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Review Article

Physiology Section

Role of Biological Sex in Normal Cardiac Function and in its Disease Outcome – A Review

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ABSTRACT

Biological sex plays an important role in normal cardiac physiology as well as in the heart's response to cardiac disease. Women generally have better cardiac function and survival than do men in the face of cardiac disease; however, this is progressively lost when comparing postmenopausal women with age matched men. Animal model of cardiac disease mirror what is seen in humans. Sex hormones contribute significantly to sex based difference in cardiac functioning and in its disease outcome. Estrogen is considered to be cardioprotective, whereas testosterone is detrimental to heart function.

Keywords: Estrogen, Gender, Testosterone

Introduction

Large studies have been carried out with respect to the cardiac functions among the different sexes in both animals and humans, though the studies on male predominate. There is increasing evidence that the biological sex; play a significant role in cardiac functioning, as well as in the occurrence and outcome of cardiac disease. Female sex tends to have an upper hand in the heart function which is progressively lost once they attain menopause. Sex differences have been reported in left ventricular hypertrophy, cardiac remodelling with aging, arrhythmogenic activity and post-infarct myocardial salvage. This has led to the hypothesis that the female sex hormone estrogen has a cardio protective mechanism which in turn is responsible for sex specific differences in the normal cardiac function and in its disease outcome.

Normal structure and function of human heart

There is no significant difference in the cardiac size between the male and female until the onset of puberty. This proves that the number of cardiac myocytes is same in both the sexes [1]. Further, it is widely accepted that postnatal growth primarily occurs by an increase in cardiac myocyte size as the tissue lose their ability to proliferate shortly after birth [2]. It is seen that after puberty there is a 15-30% increase in the heart mass in males which is proportionate to the body size. Thus the male myocyte undergoes a greater degree of hypertrophy when compared to female. The myocyte hypertrophy is proportionally symmetrical throughout the heart suggesting that there is no sex difference with respect to relative wall thickness of the heart [1].

The human heart beats approximately 70 to 85 times per minute in an average adult, with a notable difference between the genders. The average adult male heart rate is between 70 and 72 beats per minute, while the average for adult women is between 78 and 82 beats. This difference is largely accounted for by the size of the heart, which is typically smaller in females than males. The smaller female heart, pumping less blood with each beat, needs to beat at a faster rate to match the larger male heart's output. Further women have a different intrinsic rhythmicity to the pacemaker of their hearts, which causes them to beat faster [3].

As age advances there is an increase in both septal and wall thickness in both sexes, however the left ventricular diameter increases only in males [4]. The above result suggests that there is a loss of myocardial mass in males but not in females. As men ages they lose an average of 1gm of cardiac mass every year, which is approximately equivalent to 64 million cardiac myocytes. This loss is attributed to compensatory hypertrophy in men to maintain adequate heart mass. Unlike in women the myocyte number and size is preserved with ageing [5]. With respect to the cardiac function, women have a better diastolic function than men, however this reduces with ageing in both the sexes [4]. In addition, men have decreased systolic function than women as age advances. Varying results have been observed with respect to exercise performance and cardiac adaptation in men and women. Studies reveal that there is an increase in cardiac output during exercise in both the sexes [6]; however different mechanisms coexist. Well-trained athletes are known to have slower heart rates than non-athletes. The heart, as a muscle, improves its strength as a result of exercise training, particularly with aerobic training. The heart rate in female athletes and regular exercisers will be lower than that of an untrained male; however it will still beat at a faster rate than an equally trained male athlete or regular exerciser [7].

Diseases

Women tend to experience heart disease 10yr later than men. Cardiovascular disease outcome has revealed the fact that premenopausal women fare better than men, they tend to have better prognosis than men in response to diseases like hypertension; aortic stenosis and hypertrophic cardiomyopathy (HCM). Women with congestive heart failure tend to survive better than men [8]. Also, following an ischemic event, women tend to have a better long term prognosis, even though their immediate death rate is elevated, when compared to men [9]. Another study, however reports no difference in congestive heart failure prognosis for men and women [10]. Thus, cardiac function is preserved in women, whereas men experience poor cardiac contractility owing to chamber dilatation and wall thinning. Animal models also support these findings [11].

Also, studies from National Centre for health statistics reports that age also plays a major role in cardiovascular diseases. Upto to 64yr, men with cardiovascular diseases die earlier than women but after 65yr the death rate is higher in women than in men. Further the above studies reports a greater prevalence of congestive heart failure in men than women aged between 65-74 yrs but no difference

after the age of 74 [12]. The discrepancies in the outcome of the above studies have attributed to the fact that women have been underrepresented in clinical trial [13] which may be due to their poor enrolment. Further women generally do not develop cardiovascular disease until older age.

However, women do not always fare better than men. They tend to have a poor prognosis in case of dilated cardiomyopathy [14]. Women are more sensitive to alcohol induced cardiac disease [15] than men, which may or may not be attributed to estrogen. Further, women are more likely to die after their first heart attack which may be because the symptoms of heart attack are different in women when compared to men. This is due to doctors and patients often attribute chest pains in women to noncardiac causes, leading to misinterpretation of their condition. Men usually experience crushing chest pain during a heart attack. Women may have a greater tendency to have pain just under the breastbone, or complain of abdominal pain, indigestion, difficulty breathing, nausea and unexplained fatigue.

Sex differences in animal models

Studies reveal that sex difference do occur in animals similar to humans. Animal models provide a valuable tool for studying the mechanisms of sexual dimorphisms in healthy as well as diseased hearts.

Exercise also elicits a sexually dimorphic response in animals. Swim training shows an improved performance in female rats which are due to increased tension developed in female heart [16]. Female mice exhibit increased capacity in both voluntary wheel and tread mill paradigm. They also perform a better treadmill-based endurance test and stress test, which is attributed to greater percent increase in female heart weight compared to male.

Studies, on diseased animal models reveal that pathologically hypertrophied female heart fare better than male. It is seen that, in pressure overload model in rats, male heart develop dilatation, diastolic dysfunction and elevated wall stress 20wks after thoracic aortic constriction (TAC), where as female heart develop only elevated systolic pressure without progression to heart failure [11]. Further, male heart ruptures more readily, have poorer left ventricular function when compared to female heart [17].

Hypertensive rat model also reveal that, female Dhal rat develop significant hypertrophy where as male rats undergo chamber dilatation and heart failure more rapidly eventually [18]. Likewise the spontaneously hypertensive heart failure (SHHF) rat is another well studied model, which states that heart failure develop independent of obesity gene though the progression is accelerated in males when compared to females [18].

Sex differences have also being documented in mouse models of genetic heart disease such as HCM. Transgenic mice with a mutant myosin heavy chain (My Hc) gene display a significant ventricular hypertrophy in both sexes [19] but with males displaying pounced histological disease features and altered electrophysiological parameters [20]. Additionally, males develop progressive ventricular dilatation and contractile dysfunction, whereas females maintain a hypertrophic state and have preserved contractile function [19]. Also, studies reveal that mutation in cardiac troponin T (CTnT) contributing to HCM also displays sex dependent phenotypes. Further an R92Q misuse mutation results in smaller ventricles in males but not in females [21].

Signalling pathway

Alteration in signal transduction pathway may be responsible for sex based difference in cardiac function mechanism. However, this is not well established. Transgenic mouse model with altered signal transduction aids in identifying these mechanism.

TNF-α

TNF-α is a proinflammatory cytokine with pleotropic biological effect and is found to be elevated in patients with congestive heart failure, the levels correlating with the severity of disease [22]. Mice over expressing TNF in the heart show an increased incidence for ventricular hypertrophy, dilatation and fibrosis and also increased expression of ANF [23]. Both sexes have equal expression of TNF and other cytokines but the receptor for this is over expressed in males compared to females resulting in dilatation of heart in males.

Adrenergic signalling

Adrenergic receptor signalling in mice [24] states that males have reduced ability to contend with increased adrenergic drive. Further, the β2 receptor is over expressed in males compared to females, which states that the survival rate for males is less compared to females. Also, these mice develop left ventricular dilatation and reduced contractile function, symptoms of heart failure, increased myocyte size and fibrosis [24].

Mice doubly null for α1A/C and α1B adrenergic receptors have small heart owing to smaller myocyte size. In addition, males have decreased exercise capacity and increased mortality following pressure overload [25], suggesting a reduced adaptive response to cardiac stress.

PPAR α

Heart is a highly aerobic tissue that requires fatty acids as fuel. Thus, cellular lipid homeostasis is critical for normal functioning of heart. PPAR α being a member of nuclear receptor superfamily of transcription factor targets the genes involved in fatty acid metabolism. Mice lacking this receptor have an altered lipid metabolism. Thus, PPAR α null mice have cardiac lipid accumulation, leading to death in 100% males and only 25% of females [26]. Also, over expression of lipoprotein lipase enzymes liberates more free fatty acids from lipoproteins showing a sex based differences. This genetic combination results in premature death in males whereas females show a better survival [27].

Relaxin

Is an important peptide hormone that plays a role in tissue remodelling during female reproduction. Recently, it is known to act on the cardiovascular system in both sexes. Both relaxin mRNA and relaxin receptor are expressed in heart [28]. Functionally, this hormone increases both the rate and force of cardiac contraction. Mice null for this gene displays sexual dimorphism like impaired diastolic filling and increased atrial weights owing to increased fibrosis of the ventricles in males where as females do not display these characteristics [29].

GSK-3β

It is an antihypertrophic signalling molecule in response to pathological stimuli. Mice expressing this have reduced cardiac growth in response to several pathological stimuli like β adrenergic stimulation, pressure overload [30] etc. Mutation in this gene, displays a sexually dimorphic phenotype, with increased mortality rate in males by 18 months of age in comparison to females [31]. However females appear to have an increased capacity to cope with lack of hypertrophic growth [31]. Also mice with a mutation in α-My HC gene mutation results in sexual dimorphism with males having increased mortality rate [31].

Sex Hormones

Sex hormones are steroidal hormone, that are being hypothesized to contribute to the sex based differences in the heart.

Estrogen

Estrogen acts on the estrogen receptor located on the cell membrane to bring about its various actions. There are two receptor ERα and

ERβ which are expressed by separate genes and have distinct tissue distribution. 17β estradiol is the major circulating estrogen. The estrogen –ER complex acts as a transcription factor by directly binding a specific DNA sequence or act via other transcriptional activators. Nongenomic ER signalling can induce pathways involved in cardiac hypertrophy, including phospholipase C (PLC), G protein and MAP kinase pathways, as well as Ca_2^{++} flux and inositol triphosphate (IP3) generation. ERs also utilize growth factor receptor (IGFR), to enhance the activation of downstream targets. This response is quick, within minutes after the stimulation of cells. ERα is expressed equally in the hearts of both sexes, whereas ERβ are expressed higher in the hearts of men than women. Both men and women produce estrogen but men and postmenopausal women have lower circulating level than premenopausal women.
ERs and estrogen are responsible for cardioprotective mechanism observed in females. Cardioprotection against ischemia/reperfusion injury in Wild-Type female mice requires both the receptors (α and β) [32]. Females with ERβ show a better response to pressure overload than males. Further ERβ attenuates heart failure in males following MI [33].

Animal model studies reveal that ovariectomised mice mimics the postmenopausal women with increased risk for cardiovascular disease. In a rat model of chronic volume overload, the ovariectomised female develops significantly more left ventricular hypertrophy and dilatation compared with intact controls. Moreover, these animals displayed symptoms of heart failure like pulmonary oedema, decreased left ventricular failure when compared to males [34]. In a pressure overload model, female showed a significant cardiac hypertrophy than intact or estrogen-supplemented females. In addition ovariectomised rats showed deteriorated heart function and increased mortality following treatment with a β–adrenergic agonist [35]. Many studies reveal that there was a 40% reduction in cardiovascular events in postmenopausal women receiving the hormone replacement therapy [32]. However, women health initiative study as well as a recent study by British Medical Journal [36] disproves it, stating that there were increased cardiovascular events [36]. However, the main drawback of the study is that the hormone replacement was not initiated until the women were many years past menopause.

Absence of ER in the cardiac myocyte and ovariectomized rat [37] express increased expression of L-type calcium channel (LTCC), the inward Ca_2+ channel in the plasma membrane, as well as inward Ca_2+ current through the channel. Thus the mouse model with absent ER showed a prolonged QT interval, which may lead to increased risk of arrthymia and cardiovascular disease [38]. Further estrogen supplement in guinea pigs, reduced the inward Ca_2^{++} current and intracellular Ca_2+ concentration. Thus the above evidences suggest estrogen inhibits Ca_2+ channel in the plasma membrane [39].

In addition to the above studies, it was seen that ovariectomized rat also increased Ca flux in the heart via the raynodine receptor (RyR), the Ca leak channel present in the sarcoplasmic reticular membrane and Na/Ca exchanger (NCX), a Ca extruder in the plasma membrane. Both of these changes were reversed by estrogen replacement or by protein kinase A (PKA) inhibition. Thus ovariectomy in rat increases PKA expression and hyperactivity of RyR and NCX [40]. Ovariectomized mice with estrogen supplementation showed reduced apoptosis of cardiac myocytes following MI when compared with non ovariectomized controls.

The ability of estrogen to promote cell survival is dependent on phosphoinositol 3-kinase (PI3K) and Akt. Akt is activated in vitro as well as in vivo (NVRM) following treatment with estrogen [41]. Akt when activated/phosphorylated increases the survival of cardiac myocytes when it is located to the nucleus [42]. It is seen that the level of nucleus localised phosphor-AKT is more in young women when compared to age matched men and postmenopausal women. The same is observed in mouse heart as well. Additionally cultured NRVm's treated with estrogen also express increased nucleus localised phospho Akt [43].

Testosterone

Testosterone binds with the nuclear androgen receptor and modulates transcription. The receptor is present in both sexes. The hormone is produced by both men and women with men having tenfold higher levels of circulating testosterone than women.

The physiological action of testosterone on heart is less studied than estrogen. Further these studies suggest a negative impact on heart. It is seen that on treatment of NRVM with testosterone there was a hypertrophic response including increased expression of the pathological marker atrial natriuretic factor ANF. Further, mouse model of MI showed that testosterone and estrogen have opposing effect on cardiac remodelling and function [44]. In gonadectomised animals, testosterone supplement resulted in decreased cardiac function, increased myocyte cross sectional area in both the sexes, whereas estrogen had opposite effect. Additionally postmenopausal women produced more testosterone [45] which proves a second mechanism for increased risk of cardiovascular disease in postmenopausal women.

Studies of athletes using anabolic steroids provide further evidence for detrimental effects of testosterone on cardiac myocytes. These anabolic steroids are modified derivative of testosterone that is less susceptible of metabolic inactivation. Weight lifters using these steroids showed increased cardiac hypertrophy and also impaired diastolic function [46]. Moreover, anabolic steroid use has been associated with an increased risk for MI and sudden cardiac death [47].

Conclusion

Women tend to have a better cardiac function and are able to have a better disease prognosis when compared with men. But with ageing this difference disappears as there is loss of estrogen in the postmenopausal women, suggesting the role of sex hormones in cardiac functions. Further studies reveal that a difference in signalling pathway in both sexes is a cause for deteriorated cardiac functions in males.

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