Hypothesis

Effect of sex hormones on cardiac mass

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Increased left-ventricular mass is an important cardiovascular risk factor for morbidity and mortality. Apart from obvious differences in cardiac size, the changes in left-ventricular mass in response to age and hypertrophic stimuli are very different in men and women. Whereas left-ventricular mass increases with age in apparently healthy women, it remains constant in men. Under increased cardiac loading conditions, such as hypertension or aortic stenosis, this disparity between sexes is even more striking. Findings are especially pronounced in people aged 50 years or older, in whom reproductive hormone concentrations have fallen. Whether the differences in left-ventricular mass changes are related to endogenous sex-hormone concentrations has never been shown. Androgens have anabolic effects on cardiac cells, and oestrogens have antiproliferative properties, we therefore postulate that the normal decline in endogenous sex hormones with age has contrary effects on ventricular mass in men and women in normal and pathological states.

Because of longevity not seen in many other animal species, women live a large proportion of life beyond their reproductive years. The menopause is associated with cessation of ovarian function and resultant low plasma oestrogen, which has systemic repercussions, including vasomotor disturbances, osteoporosis, and possibly increased blood pressure and atherosclerosis. In men, falling concentrations of testosterone and other androgenic steroids also happens with age (figure 1).[1] Severe hypotestosteronaemia is associated with osteoporosis and coronary heart disease in later life. At puberty, left-ventricular mass increases at a much greater rate in men than in women, largely in response to allometric changes in body size. In one study,[2] sexual maturation was not an independent predictor of left-ventricular mass in puberty, after adjustment for other determinants. These results do not negate, however, the possibility of more gradual modulation of ventricular mass in later life.

Left-ventricular mass and age

Results of population studies have shown a consistent age-related increase of left-ventricular mass in healthy women that is not seen in men.[3,4] Although coincident risk factors for hypertrophy could contribute to these findings, in a highly selected, non-obese, normotensive healthy subset of the Framingham population,[4] ventricular mass increased with age in women, whereas it remained constant in men (figure 2). In a separate necropsy series, in which primary cardiac pathology was excluded, measured ventricular mass (rather than calculated with echocardiography) decreased with age in men, but remained constant in women (figure 3),[5] confirming the difference between sex shown in the non-invasive population studies. In Olivetti and co-workers' study,[5] cardiomyocyte number and volume remained stable in women, whereas in men myocyte number fell strikingly as cell volume increased. Right-ventricular and left-ventricular morphometry changed similarly, which suggests that sex differences seen were due to factors that affect the myocardium in general rather than being secondary to silent ischaemia in men or hypertension, which would mainly affect the left ventricle.

Although vascular loading conditions differ between men and women, possibly because of differences in stature,[6] neither arterial compliance nor height contributed to left-ventricular mass in multivariate analysis.[7] The complexity of control of left-ventricular mass was emphasised in a large echocardiographic study, which showed that only 50% of the variance in mass could be accounted for, even after adjustment for age, blood pressure, body size, and stroke volume.[8] These results imply that other factors not previously considered, such as sex hormones, could be important in determination of ventricular mass.

Sex differences in the effect of age on ventricular mass are paralleled by differences seen in the prevalence of ventricular hypertrophy. In the Framingham cohort,[9] the prevalence of left-ventricular hypertrophy increased by 15% for every decade of life after age 60 years in men, compared with 69% in women. More frequent and more pronounced left-ventricular hypertrophy is also seen in women than in men in pressure overload hypertrophy states such as hypertension or aortic stenosis, despite closely similar blood pressures[10] or the presence of aortic valve stenosis.[11] In all these studies, however, the women are substantially older than the normal age of menopause. Garavaglia and colleagues[10] investigated the effect of sex hormones on left-ventricular mass, and showed that remodelling differences

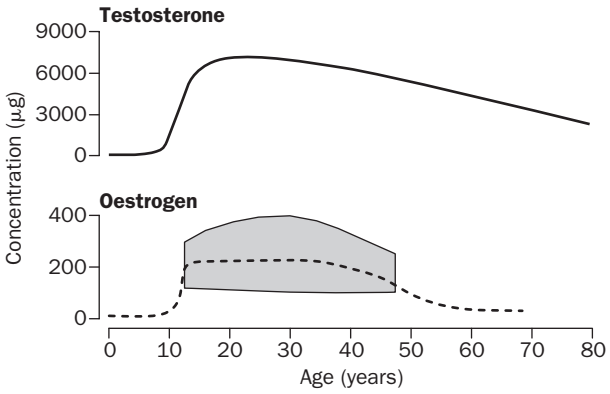

Figure 1: **Representative concentrations of testosterone and oestrogen secretion per day by age[1]**
Shaded area indicates reproductive years.

Lancet 2001; **357:** 1354–56

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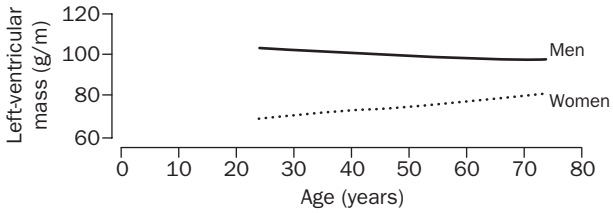

Figure 2: **Effect of age on left-venticular mass calculated from echocardiography for a healthy subgroup from Framingham population[4]**
Left-ventricular mass indexed to height.

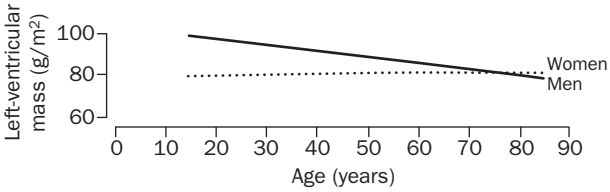

Figure 3: **Effect of age on left-ventricular mass measured at necropsy in patients in whom cardiac disease had been excluded**
Left-ventricular mass indexed to body surface area.[5]

were apparent only in postmenopausal women compared with age-matched men, and not in premenopausal age-groups. A distinct syndrome called hypertensive hypertrophic cardiomyopathy is almost exclusively seen in older postmenopausal women.[12] A disparity between the sexes in ventricular hypertrophic remodelling, in both normal and pressure-overloaded hearts, therefore exists.

Ventricular hypertrophy in animals

Results from studies in animals show a similar disparity between sexes in ventricular remodelling in response to increased cardiac load, as that seen in people.[13] In addition to greater hypertrophy, female rats typically display less or later cardiac dysfunction than male rats.[13,14] Consistent with these phenotypic changes, gene expression is also distinct, with less β-myosin and raised sarcoplasmic reticulum Ca^{2+} ATPase expression in one study,[15] and increased acetylcholinesterase expression in female pressure-overloaded rats in another.[16] In the latter study, sex differences in gene expression were not seen in control rats with no pressure overload. Workers in further studies of cardiac hypertrophy (caused by sinoaortic denervation in male and female rats) have shown that oestradiol inhibits the hypertrophic response, whereas testosterone facilitates hypertrophy.[17] Another model of rat cardiac hypertrophy (due to swimming or hypertension) could not confirm an antihypertrophic response of oestrogen.[18] That endogenous sex hormones are important in the control of cardiac contractility seems unlikely in view of the high concentrations required,[19] and the variable findings with supplementation (negative inotropism for both oestrogen and testosterone)[19] or replacement (positive inotropism for both oestrogen and testosterone).[20]

Cardiovascular receptor studies

The idea that sex hormones could be involved in modulation of cardiac mass is lent support by results of receptor studies that confirm the presence of oestrogen and androgen receptors in the myocardial cells of animals[15,21] and human beings.[21,22] Whereas oestrogen typically has antiproliferative effects on cardiac fibroblasts[23] and vascular smooth-muscle cells,[24,25] testosterone (or androgens) increases proliferation of vascular smooth-muscle cells.[26] Care should be taken in interpretation of these study results, however. Somjen and colleagues[25] have recorded, for example, a biphasic pro-proliferative and antiproliferative response for both oestrogen and testosterone on vascular smooth-muscle and endothelial cells. Although the myocardial hypertrophic effect of androgens has been confirmed in vitro,[22] there are, as yet, no studies indicating inhibition of myocyte hypertrophy or decrease in protein synthesis by oestrogens at cellular level.

Hormone-replacement studies

Despite the widespread interest in hormone-replacement therapy as a means of decreasing cardiovascular disease in women, little assessment has been done of the effect such treatment could have on cardiac remodelling or mass. Lim and co-workers[27] did a small case-control study and saw an association between long-term hormone-replacement therapy (>10 years) and lower cardiac mass in users than in non-users after controlling for known determinants of left-ventricular mass. In a second study[28] transdermal hormone replacement seemed to be associated with a decrease in left-ventricular hypertrophy in hypertensive postmenopausal women. In no study has the effect of hormone-replacement therapy on left-ventricular hypertrophy been assessed. Although non-therapeutic androgen use is associated with increased left-ventricular mass,[29] this effect generally arises in the context of associated physical training. There have been no prospective studies of the effect of therapeutic androgen replacement on cardiac mass.

The hypothesis

We postulate that sex hormones could be influential in modulating left-ventricular mass. Results of population studies in healthy volunteers, and studies in patients with pressure-overload states, consistently show sex-distinctive changes in cardiac mass correlated with ageing and increased cardiac afterload states (figures 2, 3). Older people of both sexes have been associated with relative hypogonadal hormone concentrations (figure 1). Oestrogen and androgen receptors could be involved in modulation of left-ventricular mass, since both have been seen in the myocardium. Results of in-vitro studies in animals and in-vitro organ bath studies suggest opposing cellular proliferative and hypertrophic effects of oestrogen and testosterone that are consistent with direct modulation of ventricular mass. These results could help to explain clinical findings, and might contribute to the unexplained variance in left-ventricular mass seen in population studies.

A possible confounding reason for the sex differences in left-ventricular mass is the healthy-survivor hypothesis. This hypothesis states that men with increased left-ventricular mass die earlier than similarly affected women, which results in a higher left-ventricular mass in women with increasing age. This theory cannot be argued against with prevalence rates of left-ventricular hypertrophy. However, the concordance of data from work in animals looking at left-venticular remodelling,[13,14,17] patients with aortic stenosis and hypertension being followed up,[10,11] and necropsy data that confirms sex disparity in the absence of fatal cardiovascular disease,[5] suggest that the hypothesis we propose is reasonable and warrants further consideration.

To confirm our hypothesis, several studies need to be done. To show that oestrogen has a direct modulating role on left-ventricular mass, we needed to know whether changes in protein synthesis in human adult myocardium arise in response to oestrogen receptor activation. Cellular studies should show inhibition of cardiomyocyte hypertrophy by oestrogen under appropriate stimuli, combined with physiological studies to assess prospectively the effect of hormone replacement (placebo controlled) on

ventricular mass in pressure overload states. This combination of investigations would help to differentiate a direct modulating effect of oestrogen on left-ventricular mass from a secondary effect caused by modulation of other hormone systems, such as the renin-angiotensin system.[30]

Prospective longitudinal studies with accurate non-invasive techniques, such as magnetic resonance imaging, should include men and women across a broad age range. We also needed to undertake clinical studies to measure the effect of pressure overload states on the left-venticular mass in the two sexes during reproductive years. Difficulties arise, not only because of the scarcity of isolated hypertension and aortic stenosis in youth, but also the ethical imperative to treat such disorders, either pharmacologically or surgically, as soon as they are diagnosed. Male and female patients with aortic stenosis of insufficient severity to warrant surgery would provide an optimum observation group, provided that follow-up is sufficiently long. Primary hypogonadal states such as seen in Turner's syndrome are routinely treated with hormone therapy, making such patients unsuitable for longitudinal studies. Cardiac mass could be monitored prospectively in large hormone-replacement therapy studies. If inhibition of left-ventricular hypertrophy by oestrogens is shown in appropriately constructed clinical trials, these hormones could provide a further option in the management of this disease in combination with antihypertensive or surgical treatment.

In view of the beneficial effects of testosterone on myocardial ischaemia[31] and coronary-blood flow in men with coronary disease,[32] concerns about the effect of supplemental testosterone on cardiac mass need to be thought about carefully. Since cellular studies have already shown androgen-mediated hypertrophic responses, studies in men and women undergoing testosterone replacement should include prospective measurements of cardiac mass.

The traditional factors known to affect left-ventricular mass account for only half of the variance seen between the sexes. There is strong evidence linking increased left-ventricular mass with cardiovascular and all-cause mortality.[33] The possibility that left-ventricular mass could be altered by the hormonal milieu therefore needs to be considered both physiologically and pharmacologically. The presence of hormone receptors on cardiac myocytes provides proof of a possibility for ventricular sex-hormone modulation. As such, the possibility that non-cardiac hormones modulate left-ventricular mass remains a plausible, though unproven hypothesis.

CSH is supported by an overseas research fellowship from the National Heart Foundation of Australia, and CMW by a grant from the British Heart Foundation.

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