

## REVIEW ARTICLE

# The female human heart at rest and during exercise: A review

AMANDA Q. X. NIO, ERIC J. STÖHR, & ROB SHAVE

*Cardiff School of Sport, Cardiff Metropolitan University, Cardiff, UK*

### Abstract

Sexual dimorphism exists in numerous aspects of exercise physiology. One area that has long been debated is the potential of sex differences in cardiac structure and function. Anthropometric differences exist between males and females, and the relationship between absolute body size and cardiac structure dictate that men typically have larger hearts than women. However, increasing evidence suggests that males and females may also demonstrate different cardiac structure and function independent of body size, and it is likely that female sex hormones play a role in these differences. The purpose of this review is to draw together and examine the literature that has compared cardiac structure and function in men and women at rest and during exercise. We make specific reference to the influence of female sex hormones, and discuss the confounding effects of age and training status. Wherever possible, we provide conclusive remarks. Due to the paucity of data in this field, and general lack of consensus, the review concludes by making recommendations for future work.

**Keywords:** *Cardiac, left ventricle, oestrogen, sex differences*

### Introduction

Regular physical activity results in cardiac adaptations, such as resting bradycardia and increases in maximal cardiac output (Ogawa et al., 1992), and is also associated with enhanced cardiovascular (CV) health (Erikssen, 2001). Changes in physical activity to increase physical fitness and improve CV health have important implications for healthy ageing (Erikssen, 2001). Although women are generally less physically active (Townsend et al., 2012), the chronological decline in cardiac function and onset of CV disease occurs almost a decade later in life relative to men (Maas et al., 2011). The concentrations of the primary female sex hormones (i.e. oestrogen and progesterone) fluctuate across the human lifespan and cyclical changes in hormone concentrations over the menstrual cycle alter loading of the heart via changes in blood volume and blood pressure (Chapman et al., 1997; Lynn, McCord, & Halliwill, 2007). In addition, oestrogen is now considered cardioprotective (Luczak & Leinwand, 2009; Murphy et al., 2011) and as such, may explain some of the differences in cardiac health between men and women. It is likely, therefore, that the

potent effect of female sex hormones may also help explain some of the sex differences in cardiac structure and function previously suggested in the literature (Gardin et al., 1995; Hayward, Kelly, & Collins, 2000; Luczak & Leinwand, 2009; Okura et al., 2009).

Despite a growing literature base, females are still currently under-represented in Sport and Exercise Medicine research (Costello, Bieuzen, & Bleakey, 2014), and whether sex differences in gross cardiac structure and function remain after adjusting for body size is still unclear. Such comparisons are likely to be complicated by the fluctuations in female sex hormones that occur across the menstrual cycle, with the use of oral contraceptives, in response to exercise-associated amenorrhoea and with the onset of menopause. It is also probable that any differences between men and women at rest may subsequently influence the CV response to exercise, but this has received even less scientific attention. Thus, the aim of this review is to summarise and evaluate the literature comparing cardiac structure and function at rest and during exercise between men and women, and to examine the influence of female sex hormones on the heart.

## Scope of review

We have focused on cardiac investigations with direct comparisons between healthy men and women, and in women with varying concentrations of female sex hormones. Much of the work completed in this field has been limited by a small sample size and heterogeneity of study participants. Accordingly, where possible, we have selected large-scale studies, and have discussed contradictory and/or confusing results. As our focus is specifically women and the influence of female sex hormones, we have not explicitly examined the influence of the male sex hormone testosterone on cardiac physiology (McGill, Anselmo, Buchanan, & Sheridan, 1980; Scheuer, Malhotra, Schaible, & Capasso, 1987). For more information on the specific cardiac effects of testosterone, readers are directed to the reviews by Hayward et al. (2000) and Luczak and Leinwand (2009). Within this review, if possible, we draw firm conclusions based on the existing literature. Where consensus does not exist, we highlight the need for further studies and make recommendations related to future directions.

## Resting cardiac structure and function in men and women

### *Cardiac structure*

When comparing cardiac structure between men and women, it is essential to remember that a greater body size is associated with a larger heart (Celentano et al., 2003; Gardin et al., 1995; Kaku et al., 2011; Sandstede et al., 2000). As such, many studies have reported smaller absolute left ventricular (LV) mass and wall dimensions in women than men (Celentano et al., 2003; Gardin et al., 1995; Grandi et al., 1992; Hutchinson, Cureton, Outz, & Wilson, 1991; Lang et al., 2006; Wilhelm et al., 2011), and sex-specific absolute reference ranges are therefore employed when assessing cardiac pathology (Lang et al., 2006). In an attempt to account for the effect of body size, previous authors have often employed ratiometric scaling of cardiac parameters to body surface area (Dewey, Rosenthal, Murphy, Froelicher, & Ashley, 2008). Although these results are discussed in this review and inform the current knowledge base, it is important to note that normalising to body surface area may not fully eliminate the impact of body size (Dewey et al., 2008). Therefore, previous findings need to be synthesised with caution and studies likely need to be repeated using more appropriate allometric scaling techniques (Batterham, George, & Mullineaux, 1997; Dewey et al., 2008).

Notwithstanding the issues related to ratiometric scaling, sex differences in LV mass have been shown to persist after indexing to body surface area

(Celentano et al., 2003; de Simone et al., 1991; Grandi et al., 1992; Hutchinson et al., 1991; Sandstede et al., 2000; Wilhelm et al., 2011). In fact, in one large study of young adults, differences in LV mass were still present after adjusting for body composition and size, blood pressure, alcohol consumption, pulmonary function, smoking history, physical activity, total cholesterol and family history of hypertension (Gardin et al., 1995). Beyond mass, the LV also appears to exhibit a greater ellipsoid geometry at end-diastole in young adult men compared to women (Kaku et al., 2011). Together, these findings indicate that differences in gross cardiac structure between men and women may not be fully explained by body habitus. Given the potent effects of female sex hormones on many aspects of global (e.g. blood volume and blood pressure; Chapman et al., 1997; Lynn et al., 2007) and cellular cardiac physiology (e.g. inotropic state and calcium handling; Jiang et al., 1992; Parks & Howlett, 2013), it is possible that the differences observed in structure may be related to circulating hormones.

### *Cardiac function*

In addition to LV mass, LV volumes at end-diastole and end-systole, and the resultant stroke volume (SV) are also larger in men than women (Cain et al., 2009; Celentano et al., 2003; Hutchinson et al., 1991; Kaku et al., 2011; Lang et al., 2006; Lynn et al., 2007; Sandstede et al., 2000). Again, whether these differences are simply due to body size is currently not clear and inappropriate scaling approaches cloud the debate (Cain et al., 2009; Celentano et al., 2003; Hutchinson et al., 1991; Kaku et al., 2011; Lang et al., 2006; Sandstede et al., 2000). If men do have a relatively larger SV, this may help to explain the lower resting male heart rate (HR) observed in some studies (Celentano et al., 2003; Fleg et al., 1995; Hanley et al., 1989). It should be noted, however, that similar resting HRs in men and women have also been reported (Grandi et al., 1992; Lynn et al., 2007; Sandstede et al., 2000). Although consensus regarding differences in resting HR between the sexes does not exist, it has been shown that women have greater sympathetic (Mitoff et al., 2011) as well as parasympathetic (Ryan, Goldberger, Pincus, Mietus, & Lipsitz, 1994) activation of the heart. It is likely therefore, that resting HR is modulated differently between the sexes. The apparent discrepancies in resting SV and HR may be attributed, in part, to the limited control of participant characteristics in previous studies. Age, training status and hormonal status were often not examined or controlled in previous studies (Celentano et al., 2003; Fleg et al., 1995; Grandi et al., 1992; Hanley et al., 1989; Sandstede et al.,

2000;), all of which likely influence subsequent findings (Lynn et al., 2007).

With a lack of consensus regarding differences in resting SV and HR between men and women, it is not surprising that cardiac output data are also conflicting. Previous authors have reported larger resting cardiac output in males (Lynn et al., 2007), whilst others maintain a lack of sexual dimorphism regarding this variable (Sandstede et al., 2000; Sullivan, Cobb, & Higginbotham, 1991; Yilmaz, Buyukakilli, Gurgul, & Rencuzogullari, 2013). Indexing cardiac output to body surface area has resulted in values that are mostly similar between the sexes (Carlsson et al., 2012; Hossack & Bruce, 1982; Sandstede et al., 2000; Sullivan et al., 1991; Yilmaz et al., 2013). Adult women, however, appear to have a higher resting ejection fraction (EF) than age-matched men (Cain et al., 2009; Hanley et al., 1989; Fleg et al., 1995; Kaku et al., 2011; Sandstede et al., 2000), even after controlling for HR, body surface area, body mass index or fat-free mass (Bella et al., 2006; Celentano et al., 2003). While the current data do not permit absolute conclusions regarding HR or relative SV and cardiac output, on balance it appears that global parameters of cardiac function are largely similar between men and women. Despite these similarities, however, consistent reports of a greater resting EF in women and differences in autonomic regulation suggest that sex differences in cardiac function may nonetheless exist. These findings provide impetus for future studies to closely examine systolic and diastolic function (e.g. transmitral filling velocities, myocardial tissue velocities and ventricular mechanics), in order to provide further insight into the potential sex differences in cardiac function.

In addition to the influence of body size on cardiac comparisons between men and women, age and training status clearly affect cardiac structure and function. Increasing age is associated with a lower cardiac mass and reduction in function (Kaku et al., 2011), and exercise trained men and women have a lower resting HR and greater LV mass than their less active counterparts (Carlsson et al., 2012; Yilmaz et al., 2013). The impact of both of these variables on the heart is further complicated by potential interactions with the female sex hormones. In women, for example, the ageing process of the heart is mediated by the onset of the menopause and a decreased circulating concentration of oestrogen (Düzenli et al., 2007; Harlow et al., 2012; Schillaci, Verdecchia, Borgioni, Ciucci, & Porcellati, 1998). As both chronological and reproductive ageing occur concurrently, it is extremely difficult to differentiate the effects of low levels of female sex hormones from those of ageing. In the following subsections, we first discuss the direct impact of age and training status on comparisons of cardiac structure and function

between men and women, with a focus on studies that have not explicitly considered female sex hormone concentrations. Later, we specifically address studies that have directly explored the impact of changes in female sex hormone concentrations across the lifespan upon cardiac structure and function.

#### *Interaction between age and sex on cardiac function*

In contrast to the higher resting EF in women discussed previously, other markers of systolic function, such as fractional shortening and peak shortening rates of the LV (de Simone et al., 1991; Grandi et al., 1992), appear comparable between men and women aged 18–50 years. Women, however, have faster peak lengthening rates of the LV (Grandi et al., 1992), a higher early-to-late (E/A) transmitral filling velocity ratio (Daimon et al., 2011) and faster early diastolic myocardial velocities (E'; Figure 1; Daimon et al., 2011; Okura et al., 2009), all suggestive of a superior diastology in comparison to men. In contrast, men have a faster late diastolic myocardial velocity (A'), which may reflect a greater atrial contribution in order to achieve optimal LV filling (Wilhelm et al., 2011; Yilmaz et al., 2013). Accordingly, it appears that women have a greater reliance on LV relaxation during early diastole, but men depend on LV compliance and atrial contraction during late diastole to maintain EDV. This difference is particularly intriguing as it may indicate a greater atrial reserve to aid LV filling during periods of increased HR in women, such as those experienced with exercise.

With increasing age (>50 years), fractional shortening, peak shortening rates of the LV and circumferential end-systolic stress/end-systolic volume index (measures of systolic function), all appear lower in men compared with women (Bella et al., 2006; Celentano et al., 2003; de Simone et al., 1991;

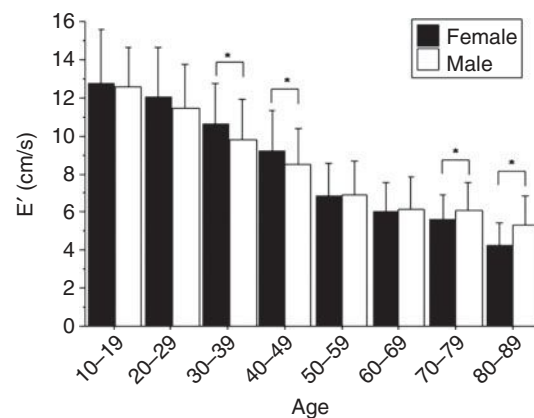


Figure 1. Comparison of early diastolic myocardial velocity (E') between men and women over 10-year age ranges (from Okura et al., 2009). Values are mean  $\pm$  standard deviation. \* $P < 0.01$ .

Grandi et al., 1992). This is in direct contrast with measures of diastolic function, which appear to worsen to a greater extent in women than men after the age of 50 (Figure 1; Grandi et al., 1992; Daimon et al., 2011; Okura et al., 2009). Thus, age appears to impact cardiac function differentially between the sexes with a greater decrease in systolic function in men but a larger decrease in diastolic function in women (Luczak & Leinwand, 2009). It is likely that this may be attributed partly to the decline in circulating concentrations of oestrogen with the menopause in women, which coincidentally occurs at an average age of 51 years (Kato et al., 1998).

Studies examining the impact of age on cardiac function have focused primarily on adult men and women. Of the few studies that have included children and adolescents, many have not controlled for maturational status (Kaku et al., 2011; Okura et al., 2009). Those that have, however, report a clear impact of puberty on cardiac structure and function, as evidenced by a greater increase in LV mass in boys than girls from the age of 12 years (de Simone, Devereux, Daniels, & Meyer, 1995), and a significant impact of sex on cardiac output in adults but not in children (de Simone et al., 1997). These results are likely related to the influence of testosterone in males, but it is also possible that oestrogen is a factor that needs to be considered. Limited data are available on the direct influence of oestrogen on cardiac structure and function during and after puberty. Nonetheless, the studies that have been completed highlight the potent influence of puberty on cardiac comparisons involving pre-, peri- and post-pubertal children/adolescents.

#### *Interaction between training status and sex on cardiac structure and function*

In conjunction with other known sex differences in the physiological response to exercise training, such as greater peripheral adaptations (i.e. arteriovenous oxygen difference; Ogawa et al., 1992) and a higher risk of iron deficiency in women (see review by McClung, 2012), it is possible that cardiac adaptations may also differ between men and women. A greater cardiac hypertrophy has been suggested in a cross-sectional study of male athletes compared to their female counterparts in similar sporting disciplines (Pelliccia, Maron, Culasso, Spataro, & Caselli, 1996). The majority of rodent studies, however, report a more pronounced hypertrophic response in females (see review by Foryst-Ludwig & Kintscher, 2013). While it is difficult to directly translate findings from animals to humans, it is clear that further work, including well-controlled longitudinal studies, is needed to reconcile these contrasting results.

A lack of control of training status in many studies may explain the ambiguity regarding resting HR highlighted earlier, as even lower HRs have been reported in active young men compared to their equally active female counterparts (Yilmaz et al., 2013). This lower resting HR in active men, coupled with a similar normalised cardiac output between the sexes regardless of training status (Carlsson et al., 2012; Yilmaz et al., 2013), suggests that they may also have a greater relative SV. Yet mixed results for relative SV with the use of different ratiometric scaling approaches, such as fat-free mass (Ogawa et al., 1992) and body surface area (Yilmaz et al., 2013) exist, highlighting the need for further investigations before conclusions can be drawn.

#### **Impact of female sex hormones on cardiac structure and function**

Receptors for both oestrogen and progesterone have been identified in the human heart (Ingegno et al., 1988; Taylor, & Al-Azzawi, 2000). Research examining the influence of progesterone on cardiac function is limited and the results inconclusive (Wittnich, Tan, Wallen, & Belanger, 2013). Oestrogen has received more scientific attention and is generally considered to be cardioprotective, yet the mechanism by which it confers protection is still under debate (Luczak & Leinwand, 2009; Murphy et al., 2011). Notwithstanding, it is likely that oestrogen exerts its effects on the heart via genomic and non-genomic pathways (Luczak & Leinwand, 2009; Murphy et al., 2011). Animal studies have shown oestrogen to negatively effect inotropic state (Jiang et al., 1992), down-regulate calcium handling (Parks & Howlett, 2013) and increase nitric oxide synthase expression (Nuedling et al., 1999). It may, however, be possible that responses to oestrogen are exclusive to cells from female hosts, as an elevated L-type  $Ca^{2+}$  current density following incubation with oestrogen was only observed in cardiomyocytes extracted from female and not male rabbits (Yang et al., 2012). Accordingly, any physiologic stimulus, such as puberty, menstrual cycle or the menopause, that alters the concentration of circulating oestrogen (Carmina, Stanczyk, & Lobo, 2014; Harlow et al., 2012), will likely impact cardiac function and ultimately structure.

#### *Influence of the menstrual cycle and oral contraceptives on cardiac function*

Three distinct menstrual phases exist: early follicular (low oestrogen and progesterone); late follicular (high oestrogen and low progesterone) and mid-luteal (high oestrogen and progesterone; Janse de Jonge, 2003). Blood volume and blood pressure may be lower during the mid-luteal phase, indicative of

Table I. Summary of studies that have compared cardiac structure and function during different phases of the menstrual cycle

Reference	Sample size	Age (years)	Menstrual cycle phase	Verification method	Key findings
Chapman et al. (1997)	16	31 ± 4	Early-fol vs. mid-lut	Oestrogen and progesterone (blood)	HR: ↔ CO: early-fol < mid-lut
Fuenmayor et al. (2000)	20	29 ± 6	Early-fol vs. mid-lut	Oestrogen and progesterone (blood)	Wall thickness, EDV, ESV, EF: ↔ E/A: early-fol < mid-lut
George et al. (2000)	17	21 ± 1	Mid-fol vs. mid-lut	Luteinising hormone (urine)	LVM, wall thickness, SV, EDV, EF: ↔ E/A: trend towards mid-fol > mid-lut
Esformes et al. (2006)	8	20 ± 1	Early-fol vs. late-fol vs. mid-lut	Luteinising hormone (urine)	HR, CO, SV, EDV, ESV, EF: ↔
Lynn et al. (2007)	14	24 ± 4	Early-fol vs. ovulatory vs. mid-lut	Oestrogen and progesterone (blood)	HR: early-fol = ovulatory < mid-lut CO: trend towards mid-lut ↑ SV: ↔
Zengin et al. (2007)	27	24 ± 6	Early-fol vs. mid-lut	Oestrogen and progesterone (blood)	MPI: mid-lut ↑
Fu et al. (2010)	11	33 ± 10	Early-fol vs. mid-lut	Oestrogen and progesterone (blood)	HR, CO, SV: ↔

Age is presented as mean ± standard deviation. Fol: follicular; lut: luteal; HR: heart rate; CO: cardiac output; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction; E/A: ratio of peak early to late diastolic mitral inflow velocity; LVM: left ventricular mass; SV: stroke volume; MPI: myocardial performance index.

changes in cardiac loading across the menstrual cycle (Chapman et al., 1997; Lynn et al., 2007). Although equivocal, if differences in cardiac function are present across the menstrual cycle, it appears that systole and diastole are enhanced during the mid-luteal phase when oestrogen and progesterone concentrations are high (Table I; Chapman et al., 1997; Fuenmayor, Ramírez, & Fuenmayor, 2000; Lynn et al., 2007; Zengin et al., 2007). It should be noted, however, that the difficulty in accurately assessing menstrual phase has limited the number of studies conducted and further work is needed, especially with larger sample sizes. It is also worthy of note that the analysis of urinary luteinising hormone (e.g. George, Birch, Jones, & Lea, 2000; Esformes, Norman, Sigley, & Birch, 2006) is not sufficient to distinguish between ovulatory and luteal phase deficient cycles in very active women (De Souza et al., 2010). Future studies should thus directly assess oestrogen and progesterone concentrations to ensure that the intended phase of the menstrual cycle is examined (Janse de Jonge, 2003).

In contrast to the large variability in levels of female sex hormones across the menstrual cycle, oestrogen concentrations are consistently high during the consumption phase of monophasic oral contraceptives and low during the withdrawal phase (George et al., 2000). Cardiac structure and function appear largely unchanged during these two phases (Birch, Cable, & George, 2002; George et al., 2000). Why the elevated levels of oestrogen present during both, the mid-luteal menstrual phase and consumption phase of oral contraceptive administration, do not result in similar changes in cardiac function

relative to their respective low oestrogen phases is presently not clear.

#### *Influence of the menopause on cardiac structure and function*

As discussed earlier, ageing may influence cardiac structure and function differentially between the sexes (Cain et al., 2009; Carlsson et al., 2012; Daimon et al., 2011; Fleg et al., 1995; Kaku et al., 2011). Advancing age is also associated with changes in circulating female sex hormone concentrations as a result of reproductive ageing, culminating with the menopause (Harlow et al., 2012). Menopause has been associated with concentric LV remodelling, characterised by greater wall thicknesses and maintained end-diastolic volume (EDV; Düzenli et al., 2007; Schillaci et al., 1998), and a reduction in both systolic and diastolic function, including the myocardial performance index and the E/A transmitral filling velocity ratio (Düzenli et al., 2007; Hayward et al., 2000; Schillaci et al., 1998). It is difficult to show cause and effect; however, it is possible that this cardiac remodelling is a result of the altered hormonal balance associated with the menopause.

Studies examining the use of hormone replacement therapy (HRT) have shown that pharmacologically reversing the menopause may slow the negative LV remodelling (Light et al., 2001), in part through modulation of angiotension II receptors, as well as estrogen receptors (Xu, Arenas, Armstrong, & Davidge, 2003). The use of HRT may also mitigate against the associated decline in systolic and diastolic

function (Duzenli et al., 2010; Özdemir et al., 2004). These data are unfortunately derived from small studies, with significant age differences between the pre- and post-menopausal women examined, and/or non-blinded hormone treatment groups (Duzenli et al., 2010; Hayward et al., 2000; Özdemir et al., 2004). More robust research is, therefore, necessary to delineate the direct cardiac impact of female sex hormones from the influence of ageing per se. With that, further information related to older pre-menopausal women, for example, across the menstrual cycle (Table I), is also required. Whether the menopause is a confounding variable to age- and sex-related differences in cardiac adaptations to exercise training (Ogawa et al., 1992) is unclear but likely will play a role.

*Influence of training status on female sex hormone concentrations*

High levels of exercise training can impact circulating female sex hormone concentrations and exercise-associated amenorrhoea has been reported in 37% of very active women (De Souza et al., 2010). More subtle menstrual disturbances may occur in up to 50% of active women (De Souza et al., 2010). Accordingly, cardiac data from a female athletic population may demonstrate even greater variability due to the wide variation in hormonal profiles. A striking gap in the literature exists examining the hearts of amenorrhoeic women. Whilst oestrogen deficiency associated with amenorrhoea appears to alter vascular function (O'Donnell, Goodman, & Harvey, 2011), it is not known whether this condition also directly affects the heart and its adaptation to regular physical training. It is thus apparent that the assessment of female sex hormone concentrations, coupled with better control of both age and training status in future studies, may help to reconcile the contradictions in the literature regarding cardiac structure and function in men and women.

**Cardiac function in men and women during exercise**

Sex differences in the direct sympathetic activation of the myocardium (Mitoff et al., 2011) and myocardial oxygen consumption (Peterson et al., 2007) have been shown at rest. Whilst concentrations of circulating catecholamines are similar between men and women at rest, these levels are distinctly higher in men during exercise (Davis, Galassetti, Wasserman, & Tate, 2000). Taken together, if differences in cardiac structure and function exist at rest it is likely that they may be exacerbated with exercise. The few studies that have explored this largely show similar increases in HR and scaled cardiac output between the sexes in response to exercise (Table II;

Table II. Comparison of cardiac function during exercise in men (M) and women (F)

Reference	Heart rate		Cardiac output		Stroke volume		End-diastolic volume		End-systolic volume		Ejection fraction	
	Submaximal	Peak	Submaximal	Peak	Submaximal	Peak	Submaximal	Peak	Submaximal	Peak	Submaximal	Peak
Hossack and Bruce (1982)	M = F	M = F	M > F	M > F	M > F	M > F						M > F
Zwilen et al. (1983)	M = F	M = F	M > F	M = F	M = F	M = F						M > F
Higginbotham et al. (1984)		M = F	M = F	M = F	M = F	M = F						M > F
Adams et al. (1987)		M = F										M > F
Hanley et al. (1989)		M = F										M ≥ F*
Younis et al. (1990)	M = F	M < F			M = F	M = F	M = F		M = F			M = F
Sullivan et al. (1991)		M = F			M = F	M ≥ F†						M = F
Ogawa et al. (1992)		M = F			M = F	M = F						M = F
Fleg et al. (1995)		M = F			M ≥ F*	M = F						M = F
Aksut et al. (1996)		M = F			M = F	M = F						M = F
Wiebe et al. (1998)		M = F			M > F	M = F						M = F

Submaximal exercise is at similar relative intensities in men and women. For clarity, only comparisons of scaled cardiac output and LV volumes have been included. Responses are also influenced by \*age or †training status. M = F: similar in men and women; M > F: greater in men than women; M < F: smaller in men than women; M ≥ F: greater than or similar in men compared to women.

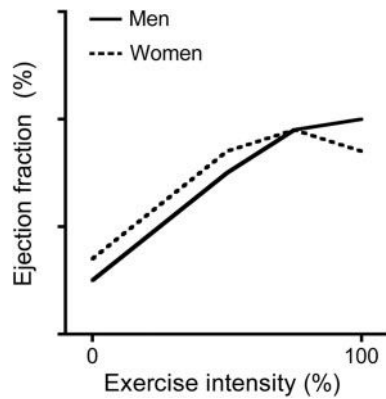


Figure 2. Schematic representation of ejection fraction during exercise in men and women. Graphs are based upon the results by Higginbotham et al. (1984) and Sullivan et al. (1991).

Aksut et al., 1996; Fleg et al., 1995; Hanley et al., 1989; Higginbotham, Morris, Coleman, & Cobb, 1984; Hossack & Bruce, 1982; Ogawa et al., 1992; Proctor et al., 1998; Wiebe, Gledhill, Warburton, Jamnik, & Ferguson, 1998; Younis, Melin, Robert, & Detry, 1990; Zwiren, Cureton, & Hutchinson, 1983). The data related to SV and EF are, however, less clear. It is possible that during exercise women augment EF via an increase in EDV, men in contrast do not increase EDV to the same degree, but rather reduce end-systolic volume to a greater extent (Adams, Vincent, McAllister, el-Ashmawy & Sheps, 1987; Aksut et al., 1996; Fleg et al., 1995; Hanley et al., 1989; Higginbotham et al., 1984). This would explain the greater increase in EF from rest to peak exercise observed in males (Figure 2; Adams et al., 1987; Aksut et al., 1996; Fleg et al., 1995; Hanley et al., 1989; Higginbotham et al., 1984; Sullivan et al., 1991; Younis et al., 1990). Accordingly, it is possible that increases in cardiac output with exercise, albeit similar between men and women (Fu & Levine, 2005), are achieved via different regulatory mechanisms (O'Toole, 1989).

### Summary and future directions

As men typically have a larger body size than women, it is not surprising that absolute measures of cardiac size and output are greater in men than women. Numerous studies have attempted to examine if sex differences exist beyond body size, but previous scaling techniques have not been ideal and the results need to be interpreted carefully. Moving forward, researchers interested in comparing male and female hearts should attempt, where possible, to adopt sample-specific allometric scaling to fat-free mass as this better controls for the confounding effect of body size (Batterham et al., 1997; Dewey et al., 2008).

Consistent reports of a higher resting EF in women compared to men imply that sex differences in cardiac function likely exist. Components of systolic

and diastolic function (e.g. fractional shortening and E/A transmitral filling velocity) may be higher in women compared to men, but this is not consistent across the human lifespan (i.e. age-dependent) and is likely influenced by circulating concentrations of female sex hormones and training status. During exercise, differences in the pattern of LV filling and ejection characteristics between men and women may result in different end-systolic/diastolic volumes, and thus the EF response to exercise will also differ between the sexes. Despite insufficient control of participant characteristics in many studies and conflicting results in the literature, it is nonetheless likely that sex differences in gross cardiac structure and function cannot be fully explained by body size. Further prospective work, with better control of age, training status and circulating concentrations of female sex hormones, is needed to improve our understanding of the underlying factors contributing to cardiac dimorphism in men and women. In addition, novel imaging techniques, such as three-dimensional speckle tracking echocardiography for the quantitative evaluation of cardiac mechanics (Mor-Avi et al., 2011), offer an exciting possibility to extend previous work and improve the current understanding of regional myocardial function in men and women.

### Funding

Amanda Nio is a beneficiary of a doctoral grant from the AXA Research Fund.

### References

- Adams, K. F., Vincent, L. M., McAllister, S. M., el-Ashmawy, H., & Sheps, D. S. (1987). The influence of age and gender on left ventricular response to supine exercise in asymptomatic normal subjects. *American Heart Journal*, *113*, 732–742. doi:10.1016/0002-8703(87)90714-9
- Aksut, S. V., Pancholy, S., Johnson, J., Walter, J. D., DiMarzio, D., Cave, V., ... Iskandrian, A. S. (1996). Comparison of left ventricular performance in healthy young women and men during exercise. *Journal of Nuclear Cardiology*, *3*, 415–421. doi:10.1016/S1071-3581(96)90077-X
- Batterham, A. M., George, K. P., & Mullineaux, D. R. (1997). Allometric scaling of left ventricular mass by body dimensions in males and females. *Medicine and Science in Sports and Exercise*, *29*, 181–186. doi:10.1097/00005768-199702000-00003
- Bella, J. N., Palmieri, V., Roman, M. J., Paranicas, M. F., Welty, T. K., Lee, E. T., ... Devereux, R. B. (2006). Gender differences in left ventricular systolic function in American Indians (from the Strong Heart Study). *The American Journal of Cardiology*, *98*, 834–837. doi:10.1016/j.amjcard.2006.03.069
- Birch, K., Cable, N., & George, K. (2002). Combined oral contraceptives do not influence post-exercise hypotension in women. *Experimental Physiology*, *87*, 623–632. doi:10.1113/eph8702400
- Cain, P. A., Ahl, R., Hedstrom, E., Ugander, M., Allansdotter-Johnsson, A., Friberg, P., & Arheden, H. (2009). Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging:

- A cross sectional study. *BMC Medical Imaging*, 9, 2. doi:10.1186/1471-2342-9-2
- Carlsson, M., Andersson, R., Bloch, K. M., Steding-Ehrenborg, K., Mosén, H., Stahlberg, F., ... Arheden, H. (2012). Cardiac output and cardiac index measured with cardiovascular magnetic resonance in healthy subjects, elite athletes and patients with congestive heart failure. *Journal of Cardiovascular Magnetic Resonance*, 14, 51. doi:10.1186/1532-429X-14-51
- Carmina, E., Stanczyk, F. Z., & Lobo, R. A. (2014). Laboratory assessment. In J. F. Strauss & R. Barbieri (Eds.), *Yen & Jaffe's reproductive endocrinology: Physiology, pathophysiology, and clinical management* (7th ed., pp. 822–850). Philadelphia, PA: Elsevier Saunders.
- Celentano, A., Palmieri, V., Arezzi, E., Mureddu, G. F., Sabatella, M., Di Minno, G., & De Simone, G. (2003). Gender differences in left ventricular chamber and midwall systolic function in normotensive and hypertensive adults. *Journal of Hypertension*, 21, 1415–1423. doi:10.1097/00004872-200307000-00033
- Chapman, A. B., Zamudio, S., Woodmansee, W., Merouani, A., Osorio, F., Johnson, A., ... Schrier, R. W. (1997). Systemic and renal hemodynamic changes in the luteal phase of the menstrual cycle mimic early pregnancy. *The American Journal of Physiology*, 273, F777–F782.
- Costello, J. T., Bieuzen, F., & Bleakey, C. M. (2014). Where are all the female participants in sports and exercise medicine research? *European Journal of Sport Science*, April 25, 1–5. [Epub ahead of print]. doi:10.1080/17461391.2014.911354
- Daimon, M., Watanabe, H., Abe, Y., Hirata, K., Hozumi, T., Ishii, K., ... Yoshikawa, J., Japanese Normal Values for Echocardiographic Measurements Project (JAMP) Study Investigators (2011). Gender differences in age-related changes in left and right ventricular geometries and functions. Echocardiography of a healthy subject group. *Circulation Journal*, 75, 2840–2846. doi:10.1253/circj.CJ-11-0364
- Davis, S. N., Galassetti, P., Wasserman, D. H., & Tate, D. (2000). Effects of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. *The Journal of Clinical Endocrinology and Metabolism*, 85, 224–230.
- de Simone, G., Devereux, R. B., Daniels, S. R., & Meyer, R. A. (1995). Gender differences in left ventricular growth. *Hypertension*, 26, 979–983. doi:10.1161/01.HYP.26.6.979
- de Simone, G., Devereux, R. B., Daniels, S. R., Mureddu, G., Roman, M. J., Kimball, T. R., ... Contaldo, F. (1997). Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. *Circulation*, 95, 1837–1843. doi:10.1161/01.CIR.95.7.1837
- de Simone, G., Devereux, R. B., Roman, M. J., Ganau, A., Chien, S., Alderman, M. H., ... Laragh, J. H. (1991). Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults. *The American Journal of Cardiology*, 68, 1704–1708. doi:10.1016/0002-9149(91)90333-G
- De Souza, M. J., Toombs, R. J., Scheid, J. L., O'Donnell, E., West, S. L., & Williams, N. I. (2010). High prevalence of subtle and severe menstrual disturbances in exercising women: Confirmation using daily hormone measures. *Human Reproduction*, 25, 491–503. doi:10.1093/humrep/dep411
- Dewey, F. E., Rosenthal, D., Murphy, D. J. Jr., Froelicher, V. F., & Ashley, E. A. (2008). Does size matter? Clinical applications of scaling cardiac size and function for body size. *Circulation*, 117, 2279–2287. doi:10.1161/CIRCULATIONAHA.107.736785
- Duzenli, M. A., Ozdemir, K., Sokmen, A., Gezginc, K., Soyulu, A., Celik, C., ... Tokac, M. (2010). The effects of hormone replacement therapy on myocardial performance in early postmenopausal women. *Climacteric*, 13, 157–170. doi:10.3109/13697130902929567
- Düzenli, M. A., Ozdemir, K., Sokmen, A., Soyulu, A., Aygul, N., Gezginc, K., & Tokac, M. (2007). Effects of menopause on the myocardial velocities and myocardial performance index. *Circulation Journal*, 71, 1728–1733. doi:10.1253/circj.71.1728
- Erikssen G. (2001). Physical fitness and changes in mortality. *Sports Medicine*, 31, 571–576. doi:10.2165/00007256-200131080-00001
- Esformes, J. I., Norman, F., Sigley, J., & Birch, K. M. (2006). The influence of menstrual cycle phase upon postexercise hypotension. *Medicine and Science in Sports and Exercise*, 38, 484–491. doi:10.1249/01.mss.0000193559.98095.ea
- Fleg, J. L., O'Connor, F., Gerstenblith, G., Becker, L. C., Clulow, J., Schulman, S. P., & Lakatta, E. G. (1995). Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *Journal of Applied Physiology*, 78, 890–900.
- Foryst-Ludwig, A., & Kintscher, U. (2013). Sex differences in exercise-induced cardiac hypertrophy. *Pflügers Archiv – European Journal of Physiology*, 465, 731–737. doi:10.1007/s00424-013-1225-0
- Fu, Q., & Levine, B. D. (2005). Cardiovascular response to exercise in women. *Medicine and Science in Sports and Exercise*, 37, 1433–1435. doi:10.1249/01.mss.0000174886.08219.85
- Fu, Q., VanGundy, T. B., Shibata, S., Auchus, R. J., Williams, G. H., & Levine, B. D. (2010). Menstrual cycle affects renal-adrenal and hemodynamic responses during prolonged standing in the postural orthostatic tachycardia syndrome. *Hypertension*, 56(1), 82–90. doi:10.1161/HYPERTENSIONAHA.110.151787
- Fuenmayor, A. J., Ramirez, L., & Fuenmayor, A. M. (2000). Left ventricular function and autonomic nervous system balance during two different stages of the menstrual cycle. *International Journal of Cardiology*, 72, 243–246. doi:10.1016/S0167-5273(99)00193-X
- Gardin, J. M., Wagenknecht, L. E., Anton-Culver, H., Flack, J., Gidding, S., Kurosaki, T., ... Manolio, T. A. (1995). Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women: The CARDIA study. *Circulation*, 92, 380–387. doi:10.1161/01.CIR.92.3.380
- George, K. P., Birch, K. M., Jones, B., & Lea, R. (2000). Estrogen variation and resting left ventricular structure and function in young healthy females. *Medicine and Science in Sports and Exercise*, 32, 297–303. doi:10.1097/00005768-200002000-00008
- Grandi, A. M., Venco, A., Barzizza, F., Scalise, F., Pantaleo, P., & Finardi, G. (1992). Influence of age and sex on left ventricular anatomy and function in normals. *Cardiology*, 81(1), 8–13. doi:10.1159/000175770
- Hanley, P. C., Zinsmeister, A. R., Clements, I. P., Bove, A. A., Brown, M. L., & Gibbons, R. J. (1989). Gender-related differences in cardiac response to supine exercise assessed by radionuclide angiography. *Journal of the American College of Cardiology*, 13, 624–629. doi:10.1016/0735-1097(89)90603-7
- Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., ... de Villiers, T. J., STRAW + 10 Collaborative Group (2012). Executive summary of the Stages of Reproductive Aging Workshop + 10: Addressing the unfinished agenda of staging reproductive aging. *The Journal of Clinical Endocrinology and Metabolism*, 97, 1159–1168. doi:10.1210/jc.2011-3362
- Hayward, C. S., Kelly, R. P., & Collins, P. (2000). The roles of gender, the menopause and hormone replacement on cardiovascular function. *Cardiovascular Research*, 46(1), 28–49. doi:10.1016/S0008-6363(00)00005-5



- Higginbotham, M. B., Morris, K. G., Coleman, R. E., & Cobb, F. R. (1984). Sex-related differences in the normal cardiac response to upright exercise. *Circulation*, *70*, 357–366. doi:10.1161/01.CIR.70.3.357
- Hossack, K. F., & Bruce, R. A. (1982). Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *53*, 799–804.
- Hutchinson, P. L., Cureton, K. J., Outz, H., & Wilson, G. (1991). Relationship of cardiac size to maximal oxygen uptake and body size in men and women. *International Journal of Sports Medicine*, *12*, 369–373. doi:10.1055/s-2007-1024696
- Ingegno, M. D., Money, S. R., Thelmo, W., Greene, G. L., Davidian, M., Jaffe, B. M., & Pertschuk, L. P. (1988). Progesterone receptors in the human heart and great vessels. *Laboratory Investigation*, *59*, 353–356.
- Janse de Jonge, X. A. K. (2003). Effects of the menstrual cycle on exercise performance. *Sports Medicine*, *33*, 833–851. doi:10.2165/00007256-200333110-00004
- Jiang, C., Poole-Wilson, P. A., Sarrel, P. M., Mochizuki, S., Collins, P., & MacLeod, K. T. (1992). Effect of 17 $\beta$ -oestradiol on contraction, Ca<sup>2+</sup> current and intracellular free Ca<sup>2+</sup> in guinea-pig isolated cardiac myocytes. *British Journal of Pharmacology*, *106*, 739–745. doi:10.1111/j.1476-5381.1992.tb14403.x
- Kaku, K., Takeuchi, M., Otani, K., Sugeng, L., Nakai, H., Haruki, N., ... Lang, R. M. (2011). Age- and gender-dependency of left ventricular geometry assessed with real-time three-dimensional transthoracic echocardiography. *Journal of the American Society of Echocardiography*, *24*, 541–547. doi:10.1016/j.echo.2011.01.011
- Kato, I., Toniolo, P., Akhmedkhanov, A., Koenig, K. L., Shore, R., & Zeleniuch-Jacquotte, A. (1998). Prospective study of factors influencing the onset of natural menopause. *Journal of Clinical Epidemiology*, *51*, 1271–1276. doi:10.1016/S0895-4356(98)00119-X
- Lang, R. M., Bierig, M., Devereux, R. B., Flachskampf, F. A., Foster, E., Pellikka, P. A., ... Stewart, W. (2006). Recommendations for chamber quantification. *European Journal of Echocardiography*, *7*(2), 79–108. doi:10.1016/j.euje.2005.12.014
- Light, K. C., Hinderliter, A. L., West, S. G., Grewen, K. M., Steege, J. F., Sherwood, A., & Girdler, S. S. (2001). Hormone replacement improves hemodynamic profile and left ventricular geometry in hypertensive and normotensive postmenopausal women. *Journal of Hypertension*, *19*, 269–278. doi:10.1097/00004872-200102000-00014
- Luczak, E. D., & Leinwand, L. A. (2009). Sex-based cardiac physiology. *Annual Review of Physiology*, *71*, 1–18. doi:10.1146/annurev.physiol.010908.163156
- Lynn, B. M., McCord, J. L., & Halliwill, J. R. (2007). Effects of the menstrual cycle and sex on postexercise hemodynamics. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *292*, R1260–R1270. doi:10.1152/ajpregu.00589.2006
- Maas, A. H., van der Schouw, Y. T., Regitz-Zagrosek, V., Swahn, E., Appelman, Y. E., Pasterkamp, G., ... Stramba-Badiale, M. (2011). Red alert for women's heart: The urgent need for more research and knowledge on cardiovascular disease in women: Proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *European Heart Journal*, *32*, 1362–1368. doi:10.1093/eurheartj/ehr048
- McClung, J. P. (2012). Iron status and the female athlete. *Journal of Trace Elements in Medicine and Biology*, *26*, 124–126. doi:10.1016/j.jtemb.2012.03.006
- McGill, H. C. Jr., Anselmo, V. C., Buchanan, J. M., & Sheridan, P. J. (1980). The heart is a target organ for androgen. *Science*, *207*, 775–777. doi:10.1126/science.6766222
- Mitoff, P. R., Gam, D., Ivanov, J., Al-hesayen, A., Azevedo, E. R., Newton, G. E., ... Mak, S. (2011). Cardiac-specific sympathetic activation in men and women with and without heart failure. *Heart*, *97*, 382–387. doi:10.1136/hrt.2010.199760
- Mor-Avi, V., Lang, R. M., Badano, L. P., Belohlavek, M., Cardim, N. M., Derumeaux, G., ... Zamorano, J. L. (2011). Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Journal of the American Society of Echocardiography*, *24*, 277–313. doi:10.1016/j.echo.2011.01.015
- Murphy, E., Lagranha, C., Deschamps, A., Kohr, M., Nguyen, T., Wong, R., ... Steenbergen, C. (2011). Mechanism of cardioprotection: What can we learn from females? *Pediatric Cardiology*, *32*, 354–359. doi:10.1007/s00246-010-9877-4
- Nuedling, S., Kahlert, S., Loebbert, K., Doevendans, P. A., Meyer, R., Vetter, H., & Grohé, C. (1999). 17 $\beta$ -estradiol stimulates expression of endothelial and inducible NO synthase in rat myocardium in-vitro and in-vivo. *Cardiovascular Research*, *43*, 666–674. doi:10.1016/S0008-6363(99)00093-0
- O'Donnell, E., Goodman, J. M., & Harvey, P. J. (2011). Cardiovascular consequences of ovarian disruption: A focus on functional hypothalamic amenorrhea in physically active women. *The Journal of Clinical Endocrinology and Metabolism*, *96*, 3638–3648. doi:10.1210/jc.2011-1223
- Ogawa, T., Spina, R. J., Martin, W. H. 3rd, Kohrt, W. M., Schechtman, K. B., Holloszy, J. O., & Ehsani, A. A. (1992). Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation*, *86*, 494–503. doi:10.1161/01.CIR.86.2.494
- Okura, H., Takada, Y., Yamabe, A., Kubo, T., Asawa, K., Ozaki, T., ... Yoshida, K. (2009). Age- and gender-specific changes in the left ventricular relaxation: A Doppler echocardiographic study in healthy individuals. *Circulation: Cardiovascular Imaging*, *2*, 41–46. doi:10.1161/CIRCIMAGING.108.809087
- O'Toole, M. L. (1989). Gender differences in the cardiovascular response to exercise. *Cardiovascular Clinics*, *19*, 17–33.
- Özdemir, K., Çelik, Ç., Altunkeser, B. B., Içli, A., Albeni, H., Düzenli, A., ... Gök, H. (2004). Effect of postmenopausal hormone replacement therapy on cardiovascular performance. *Maturitas*, *47*(2), 107–113. doi:10.1016/S0378-5122(03)00248-2
- Parks, R. J., & Howlett, S. E. (2013). Sex differences in mechanisms of cardiac excitation-contraction coupling. *Pflügers Archiv - European Journal of Physiology*, *465*, 747–763. doi:10.1007/s00424-013-1233-0
- Pelliccia, A., Maron, B. J., Culasso, F., Spataro, A., & Caselli, G. (1996). Athlete's heart in women. Echocardiographic characterization of highly trained elite female athletes. *JAMA: The Journal of the American Medical Association*, *276*, 211–215. doi:10.1001/jama.1996.03540030045030
- Peterson, L. R., Soto, P. F., Herrero, P., Schechtman, K. B., Dence, C., & Gropler, R. J. (2007). Sex differences in myocardial oxygen and glucose metabolism. *Journal of Nuclear Cardiology*, *14*, 573–581. doi:10.1016/j.nuclcard.2007.03.001
- Proctor, D. N., Beck, K. C., Shen, P. H., Eickhoff, T. J., Halliwill, J. R., & Joyner, M. J. (1998). Influence of age and gender on cardiac output-VO<sub>2</sub> relationships during submaximal cycle ergometry. *Journal of Applied Physiology*, *84*, 599–605.
- Ryan, S. M., Goldberger, A. L., Pincus, S. M., Mietus, J., & Lipsitz, L. A. (1994). Gender- and age-related differences in heart rate dynamics: Are women more complex than men? *Journal of the American College of Cardiology*, *24*, 1700–1707. doi:10.1016/0735-1097(94)90177-5
- Sandstede, J., Lipke, C., Beer, M., Hofmann, S., Pabst, T., Kenn, W., Hahn, D. (2000). Age- and gender-specific differences in left and right ventricular cardiac function and mass determined

- by cine magnetic resonance imaging. *European Radiology*, 10, 438–442. doi:10.1007/s003300050072
- Scheuer, J., Malhotra, A., Schaible, T. F., & Capasso, J. (1987). Effects of gonadectomy and hormonal replacement on rat hearts. *Circulation Research*, 61(1), 12–19. doi:10.1161/01.RES.61.1.12
- Schillaci, G., Verdecchia, P., Borgioni, C., Ciucci, A., & Porcellati, C. (1998). Early cardiac changes after menopause. *Hypertension*, 32, 764–769. doi:10.1161/01.HYP.32.4.764
- Sullivan, M. J., Cobb, F. R., & Higginbotham, M. B. (1991). Stroke volume increases by similar mechanisms during upright exercise in normal men and women. *The American Journal of Cardiology*, 67, 1405–1412. doi:10.1016/0002-9149(91)90472-W
- Taylor, A. H., & Al-Azzawi, F. (2000). Immunolocalisation of oestrogen receptor beta in human tissues. *Journal of Molecular Endocrinology*, 24(1), 145–155. doi:10.1677/jme.0.0240145
- Townsend, N., Bhatnagar, P., Wickramasinghe, K., Scarborough, P., Foster, C., & Rayner M. (2012). *Physical activity statistics 2012*. London: British Heart Foundation.
- Wiebe, C. G., Gledhill, N., Warburton, D. E., Jamnik, V. K., & Ferguson, S. (1998). Exercise cardiac function in endurance-trained males versus females. *Clinical Journal of Sport Medicine*, 8, 272–279. doi:10.1097/00042752-199810000-00004
- Wilhelm, M., Roten, L., Tanner, H., Wilhelm, I., Schmid, J. P., & Saner, H. (2011). Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. *The American Journal of Cardiology*, 108, 1489–1495. doi:10.1016/j.amjcard.2011.06.073
- Wittnich, C., Tan, L., Wallen, J., & Belanger, M. (2013). Sex differences in myocardial metabolism and cardiac function: An emerging concept. *Pflugers Archiv – European Journal of Physiology*, 465, 719–729. doi:10.1007/s00424-013-1232-1
- Xu, Y., Arenas, I. A., Armstrong, S. J., & Davidge, S. T. (2003). Estrogen modulation of left ventricular remodeling in the aged heart. *Cardiovascular Research*, 57, 388–394. doi:10.1016/S0008-6363(02)00705-8
- Yang, X., Chen, G., Papp, R., Defranco, D. B., Zeng, F., & Salama, G. (2012). Oestrogen upregulates L-type Ca<sup>2+</sup> channels via oestrogen-receptor- $\alpha$  by a regional genomic mechanism in female rabbit hearts. *Journal of Physiology*, 590, 493–508. doi:10.1113/jphysiol.2011.219501
- Yilmaz, D. C., Buyukakilli, B., Gurgul, S., & Rencuzogullari, I. (2013). Adaptation of heart to training: A comparative study using echocardiography & impedance cardiography in male & female athletes. *The Indian Journal of Medical Research*, 137, 1111–1120.
- Younis, L. T., Melin, J. A., Robert, A. R., & Detry, J. M. (1990). Influence of age and sex on left ventricular volumes and ejection fraction during upright exercise in normal subjects. *European Heart Journal*, 11, 916–924.
- Zengin, K., Tokac, M., Duzenli, M. A., Soylu, A., Aygul, N., & Ozdemir, K. (2007). Influence of menstrual cycle on cardiac performance. *Maturitas*, 58(1), 70–74. doi:10.1016/j.maturitas.2007.06.002
- Zwiren, L. D., Cureton, K. J., & Hutchinson, P. (1983). Comparison of circulatory responses to submaximal exercise in equally trained men and women. *International Journal of Sports Medicine*, 4, 255–259. doi:10.1055/s-2008-1026045