Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently

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Abstract

The ability to recognize and appreciate from a reproductive standpoint that males and females possess different attributes has been long standing. Only more recently have we begun to look more deeply into both the similarities and differences between men and women, as well as between boys and girls, with respect to the structure and function of other organ systems. This article focuses on the cardiovascular system, with examples of sex differences in the control of coronary function, blood pressure, and volume. Recognizing the differences between the sexes with respect to cardiovascular function facilitates understanding of the mechanisms whereby homeostasis can be achieved using different contributions or components of the living system. Furthermore, recognition of the differences as well as the similarities permits the design of appropriate diagnostic instruments, recognition of sex-specific pathophysiology, and implementation of appropriate treatment of cardiovascular disease in men and women.

Keywords

heart rate; blood pressure; volume homeostasis; microvascular function

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SOMETIMES, differences are, simply, annoying. Sometimes, they are illuminating and provide insight into hitherto hidden mechanisms. So it appears to be when considering the cardiovascular function and dysfunction of women and men. The purpose of this article is to highlight the features of cardiovascular function (e.g., pumping of the heart, blood flow control, pressure regulation, and solute delivery) and manifestation of dysfunction (e.g., symptomology, prevalence, and comorbities) in men and women with the dual intent of learning more about how the integrated system functions and identifying fundamental questions yet to be answered.

It comes as little surprise to learn that the size of the heart and major blood vessels of women are smaller than those of men of the same race and age (39). The anatomic location of the major vessels in the heart, lung, and most organs are indistinguishable among the

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sexes. Similarly, the cardiovascular systems of males and females have the same formed elements circulating in the blood, the vessels are composed of the same cell types, and the union of the elements perform the same functions. Healthy men and women are in homeostasis. Consequently, it makes sense to conclude that the functions and functional responses of all of these common elements are the same in men and women, right? Well, no, not necessarily, and that is where the tale becomes interesting. The take-home message of this monograph will be that while men and women are indeed in homeostasis and they possess the same structural elements, how those components function to achieve homeostasis with respect to the cardiovascular system differs (from subtly to profoundly). The manifestation of these differences has a real outcome: how and when cardiovascular disease occurs, how disease can be prevented, and what can be done to ameliorate or treat its manifestations effectively. As physiology students, the functional differences as well as the similarities are of utmost importance as they provide fundamental insight into the mechanisms regulating the integrated functions of the intact organism.

At the core, few students of physiology are surprised that men and women can differ. At the very least, males produce testosterone and females produce the sex hormones estrogen and progesterone. What has become evident, with respect to the cardiovascular system, is that the differences and similarities involve more than the sex hormones, per se. It is essential to realize that every cell has a "sex" thanks to the presence of either an XX or an XY chromosome, that this sex is manifested in the womb, and that, beyond behavioral differences, prepubertal differences exist between the cardiovascular systems of boys and girls.

History

Before going further, it is important to understand historically how we have failed to recognize more widely that the physiology of males and females might differ. Part of the reason is that the "women's cycle," e.g., the sex hormone status of females, changes in a cyclical fashion over the lunar month; thus, when experiments are designed, the question has been how to make observations against a changing background. The status of the reproductive hormone testosterone was viewed as relatively constant; therefore, males provided a "cleaner model" for the study of cardiovascular function. In fact, serum testosterone levels rise to 20% above mean levels (500 ng/dl), peaking at 20:00 hours, and fall to 35% below mean levels, at 7:00 hours, in healthy men daily (16). While a circadian rhythm is maintained with age, the mean levels of younger men (~25 yr) are ~100 ng/dl higher than those of healthy elderly (70 yr) men, and the excursion from the nadir to peak is greater at the younger age. In men, a state similar to menopause (e.g., andropause) has not been demonstrated convincingly. Thus, men not only cycle, but cycle faster, for longer than women.

We need to also think further on the characteristics of the subjects tested whose data occupy the tables and graphs in handbooks, medical "scut" books, textbooks, encyclopedias, and internet files. Much of the human data found in medical texts represent the environment in which the testing was conducted. Medical schools and military institutions located largely in Europe and North America have provided the largest numbers of "healthy" individuals in

which to make measures of function. Consequently, most of the data represent young (18–22 yr), healthy, 70-kg Caucasian males. The majority of studies of human cardiovascular disease have been carried out, largely from the end of the 1800s through the 1970s. Until recently, these studies were conducted on males to "eliminate the confounding problem of cycling;" similarly, when cardiovascular adaptations to exercise, altitude, or space were the subjects, young Caucasian males who were now endurance-trained athletes again populated the data set. As shown in Fig. 1, the actual distribution of humans is broader than that represented by these subsets, and the distribution of females likely overlaps, but not coincides, with the distribution for males. While the data obtained from these subjects have greatly furthered our knowledge of physiology and pathophysiology, this information has been used to represent the behavior of humans as a collective rather than a selective. The consequences, as we will see, have led to a limited view of the mechanisms controlling organ and tissue function and to limitations in the diagnosis and care of humans with disease.

Sexual Dimorphism With Respect to Cardiac Function

The dual-chambered pump sending blood into the lungs for gas exchange and into the body for gas, water, and solute exchange appears, grossly, to just be smaller in women than in men (9, 17, 20a). In the living state, it is evident that this translates into a smaller stroke volume (SV) and thus a lower cardiac output (CO) (see Eq. 1). Less evident, until the living human is observed, is that the rate of pumping [heart rate (HR)] is greater in females than in males (38). Contrary to common belief, though, the HRs of male and female fetuses do not differ in utero (29). Given (as shown in Eq. 1) that the frequency of beats (HR; beats/time) multiplied by the amount ejected with each beat (SV; amount) is what determines CO (amount/time),

$$HR \times SV = CO \quad (1)$$

In studies of large numbers of normal healthy adults, even after accounting for the larger body surface area of men than women, the SV was ~10% smaller and HR similarly greater, resulting in no difference in cardiac index (volume·time^{-1}·surface area^{-1})(7). The gradient in pressure across the systemic circulation between the aorta [or mean arterial pressure outside the left heart (P_a)] and the vena cava [coming into the right heart (P_v)] is a function of the amount of blood pumped into the systemic vasculature (CO) and the resistance to blood flow offered by the vessels of the tissues [total peripheral resistance (TPR)], as shown by Eq. 2:

$$CO = (P_a - P_v)/TPR \quad (2)$$

In the normal circulatory system, P_v is on the order of 5% of P_a and is therefore considered negligible; under these conditions, the relationship can be rewritten to indicate that P_a is determined by the product of CO and TPR, as shown by Eq. 3:

$$P_a \sim CO \times TPR \quad (3)$$

Under conditions of cardiovascular stress (e.g., exercise, loud noises, or psychological stress) men respond by increasing mainly vascular resistance (TPR in Eqs. 2 and 3), which is manifested as an increase in mean P_a (blood pressure) (2), whereas women predominantly increase HR (Eq. 1), thereby increasing CO. In both cases, there is an appropriate cardiovascular response, but there are potentially different outcomes.

Recall further that the control of blood pressure involves actions of the autonomic nervous system. On the one hand, there is a sympathetic drive (by analogy, the accelerator) to the heart and periphery. Increases in sympathetic activity in the heart results in both elevated contractility, which leads to increases in SV, and increases in HR. Either or both actions lead to an increase in CO. In the periphery, increases in sympathetic activity results in resistance vessel constriction with an increase in TPR. Reduction or withdrawal of sympathetic activity is analogous to taking one's foot off of the accelerator, thereby reducing SV, HR, and TPR. On the other hand, the parasympathetic (vagal) system (by analogy, the brake) slows the heart; withdrawal of parasympathetic activity unmasks the sympathetic drive.

Recent studies of blood pressure control and cardiac function in healthy men and women have demonstrated that women and men use the two arms of the baroreflex system differently. At all ages, women were found to have reduced sympathetic activity (reflected by lower TPR and P_a) and enhanced para-sympathetic activity relative to men. Similarly, men were found to have higher plasma norepinephrine levels than women(12). The consequence, though, was that in response to changes in body position (e.g., in response to fluid shifts), women appeared to be more vulnerable to orthostatic hypotension and fainting (2).

Should the stresses be maintained and the system adapts or remodels, pathophysiology will develop. Given that the different mechanisms put strains on different components of the cardiovascular system, the long-term consequences of repeated and prolonged exposure to stress in the conduit and resistance vessels of males is vessel remodeling, resulting in sustained hypertension with less tissue perfusion. The consequences of reductions in tissue perfusion can be appreciated when recalling that metabolically active cells of an organ are downstream of the constricting arterial vessels. In women, it is the heart rather than the large arterial vessels that takes the burden (32).

As mentioned above, women also respond to changes in body position, application of lower body negative pressure, prolonged standing, or return to gravity from outer space with fainting (orthostatic hypotension) as a consequence of the reduced ability to maintain venous return to the heart and CO (orthostatic intolerance) (5, 10, 27, 40). Exactly which mechanisms account for the sex differences in orthostatic intolerance or even normal control of blood pressure, while widely studied, are not known (11). It should be evident, though, that if men and women use different components of the cardiovascular system to achieve

homeostasis, then a single approach to the treatment of dysfunction will not be optimal for both men and women.

In the general population, women are less likely to experience heart failure than men (14). The situation reverses itself following myocardial infarction, when it is women who are at greater risk than men to experience heart failure (36). From studies to determine left ventricular geometry and function in normal and hypertensive males and females by echocardiography while also controlling for differences in body size, HR, and age, it was confirmed that left ventricular systolic function (as deduced from measures of ejection fraction and fractional shortening by echocardiography) are influenced by the anatomic geometry of the left ventricle and that left ventricle geometry differs between men and women (7). Works of this type provided sex-specific data to define normal and patho-physiological cardiac function that can be used to correctly identify otherwise asymptomatic patients. In addition to the anatomic size differences between men's and women's hearts (31), the electrical activity of cardiac myocytes differ (35). In the intact beating heart, the ECG of women demonstrates a longer QT interval than that of men; prior to sexual maturity, the QT interval is similar, and it is after puberty that the interval in boys shortens to the times observed in adult males. There are also differences in the patterns of cardiac repolarization between males and females. It has been postulated that females have a lower density of subclasses of repolarizing potassium currents (K_r and K_s currents) and more variance in L-type calcium current in the different layers of the heart. The implications are that these differences, in turn, account for the sex-specific incidence in cardiac arrhythmias and differences in responses to drugs used to treat heart disease in men and women (1).

The composition of the blood circulating in the body also displays sex-specific differences in the levels of the formed elements, the most obvious being that lower numbers of circulating red blood cells per unit volume of plasma in females than in males (20a). This is manifested as lower hematocrit in women than in men. Both lipid and plasma protein compositions demonstrate sexual dimorphism. With respect to lipids, high-density lipoprotein (HDL) is higher and triglycerides are lower in females than in males; this "antiathrogenic" blood lipid profile is also associated with a lower incidence of cardiovascular disease. Following menopause, the lipid profile of females becomes more athrogenic and is correlated with the higher incidence of heart disease in that population (6). Less obvious is the lower plasma protein levels in females than in males (Fig. 2); the implications of this are discussed below.

With respect to hemodynamic responses, while most of the studies have been conducted on males, reexamination appears to be underway in several areas. One example is the response of the cardiovascular system to ingestion of a meal. Whereas mean arterial pressure is lower in females than in males, ingestion of a meal results in no change in females and a fall (reduced diastolic pressure) in males. Blood flow into the superior mesenteric artery is higher in females than in males; and, following a meal, it increases to a similar extent in both sexes, thereby maintaining the difference. In the portal venous system, no apparent differences exist for males and females, and for both sexes, venous flow increased to a similar extent in males and females. Although the control of blood flow within the splanchnic circulation for males was reflected in the systemic circulation by a drop in peripheral resistance, the same was not true in females.

With respect to cardiovascular disease, men are at greater risk, and their incidence of hypertension is greater than for premenopausal women of the same age (26). Ambulatory blood pressure measurements have consistently found that men have higher blood pressures than premenopausal, age-matched women (20). After menopause, the sex difference in the incidence of hypertension is lost (34). In animal models of hyper-tension, studies have also shown males to have higher blood pressure than females. For example, in Dahl salt sensitive-hypertensive rats, spontaneously hypertensive rats, and rats with reduced renal mass fed high-salt diets, males have higher blood pressures than females (18).

While the mechanisms underlying sex differences are poorly understood, there is significant evidence for a role for both testosterone in the development of and estrogen in the protection against high blood pressure (18). Evidence supporting the hypothesis of estrogen involvement in the differential expression of coronary vascular disease (CVD) and hypertension between men and women has been shown by several laboratories (18). While estrogen replacement therapy has been shown to reduce low-density lipoprotein-cholesterol and increase HDL levels, (18) these protective findings contrast with the findings of the Women's Health Initiative (6, 22) and Heart and Estrogen/Progestin Replacement Studies I and II (15, 19), two clinical trials that failed to find a protective effect for hormone replacement therapy (HRT) against CVD. It has been suggested that the type of estrogen used in the replacement trials, the fact that a significant number of participants were obese, and that many of the women had already gone through menopause could account for these outcome discrepancies (34,37). Furthermore, it has been suggested that HRT started during perimenopause rather than after menopause may have provide CVD protection (28).

Having suggested that sex hormones play a role in the development of hypertension, it should be recognized that 24-h monitoring of blood pressures and HRs in pediatric patients has demonstrated differences between boys and girls. Systolic blood pressure was normally distributed for girls and skewed toward higher levels in boys; median levels only became statistically different at the onset of puberty. Diastolic blood pressures also tended to be skewed toward higher levels at night than during the day and showed a movement to low or very low levels in children approaching puberty (41). What is notable is that there were not only differences in absolute values between boys and girls but the time of day when those differences were apparent (day vs. night, for example) was significant. Overall, HR decreased almost linearly with age and to a greater extent in boys than in girls. In a study of children in Italy, HR and blood pressure were positively correlated in boys and girls, with HR being consistently higher in girls than boys. Having said that, HR was independently correlated age, sexual maturation, height, physical activity, and "parental sociocultural level" (31).

In response to exercise, 11-yr-old children showed circulatory responses similar to those of adults, but, compared with adult men, boys have lower CO and higher HR for a given maximal oxygen output than men. At each work level, CO was ~0.5 higher than the values for boys. In boys, the increase in CO was achieved by an increase in HR, whereas girls achieved their increase in CO by increasing SV and HR to a similar extent. Consistent with the previous studies on children and adults, girls had a higher HR than boys; the difference

was maintained with increasing exercise, although the age, height, weight, and surface area of the children studied were not different between boys and girls (3).

Physiological Consequences of Sexual Dimorphism With Respect to Volume Balance

First of all, we know that healthy males and females are in volume balance. According to Starling's law of filtration, volume balance between the vascular and tissue spaces is determined by two set of forces existing across the walls of the exchange vasculature. These forces expressed per unit surface area are given as pressures: hydrostatic and oncotic. The hydrostatic pressure of the vascular space is generated by the force of the beating of the heart (P_{cap}) and that of interstitial space between the cells of the tissue (P_{int}) is a product of the fluid captured within the organ. Given that the oncotic pressure is determined from van't Hoff's Law,

$$\pi = \phi\, n\mathrm{C} \quad (4)$$

where n is the number of osmotically active particles, ϕ is an correction factor for the nonideality of particles in solution, and π is a function of the protein concentration (C) in the plasma (π_p) and interstitial spaces (π_i), respectively. The modern statement of Starling's law is that volume flux (J_v; volume/time) occurs when there is a gradient in the forces across a barrier with hydraulic conductivity (L_p; "leakiness" to water, distance·time^{-1}·unit pressure $^{-1}$), surface area (S, distance squared), and reflection coefficient (σ) to protein as follows:

$$J_v = L_p S\left[\left(P_{cap} - P_{int}\right) - \sigma\left(\pi_p - \pi_i\right)\right] \quad (5)$$

In a perfectly semipermeable membrane, σ to the primary protein constituent of plasma (albumin) is 1 (e.g., the full oncotic pressure is expressed); in organs such as the spleen or liver, where the spaces between endothelial cells are macroscopic, σ is 0 and no oncotic pressures are expressed as the protein concentrations in the vascular and tissue spaces are equal.

As shown in Fig. 2, there is also a difference in the protein content of plasma between women and men (20a). The discussion above should lead the reader to the conclusion that the net plasma oncotic pressure of blood in women will be less than in men, yet they are both in volume balance. As it happens, there are good physiological data demonstrating that not only is the mean arterial pressure of women less than that of men but that pressure in the exchange microvessels is also lower in women than men (33). The outcome is that in females, relative to males, there is a lower absorbing force (plasma oncotic pressure) in the exchange vessels that is offset by a lower filtering force (capillary hydrostatic pressure). In both cases, assuming that the hydrodraulic conductivities and surface areas of the vasculatures are equal, volume balance is maintained (Fig. 3). The other potential variable that may offset the pressures with respect to volume flux is the surface area for exchange, which, in turn, is a function of the size, number, and length of the microvessels in a whole

organ. The actual pressures in those vessels is also a function of how the vessels are arranged in a network. In normal animals, it appears that microvessel density is not remarkably different between males and females.

Remodeling of the network architecture has been observed in male, but not female, models of hypertension. In this pathophysiological state, males have fewer microvessels (rarefaction), resulting in changes in exchange surface area and TPR. In hypertensive humans, without respect to sex, forearm skin capillary density is reduced by ~20% compared with normotensive subjects and correlates inversely with blood pressure. Rarefaction of this magnitude, if present in all vascular beds, would result in an ~20% increase in TPR (30).

The contribution of sex in this process was studied in a hypertensive rat model of reduced renal mass plus feeding of a high-salt diet. In males, mean arterial pressure increased by >50% and skeletal muscle capillary density decreased by 33%, results similar to those observed in male normotensive and spontaneously hypertensive rats on a high-salt diet. In contrast, mean arterial pressures of females rose only slightly, and no changes in microvessel density were observed (29).

Returning to the discussion of fluid movement into tissue (volume flux, Eq. 5), fewer vessels implies reductions in both surface area and capillary pressure (or unchanged capillary pressure) relative to normotensive males, serving to maintain a constant flux of water in the face of an increase in arterial pressure. The modification in the network architecture appears to "protect" the exchange vasculature from an elevation in driving force. The problem with the compensatory mechanism is that "rebuilding" of the vasculature means that it is difficult to return blood pressure to "normal" as the variable resistance elements, the arterioles, have been removed. In addition, elevation of P_{cap} alone would be expected to result in an increase in filtration from the exchange microvasculature (leading to an increase in tissue water, edema) (Fig. 4*A*). Of interest, measures of the capillary filtration coefficient (CFC, the product of L_pS) in the forearm of hypertensives averaged 41% of controls, and the relation between CFC and arterial blood pressure values is inversely nonlinear (30). In aggregate, whether there is a net change in fluid filtration in hypertensive relative to normal subjects will depend on the combination of the changes in driving force (capillary pressure), capillary area (rarefaction), and permeability properties (Fig. 4*B*). The mechanisms controlling these changes and the role of the sex hormones are poorly understood.

Sexual Dimorphism in the Presentation of Cardiovascular Disease

We are all taught that there are three hallmarks of a heart attack:

1.   Chest discomfort or uncomfortable pressure, fullness, squeezing, or pain in the center of the chest that lasts longer than a few minutes or that comes and goes.

2.   Spreading pain to one or both arms, back, jaw, or stomach.

3.   Cold sweats and nausea.

It turns out that these three hallmarks are experienced more often by men than by women, and, in fact, only one in three women have these symptoms when experiencing a myocardial infarction. Instead, women experience shortness of breath, nausea, vomiting, sleeplessness, back or jaw pain, and/or a feeling of generalized fatigue or weakness weeks prior to an acute myocardial infarction! The serious consequence is that appropriate treatment for women is delayed, inappropriate, or incorrect, leading to preventable deaths.

Current studies of disease processes and diagnostic procedures are demonstrating that there is a need not only to recognize that differences exist between men and women but also to perform appropriate studies documenting normal and pathophysiological parameters, especially as they relate to diagnostic procedures. Studies of this nature are leading to the evaluation of diagnostic modalities, such as exercise ECGs and cardiac-imaging modalities, with respect to sex differences to improve the diagnosis and risk assessment of women and men, specifically, with suspected cardiovascular disease (25).

Summary

Over the past 10 years, differences between the physiology of women and men have been recognized with respect to normal cardiovascular physiology as well as with respect to the incidence, severity, and comorbidities of obesity, diabetes, and cancer of cardiovascular disease. What is important, in addition to knowing that these differences exist, is the elucidation of the physiological mechanisms responsible for the differences as well as the similarities. With these data, appropriate treatments can be designed to maintain function as well as to treat disease.

Acknowledgments

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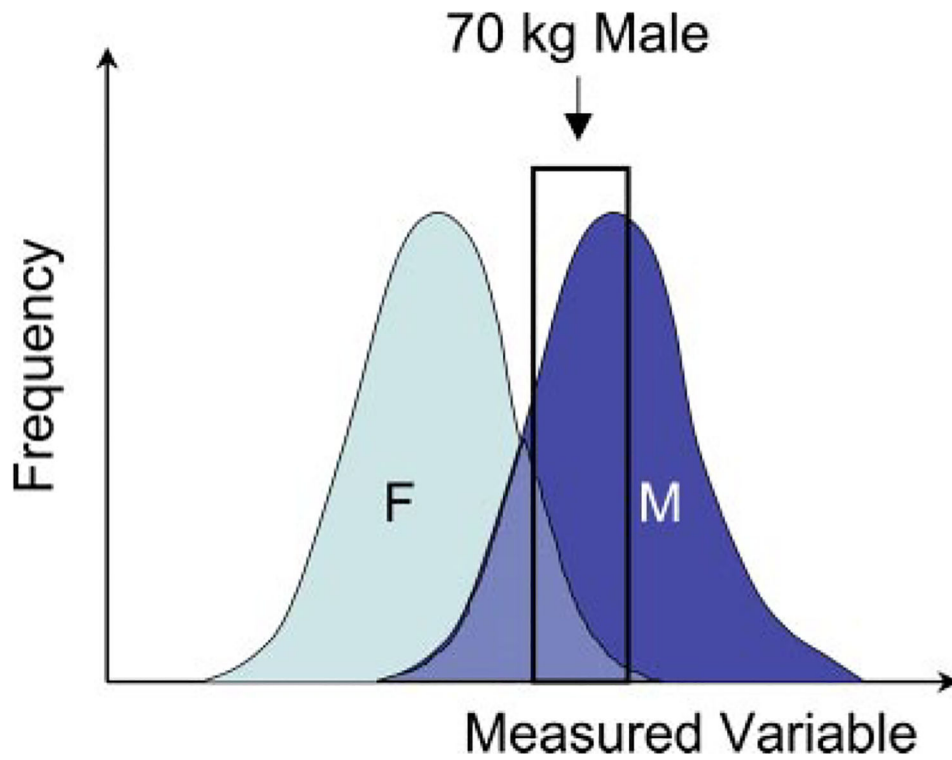**Fig. 1.**
Sampling a subset of a population may represent only a portion of the population. Many of the data on healthy humans came from studies of Caucasians men of 18–22 yr of age that were part of the military, athletes, or European medical students. Depending on the variable measured, the degree of overlap between females (F) and males (M) could range from negligible to complete, and, a priori, it cannot be predicted whether they accurately reflect the responses of both sexes, even of the same age and race.
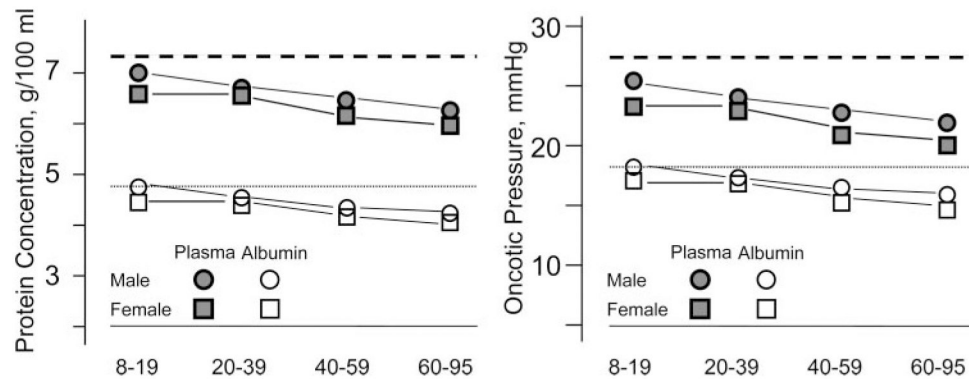
Fig. 2.
Total plasma protein and plasma albumin concentrations for males and females at 4 ages. Data are redrawn from Ciba-Giegy data tables (20a) (*A*). In *B*, the data shown in *A* were used to construct a plot of the net plasma oncotic pressures for the same groups. Dashed lines represent the "normal" values for humans (20a).

$$J_v = L_p S \left[\Delta P - \sigma \Delta \Pi \right]$$

♥P_{cap}: Females<Males

♥$\Delta\pi$: Females<Males

Fig. 3.
Is the Starling balance the same for males and females? In normal males and females, yes, the Starling balance is maintained; apparently, in females, the lower oncotic pressure (π) is offset by the lower capillary hydrostatic pressure (P_{cap}) relative to that of healthy normal males.
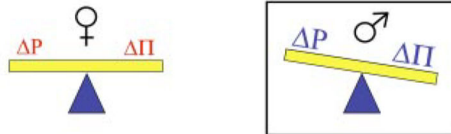
Pathophysiology: Hypertension

$$J_v = L_p S \left[(P_{cap} - P_{int}) - \sigma \Delta \Pi \right]$$

A Acute Case

✱P_{cap}: Females<<Males

✱Oncotic pressure (Π) : Females<Males

B Compensation with prolonged Hypertension

Capillary density (S) in Hypertensive Males< Females

Fig. 4.

In hypertension, the P_{cap} of females, while raised, is still less than that of males, as is π. Without any changes in the system [e.g., hydraulic conductivity (L_p) and surface area (S) remain as in health], the forces favor fluid movement into the tissues of males relative to females (*A*). While π remains, there is a reduction in the total number of skeletal muscle microvessels in hypertensive males, resulting in a reduction in *S* in the face of a rise in P_{cap}, bringing the Starling forces back into balance in males and females (*B*).