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Sex-Specific Characteristics of the Microcirculation

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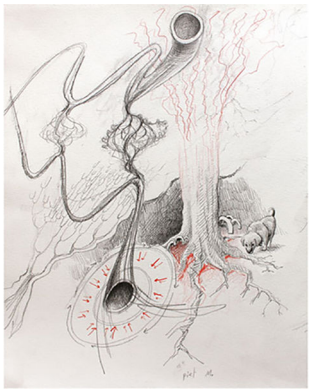
Abstract

The requirements of metabolizing tissue are both continuous and variable; accordingly, the microvasculature serving that tissue must be similarly dynamic. Just as it is recognized that males and females of the same species have differing metabolic requirements, is it not likely that the microvasculature serving these tissues will differ by sex? This section focusing on the constituents of the microcirculation identifies what is known presently about the role sex plays in matching metabolic demand with microvascular function and areas requiring additional study. Many of the identified sex differences are subtle and easily ignored. In the aggregate, though, they can profoundly alter phenotype, especially under stressful conditions including pregnancy, exercise, and disease states ranging from diabetes to heart failure. Although the features presently identified to “have sex” range from differences in growth, morphology, protein expression, and intracellular signaling, males and females alike achieve homeostasis, likely by different means. Studies of microvascular sexual dimorphism are also identifying age as an independent but interacting factor requiring additional attention. Overall, attempting to ignore either sex and/or age is inappropriate and will prevent the design and implementation of appropriate interventions to present, ameliorate, or correct microvascular dysfunction.

Graphical Abstract



Art work by Piet Michiels, Leuven, Belgium

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Keywords

Aquaporin; Arterioles; Barrier function; Blood flow regulation; Capillaries; Coronary microvascular dysfunction; Endothelium; Fibrinolysis; Fluid homeostasis; Glycocalyx; Hydrostatic pressure; Lymphatics; Venules; Microcirculation; Microvascular network; Myogenic response; Orthostatic intolerance; Pericyte; Peripheral resistance; Pregnancy; Rarefaction; Hypertension; Sepsis; Sex difference; Sexual dimorphism; Syndecan-1; Vascular homeostasis

Introduction

The microvasculature constitutes the largest number of vessel segments and surface area of the blood vasculature. Despite its anatomical prominence, it is the least studied portion of the vasculature circulating blood reflecting the difficulties of access and visualization. Its tubular structures, the arterioles, capillaries, and venules, perform the majority of the "work." They control how much blood moves into and out of the tissues they penetrate and the movement of everything from respiratory gases, fluid, solutes, drugs, hormones, proteins, and cells between circulating blood and metabolizing tissue. In addition, they govern the production and modification of a growing list of circulating vasoactive mediators, peptides, growth factors, and hormones. The microvessels are also the sites most likely to experience changes in function early in the development of numerous acute life-threatening conditions such as sepsis and disseminated intravascular coagulation (DIC) [28, 36, 68] to chronic diseases spanning from diabetes, obesity, and Alzheimer's to heart failure [22, 41, 52, 67, 82, 113]. Even less studied is the influence of sex on these myriad functions in health or dysfunctions in disease. What work has been done and is now underway makes it clear that ignoring sex will lead to misunderstanding of the basis of vascular homeostasis or how it is modified in whichever sex is not being studied.

Constituents of the Microvasculature

Multiple definitions of the "microvasculature" exist based on size and anatomical location [105]. In most mammalian systems, microvessels are arranged in a network whose anatomical structure is optimized to the organ's function and distributes circulating blood close to metabolically active tissue and then removes it to the venous system. The three primary microvascular constituents are arterioles, capillaries, and venules.

Arterioles

Arterioles branch off of the feed arteries connecting an organ to the conduit vessels carrying blood from the heart at high velocity with high pulsatile pressure. Arterioles in mammals are <100 μm in diameter (in situ resting tone results in diameters ranging between 15 and 40 μm) [97]. Their walls consist of vascular smooth muscle (VSM) wrapping a smooth, continuous layer of endothelial cells (EC). The smallest of these vessel segments, the terminal arterioles, possess a single layer of VSM and resting diameter between 5 and 8 μm. Arteriolar constriction and dilation lead to fine, variable control of blood flow to and within the microvascular network. As capillaries lie downstream of the arterioles, changes in arteriolar tone also lead to control of the amount of materials delivered to the capillaries and

of capillary hydrostatic pressure which controls transmural fluid movement. These vessels are dynamic as their structure can be changed both acutely and chronically in the face of changing hemodynamic conditions [76, 105].

Capillaries

Capillaries branch off of the terminal arterioles and are distinguished by the lack of VSM but presence of pericytes on the abluminal surface in contact with the EC lining [105]. The degree of pericyte coverage is organ dependent with coverage being highest in the capillaries of the retina and brain. It is not unusual for a single pericyte to have processes contacting more than one EC. The contribution of pericytes to the regulation of microvascular function, especially at the level of the capillaries, is just beginning to come into its own. These cells are referred to in the early literature as Rouget cells and discussed heavily by Krogh [65], with respect to their roll in participating in the regulation of capillary blood flow. Most recently the notion that pericyte contraction could influence blood flow within the capillary bed has re-emerged in discussion of the capillary no-reflow following ischemic insult in both the brain [37] and the heart [85]. Pericytes are also thought to play a role in regulation of barrier properties of intact exchange micro-vessels. Cross sections of fixed capillaries and venules often show pericyte foot processes in close proximity to the endothelial junctions of vessels that display a transient loss of barrier function in response to agents such as histamine and display massive endothelial gaps at times when permeability has returned back to normal levels [125]. The implication being that acute loss of barrier function is limited by the presence of the pericytes. To date, though, no studies have focused on sex differences in pericyte function or dysfunction.

Within the microvascular network are several orders of capillaries. Capillaries branching off of the terminal arterioles, the arterial capillaries, have blood flow diverging at the segment entrance and exit. True capillaries come off of the arterial capillaries, with flow diverging at the entrance and converging with flow in the next segment, the venular capillaries [98]. Mammalian capillary diameter across the capillary network ranges from 3 to 5 μm, and the EC thickness in areas away from the nucleus ranges from 0.1 to0.3 μm facilitating the exchange of fluid and solutes. Exchange is driven by gradients in pressure driving fluid and gradients in concentration driving solute across the wall [105]. Additional factors favoring exchange are the high density/large number of capillary segments providing small distances between exchange elements and a huge surface area, the thin attenuated EC structure that provides a large area of lipid facilitating exchange of hydrophobic materials, and thin junctions favoring diffusion of hydrophilic solutes. The membranes of capillary EC also contain water channels, the aquaporins, through which water can flow exclusively, and vesicular structures, caveoli, that contain receptor and enzyme complexes that facilitate localization of interactions in the face of a flowing medium. In addition, the surface of the EC also possesses an extensive, charged carbohydrate structure, the glycocalyx, that also serves as a relatively unstirred region near the surface that also facilitates ligand interaction in a changing environment. The glycocalyx can act as a sensor of fluid flow and offers significant resistance to solute and fluid transport [44–46, 48, 55], and its structure/composition can be altered by disease [79, 102].

Venules

Flow, out of the capillary network through venular capillaries, converges into the venules [98]. These vessels, of larger diameter than their terminal arteriolar cousins, are generally not round but elliptical in cross section reflecting the sparse coverage by VSM. Pericytes are still found in the venular capillary segments that flow into the venules, but their coverage falls off with successive branches. These vessels coalesce into collecting venules (30–50 μm) and then into the muscular venules (50–100 μm). The venular portion of the microvascular network is involved with control of volume and modulation of inflammatory and immune responses [105]. The glycocalyx is also present on the venular endothelial cells; in addition to participating as a resistor to solute and fluid flux, the structure limits access to endothelial ligands mediating not only receptor access but also white cell interactions [70].

Lymphatics

The lymphatics, the “forgotten” portion of the vasculature, were first described by Hippocrates (460–377 B.C.) and then illustrated by the Greek physicians Herophilus (335–280 B.C.) and Erasistratus (304–250 B.C.) [12]. These vessels and the fluid they produced were again forgotten until the Italian anatomist Gasparo Asellius published his work (Gaspare [27]) almost a millennium after the systemic vasculature was described. While there is a more recent study of collecting and capillary lymphatic (the lymphatic vessels of sizes and distributions similar to the systemic microvessels) function, consideration of sex has received only passing interest. Relative to what has been shown with respect to sexual dimorphism in capillary function, it would be surprising if there were no sex-related differences in lymphatic function that are central to maintenance of fluid and solute homeostasis in healthy males and females.

The Common Constituent Separating “Inside from Out”: The Endothelium

The entire network of microvessels is covered by a monolayer of EC. EC are involved in not only control of barrier function but also participate significantly in immune responses, inflammation, thrombosis, vascular remodeling, and regulation of arteriolar vessel tone. The EC are incredibly heterogeneous, likely reflecting these spectra of functions. The degree of heterogeneity reflects not only where in the vascular system (both organ and anatomical location) [96] the EC are located but also where within the microvascular network the EC reside [2, 117] and the sex of host [5, 54, 123]. One reason considering EC heterogeneity is important is that sampling a limited number of EC in vivo or in culture may reflect the behaviors of selected populations giving rise to a false or skewed understanding of the etiology of disease or approaches for ameliorating the disease state. In turn, EC dysfunction is a feature common to multiple chronic diseases including diabetes mellitus, heart failure, and stroke. This same constellation of diseases displays male/female differences with respect to incidence, onset, severity, morbidity, and mortality [72, 100, 120].

Sexual Dimorphisms in EC Phenotype that Influences Function

EC in culture are commonly referred to as taking on a “cobblestone” morphology. In fact, EC shape is a function of the composition of the substrata on or in which they are grown [73, 101]. On Matrigel™, EC will form tubelike structures; this characteristic is used as one verification of EC [6] to distinguish them from VSM, pericytes, white blood cells, or fibroblasts. EC plated on gelatin or collagen spread and, depending on vascular bed of origin, can actually take on multiple shapes. Recently it has been found that microvascular EC from skeletal muscle display sexual dimorphism with respect to shape in vitro when plated on gelatin [50]. Prior to plating, no sex difference existed in size - for both sexes the microvascular SKM EC were 16 μm in diameter (~2000 μm^3 volume); on plating EC from females spread further than SKM EC from males. While apparently not a large difference (>10%), the predictions are that the area of water-filled perimeter per capillary segment will be greater in females suggesting that hydrophilic solute flux would be greater in females than males. In another example, we find, on a per cell basis, the amount of lactate generated by microvascular EC in culture does not differ by sex [50]. The “but” is that if the differences in EC size are taken into account, a greater number of EC are required to cover a skeletal muscle capillary for a male than a female. The back-of-the-envelope calculation predicts a 50% greater lactate production per unit volume in equivalentsized vessel segments of males relative to females. This prediction needs to be tested in vivo for both lactate and other EC-generated hormones and mediators.

Sexual Dimorphism in Arterioles

For a variety of historical reasons, most studies of microvascular arteriolar function have been conducted on animals of one sex or the other. Many studies of in vivo blood flow control, for example, have used the cremaster muscle in males because the tissue is thin facilitating study in the living tissue by light microscopy. Many small animal studies of exercise and low gravity are performed on females because females tend to use the exercise wheels spontaneously, and the hind limb-unweighted female does not suffer involution of the testis on unloading. In human studies of exercise, the subjects were often young males in a medical school or the military. Similarly, males were used in many studies because of the fear that reproductive hormone cycling would influence outcomes. The concern is that our perceptions of how the systems work are erroneous because a male is not a female and vice versa.

Architecture and Morphology (Rarefaction)

The microvasculature, particularly the arteriolar elements, changes with respect to structure and reactivity with sustained hypertension. The conclusion from the majority of studies is that the adaptation is a successive process of first increasing arteriolar tone to protect the downstream vessels from increases in capillary pressure, followed by structural remodeling of the arteriolar wall replacing VSM with matrix to maintain a fixed reduction in diameter, and finally vessel pruning (rarefaction). While female humans and mammals can develop hypertension, it occurs later in life and to a lesser degree [29, 95, 127]. In many animal models, it is difficult to make females hypertensive [26, 40, 119]. In one study, male and

female rats were rendered hyper-tensive by removing a kidney and placing them on a high-salt diet [90]. The males developed hypertension well in advance of the females - by day 3 on the high-salt diet, mean arterial pressure (MAP) in the 85-day-old males was 135 ± 6 mmHg, whereas it was only 103 ± 3 mmHg in the females. At that point the skeletal muscle microvasculature was examined for changes in morphology. In the white *gastrocnemius* muscle, there was evidence of micro-vessel loss in the males but not the females. In fact, even following 4 weeks of the high-salt diet, the females remained free of evidence of micro-vascular remodeling and normotensive at 105 ± 5 mmHg, whereas MAP had risen to 160 ± 8 in their male counterparts where rarefaction was now discernable in both the white and red *gastrocnemius* as well as the *soleus* and *plantaris* muscles [90].

Vascular Reactivity (VSM Dilation/Constriction)

Arteriolar function is of particular importance because the state of vascular tone (constriction relative to dilatation) regulates blood flow distribution as well as capillary hydrostatic pressure. Sex plays a role in pressure-induced myogenic constriction of arterioles. The myogenic response in arterioles from female rats, for example, is smaller than that of males. It was suggested an increased release of NO and/or elevated eNOS activity related to the higher levels of estrogen in the female animals could account for the reduction in myogenic response [42, 126].

Adaptation to an environmental change also has been shown to differ by sex. In response to chronic hypoxia (CH) at the whole animal level equivalent, sex-independent changes in total peripheral resistance were observed, and in both sexes pressor responses were similarly reduced following CH. At the level of the mesenteric microvasculature, though, arteriolar reactivity, while reduced in males, remained unchanged by CH in females; eNOS protein expression in these vessels was unchanged although EC calcium was elevated in CH females compared to controls [34]. This example illustrates that because one parameter, in this case total peripheral resistance, is sex-independent, it is incorrect to assume that all parameters are likewise independent of sex.

Only recently it has become accepted that coronary heart disease (CHD) and its manifestations differ by sex. Heart disease generally shows up at an earlier age in men than women [35]. In human females, CHD is a microvascular disease which manifests by increased arteriolar constriction and vasospasm not generally found in males [81, 91, 108]. In contrast, CHD in males is a macrovascular disease characterized by the presence of coronary occlusion and deposition of plaque [23]. Males adapt to CHD by growing coronary collateral vessels that bypass areas of occlusion. In contrast, collateral vessel formation in females is rare [61, 81]. The small size and large numbers of microvessels make them difficult to image and confirm coronary micro-vascular dysfunction in women especially using approaches developed for detecting CHD in males [91, 92]. Sex-sensitive arteriolar vascular reactivity is not limited to the heart. In the gut, responses to ischemia/reperfusion injury differ by sex. In male mice, 30 min of ischemia followed by 90 min of reperfusion was characterized by a loss of intestinal epithelial barrier integrity that paralleled increased endothelial/leukocyte interactions and reduction in blood flow resulting from a reduction in flow rate and the number of capillaries perfused. In females subjected to the same treatment,

while loss of epithelial barrier function occurred, it was later in time and accompanied by similar changes in inflammatory response and degree of organ perfusion [116].

Onset, frequency, and pathophysiology of cardiovascular disease (CVD) outside of the heart involving the microcirculatory system are also influenced by sex [14, 25]. In the cerebrovasculature, sex differences have been described with respect to vascular anatomy [21] and also pharmacology [60]. In the brain, arteriolar responses to vasoactive compounds, including angiotensin [19, 114] and endothelin-1 [29, 71], and nitric oxide synthase activity [88, 115], are sexually dimorphic.

The incidence of stroke is higher in women than men, especially later in life [14, 21, 61, 99]. As with coronary microvessels, age and sex are significant, independent variables influencing cerebrovascular function. Recent work [1, 69] has shown cerebral blood flow to be higher in young women than men, a difference not found in older adults. Similarly, in younger women, the response to hypercapnia was greater than in age-matched males; following menopause this sex difference was no longer present [59]. An important consideration pointed out by Barnes [7] is that when sex differences in MAP and vascular architecture are considered along with the differences in responses to hypercapnia, cerebral blood flow in young women is actually lower than age-matched men. This consideration of multiple variables controlled by microvascular cerebral vessel function is especially important as a reduced response to hypercapnia is associated with elevated risk of stroke and increased cognitive decline, two identified sexually dimorphic risk factors [78].

In addition to the anatomical differences, sexual dimorphism exists with respect to the mediators of microvascular tone and pharmacological responses to vasoactive drugs verified in clinical studies using male subjects [86]. The potent vasoactive peptide endothelin (ET-1) is interesting as plasma levels of ET-1 differ by sex [3, 32, 33], as do the distribution, expression [33, 66], and activation of ET receptors and as do the mediators of the ET system. In females the ratio of ET-1 to ETB receptor activation is primary; in contrast, in males, ET-1/ETA receptor activation is of greatest importance [29]. The implication is that these differences contribute to the overall observation of lower blood pressure of females relative to males reflecting in part the predominance of ETA receptors on vascular smooth muscle that enhances constrictor action of ET-1 relative to ETB receptors predominant on EC-mediating vasodilator actions of ET-1. In rat coronary arterioles, age, as well as sex, influences the functional response. As females age, coronary arteriolar constriction to ET-1 increases, while in males with aging reduction in the constrictor response to ET-1 is observed [66]. In retinal arterioles, ET-1 sensitivity declines with age, especially in females, while expression levels of the two receptors, ETA and ETB, displayed no differences with either age or sex [71]. It was determined using a pharmacological approach that the age-related reduction in ET-1 response in males was mediated by ETA signaling pathways, while in females it was the ETB signaling pathways that mediated the attenuated ET-1 contractility with age.

A component that has been studied more intensely with respect to sex differences in blood pressure control is the autonomic nervous system (review, [57]). These studies are germane to microvascular, particularly arteriolar, function, given that sympathetic tone (including

muscle sympathetic nerve activity) influences VSM contractile state via alpha-adrenergic receptor activation to increase peripheral vascular resistance. Elevated resistance, of course, leads to increased systemic blood pressure upstream of the arterioles and reduction of blood flow and hydrostatic pressure in the exchange microvessels downstream from the arterioles. A recent review by Barnes covers this subject in greater detail [7]. The highlights of the review are that alpha-adrenergic vasoconstriction is lower in young females than males [24], there are differences in beta-adrenergic receptors [39, 63], and while female sex hormones contribute to a reduction in tonic autonomic nervous support, the autonomic nervous system becomes a greater controller of blood pressure in females postmenopause.

Microvascular exchange tends to be equated with the capillary and venular elements of the network; in certain organs, like the heart, flux across arterioles appears to also contribute to net whole organ clearance. In the heart, arterioles are positioned anatomically in areas removed from the capillaries [58] and to be relatively leaky (protein reflection coefficient, σ, circa ~0.6 [16] compared to $\sigma > 0.8$ in skeletal muscle [124]). In porcine coronary arterioles, while basal arteriolar permeability to albumin did not differ by sex, the permeability response to adenosine with endurance exercise was greater in females than males [53, 123]. While skeletal muscle arterioles are tighter than capillaries and venules (e.g., have lower permeability), their EC layer requires a finite permeability to solutes to support VSM function. Arterioles from rat skeletal muscle demonstrated sex differences in the magnitude and direction of permeability responses to adenosine [121]. Differences in adenosine receptor isoform distribution, while demonstrating that A2b mediates EC permeability, were not found. Only when adenosine receptor signaling pathways were examined did it become evident that expression levels of the phosphodiesterase isoform 3 (PDE3) differed by sex [122].

Sexual Dimorphism in Capillary Function

Sex differences with respect to the primary function of capillary endothelial cells, fluid and solute exchange, have been demonstrated at multiple levels in a limited number of studies [15, 53, 54, 74, 89, 104, 112, 116]. In each it becomes evident that the differences can reflect the driving forces for exchange, EC morphology, and cell signaling, as well as EC responses to a myriad of mediators. While we often focus on the pathophysiology of loss of barrier function (e.g., increases in permeability with inflammation or trauma), interventions that "tighten" the barrier can also create pathology by limiting the passage of necessary materials (as appears to happen with hyper-insulinemia [104]) either out of or into the circulation. A well-functioning barrier exists in a state analogous to arteriolar tone — wherein permeability can increase or decrease in response to changes in tissue demand and environment [43, 47].

The amount of fluid or solute moved across the endothelial barrier is a function of the architecture of the pathways through and between the endothelial cells, the surface area for exchange, and the physicochemical properties of the barrier media (including the glycocalyx at the blood/EC interface and the extracellular matrix at the luminal and abluminal surfaces, respectively) and of the moving material (where size, shape, and charge can be influential). In a study of acute coronary syndrome, males were found to shed more syndecan-1 (a

marker of glycocalyx damage) than females [79]. These data imply either a greater amount of sydecan-1, a denser glycocalyx, or higher protease activity in EC of males.

In the presence of natriuretic peptides (ANP, BNP, or CNP), components of the glycocalyx, including syndican-1, have been shown to be released into coronary effluent of isolated, perfused guinea pig hearts [56]. This result is interesting as (a) the atrial peptides can reversibly increase microvascular permeability [45, 46, 77] and hydraulic conductivity [47, 49, 51] and(b) the “normal” levels of ANP and BNP are higher in healthy women than men (Table 20.1). Further, preliminary studies from the same group find that syndican-1 and hyaluronan levels in the blood of healthy premenopausal women vary with the menstrual cycle, that syndican-1 levels of males are higher than cycling and postmenopausal females, and that the levels of syndican-1 have no temporal component in either males or postmenopausal females (personal communication). These results are intriguing because the changes in glycocalyx thickness with shedding could account for the well-known increases in premenstrual edema in females and be of importance in the changes in fluid balance observed during pregnancy.

In addition, especially for water and hydro-philic solutes the size of peptides, hormones, and proteins, the net transmural pressure gradient is of importance. Two of these factors appear to differ in males and females: the concentration of plasma protein (higher in males than females [52]) which sets the oncotic pressure gradient (1–3 mmHg greater in males than females [52]) drawing fluid out of the tissue toward the lumen and the hydrostatic pressure gradient largely a function of capillary blood pressure. Not only is arterial blood pressure 6–10 mmHg lower in females than males prior to menopause [95], but, from a more limited study, capillary pressures are 2 mmHg lower in females than males [111]. The net driving force for fluid and solute, the difference in these two values, appears to favor filtration in females over males; this conclusion is another thing that needs to be evaluated in vivo. A summary of published hemodynamic data for healthy males and females is presented in Table 20.2.

In a study of seizure activity in rats, it was found that nitric oxide synthase blockade with L-NAME induced an increase in blood-brain barrier (BBB) permeability (Evans blue dye extravasation), in females, not in males [15]. Surgical cessation of ovarian function in adult female swine also results in loss of meningeal microvascular barrier to fluorescently labeled protein [30]; replacement of estrogen in a pulsed dose (estrogen patches) restored barrier function (and changes in vessel architecture), whereas flat dose estrogen replacement was not effective [31]. Thus, not only can a hormone or vasoactive compounds be important in regulating microvascular function, but the rate of change (a spike) can be of importance. This appears to be also the case for vascular endothelial growth factor (VEGF) [8, 10], a potent mediator of permeability. Plasma levels of VEGF are higher in men than women and are correlated with the development of atherosclerosis [62], a disease process shown to occur more frequently in males.

At the level of the whole human, fluid balance can differ by sex. It is well known that the state of pregnancy results in profound changes in fluid distributions with resulting changes in hemodynamics [18, 80]. One supposition is that because females must possess the

mechanisms to reversibly alter fluid distributions to accommodate pregnancy, the multiple factors regulating fluid and solute flux will differ between males and females.

Venules

The majority of vascular volume resides in the venous component of the microvasculature, and fluid exchange occurs predominantly across the capillaries. In the environment of microgravity, sex differences in volume regulation become apparent. Female astronauts during space flight experience a greater shift of fluid out of the plasma space than men and following return to gravity experience greater orthostatic intolerance [38, 75]. In response to orthostatic stress, males compensate by changing vascular resistance (microvascular), while females change heart rate. In a follow-up study to match sex-specific countermeasures (lower body negative pressure, LBNP) for changes in orthostatic stress (head-down tilt), it was found that compared to men tibial microvascular blood flow and oxygenation were both lower in women [38]. The conclusion of the study was that whereas LBNP is a suitable intervention to combat orthostatic changes in men, another approach needs to be designed for women.

It is in the venules draining the capillary tree that the majority of white blood cell/endothelial cell (WBC/EC) interactions are observed, and it is in these vessels, with their lower hydrostatic pressure and relatively low flow rates, that increases in vascular leakage to proteins as well as white cell diapedesis are observed [105]. Venules are also the site of integrin expression by EC in response to cytokines that promote WBC/EC interactions [20, 87]. In turn, inflammatory cytokine action is sensitive to the presence of estrogen and testosterone, respectively [64, 118].

Under basal conditions observations of in situ venular perfusion demonstrate no discernable difference between males and females with respect to WBC/EC interactions in the hamster cheek pouch [89]. While basal white cell/EC interactions did not differ in this preparation, permeability responses to ischemia/reperfusion (I/R) injury in the venous vasculature did. Following the I/R insult, fluorescently labeled dextrans were observed to egress more from the venules of males relative to the females clearly demonstrating that the loss of barrier function was apparently independent of WBC/EC interactions [89].

That said, in porcine coronary venules and rat skeletal muscle venules, differences in both basal venular permeability to protein and permeability responses with sex have been documented [53, 54, 123]. A study of protein clearance from mesenteric venular vessels in sexually mature rats [103] illustrates the complexity of protein and fluid movement under basal and stimulated conditions. While basal leak index (LI) of fluorescently labeled albumin did not differ by sex, acute treatment with insulin increased LI in males and was without effect in females. Analysis of protein clearing into the suffusate demonstrated lower total protein clearance and no difference albumin clearance, for males and females, respectively. In males, insulin reduced both total protein and albumin clearance rates; insulin reduced total protein clearance and was without effect on protein clearance in the females. Further, in response to acute insulin, the reduction in protein clearance was greater in the males than in females [103]. This study, given the mismatches between venular albumin LI,

albumin clearance, and total protein clearance, illustrates that protein flux occurs across microvascular elements other than the venules and that male/female sex (and insulin) interacts with different elements governing protein and consequent fluid flux.

Sepsis results in loss of barrier integrity and, like inflammation, is accompanied by increases in WBC/EC interactions. Female animals and women appear less prone to develop sepsis than males [68, 94, 106, 110]. Among the factors implicated in this difference are estrogen and its interactions with EC and WBC [83], estrogen receptor distribution [106], sex differences in glucocorticoid action [17], and inflammatory status [9], to name but a few identified factors. A final component of venous function that has received attention with respect to sexual dimorphism is clot formation [94, 99] as well as fibrinolysis [99]. The complex interactions of the coagulation cascade and their associations with respect to genomic sex and sex hormones exist and are discussed in the review by [99].

Conclusions and Missing Information (e.g., Future Studies Are Needed)

There are multiple components displaying sex differences with respect to the myriad of micro-vascular functions. Figure 20.1 illustrates a selection of sexually dimorphic features across the microvasculature from the arterioles regulating blood flow into the exchange vessels; the capillaries where gas, fluid, and solute move between tissue and the circulating blood; and the venules where inflammatory processes occur. At present, several studies appear to have disparate, contradictory outcomes. This apparent “noise” likely reflects the early point in time of this research as all the systems described actually are multifactorial and most of the factors in health, no less disease, have yet to be studied equally in males and females. Further, as stated earlier, much of the microvasculature is heterogeneous with the form and function of the microvascular elements being married to organ function. Obviously healthy males and females are in fluid homeostasis but how they achieve this state differs by sex. The major implication is that for a given stressor, the responses in males and females, and the resulting pathology should the stressor not be removed, are likely to differ. Multiple comorbidities such as diabetes, hypertension, and heart failure, which have already been shown to display sex differences with respect to onset, frequency, morbidity, and mortality, also impact microvascular function [4, 11, 13, 84, 93, 107].

The present state of confusion likely reflects the lack of data. Resolution requires more comprehensive research to assemble the comprehensive anatomical, functional, and biochemical pictures of the female and the male microvasculatures. Once developed, sex needs to be considered when diagnosing, implementing preventive strategies, and treating diseases involving microvascular functions. The review of the literature further illustrated the importance of age (in Tables 20.1 and 20.2, several reported age-dependent changes are summarized), an independent but interacting variable. Consideration of sex and age as interdependent variables is just beginning, and we would be remiss to not note that the contribution of ethnicity has been omitted in this review as there are several differences between Caucasian, Asian, African, and Hispanics that have been observed. A good example are the differences to platelet concentration, noted in Table 20.2, that while significantly higher in women than men also vary significantly by ethnicity [109].

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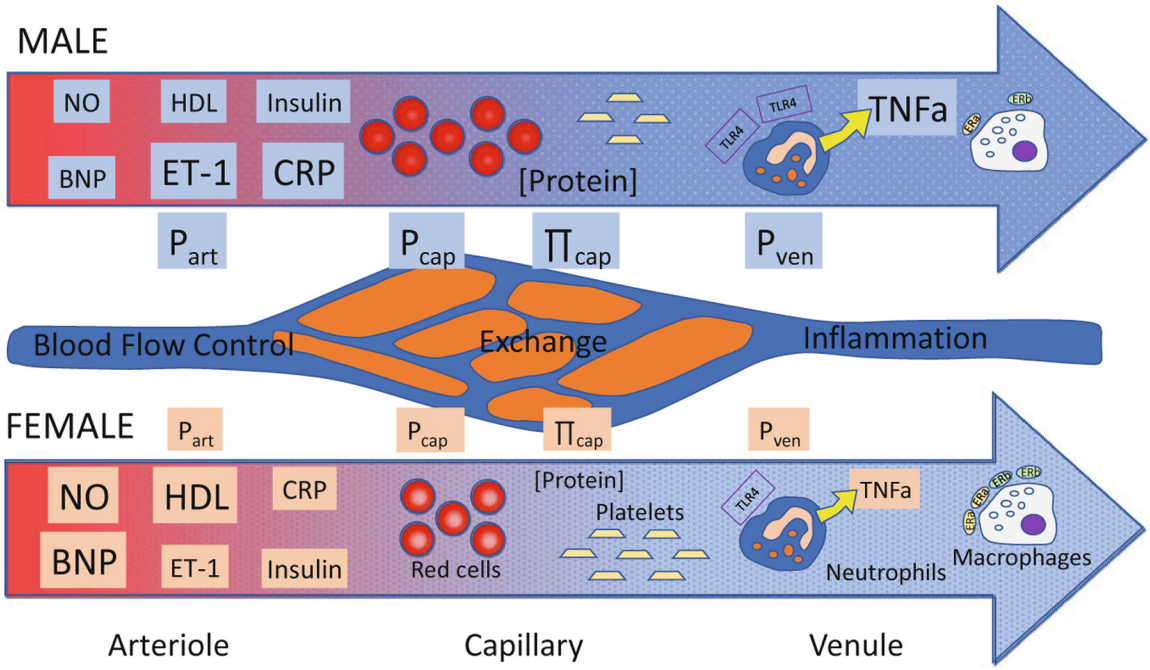

Fig. 20.1.

Diagram of sexually dimorphic constituents identified in male and female humans influencing the three primary functions of the microvasculature:

1. Control of blood flow via changes in VSM tone of the arterioles
2. Control of gas, fluid, and solute exchange via changes in capillary barrier function
3. Control of inflammation and immune function in the venules

Overall, hydrostatic pressures, Part, Pcap and Pven, and VSM tone are higher in males than females reflecting in part the relatively higher levels of vasoconstrictors (ET-1) to vasodilators (BNP, NO) in the blood of males. Blood from males carries a greater number of red blood cells; while the amount of hemoglobin per cell does not vary greatly by sex, the larger number of cells means a higher net Hgb and thus a higher O_2 carrying capacity favoring a higher O_2 delivery in males. The higher protein content of plasma in the males results in a higher oncotic protein force that will offset the higher fluid movement out of the capillaries by Pcap in males. The number of platelets tends to be higher in females than males suggesting a higher tendency for formation of clots in females than males. While white cell numbers tend to be higher or not different between males and females, it is the sex differences in receptor density that appears to play a role in sex differences in WBC responses. On exposure to LPS, neutrophils via TLR4 receptor activation release greater amounts of the cytokine TNFa in males than females. Macrophages of females express higher ERa and ERb receptors; the response to LPS is mediated by ERa in both sexes but to a greater extent in females. Abbreviations: *art* arterioler, *BNP* B-type natriuretic peptide, *cap* capillary, *ERa* estrogen receptor alpha, *ERb* estrogen receptor beta, *Hgb* hemoglobin, *LPS* lipopolysaccharide, *NO* nitric oxide, *TLR* Toll-like receptor, *TNFa* tumor necrosis factor alpha, *ven* venule, *VSM* vascular smooth muscle, *WBC* white blood cell (count)

Table 20.1 has most of these data (not the macrophage (Campesi et al., 2017) or neutrophil (Aomatsu et al., 2013) data, though)

Aomatsu M, Kato T, Kasahara E, Kitagawa S. Gender difference in tumor necrosis factor-α production in human neutrophils stimulated by lipopolysaccharide and interferon-γ. Biochem Biophys Res Commun. 2013;441:220–5.

Campesi J, Marino M, Montella A, Pais S, FranconiiF. Sex differences in estrogen receptor α and β levels and activation status in LPS-stimulated human macrophages. J Cell Physiol. 2017;232:340–5.

Table 20.1

Clinical chemistry/hematology reference values for adult healthy humans

			Male		Female						
Hormone	**Units**	**Change with age**		**Peak a.m.**		**Follicular**	**Ovulatory/mid-cycle**	**Luteal**	**Postmenopause**	**Statistics**	**Ref**
Testosterone *T*	ng/dL	M↓	350–1000		9–55				5–32	Range	*1*
		F↓	618(488–786) *		24.6 (17.7–34.3)					M(75–25)	*10*
					18.3 ± 1.2	15.4 ± 1.6	22.7 ± 1.7 +	18.7 ± 1.5	10.5 ± 1.3 +	X ± SE	*16*
			750 ± 380 *		10 ±4					X ± SD	*9*
				571 ± 29						X ± SE	*11*
Free-T	pg/mL	M↓	32–168 *		<3					Range	*1*
		F↓	119(95–152 *)		2.2 (1.4–3.2)	2.2				M(75–25)	*10*
					1.8 ±0.15	1.5 ±0.13	2.0 ± 0.17 +	1.6 ± 0.21	1.2 ± 0.1	X ± SD	*16*
				78 ±8						X ± SE	*11*
Sex hormone binding globulin	nmol/L	M↑	10–80 *		20–130					Range	*1*
		F↓	37.0 (0.78–1.66) *		89.7 (58.7–132.7)					M(75–25)	*10*
					85.4 ± 6.0	85.3 ± 9.2	99.0 ± 8.8	103 ± 10.7 +	67.7 ± 8.4 +	X ± SD	*16*
				23.1 ± 2.3						X ± SE	*11*
Estrogen E2	pg/mL	M NC	11–43			12–233	41–398	22–341	<5–138	Range	*1*
		F↓				31.8 ± 19.8			22.0 ± 14.0	X ± SE	*21*
						48 (37)	96(111.0) +	122 (91.5) +		M(75–25)	*12*
					55.4 ± 10.3	68.1 ± 18.6	98.1 ± 19.0 +	106.8 ± 8.3 +	1.3 ± 0.3 +	X ± SE	*16*
						56.1 ±6.4		132.2 ± 13.0		X ± SE	*4*
		Day				51 ± 10		86 ± 15 +		X ± SE	*5*
		Night				50 ± 16		60 ±8 ^			
			16 ± 14.4 *		76.9 ±71.0					X ± SD	*9*
				16 ± 1.7						X ± SE	*11*
Progesterone P4	ng/mL	M NC	<0.2–0.8			0.2–1.5	0.8–3.0	1.7–27.0	<0.2–0.8	Range	*1*
		F↓				0.76 ± 0.59			0.67 ± 0.57	X ± SE	*21*

			Male		Female						
Hormone	**Units**	**Change with age**		**Peak a.m.**		**Follicular**	**Ovulatory/mid-cycle**	**Luteal**	**Postmenopause**	**Statistics**	**Ref**
						0.4 (0.3)	1.7(3.0)	8.9 (7.4)$^{+}$		M(75–25)	*12*
						0.22 ± 0.02		8.13 ± 1.55		X ± SE	*4*
		Day				0.3 ± 0.0		8.8 ± 1.9		X ± SE	*5*
		Night				0.2 ± 0.0		7.7 ± 1.5			
Follicle Stimulating Hormone FSH	mIU/mL	M↑	1.5–12.4			3.5–12.5	4.7–21.5	1.7–7.7	25.8–134.8	Range	*1*
		F↑				6.4 (2.5)	6.3 (5.3)	3.1 (2.5)		M(75–25)	*12*
					7.6 ± 0.88	6.5 ± 0.58	6.9 ± 0.7	3.0 ± 0.45	81.0 ± 6.9	X ± SE	*16*
				5.6 ± 0.9						X ± SE	*11*
Luteinizing Hormone LH	mIU/mL	M↑	1.7–8.6			2.4–12.6	14–95.6	1–11.4	7.7–58.5	Range	*1*
		F↑				4.7 (3.0)	8.5 (10.9)	4.3 (4.6)		M(75–25)	*12*
	IU/L				5.4 ± 0.35	5.1 ±0.5	11.2 ± 2.8	3.8 ± 0.56	37.2 ± 3.7	X ± SE	*16*
				11.7 ± 0.9						X ± SE	*11*
Aldosterone	ng/dL					3.1 ± 0.3		8.5 ± 1.0		X ± SE	*4*
		Day	9.4 ± 2.3			8.1 ± 1.5		18.9 ± 2.8		X ± SE	*5*
		Night	7.8 ± 1.0			6.1 ± 1.5		11.2 ± 2.6			
			9(7–13)		10 (7–15)					M(75–25)	*23*
Cortisol	ug/dL	M NC F?		16.6 ± 1.6						X ± SE	*11*
		Day	7.7 ± 1.2			8.4 ± 1.4		9.9 ± 0.9		X ± SE	*5*
		Night	3.5 ± 0.7			5.1 ± 0.9		4.1 ± 0.7			
Renin Activity	ng/(mL hr)					0.36 ± 0.05		1.21 ± 0.18		X ± SE	*4*
		Day	1.2 ±0.2			1.1 ± 0.3		1.4 ± 0.2^{+}		X ± SE	*5*
		Night	1.7 ±0.4^{+}			0.8 ± 0.1		2.0 ± 0.4$^{+\wedge}$			
NT-proBNP	ng/L	M↑	0–95		0–178					Range	*1*
		F↑	16.2(8.1–28.8)		42.9 (25.7–72.2)					M(75–25)	*10*
Brain Natriuretic Peptide, BNP	pg/mL	M↑	8.0 ± 12.8		13.9 ± 18.9					X ± SE	*20*
		F↑	5.4(4.0, 13.4)		9.7(4.0, 18.9)					M(75–25)	*23*
			7.7 ± 7.0		12.2 ± 10.2					X ± SE	*6*
NT-proANP	pmol/L	M↑	284 ± 157		379 ± 177					X ± SE	*20*
		F↑	273 (188–392)		343 (248–476)					M(75–25)	*23*
ANP	pg/ml	M↑				53.0 ± 5.8		35.2 ± 4.6		X ± SE	*4*

			Male		Female						
Hormone	**Units**	**Change with age**		**Peak a.m.**		**Follicular**	**Ovulatory/mid-cycle**	**Luteal**	**Postmenopause**	**Statistics**	**Ref**
		F↑	16.7 ± 10.0		18.8 ± 11.7					X ± SE	*6*
Insulin	pmol/L	M↓	59.3 ± 58.3		53.4 ± 24.9					X ± SD	*9*
		F↑	60.0 ± 53.5		69.8 ± 54.4					X ± SD	*15*
	mU/L		12.5		10.1				13.9	Median	*22*
HOMA-IR			1.01 (0.78–1.66)		0.89 (0.65–1.31)					M(75–25)	*10*
			1.8 ± 2.0		1.5 ±0.7					X ± SD	*9*
			1.35 ± 1.31		1.49 ± 1.27					X ± SD	*15*
Fasting Glucose	mg/dL	M NC				80 ± 2			89 ±3	X ± SE	*21*
		F↑	100 ± 8.2		95.5 ± 7.5					X ± SD	*14*
			105.6 ±25.1		99.6 ± 26.0					X ± SD	*23*
	mmol/L		4.6 ± 0.4		4.4 ± 0.5					X ± SD	*9*
			5.98 ± 0.46		4.76 ± 0.45					X ± SD	*15*
			5.42		5.12				5.33	Median	*22*
Endothelin-1 ET-1	pg/mL	M↑				1.39 ± 0.41			1.74 ± 0.42	X ± SE	*21*
		F↑	1.4 ± 0.07*		1.0 ±0.08					X ± SE	*19*
Leptin	ng/mL		4.5 ± 4.0		15.3 ± 8.2					X ± SD	*9*
Total Cholesterol	mg/dL	M NC				163 ± 6			216 ± 7	X ± SE	*21*
		F↑				166 (39.0)	162.0 (64.0)	161.0 (36.0)		M(75–25)	*12*
			200 ± 35		211 ±38					X ± SD	*23*
	mmol/L		5.42 ± 1.13		5.43 ± 0.92					X ± SD	*15*
			5.54		5.38				6.12	Median	*22*
HDL	mg/dL	M↓				67 ± 3			85 ± 4	X ± SE	*22*
		F↑				50.0 (17.0)	52.0(16.0)	51.0(16.0)		M(75–25)	*12*
			56.8 ± 12.6		72.4 ± 16.6					X ± SD	*14*
			44 ± 12		58 ± 16					X ± SD	*23*
	mmol/L		1.22		1.5				1.44	Median	*22*
LDL	mg/dL					82 ± 6			117 ± 6	X ± SE	*21*
		F NC				102.0 (33.0)	98.5 (32.0)	97.0 (34)		M(75–25)	*12*
Triglycerides	mmol/L	M↓				79 ± 9	53.0		73 ± 7	X ± SE	*21*
		F NC, ↑				56.0 (33)	(27.0)	51.0(28.0)		M(75–25)	*12*

			Male		Female						
Hormone	**Units**	**Change with age**		**Peak a.m.**		**Follicular**	**Ovulatory/mid-cycle**	**Luteal**	**Postmenopause**	**Statistics**	**Ref**
			1.31 ±0.74		1.01 ±0.53					X ± SD	*15*
			1.58		1.06				1.45	Median	*22*
	mg/dL		0.9 ±0.13		0.70 ±0.11					M(75–25)	*10*
Creatinine			1.25 ± 17		1.07 ±0.15					X ± SE	*20*
ICAM-1	ng/mL	M↑				214.8 ± 9.2		215.7 ± 6.0		X ± SE	*8*
		F NC	264 ± 63		249 ± 60					X ± SD	*15*
			285 ± 92		309 ± 111					X ± SD	*2*
E-selectin	ng/mL					44.6 ± 5.1		41.4 ±4.8		X ± SE	*8*
			56.8 ± 28.2		46.2 ± 23.7					X ± SD	*15*
			56 ±20		50 ±20					X ± SD	*2*
L-selectin	ng/mL		1107 ±471		1140 ±485					X ± SD	*15*
P-selectin	ng/mL		143 ± 44		123 ± 34					X ± SD	*15*
			205 (40–2550)		206 (22–5700)					M(75–25)	*2*
Thrombomodulin	ng/mL		48 ± 16		40 ± 12					X ± SD	*2*
Total Homocysteine	µmol/L		11.3(11.2–11.5) *		9.6(9.5–9.69)					X ± 95% CI	*13*
			9.72(8.24–11.7) *		8.29 (6.96–10.1)					M(75–25)	*23*
CRP	mg/L	M↑	1 ± 1.5 *		0.7 ± 1.2					X ± SD	*14*
		F↑	1.79(0.84–3.50) *		2.25 (0.93–5.39)					M(75–25)	*23*
HCT	%		40–52 *		35–47					Range	*1*
			40.3 ± 1.0 *		39.5 ± 0.7					X ± SE	*4*
		Day	43 ± 1 *			37 ± 1		39 ± 0		X ± SE	*5*
		Night	42 ± 1 *			36 ± 0		37 ± 1			
Hemoglobin	g/dL		13.2–17.7		11.9–15.5					Range	*1*
			15.2 ± 1.0 *		12.8 ±0.6					X ± SD	*3*
RBC count	10^{12}/L		5.01 ±0.31 *		4.44 ± 0.33					X ± SD	*15*
Platelet Count	10^{9}/L	M↓	239 ±51.0 *		249.3 ± 54.3					X ± SD	*15*
		F↓	249 (244–254) *		272 (268–276)					X ± 95% CI	*18*

			Male		Female						
Hormone	**Units**	**Change with age**		**Peak a.m.**		**Follicular**	**Ovulatory/mid-cycle**	**Luteal**	**Postmenopause**	**Statistics**	**Ref**
			235 ± 59 *		261 ± 64					X ± SD	*17*
Leukocyte count	10^9/L		6.69 ± 1.66 *		6.91 ± 1.48					X ± SD	*15*
Osmolarity	mOsm/kgH_2O					287.4 ± 0.9		282.3 ± 0.9 +		X ± SE	*4*
			288 ± 1			288		284 ± 1 +		X ± SD	*3*

* M≠F;

+ differs from follicular;

^ day≠night; # ≠postmenopause; $P < 0.05$ or better (refer to specific papers); *NC* no change, *HOMA* homeostasis model assessment of insulin resistance

Mean ± standard deviation (X ± SD); mean ± standard error of the mean X ± SE; mean ± 95% confidence interval X ± 95%CI; median (75%, 25%) M (75–25)

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Table 20.2

Hemodynamic reference values for adult healthy humans at rest

				Female					
Paramter	**Units**	**Change with age**	**Male**		**Follicular**	**Luteal**	**Menopause**	**Statistics**	**Ref**
HR	bpm	M↓			66 ± 9	65 ± 9		X ± SE	*7*
		F↓			60 ± 2		57 ± 2	X ±SE	*7*
					62 ± 2	65 ± 2		X ± SE	*2*
			67.2 ± 16.6	71.0 ± 16.6				X ± SD	*9*
SV	mL		94 ± 17	97 ± 16				X ± SD	*1*
CO	L/min		6.9 ± 0.8	7.2 ± 1.1				X ± SD	*1*
					5.6 ± 0.4	6.6 ± 0.4 [+]		X ± SE	*2*
Systolic BP	mmHg	M↑	121 ± 13	113 ± 14				X ± SD	*3*
		F↑	118 ± 10	115 ± 12				X ± SD	*6*
				109 ± 3			123 ± 3 [#]	X ± SE	*7*
			121 ± 8.7 [*+]		113.5 ± 8.7			X ± SE	*5*
			136.5 ±12.5 [1]				125 ± 12.3 [1#]		
			130 ± 17	126 ± 20				X ± SD	*8*
Diastolic BP	mmHg	M↑	78 ±9	73 ± 9				X ± SD	*3*
		F↑	73 ±7	70 ± 7				X ± SD	*6*
					67 ± 2		80±2 [+]	X ± SE	*7*
			70.6 ± 10.0 [*]	66.3 ± 7.6				X ± SE	*5*
			81.1 ± 5.9 [1*]				73.0 ± 5.9 [1]		
			78 ± 9	74 ± 9				X ± SD	*8*
MAP	mmHg	M↑	92.5 ± 6.7	88.6 ± 7.2	81 ± 2		94±2 [+]	X ± SE	*7,10*
		F↑			81.7 ± 2.0	75.4 ± 2.3		X ± SE	*2*
Capillary Pressure	mmHg	M NSD	18.0 ± 2.5 [*]	15 ± 2.4				X ± SE	*5*
		F↑	18.4 ± 2.0 [1]				17.6 ± 3.4 [1]		

[*] M≠F, 20–50 years;

[+] differs from follicular;

[#] ≠ postmenopause (>55 years); $P < 0.05$ or better (refer to specific papers);

[1] >50 years

Mean ± standard deviation (X ± SD); mean ± standard error of the mean X ± SE; *NSD* not significantly different, *HR* heart rate, *BP* (arterial) blood pressure, *MAP* mean arterial pressure, *bpm* beats per minute, *SV* stroke volume, *CO* cardiac output

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