-related differences in the heart susceptibility to ischemia/reperfusion are implemented by the increased protein kinase B (Akt) and protein kinase Cε levels. The proposed cardioprotective effect includes inhibition of apoptosis and hence reduction of myocardial infarction. The possible protective role of Akt is supported by the observation of Camper-Kirby *et al.* (47) that young women possess higher levels of nucleus-localized Akt relative to comparably aged men or postmenopausal women. Xu *et al.* (48) assume that the cardioprotective effects of estrogen are in part mediated by inhibiting the expression of pro-inflammatory tumor necrosis factor α (TNFα) and modulating TNFα receptor expression; TNFα inhibition improved functional recovery and reduced apoptosis and myocardial necrosis.

The majority of experimental studies deal exclusively with the effect of estrogens and estrogen receptors. However, it is obvious that the cardiovascular system is influenced not only by estrogens or hormones with estrogen effects, but at least by one additional player, androgens. Similarly to estrogens, androgens are present in both sexes, albeit at different concentrations and ratios. Endogenous androgens (dehydroepiandrosterone, androstenedione, and testosterone) are readily converted to estradiol by the sequential actions of 17β-hydroxysteroid dehydrogenase and aromatase. Grohé *et al.* (49) have shown that cyp450 aromatase active in generating estrogen is expressed in cardiac myocytes; incubation of cardiac myocytes with estrogen precursors androstenedione and testosterone stimulated expression of ER-α and ER-β and iNOS in a gender-specific fashion. These data suggest that local estrogen biosynthesis may contribute to the cardioprotective effects of estrogens. It is, therefore, obvious that some of the beneficial effects of testosterone observed in males may be due to its conversion to estradiol and estradiol metabolites. Testosterone activates androgen receptors that are expressed in cardiac myocytes; it increases endothelin-1 levels, circulating levels of homocysteine and, by stimulation of tyrosine hydroxylase, elevates the synthesis of catecholamines. Testosterone thus markedly influences the cardiovascular system; its reduced level has a cardioprotective effect (13). However, recently Tsang *et al.* (50) observed that testosterone conferred cardioprotection by up regulating the cardiac α(1)-adrenoceptor and enhancing the effects of stimulation of this adrenoceptor. These effects of testosterone were abolished or attenuated by blockade of androgen receptors. Several newer steroid hormones signaling concepts with implications for cardiovascular physiology have emerged recently. Steroid hormone receptors do not act alone but interact with a broad array of co-regulatory proteins to alter transcription. Understanding co-regulator biology is important to the development of cardiovascular-selective estrogen receptor modulators and modulators for other sex steroid hormones (51).

The number of different hypotheses, trying to explain the mechanisms of gender differences in cardiac sensitivity to oxygen deprivation, steadily increases. Nevertheless, we are still waiting for a competent and verified explanation of the molecular basis of this clinically highly relevant biological phenomenon. New better tailored HRT and selective modulators of steroid hormones for prevention and treatment of cardiovascular diseases in women are needed (51).

Protection of the Female Heart

To answer the question whether it would be possible to increase the already high tolerance of the female heart to ischemia by different types of known cardioprotective mechanisms is not easy. Experimental studies dealing with this problem are sporadic and not conclusive, clinical observations are completely missing. We have observed that adaptation of rats to chronic hypoxia increases cardiac tolerance to acute hypoxia (expressed as increased repa-

ration of contractility after acute anoxia) in both sexes, yet the sex difference was preserved: female heart was significantly more tolerant (26, 27). Data on the protective effect of ischemic preconditioning are inconsistent. Humphreys *et al*. (52) have observed a comparable degree of protection in both male and female rat heart. On the other hand, Wang *et al*. (44) were unable to increase the tolerance of the female rabbit heart by preconditioning induced by isoflurane. And, finally, Song *et al*. (53) have found that cardioprotection by preconditioning produced by endotoxin was attenuated in isolated female rat hearts as compared with those of their male counterparts. Similar results were obtained by Crisostomo *et al*. (54) with ischemic postconditioning. Recently, Cao *et al*. (55) have found that there is no sex difference in the degree of Met^5-enkephalin (ME)-induced protection but there is a sex difference in the cardioprotective signaling pathways after the administration of ME. ME-induced cardioprotection in males primarily utilizes a PI3K/Akt1/2 pathway, whereas in females the PI3K/Akt3 one.

It seems to us that most relevant is the observation of Turcato *et al*. (56) that preconditioning in females depends on age: its protective effect was absent in young, highly tolerant heart but it appeared with the decrease of natural tolerance during ageing. This fact is most likely a general biological phenomenon; we observed a similar effect in neonatal rats (57, 58): their already high hypoxic tolerance could not further increase either by adaptation to chronic hypoxia or by ischemic preconditioning. Protective effect occurred only with the decrease of natural cardiac tolerance during the first postnatal week.

Adaptive Response of the Cardiac Muscle

Remodeling after myocardial infarction is initially a compensatory response which facilitates maintenance of a normal stroke volume despite the loss of myocytes. However, when progressive remodeling occurs, it may lead to the development of heart failure (59, 60). Clinical studies suggest that gender affects also these adaptive responses; differences involve first of all the rate of changes, the degree of hypertrophy and fibrotization, and the extent of cell death. It is generally accepted that the female heart tolerates the stress much better than male myocardium, but the reasons for the different patterns of remodeling are not known. Females exhibit increased left ventricular hypertrophy and have an increased cardiac reserve, with augmented preservation of cardiac function and slowed transition to heart failure (61, 62). Women living with heart failure have significantly better survival than men with this condition, despite being older (63). Gender differences do exist also in the extent of myocyte death following heart failure. Guerra *et al*. (64) demonstrated that necrosis and apoptosis in the failing human heart was twice higher in men than in women, necrosis being in both sexes 7-fold greater than apoptosis. The mechanism responsible for the reduction of myocyte death in women with cardiac failure is, however, unknown. In clinical trials it is difficult to clearly determine if there are true biological differences in the response of males and females to myocardial infarction because of complicated variables, such as baseline differences in age, risk factor prevalence and the presence of coexisting diseases. In addition, medical treatment may have different effects in men and women (65).

Animal model of postinfarction heart failure has been well characterized and may offer an advantage in this type of investigation (66). Litwin *et al*. (65) found that large myocardial infarction in both male and female rats produced progressive left ventricular dilatation with global and regional systolic dysfunction. However, the overall chamber geometry differed, with male rats showing a greater increase in thickness of the noninfarcted portions of the left ventricle than females. The authors hypothesize that the different pattern of left ventricular remodeling in the female rats may have attenuated the diastolic filling abnormalities by decreasing left ventricular chamber stiffness. This may lead to the better survival of female rats after myocardial infarction compared with males. The reason for the different response is obviously the effect of sex hormones. For example, it has been observed that testosterone stimulates left ventricular hypertrophy while estradiol has an inhibitory effect. Furthermore, estrogen decreases collagen accumulation and increases elastin in blood vessels; the net effect being an increase in vascular distensibility. Cavasin *et al*. (67), using a mouse model of myocardial infarction, found that cardiac rupture rate after myocardial infarction was significantly lower in females than in males, suggesting that females have an attenuated structural remodeling. The gender difference in cardiac rupture could be attributable to premature degradation of extracellular matrix in males, promoted by the increased matrix metalloproteinase activity. The mechanism underlying the poorer left ventricular performance is not completely understood but may be related in part to the increase of collagen type I/III ratio, since estrogen supplementation prevents this increase in old female rats (68). Jain *et al*. (69) observed that myocardial infarction induced in rats with systemic hypertension results in marked differences in the pattern of left ventricular hypertrophy between female and male rats. In females there develops concentric hypertrophy with no additional cavity dilatation and no measurable scar thinning. In contrast, in males there develops eccentric hypertrophy, further dilatation of the left ventricular cavity and scar thinning. Consequently, concentric hypertrophy in females resulted in elevated contractile function, whereas eccentrically hypertrophied males had no such increase. The authors suggest that this difference is due to the positive effect of estrogens on the expression of growth factors (IGF-1). Recently, Shioura *et al*. (70) have observed gender differences in cardiac function following myocardial infarction in mice despite similarly sized ischemic injury. Whereas the compensatory hypertrophy was associated with an improve-

ment in contractility and a delayed decompensation to heart failure in females, compensatory hypertrophy in males was accompanied by a steady decline in contractility leading to heart failure.

In summary, both experimental and clinical studies have indicated that female gender influences favorably the remodeling and the adaptive response to myocardial infarction. Further work will be required to clarify the mechanisms underlying the different remodeling in males and females. Better understanding of physiological and pathophysiological function during the transition to heart failure following myocardial infarction will provide the necessary groundwork for further mechanistic studies aimed at dissecting sex differences.

Conclusions

Many experimental studies dealing with gender differences in the cardiovascular system under physiological and pathological conditions emerged during recent years. This testifies to the relevance of this topic as well as the urgent need to explain the mechanisms of these differences. This, unfortunately, failed so far; to accomplish these goals greater focus on understanding the molecular and cellular mechanisms of these differences in the cardiovascular system will be required. It is more than clear that from the experimental point of view investigation of gender differences is a complicated problem: cardiac muscle is influenced not only by estrogens (they are studied most frequently) but also by other sex hormones. Their effect differs in different periods of ontogenetic development, in females also during the menstrual cycle; the individual phases are, however, often difficult to consider in experimental studies. Furthermore, the experiments are performed predominantly on healthy individuals; translation of their results into clinical practice should be, therefore, done very cautiously. On the other hand, the importance of the experimental studies is obvious; the clinical data are predominantly descriptive and their analytical approach can be for apparent reasons only very limited. Close collaboration of experimental and clinical cardiologists is, therefore, essential. It follows from the data available, that male and female hearts differ significantly in many parameters under both physiological and pathological conditions. Detailed mechanisms of these differences are still unknown but one is clear already today: they are so important that they should be considered by the selection of optimum diagnostic and therapeutic procedures in clinical practice.

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