Published in final edited form as:

Semin Neurol. 2017 December ; 37(6): 679–688. doi:10.1055/s-0037-1608881.

Cerebrovascular Hemodynamics in Women

Cristina Duque, MD^{1,2}, Steven K. Feske, MD³, Farzaneh A. Sorond, MD PhD¹

¹Division of Stroke and Neurocritical Care, Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

²Department of Neurology, Coimbra University Hospital Center, Coimbra, Portugal

³Division of Stroke, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

Sex and gender, as biological and social factors, significantly influence health outcomes. Among the biological factors, sex differences in vascular physiology may be one specific mechanism contributing to the observed differences in clinical presentation, response to treatment, and clinical outcomes in several vascular disorders. This review focuses on the cerebrovascular bed and summarizes the existing literature on sex differences in cerebrovascular hemodynamics to highlight the knowledge deficit that exists in this domain. The available evidence is used to generate mechanistically plausible and testable hypotheses to underscore the unmet need in understanding sex-specific mechanisms as targets for more effective therapeutic and preventive strategies.

Keywords

cerebrovascular hemodynamics; women; cerebral autoregulation; cerebral vasoreactivity; neurovascular coupling

Increasing evidence from epidemiological and experimental studies highlight the importance of sex and gender in vascular health and disease. Differences based on sex and gender span clinical manifestations, pathophysiology, responses to treatment, and outcomes in all vascular beds, but more specifically brain, heart, and kidney. Men have a higher prevalence of coronary heart disease and stroke, with higher mortality rates than women until mid to late life, around the time of menopause, when this association is reversed.¹⁻³ Similarly, while aging is associated with increasing risk of stroke and coronary heart disease, the rate of increase for both conditions is much higher in older women.^{2,4} Moreover, while age-adjusted mortality for cardiovascular disease has been declining, the extent of this decline has been less in women, and stroke-related outcomes remain consistently worse in women, except in the case of aneurysmal subarachnoid hemorrhage (SAH) where women seem to have more favorable outcomes.^{4,5} On the other hand, despite a higher prevalence of chronic

kidney disease in women, women with chronic kidney disease seem to have a better cardiovascular prognosis than men, even though women are less likely to start dialysis.⁶⁻⁸

Age variable gender disparities in the incidence of and clinical outcomes from vascular disease among women have been largely ascribed to the actions of the sex steroid hormone 17 β -estradiol (E2) and its receptors, estrogen receptor α (ER α) and β (ER β), on the vascular endothelium.^{9,10} The underlying mechanisms are complex. In addition to effects on endothelial function, estrogens influence blood pressure (BP) regulation, platelet function, and autonomic nervous system regulation. This review will focus on the vessels of the brain, but we will draw on research on other vascular beds where cerebrovascular data are lacking.

The cerebrovascular bed is regulated through myogenic, endothelial, autonomic, and metabolic mechanisms. These regulatory mechanisms, which maintain brain perfusion and meet the metabolic demands of neurons, are termed cerebral autoregulation, vasoreactivity (VR), and neurovascular coupling (NVC).^{2,11-16} This review will summarize existing evidence that highlights possible hormonal and cellular pathways affecting regulatory mechanisms in the cerebrovascular bed and contributing to gender differences in cerebral hemodynamics and cerebrovascular disease. An appreciation of hemodynamic pathophysiology is particularly important to our understanding of sex-specific responses to stroke and to our understanding of the cerebrovascular complications of preeclampsia–eclampsia. To contribute to this field and to promote the generation of testable hypotheses and the identification of potential therapeutic targets, this review will also describe noninvasive methods for assessing cerebrovascular hemodynamics in humans.

Autoregulation

Definition

Cerebral autoregulation refers to the regulatory mechanisms which serve to maintain relatively constant blood flow to the brain by rapidly adjusting cerebrovascular resistance while compensating for fluctuations in cerebral perfusion pressure (CPP).¹⁷⁻¹⁹

Cerebrovascular resistance is primarily governed by arteriolar diameter, although larger vessels may also contribute. CPP, in turn, reflects the pressure difference between cerebral arterial and venous beds. However, since an accurate measure of cerebral venous pressure is not readily available, the intracranial pressure (ICP) is used as a surrogate, and CPP is commonly calculated as the difference between the mean arterial pressure (MAP) and ICP. Cerebral autoregulation is mediated by myogenic, metabolic, and neurogenic mechanisms.^{20,21} Given the high metabolic demand of brain tissue and the need for a constant supply of oxygen and glucose, any condition that impairs cerebral autoregulation will allow harmful changes in CPP to be transmitted to the neurovascular bed. Stroke, head trauma, SAH, severe hypertension, or space-occupying brain lesions may all result in impairments in cerebral autoregulation.²²

A variety of methods have been used to assess the integrity of cerebral autoregulation. Early investigations of autoregulation were limited to the steady-state behavior of cerebral blood flow (CBF). Using this approach, steady-state blood flow changes were measured in response to steady-state changes in the BP. However, the time-consuming and invasive

nature of these procedures^{23,24} and the need to manipulate BP using vasoactive medications are impractical for testing autoregulation in acute cerebrovascular disorders. In addition to this practical limitation, since cerebrovascular resistance is constantly changing, optimizing CBF through fast-acting dynamic processes, the traditional steady-state approaches, lack the temporal resolution necessary for assessment of this dynamic process.

The introduction of transcranial Doppler ultrasound (TCD) to measure CBF velocity²⁵ provided a powerful tool for noninvasive assessment of dynamic CBF responses to various stimuli, including changes in MAP.^{16,17} TCD, which can provide continuous beat-to-beat measurement of the CBF velocity in the basal cerebral arteries with high temporal resolution, has become the most commonly used tool to study CBF regulation in humans. Dynamic cerebral autoregulation (dCA) is assessed by measuring transient changes in the CBF velocity in response to sudden rapid changes in MAP. Sudden changes in MAP can be induced using a variety of techniques such as the rapid deflation of bilateral thighcuffs,¹⁸ hand grip,²⁶ valsalva maneuver,²⁷ transient hyperemic response test,^{28,29} and the sit-to-stand method.^{30,31} The blood flow responses are then characterized and quantified by several different derived variables and reported as specific measures of autoregulation.¹¹

As an alternative to measuring responses to induced changes in MAP, spontaneous oscillations in arterial BP ranging from 0.02 to 0.4 Hz that occur in humans without external BP manipulations can be measured and compared with associated variations in CBF velocity to achieve a measure of dCA.³²⁻³⁷ This approach, which is the most physiological and noninvasive method for assessing the integrity of cerebral autoregulation at the bedside, is the one most frequently used in patients with acute cerebrovascular injuries.

Transfer function analysis can be used to quantify the transfer of the BP oscillations to CBF velocity as a measure of autoregulation. The extent to which BP oscillations are reflected in CBF velocity oscillations is expressed using three parameters, gain, phase shift, and coherence. Given that diameter changes of the cerebral arterioles in response to pressure changes are not fast enough to block high-frequency (>0.2 Hz) oscillations in BP, fast oscillations are passed along and cerebral autoregulation is not engaged in the high frequency ranges. However, slower oscillations (0.03–0.2 Hz) can be offset by autoregulation working through diameter changes in cerebral arterioles. In these low or autoregulatory frequency ranges, gain reflects the magnitude, and phase shift reflects the time delay of the transmitted BP oscillation to CBF velocity oscillation. Higher phase shift and lower gain are reflective of more efficient autoregulation.³⁸⁻⁴¹ Coherence is a measure of the relation between cerebral blood flow velocity (CBFV) and BP oscillations across different frequencies; in other words, it can be used to estimate the extent to which these oscillations approximate one another.

Influence of Sex

The influence of sex on systemic and cerebral hemodynamics has been the focus of many publications; however, small sample sizes and methodological differences have hindered a better understanding of the mechanisms underlying some of the observed differences. Clinically, orthostatic hypotension as well as other hypotensive disorders of BP regulation are much more common in women than men.⁴² BP starts to rise in the 3rd decade of life in

men, but not until 4th or 5th decade in women, corresponding to timing of menopause. By the age of 70, more women have hypertension than men, and the incidence of hypertension continues to rise in women.⁴³ Additionally, while markers of whole body sympathetic activity and vascular resistance are tightly correlated in men across the adult life span, this is not the case for young women. In other words, the vasoconstrictive effect of the sympathetic nervous system is dampened in young women, possibly as a result of concurrent β_2 -adrenergic vasodilation that offsets α -adrenergic vasoconstriction. In older women like men, however, a clear relationship emerges between markers of whole body sympathetic activity and vascular resistance. There is evidence to suggest that the loss of estrogen may contribute to an increase in sympathetic activity and loss of β -adrenergically mediated endothelial vasodilatation.⁴⁴

Spectral analysis of beat-to-beat heart rate (HR) and arterial pressure variability has been increasingly utilized to study the dynamic interaction of the sympathetic and parasympathetic control of cardiovascular autonomic regulation.⁴⁵ Studies using this approach have demonstrated that across the adult life span, compared with men, women have lower resting HRs, lower R-R intervals, and diastolic BP (DBP) variability in the low frequency ranges, as well as lower MAP and CBF velocity variability in the very low frequency range at rest and during sit-to-stand maneuvers.⁴⁶ While attributing neurophysiological correlates to the low- and high-frequency spectral components of HR and BP have been controversial, it has been argued that an increase in sympathetic activity may be associated with the enhancement of low-frequency and the attenuation of the high-frequency oscillations.^{47,48} Applying the same spectral analysis to BP and CBF velocity oscillations to assess cerebral autoregulation (transfer function analysis) across adult life span, women demonstrate lower gain and coherence at rest and a higher phase shift during sit-stand maneuvers than men, suggesting a better dCA for women in both conditions.^{46,49} At the same time, women seem to have lower baroreflex sensitivity than men.⁴⁶

The integrative physiological model that emerges from these studies is complex. These studies show that aging is associated with increased sympathetic activity in both genders, but more pronounced in women as evidenced by increasing incidence of hypertension and lower baroreceptor sensitivity and lower HR, BP, and CBF variability. Yet, throughout life women continue to manifest more efficient dCA parameters. One possible explanation for this observation is that the cerebrovascular bed may also be more vasoconstricted as a result of increased sympathetic tone in women.⁴⁹⁻⁵¹ This suggestion is based on work demonstrating improved dCA during hypocapnia, which increases cerebrovascular resistance (higher vasoconstricted state).¹⁸ Sex hormone levels don't seem to provide an explanation, since dCA remains unchanged throughout the menstrual cycle in premenopausal women,⁴⁰ and hormone replacement therapy (HRT) in postmenopausal women does not seem to impact dCA.³⁴ Interestingly, studies using phase contrast magnetic resonance imaging (MRI) show that women have higher CBF than men across the adult age range.⁵² The higher CBF was observed despite a smaller total brain tissue volume, suggesting that there may be a higher cerebral metabolic rate in women than men.⁵³ So, while women may have better autoregulatory mechanisms, their age-related susceptibility to cerebrovascular injury may be related to loss of systemic regulatory mechanisms which exposes the higher metabolic demands of the female neurovascular unit to greater vascular injury despite better

autoregulation. Given that XX neurons seem to be more susceptible to proapoptotic cell death, whereas XY cells seem to be more vulnerable to excitotoxic cell death,⁵⁴ there may indeed be sex-dependence to ischemic tolerance, neuronal injury, and recovery.

Pregnancy and Preeclampsia–Eclampsia

The cerebrovascular system undergoes adaptive changes to maintain stable cerebral perfusion during pregnancy, while other organs, such as the uterus, heart, and kidney, undergo substantial increases in perfusion and filtration.⁵⁵ Major hemodynamic changes associated with pregnancy work to maintain a stable CBF and BP despite cardiac output increases of up to 50% to sustain a hypervolemic state in the setting of augmented circulatory demand.^{56,57} Maternal plasma volume and cardiac output increases reach a maximum at 20 weeks of gestation, accompanied by a decline in peripheral vascular resistance. Cerebral adaptation to this increased inflow occurs through an increase in resistance in the MCA. Although this adaptation maintains relatively stable CBF during pregnancy, in the postpartum period when there is a normal fall in the CPP, it is associated with a period of decreased CBF.⁵⁸ Changes in carbon dioxide (CO₂), perivascular innervation, hormones, cytokines, and other circulating factors are thought to be responsible for these adaptive alterations.⁵⁹

Although the overall number of strokes in women in reproductive age is low, pregnancy and the postpartum period confer an increased stroke risk, resulting from altered coagulation and vascular hemodynamics.⁶⁰ Preeclampsia and eclampsia account for much of this increased stroke risk. These hypertensive disorders of pregnancy have been associated with altered cerebrovascular hemodynamics and impaired autoregulation, and these physiologic impairments are believed to be a major source of the clinical consequences of the hypertensive cerebral vasculopathy of pregnancy.⁶¹ In normal pregnancy, autoregulatory index (ARI, that is, the change in the cerebrovascular resistance per second in response to a change in arterial BP) is in the high normal range, suggesting that the normal pregnant state demands more efficient cerebrovascular regulation.^{62,63} The enhanced autoregulatory capacity of normal pregnancy has been attributed to the relative hypocapnia seen in pregnancy⁶⁴ (vasoconstricted cerebrovascular bed); however, observed ARI differences persist after adjusting for end-tidal CO₂. In preeclampsia–eclampsia, cerebral arterioles undergo changes that impede their autoregulatory capacity (dilation and constriction abilities) to manage pulsatile changes in arterial pressure, leading to hyperperfusion as well as hypoperfusion injuries resulting from autoregulatory failure.⁶² CBF studies in preeclampsia have mainly used TCD to assess hemodynamic changes. Compared with normal pregnancy, CPP is significantly higher in preeclampsia, while dCA is normal.^{62,65} Only one small study has shown dCA to be less efficient in pregnant women with chronic hypertension and preeclampsia compared with normal and gestational hypertension pregnancies where ARI was also in the low normal range.⁶⁶ It appears that in most cases of preeclampsia dCA remains adequate, but when dCA becomes inefficient, perfusion injury, edema formation, and neurological complications of hypertensive encephalopathy, seizures, and strokes ensue.⁶⁷ In patients with chronic hypertension, the cerebrovascular system remodels to shift the autoregulatory curve to tolerate higher pressures.⁶⁸ It is speculated that this vascular remodeling does not occur during pregnancy, rendering the cerebrovascular bed

vulnerable to the acute perfusion injury, for example, in the setting of hypertension leading to posterior reversible encephalopathy syndrome (PRES).⁶⁹ The observed alterations in the expression of angiogenic factors and resulting systemic endothelial dysfunction may also involve the cerebrovascular endothelium, where dysfunction could also play a role in the progression to cerebral edema and, hence, from preeclampsia to eclampsia.⁷⁰

Stroke

Gender disparities in stroke incidence are age-dependent. Until the age of 45, women have a lower age-adjusted incidence of ischemic stroke and a better prognosis for neurological recovery.^{71,72} Between 45 and 54 years of age, coincident with the onset of menopause, the incidence of stroke begins to increase. During this period, there is also a surge in obesity and metabolic syndrome that contributes to increased stroke risk.⁷³ Between the ages of 55 and 85, the incidence of stroke is comparable between men and women. After 85 years of age, women are at highest risk of ischemic stroke.⁷² Furthermore, recurrence rates and poststroke motor disability are significantly higher in older women,^{54,74} as is stroke-related mortality.^{75,76}

Gender-specific risk factors for ischemic stroke in young women include oral contraceptives containing estrogens, migraine with aura, and rare causes such as fibromuscular dysplasia, antiphospholipid antibody syndrome, and Takayasu arteritis.^{5,77,78} During pregnancy (hemorrhagic), and especially postpartum (both ischemic and hemorrhagic), the risk of stroke increases with a significant contribution from preeclampsia–eclampsia. Mechanisms underlying gender disparities in stroke risk and outcome after menopause are unclear. Studies of cerebral autoregulation in acute ischemic stroke have produced conflicting results and have not shown any gender-specific differences. Studies in lacunar and large-vessel stroke in the first 72 to 96 hours have demonstrated impaired dCA^{26,79,80} in both stroke types. Low phase shift dCA has been the parameter consistently altered in ischemic stroke, contrary to gain which does not seem to have an association.^{81,82} In these studies, this difference was independent of severity of stroke, BP, sex, and age, lasting for at least 1 to 2 weeks.⁸³ In another study of minor stroke, dCA was preserved in the acute phase, but in the subacute phase, ARI was decreased with a trend for lower phase shift, representing mild autoregulatory disruption.⁸² More recently, it was demonstrated that the efficacy of dCA during the first 6 hours after stroke symptom onset was associated with smaller infarct lesion size at 24 hours and a better functional outcome at 3 months.⁸⁴ Autonomic dysfunction after stroke, a known phenomenon, was suggested as a possible mechanism for dCA impairment.²⁶ Similarly, patients with migraine have been shown to have less efficient autoregulation compared with healthy controls.^{85,86} Given the link between early dCA impairment and neurological outcome, it is possible that some of the gender differences in clinical outcome may stem from early dCA differences. If indeed women demand a more efficient autoregulatory system than men, or if their cerebrovascular beds are accustomed to higher autoregulatory efficiency, even mild decreases in the effectiveness of autoregulation could pose a greater risk of neurovascular injury for them. Further studies are needed to advance our understanding of sex differences that might contribute to the better stroke outcomes in women, comparable to those observed in men.

Similar to ischemic stroke, sex-specific differences have also been observed in hemorrhagic strokes [primary intracerebral hemorrhage (ICH), aneurysmal SAH, and hemorrhagic transformation of ischemic stroke]. Epidemiologic studies in ICH have demonstrated sex differences in hematoma location.⁸⁷ There is a reported female predilection for cerebellar and right hemispheric hematoma formation.⁸⁸ Women may have an overall lower ICH incidence.⁸⁹ BP response to treatment, cerebral edema, and development of deep venous thrombosis (DVT) also show sex differences.⁹⁰ Treatment response shows some gender disparity as well, with an inverse association between rate of MAP decline and mortality only observed in men, but not in women.⁹⁰ Finally, in a prospective study of ICH, female sex was the only independent predictor for DVT.⁹¹ Mechanisms underlying these observed differences are not completely understood. Studies so far have demonstrated that loss of female sex hormones (as in menopause) influence outcome after brain injury,⁹² and in a prospective observational study, postmenopausal women seemed to have a significantly higher risk for ICH.⁹³ SAH represents 5% of all stroke causes,⁹⁴ and female sex is a risk factor for aneurysm formation, mainly in the postmenopausal period;⁹⁵ however, females seem to have better clinical outcomes. Although no gender differences have been explored, autoregulation can be impaired in the first days after SAH,^{96,97} and those with less effective autoregulation after SAH seem to have a higher risk of delayed cerebral ischemia (DCI).⁹⁸ The hemodynamic autoregulatory profile of patients who developed DCI was that of lower gain and lower autoregulatory slope, suggesting a smaller capacity to increase flow with pressure augmentation.⁹⁸ While autoregulatory changes have not been observed in animal models of SAH, female animals tend to have less volume of subarachnoid blood, lower rise in ICP, less vascular and brain injury, and lower 24-hour mortality compared with males.⁹⁹ Males seem to have a greater ICP rise and larger vascular and inflammatory responses than females.¹⁰⁰

Similar to primary cerebral hemorrhage, in acute ischemic stroke patients with hemorrhagic transformation, where cerebral microvascular injury and less effective autoregulation may represent a biologic pathway between white matter injury and hemorrhagic transformation,¹⁰¹ early impairment in dCA (low phase shift) during the acute stroke phase has also been associated with delayed hemorrhagic transformation.¹⁰² Given the existing gender differences in clinical outcomes and risks associated with these stroke subtypes, it would be worthwhile to explore whether sex differences in autoregulatory efficiency may be possible mediators or modifiers for observed gender differences in risk and clinical outcome.

Vasoreactivity

Definition

A healthy cerebrovascular bed is inherently reactive to changes in the partial pressure of arterial CO₂ (PaCO₂).¹⁰³ Hypercapnia results in vasodilation of cerebral arterioles and consequent increase in CBF, while hypocapnia results in vasoconstriction and decrease in CBF.^{104,105} This interaction between PaCO₂ and CBF, termed cerebral VR, is regulated at the level of arterioles and precapillary sphincters¹⁰⁶ by mechanisms that are mediated at the level of K⁺ channels in the smooth vascular muscle¹⁰⁷ as well as the vascular endothelium through nitric oxide (NO)-mediated pathways.¹⁰⁸ CBF responses to step changes in CO₂ in

humans start within 30 seconds of inhalation and reach a peak within 6 seconds after onset.¹⁰⁹ TCD has been used extensively to study cerebral VR and has established clinical utility in stroke risk assessment in several cerebrovascular pathologies, such as carotid stenosis, intracranial atherosclerosis, SAH, and moyamoya disease.^{110,111} Cerebral VR protocols tend to vary based on the stimulus or challenge used and the analytical approach for assessing the CBF and CO₂ relationship. Some use an inhaled gas mixture of 8% CO₂ with 21% O₂ (hypercapnia with normoxia), while others use 5% CO₂ with 95% O₂ (hypercapnia with hyperoxia). Hypocapnia is achieved by hyperventilation in most protocols. Others use breath-holding as a hypercapnic stimulus. Acetazolamide can also lead to a mild extracellular acidosis and hence intracranial vasodilation, and is an alternative to inhaled gasses or breath-holding as a vasodilatory stimulus.¹¹² TCD is the noninvasive tool with the best temporal resolution most often used in clinical and experimental settings. Across most selected experimental studies, normal “global” CBF reactivity to changes in PaCO₂ is ~3.8%/mm Hg within the PaCO₂ range of 35 to 55 mm Hg—higher in the hypercapnic than hypocapnic range. Arterial spin labeling (ASL) MRI, which can provide much greater spatial resolution than TCD, has been utilized more recently to measure the reactivity of cerebral small vessels within the cortical gray matter.¹¹³ While VR has been studied in healthy aging and chronic cerebrovascular injuries, for practical reasons, these studies have been limited in the acute phase of neurovascular injuries.

Influence of Sex

The relationship between cerebral VR and female sex remains unclear, and contradictory results have been reported. While some studies have shown lower VR in young women, particularly in those younger than 65 years of age,^{49,114} and in postmenopausal women younger than 65 years of age, others have reported higher VR in younger women,¹¹⁵⁻¹¹⁷ and some have reported no gender differences.¹¹⁸ A possible explanation for the observed controversies reported by different groups may be a consequence of different methodologies used for VR protocols. BP changes during CO₂ inhalation and the interindividual variability of the breath-holding duration are unmeasured confounders in many of these studies. Definitive conclusions warrant studies with larger sample sizes and tighter protocol adherence. The impact of hormones on cerebral VR is also controversial. While menopause has not been shown to alter VR significantly,¹¹⁹ VR has been shown to be significantly altered over the course of the menstrual cycle and the changes have been positively correlated with ovarian hormone concentrations.¹²⁰ However, reports of the impact of HRT on cerebral VR have been conflicting, with one showing no benefit,¹²¹ while another showed improved reactivity and reduced coronary heart disease and mortality when started early after menopause.¹²² The hormonal state of women in many of these studies has been heterogeneous with significant variability in the menstrual phase for premenopausal women, the hormonal state of perimenopausal women, and time postmenopause in older women.¹²³

Hypertensive disorders of pregnancy seem to impact cerebral VR as well. Cerebral VR seems to be significantly reduced in preeclampsia–eclampsia when compared with normotensive pregnancies.^{124,125} This finding is consistent with a state of vasoconstriction in the hypertensive disorders of pregnancy that is unresponsive to vasodilatory stimuli such as hypercapnia.

Unlike dCA, cerebral VR has been more challenging to study in patients with acute stroke and hemorrhage, and as a result there are no studies examining gender differences in cerebral VR in acute neurovascular injuries. The few studies that have examined cerebral VR in acute cerebrovascular injuries, such as acute ischemic stroke and SAH, seem to show that VR is impaired early in these conditions.¹²⁶⁻¹²⁹ Animal studies also support these findings and show that while NVC is not altered in the first few hours after SAH, cerebral VR is completely lost.¹³⁰

Given that cerebral VR is a measure of endothelial function in the cerebrovascular bed, and therefore, NO-mediated, it is expected that this measure should be regulated by estrogen and the hormonal state of female patients. This hypothesis is supported by studies of peripheral endothelial function using flow-mediated dilation (FMD). This is a well-established technique that allows researchers to examine endothelial function and assess cardiovascular risk noninvasively, even during pregnancy.¹³¹ Studies have shown that FMD decreases with increasing age in both genders, up to 70 years for men and 80 for women ($p < 0.001$). However, age-related decline in FMD was steepest after age 45 for women, while in men, a steady decline was observed after age 30.¹³² Also, in women who developed preeclampsia as compared with normal pregnancies, FMD was also lower before the clinical diagnosis of preeclampsia (2029 weeks gestation), at the time of preeclampsia, and for 3 years postpartum.¹³³ Steeper age-related decline in endothelial function may be one mechanism for worse stroke-related outcomes in older women, in whom plasticity may be hampered by lower VR to increased metabolic demand. There is clearly an unmet need for more studies of sex-specific changes in cerebral VR in acute neurovascular injuries.

Neurovascular Coupling

Definition

NVC, or functional hyperemia, defines the close relationship between CBF and neuronal activity regulated at the level of the neurovascular unit.^{134,135} Astrocytes and GABAergic interneurons connect with cortex-penetrating arterioles, and intramural propagation of vascular signals, mediated by excitatory and inhibitory neurons, produces remote vasodilation of upstream pial arterioles.¹³⁶ NVC can be exemplified by visual activation of the occipital cortex, which elicits an immediate and robust increase in CBF velocity in the posterior cerebral artery (PCA).¹³⁷ Cognitive testing during TCD monitoring of the anterior cerebral circulation has also been used in several studies to demonstrate increased CBF velocity in response to motor and cognitive tasks.¹³⁸⁻¹⁴⁰ Functional MRI (fMRI), position emission tomography (PET), and TCD can all be used to assess NVC. While TCD can noninvasively measure the hyperemic response, PET and fMRI mainly measure the metabolic activity of the neurovascular unit. Aging, vascular disease, and neurodegenerative pathologies can all impair NVC. Similar to VR, assessment of the NVC in the acute state of neurovascular injuries has been limited, and most studies have focused on cognitive disorders of aging.

Influence of Sex

Impact of sex on NVC has not been specifically addressed in previous studies. However, given the central role NO plays in regulating neurovascular responses, it is very likely that hormonal changes, especially, estrogen, have a strong influence across the adult life span with prominent sex differences.¹²⁹ For example, a few studies have assessed NVC during normal pregnancy and hypertensive disorders of pregnancy. A recent history of preeclampsia has been shown to dampen NVC in the posterior circulation during visual activation.¹⁴¹ Also, at 24 to 28 weeks of gestation, women with impaired utero-placental vasoregulation seemed to have enhanced NVC during visual stimulation, but this response was not necessarily predictive or protective of eclampsia.¹⁴² Several mechanisms may account for this dysregulation, but enhanced placental NO bioavailability may be a critical factor.¹⁴³ fMRI studies have also shown gender differences in blood oxygen level-dependent (BOLD) amplitudes during neural responses to flickering stimuli, where despite a higher visual evoked potential (VEP) amplitude, the BOLD amplitude is significantly lower in women.¹⁴⁴ While the mechanisms underlying this observation have not been identified, differences in baseline hemodynamics as well as structural differences (i.e., more gray matter in women versus more white matter in men) have been suggested.¹⁴⁵

Stroke, aging, and traumatic brain injury all seem to impair NVC, but the impact of sex has not been specifically examined in all these conditions. Cognitive impairment and dementia seem to be more frequent in women, which may be related to a higher number of elderly women than men, particularly over 80 years of age.¹⁴⁶ However, at a comparable stage of Alzheimer's disease (AD), women seem to have more prominent cognitive deficits than men.¹⁴⁷ Increasing evidence links cerebral hypoperfusion and neurodegeneration to AD and vascular dementia, and assessment of cerebrovascular hemodynamics may be an important tool in early identification of at-risk individuals.^{148,149} Given gender disparities in stroke and cognitive impairment and the established link between age-related differences in cognitive performance and NVC,¹⁵⁰ a better understanding of the impact of gender on NVC could provide new targets and approaches to enhance motor recovery after stroke or to prevent cognitive decline in women. Also, in animal models of SAH, while CO₂ is impaired before NVC, impairment of NVC can occur secondarily and further aggravate SAH-induced cerebral ischemia and subsequent brain damage.¹²⁹ Recent studies demonstrate that targeting NVC is pharmacologically possible and can lead to improved cognitive function,¹⁵¹ particularly in postmenopausal women.¹⁵² These findings hold promise for novel therapeutic targets in acute and chronic neurovascular injuries.

Summary

Women have a longer life expectancy with a hormonal profile that significantly varies across their life span, in particular, during their reproductive years. The impact of sex as a biological variable in vascular risk and neurovascular response to injury seems to not only depend on the hormonal milieu, but also on age-related changes in physiological response to the hormonal milieu. Estrogens clearly play a protective role in vascular function, but the benefits of estrogens seem to be linked to other age-related cellular and systemic changes that occur across the female life span and are time variable. In the cerebrovascular bed

which can be assessed through measures of autoregulation, VR, and NVC, it appears that healthy women have better dCA and higher resting CBF. Systemically, young premenopausal women also seem to have lower sympathetic tone and a better overall BP profile, resulting in less systemic endothelial injury. Premenopausal young females are also better protected against vascular injury as a result of the higher number of endothelial progenitor cells and greater proangiogenic potential that is also regulated by E2 concentrations.¹⁵³ Overall, it seems that the female vascular system is better protected and operates at a higher efficiency in the childbearing years, possibly a biological result of the enhanced hemodynamic demand of the pregnant state. Therefore, neurological sequelae of hypertensive disorders of pregnancy can ensue when dCA and VR become less effective, even below the level of frank impairment.

While we know that impaired dCA and cerebral VR are associated with worse clinical outcomes in ischemic and hemorrhagic strokes, whether sex differences in these measures also account for gender-specific outcomes in these conditions remains unknown. Similarly, age-related cognitive decline and dementia seem to be linked to NVC, but whether aging and vascular risk factors have a sex-specific impact on NVC is unknown. Clearly, there is a significant knowledge deficit that hinders our ability to prevent and treat a devastating condition in women. This review is intended to generate testable hypotheses that can lead to more effective sex-specific preventive strategies and therapeutic targets in vascular disease. Now that bedside assessment of the cerebrovascular bed can be noninvasively and repeatedly achieved, we are poised to test some of these hypotheses and correct the existing knowledge deficit on sex-specific changes in cerebrovascular hemodynamics that could serve as the substrates for vascular health disparities that exist for women.

References

1. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011;124(19):2145–2154 [PubMed: 22064958]
2. Panerai RB. Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. *Physiol Meas* 1998; 19(03):305–338 [PubMed: 9735883]
3. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation* 1999;99(09):1165–1172 [PubMed: 10069784]
4. Mozaffarian D, Benjamin EJ, Go AS, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;131(04): e29–e322 [PubMed: 25520374]
5. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol* 2008;7(10):915–926 [PubMed: 18722812]
6. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;88(05):950–957 [PubMed: 26221752]
7. Cobo G, Hecking M, Port FK, et al. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)* 2016;130(14):1147–1163 [PubMed: 27252402]
8. Carrero JJ, de Zager DJ, Verduijn M, et al. Cardiovascular and noncardiovascular mortality among men and women starting dialysis. *Clin J Am Soc Nephrol* 2011;6(07):1722–1730 [PubMed: 21734088]

9. Koh KK. Can a healthy endothelium influence the cardiovascular effects of hormone replacement therapy? *Int J Cardiol* 2003;87(01):1–8 [PubMed: 12468049]
10. Pettersson K, Gustafsson JA. Role of estrogen receptor beta in estrogen action. *Annu Rev Physiol* 2001;63:165–192 [PubMed: 11181953]
11. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26(06):1014–1019 [PubMed: 7762016]
12. Ainslie PN, Ashmead JC, Ide K, Morgan BJ, Poulin MJ. Differential responses to CO₂ and sympathetic stimulation in the cerebral and femoral circulations in humans. *J Physiol* 2005; 566(Pt 2):613–624 [PubMed: 15890697]
13. Poulin MJ, Liang PJ, Robbins PA. Dynamics of the cerebral blood flow response to step changes in end-tidal PCO₂ and PO₂ in humans. *J Appl Physiol* (1985) 1996;81(03):1084–1095 [PubMed: 8889738]
14. Aaslid R. Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke* 1987;18(04):771–775 [PubMed: 3299883]
15. Stroobant N, Vingerhoets G. Test-retest reliability of functional transcranial Doppler ultrasonography. *Ultrasound Med Biol* 2001;27(04):509–514 [PubMed: 11368863]
16. Panerai RB, Eyre M, Potter JF. Multivariate modeling of cognitivemotor stimulation on neurovascular coupling: transcranial Doppler used to characterize myogenic and metabolic influences. *Am J Physiol Regul Integr Comp Physiol* 2012;303(04):R395–R407 [PubMed: 22718807]
17. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2(02):161–192 [PubMed: 2201348]
18. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989;20(01):45–52 [PubMed: 2492126]
19. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke* 1994;25(04):793–797 [PubMed: 7909175]
20. Halpern W, Osol G. Influence of transmural pressure of myogenic responses of isolated cerebral arteries of the rat. *Ann Biomed Eng* 1985;13(3-4):287–293 [PubMed: 4037458]
21. Kontos HA, Wei EP. Oxygen-dependent mechanisms in cerebral autoregulation. *Ann Biomed Eng* 1985;13(3-4):329–334 [PubMed: 4037462]
22. Panerai RB. Cerebral autoregulation: from models to clinical applications. *Cardiovasc Eng* 2008;8(01):42–59 [PubMed: 18041584]
23. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J Clin Invest* 1948;27(04):476–483 [PubMed: 16695568]
24. Obrist WD, Thompson HK Jr, Wang HS, Wilkinson WE. Regional cerebral blood flow estimated by 133-xenon inhalation. *Stroke* 1975;6(03):245–256 [PubMed: 1154462]
25. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982;57(06):769–774 [PubMed: 7143059]
26. Dawson SL, Blake MJ, Panerai RB, Potter JF. Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. *Cerebrovasc Dis* 2000;10(02):126–132 [PubMed: 10686451]
27. Tiecks FP, Haberl RL, Newell DW. Temporal patterns of evoked cerebral blood flow during reading. *J Cereb Blood Flow Metab* 1998;18(07):735–741 [PubMed: 9663503]
28. Giller CA. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. *Acta Neurochir (Wien)* 1991; 108(1-2):7–14 [PubMed: 2058430]
29. Rätsep T, Asser T. Cerebral hemodynamic impairment after aneurysmal subarachnoid hemorrhage as evaluated using transcranial Doppler ultrasonography: relationship to delayed cerebral ischemia and clinical outcome. *J Neurosurg* 2001;95(03): 393–401 [PubMed: 11565859]
30. van Beek AH, Olde Rikkert MG, Pasman JW, Hopman MT, Claassen JA. Dynamic cerebral autoregulation in the old using a repeated sit-stand maneuver. *Ultrasound Med Biol* 2010;36(02):192–201 [PubMed: 20045593]

31. Sorond FA, Serrador JM, Jones RN, Shaffer ML, Lipsitz LA. The sit-to-stand technique for the measurement of dynamic cerebral autoregulation. *Ultrasound Med Biol* 2009;35(01):21–29 [PubMed: 18834658]
32. Panerai RB, Dawson SL, Potter JF. Linear and nonlinear analysis of human dynamic cerebral autoregulation. *Am J Physiol* 1999;277 (3 Pt 2):H1089–H1099 [PubMed: 10484432]
33. Diehl RR, Linden D, Lücke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. *Stroke* 1995;26(10):1801–1804 [PubMed: 7570728]
34. Birch AA, Dirnhuber MJ, Hartley-Davies R, Iannotti F, Neil-Dwyer G. Assessment of autoregulation by means of periodic changes in blood pressure. *Stroke* 1995;26(05):834–837 [PubMed: 7740576]
35. Blaber AP, Bondar RL, Stein F, et al. Transfer function analysis of cerebral autoregulation dynamics in autonomic failure patients. *Stroke* 1997;28(09):1686–1692 [PubMed: 9303010]
36. Serrador JM, Sorond FA, Vyas M, Gagnon M, Iloputaife ID, Lipsitz LA. Cerebral pressure-flow relations in hypertensive elderly humans: transfer gain in different frequency domains. *J Appl Physiol* (1985) 2005;98(01):151–159 [PubMed: 15361517]
37. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol* 1998;274(1 Pt 2):H233–H241 [PubMed: 9458872]
38. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB; international Cerebral Autoregulation Research Network (CARNet). Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab* 2016;36(04):665–680 [PubMed: 26782760]
39. van Beek AH, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab* 2008;28(06):1071–1085 [PubMed: 18349877]
40. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996;27(10):1829–1834 [PubMed: 8841340]
41. Lang EW, Lagopoulos J, Griffith J, et al. Noninvasive cerebrovascular autoregulation assessment in traumatic brain injury: validation and utility. *J Neurotrauma* 2003;20(01):69–75 [PubMed: 12614589]
42. Ali YS, Daamen N, Jacob G, et al. Orthostatic intolerance: a disorder of young women. *Obstet Gynecol Surv* 2000;55(04): 251–259 [PubMed: 10758621]
43. Pospori C, Xue SA, Holler A, et al. Specificity for the tumor-associated self-antigen WT1 drives the development of fully functional memory T cells in the absence of vaccination. *Blood* 2011;117(25):6813–6824 [PubMed: 21447831]
44. Joyner MJ, Barnes JN, Hart EC, Wallin BG, Charkoudian N. Neural control of the circulation: how sex and age differences interact in humans. *Compr Physiol* 2015;5(01):193–215 [PubMed: 25589269]
45. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991 ;84(02):482–492 [PubMed: 1860193]
46. Xing CY, Tarumi T, Meijers RL, et al. Arterial pressure, heart rate, and cerebral hemodynamics across the adult life span. *Hypertension* 2017;69(04):712–720 [PubMed: 28193707]
47. Montano N, Cogliati C, Dias da Silva VJ, Gneccchi-Ruscione T, Malliani A. Sympathetic rhythms and cardiovascular oscillations. *Auton Neurosci* 2001;90(1-2):29–34 [PubMed: 11485288]
48. Pagani M, Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. *J Hypertens* 2000; 18(12):1709–1719 [PubMed: 11132592]
49. Deegan BM, Sorond FA, Galica A, Lipsitz LA, O’Laighin G, Serrador JM. Elderly women regulate brain blood flow better than men do. *Stroke* 2011;42(07):1988–1993 [PubMed: 21566238]
50. Müller HR, Brunhölzl C, Radü EW, Buser M. Sex and side differences of cerebral arterial caliber. *Neuroradiology* 1991;33(03):212–216 [PubMed: 1881537]
51. Orlandini GE, Ruggiero C, Orlandini SZ, Gulisano M. Blood vessel size of circulus arteriosus cerebri (circle of Willis): a statistical research on 100 human subjects. *Acta Anat (Basel)* 1985;123 (01):72–76 [PubMed: 4050309]

52. Xing CY, Tarumi T, Liu J, et al. Distribution of cardiac output to the brain across the adult lifespan. *J Cereb Blood Flow Metab* 2017; 37(08):2848–2856 [PubMed: 27789785]
53. Hazlett EA, Byne W, Brickman AM, et al. Effects of sex and normal aging on regional brain activation during verbal memory performance. *Neurobiol Aging* 2010;31(05):826–838 [PubMed: 19027195]
54. Bushnell CD. Stroke and the female brain. *Nat Clin Pract Neurol* 2008;4(01):22–33 [PubMed: 18199994]
55. Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: adapting to preserve normalcy. *Physiology (Bethesda)* 2015;30(02):139–147 [PubMed: 25729059]
56. Clapp JF III, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol* 1997 ;80(11):1469–1473 [PubMed: 9399724]
57. Tettenborn B. Stroke and pregnancy. *Neurol Clin* 2012;30(03): 913–924 [PubMed: 22840796]
58. Lindqvist PG, Marsál K, Pirhonen JP. Maternal cerebral Doppler velocimetry before, during, and after a normal pregnancy: a longitudinal study. *Acta Obstet Gynecol Scand* 2006;85(11):1299–1303 [PubMed: 17091406]
59. Cipolla MJ. The adaptation of the cerebral circulation to pregnancy: mechanisms and consequences. *J Cereb Blood Flow Metab* 2013;33(04):465–478 [PubMed: 23321787]
60. Leffert LR, Clancy CR, Bateman BT, Bryant AS, Kuklina EV. Hypertensive disorders and pregnancy-related stroke: frequency, trends, risk factors, and outcomes. *Obstet Gynecol* 2015;125(01):124–131 [PubMed: 25560114]
61. Sibai BM. Eclampsia. VI. Maternal-perinatal outcome in 254 consecutive cases. *Am J Obstet Gynecol* 1990;163(03):1049–1054, discussion 1054–1055 [PubMed: 2403130]
62. Belfort MA, Grunewald C, Saade GR, Varner M, Nisell H. Preeclampsia may cause both overperfusion and underperfusion of the brain: a cerebral perfusion based model. *Acta Obstet Gynecol Scand* 1999;78(07):586–591 [PubMed: 10422904]
63. van Veen TR, Panerai RB, Haeri S, et al. Cerebral autoregulation in different hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2015;212(04):513.e1–513.e7 [PubMed: 25446701]
64. Jensen D, Duffin J, Lam Y-M, et al. Physiological mechanisms of hyperventilation during human pregnancy. *Respir Physiol Neurobiol* 2008;161(07):76–86 [PubMed: 18289946]
65. Williams KP, Galerneau F, Wilson S. Changes in cerebral perfusion pressure in puerperal women with preeclampsia. *Obstet Gynecol* 1998;92(06):1016–1019 [PubMed: 9840569]
66. van Veen TR, Panerai RB, Haeri S, Griffioen AC, Zeeman GG, Belfort MA. Cerebral autoregulation in normal pregnancy and preeclampsia. *Obstet Gynecol* 2013;122(05):1064–1069 [PubMed: 24104783]
67. Hammer ES, Cipolla MJ. Cerebrovascular dysfunction in preeclamptic pregnancies. *Curr Hypertens Rep* 2015;17(08):64 [PubMed: 26126779]
68. Harper SL, Bohlen HG. Microvascular adaptation in the cerebral cortex of adult spontaneously hypertensive rats. *Hypertension* 1984;6(03):408–419 [PubMed: 6735460]
69. Cipolla MJ, Smith J, Bishop N, Bullinger LV, Godfrey JA. Pregnancy reverses hypertensive remodeling of cerebral arteries. *Hypertension* 2008;51(04):1052–1057 [PubMed: 18259042]
70. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. *Semin Nephrol* 2011;31(01):33–46 [PubMed: 21266263]
71. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M; World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke incidence, case fatality, and mortality in the WHO MONICA project. *Stroke* 1995;26(03): 361–367 [PubMed: 7886707]
72. Go AS, Mozaffarian D, Roger VL, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation* 2013;127(01):e6–e245 [PubMed: 23239837]
73. Towfighi A, Saver JL, Engelhardt R, Ovbiagele B. A midlife stroke surge among women in the United States. *Neurology* 2007;69 (20):1898–1904 [PubMed: 17581944]
74. Towfighi A, Markovic D, Ovbiagele B. Persistent sex disparity in midlife stroke prevalence in the United States. *Cerebrovasc Dis* 2011;31(04):322–328 [PubMed: 21212663]

75. Ovbiagele B, Goldstein LB, Higashida RT, et al.; American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke* 2013;44(08):2361–2375 [PubMed: 23697546]
76. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System. 2013;61(04):1–117
77. Mercuro G, Deidda M, Piras A, Dessalvi CC, Maffei S, Rosano GM. Gender determinants of cardiovascular risk factors and diseases. *J Cardiovasc Med (Hagerstown)* 2010;11(03):207–220 [PubMed: 19829128]
78. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke* 2007;38(09):2438–2445 [PubMed: 17690308]
79. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter JF. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2002;72(04):467–472 [PubMed: 11909905]
80. Xiong L, Tian G, Lin W, et al. Is dynamic cerebral autoregulation bilaterally impaired after unilateral acute ischemic stroke? *J Stroke Cerebrovasc Dis* 2017;26(05):1081–1087 [PubMed: 28262564]
81. Reinhard M, Wihler C, Roth M, et al. Cerebral autoregulation dynamics in acute ischemic stroke after rtPA thrombolysis. *Cerebrovasc Dis* 2008;26(02):147–155 [PubMed: 18560218]
82. Reinhard M, Roth M, Guschlbauer B, et al. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke* 2005;36(08):1684–1689 [PubMed: 16020768]
83. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis* 2003;16(01):69–75 [PubMed: 12766365]
84. Castro P, Serrador JM, Rocha I, Sorond F, Azevedo E. Efficacy of cerebral autoregulation in early ischemic stroke predicts smaller infarcts and better outcome. *Front Neurol* 2017;8:113 [PubMed: 28392777]
85. Reinhard M, Schork J, Allignol A, Weiller C, Kaube H. Cerebellar and cerebral autoregulation in migraine. *Stroke* 2012;43(04): 987–993 [PubMed: 22343638]
86. Müller M, Marziniak M. The linear behavior of the system middle cerebral artery flow velocity and blood pressure in patients with migraine: lack of autonomic control? *Stroke* 2005;36(09): 1886–1890 [PubMed: 16100026]
87. Gokhale S, Caplan LR, James ML. Sex differences in incidence, pathophysiology, and outcome of primary intracerebral hemorrhage. *Stroke* 2015;46(03):886–892 [PubMed: 25657181]
88. Ganti L, Jain A, Yerragund N, et al. Female gender remains an independent risk factor for poor outcome after acute nontraumatic intracerebral hemorrhage. *Neurol Res Int* 2013; 2013:219097 [PubMed: 24083025]
89. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009;40(04):1082–1090 [PubMed: 19211488]
90. Qureshi AI, Bliwise DL, Bliwise NG, Akbar MS, Uzen G, Frankel MR. Rate of 24-hour blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. *Crit Care Med* 1999;27:480–485 [PubMed: 10199525]
91. Kawase K, Okazaki S, Toyoda K, et al. Sex difference in the prevalence of deep-vein thrombosis in Japanese patients with acute intracerebral hemorrhage. *Cerebrovasc Dis* 2009;27(04):313–319 [PubMed: 19218795]
92. Herson PS, Koerner IP, Hurn PD. Sex, sex steroids, and brain injury. *Semin Reprod Med* 2009;27(03):229–239 [PubMed: 19401954]
93. Feldmann E, Broderick JP, Kernan WN, et al. Major risk factors for intracerebral hemorrhage in the young are modifiable. *Stroke* 2005;36(09):1881–1885 [PubMed: 16081867]
94. Sehba FA, Hou J, Pluta RM, Zhang JH. The importance of early brain injury after subarachnoid hemorrhage. *Prog Neurobiol* 2012;97(01):14–37 [PubMed: 22414893]

95. Weir B Unruptured intracranial aneurysms: a review. *J Neurosurg* 2002;96(01):3–42 [PubMed: 11794601]
96. Otite F, Mink S, Tan CO, et al. Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. *Stroke* 2014;45(03):677–682 [PubMed: 24425120]
97. Nakagawa K, Serrador JM, LaRose SL, Sorond FA. Dynamic cerebral autoregulation after intracerebral hemorrhage: a case-control study. *BMC Neurol* 2011;11:108 [PubMed: 21884574]
98. Santos GA, Petersen N, Zamani AA, et al. Pathophysiologic differences in cerebral autoregulation after subarachnoid hemorrhage. *Neurology* 2016;86(21):1950–1956 [PubMed: 27164675]
99. Friedrich V, Bederson JB, Sehba FA. Gender influences the initial impact of subarachnoid hemorrhage: an experimental investigation. *PLoS One* 2013;8(11):e80101 [PubMed: 24250830]
100. Hall ED, Pazara KE, Linseman KL. Sex differences in postischemic neuronal necrosis in gerbils. *J Cereb Blood Flow Metab* 1991;11 (02):292–298 [PubMed: 1997500]
101. Curtze S, Haapaniemi E, Melkas S, et al. White matter lesions double the risk of post-thrombotic intracerebral hemorrhage. *Stroke* 2015;46(08):2149–2155 [PubMed: 26111888]
102. Castro P, Azevedo E, Serrador J, Rocha I, Sorond F. Hemorrhagic transformation and cerebral edema in acute ischemic stroke: link to cerebral autoregulation. *J Neurol Sci* 2017;372:256–261 [PubMed: 28017224]
103. Brian JE Jr, Faraci FM, Heistad DD. Recent insights into the regulation of cerebral circulation. *Clin Exp Pharmacol Physiol* 1996;23(6-7):449–457 [PubMed: 8800565]
104. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J Clin Invest* 1948;27:484–492 [PubMed: 16695569]
105. Shapiro W, Wasserman AJ, Baker JP, Patterson JL Jr. Cerebrovascular response to acute hypocapnic and eucapnic hypoxia in normal man. *J Clin Invest* 1970;49(12):2362–2368 [PubMed: 5480859]
106. Atkinson JL, Anderson RE, Sundt TM Jr. The effect of carbon dioxide on the diameter of brain capillaries. *Brain Res* 1990;517 (1-2):333–340 [PubMed: 2115812]
107. Kinoshita H, Katusic ZS. Role of potassium channels in relaxations of isolated canine basilar arteries to acidosis. *Stroke* 1997; 28(02):433–437, discussion 437–438 [PubMed: 9040702]
108. Parfenova H, Shibata M, Zuckerman S, Leffler CW. CO₂ and cerebral circulation in newborn pigs: cyclic nucleotides and prostanoids in vascular regulation. *Am J Physiol* 1994;266(4 Pt 2):H1494–H1501 [PubMed: 7514362]
109. Poulin MJ, Liang PJ, Robbins PA. Fast and slow components of cerebral blood flow response to step decreases in end-tidal PCO₂ in humans. *J Appl Physiol* (1985) 1998;85(02):388–397 [PubMed: 9688710]
110. Wijnhoud AD, Koudstaal PJ, Dippel DW. Relationships of transcranial blood flow Doppler parameters with major vascular risk factors: TCD study in patients with a recent TIA or nondisabling ischemic stroke. *J Clin Ultrasound* 2006;34(02):70–76 [PubMed: 16547983]
111. Purkayastha S, Sorond F. Transcranial Doppler ultrasound: technique and application. *Semin Neurol* 2012;32(04):411–420 [PubMed: 23361485]
112. Ainslie PN, Duffin J. Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol* 2009;296(05):R1473–R1495 [PubMed: 19211719]
113. Mandell DM, Han JS, Poulblanc J, et al. Selective reduction of blood flow to white matter during hypercapnia corresponds with leukoaraiosis. *Stroke* 2008;39(07):1993–1998 [PubMed: 18451357]
114. Bakker SL, de Leeuw FE, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. Cerebral haemodynamics in the elderly: the Rotterdam Study. *Neuroepidemiology* 2004;23(04):178–184 [PubMed: 15272220]
115. Karnik R, Valentin A, Winkler WB, Khaffaf N, Donath P, Slany J. Sex-related differences in acetazolamide-induced cerebral vasomotor reactivity. *Stroke* 1996;27(01):56–58 [PubMed: 8553403]

116. Kastrup A, Thomas C, Hartmann C, Schabet M. Sex dependency of cerebrovascular CO₂ reactivity in normal subjects. *Stroke* 1997; 28(12):2353–2356 [PubMed: 9412613]
117. Matteis M, Troisi E, Monaldo BC, Caltagirone C, Silvestrini M. Age and sex differences in cerebral hemodynamics: a transcranial Doppler study. *Stroke* 1998;29(05):963–967 [PubMed: 9596243]
118. Vriens EM, Kraaier V, Musbach M, Wieneke GH, van Huffelen AC. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. *Ultrasound Med Biol* 1989;15(01):1–8
119. Oláh L, Valikovics A, Bereczki D, Fülesdi B, Munkácsy C, Csiba L. Gender-related differences in acetazolamide-induced cerebral vasodilatory response: a transcranial Doppler study. *J Neuroimaging* 2000;10(03):151–156 [PubMed: 10918741]
120. Krejza J, Rudzinski W, Arkuszewski M, Onuoha O, Melhem ER. Cerebrovascular reactivity across the menstrual cycle in young healthy women. *Neuroradiol J* 2013;26(04):413–419 [PubMed: 24007729]
121. Bain CA, Walters MR, Lees KR, Lumsden MA. The effect of HRT on cerebral haemodynamics and cerebral vasomotor reactivity in post-menopausal women. *Hum Reprod* 2004;19(10):2411–2414 [PubMed: 15284214]
122. Main C, Knight B, Moxham T, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2013;(04):CD002229 [PubMed: 23633307]
123. Peltonen GL, Harrell JW, Rousseau CL, et al. Cerebrovascular regulation in men and women: stimulus-specific role of cyclooxygenase. *Physiol Rep* 2015;3(07):e12451 [PubMed: 26149282]
124. Sariri E, Vahdat M, Behbahani AS, Rohani M, Kashanian M. Cerebro vascular reactivity (CVR) of middle cerebral artery in response to CO₂ 5% inhalation in preeclamptic women. *J Matern Fetal Neonatal Med* 2013;26(10):1020–1023 [PubMed: 23356662]
125. Riskin-Mashiah S, Belfort MA, Saade GR, Herd JA. Cerebrovascular reactivity in normal pregnancy and preeclampsia. *Obstet Gynecol* 2001;98(5 Pt 1):827–832 [PubMed: 11704176]
126. Salinet AS, Robinson TG, Panerai RB. Effects of cerebral ischemia on human neurovascular coupling, CO₂ reactivity, and dynamic cerebral autoregulation. *J Appl Physiol* (1985) 2015;118(02):170–177 [PubMed: 25593216]
127. Knottnerus IL, Ten Cate H, Lodder J, Kessels F, van Oostenbrugge RJ. Endothelial dysfunction in lacunar stroke: a systematic review. *Cerebrovasc Dis* 2009;27(05):519–526 [PubMed: 19372654]
128. da Costa L, Houlden D, Rubenfeld G, Tymianski M, Fisher J, Fierstra J. Impaired cerebrovascular reactivity in the early phase of subarachnoid hemorrhage in good clinical grade patients does not predict vasospasm. *Acta Neurochir Suppl (Wien)* 2015;120:249–253
129. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Heart Circ Physiol* 2017;312(01):H1–H20 [PubMed: 27793855]
130. Balbi M, Koide M, Schwarzmaier SM, Wellman GC, Plesnila N. Acute changes in neurovascular reactivity after subarachnoid hemorrhage in vivo. *J Cereb Blood Flow Metab* 2017;37(01): 178–187 [PubMed: 26676226]
131. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc* 2015;4(11):e002270 [PubMed: 26567372]
132. Skaug EA, Aspenes ST, Oldervoll L, et al. Age and gender differences of endothelial function in 4739 healthy adults: the HUNT3 Fitness Study. *Eur J Prev Cardiol* 2013;20(04):531–540 [PubMed: 22456692]
133. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired flow-mediated dilation before, during, and after preeclampsia: a systematic review and meta-analysis. *Hypertension* 2016;67 (02):415–423 [PubMed: 26711737]
134. Iadecola C Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004;5(05):347–360 [PubMed: 15100718]

135. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol* 2014;592(05):841–859 [PubMed: 24396059]
136. Lagaud G, Karicheti V, Knot HJ, Christ GJ, Laher I. Inhibitors of gap junctions attenuate myogenic tone in cerebral arteries. *Am J Physiol Heart Circ Physiol* 2002;283(06):H2177–H2186 [PubMed: 12427590]
137. Rosengarten B, Aldinger C, Kaufmann A, Kaps M. Comparison of visually evoked peak systolic and end diastolic blood flow velocity using a control system approach. *Ultrasound Med Biol* 2001;27(11):1499–1503 [PubMed: 11750749]
138. Sorond FA, Kiely DK, Galica A, et al. Neurovascular coupling is impaired in slow walkers: the MOBILIZE Boston Study. *Ann Neurol* 2011;70(02):213–220 [PubMed: 21674588]
139. Sorond FA, Schnyer DM, Serrador JM, Milberg WP, Lipsitz LA. Cerebral blood flow regulation during cognitive tasks: effects of healthy aging. *Cortex* 2008;44(02):179–184 [PubMed: 18387547]
140. Stroobant N, Vingerhoets G. Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review. *Neuropsychol Rev* 2000;10(04):213–231 [PubMed: 11132101]
141. Martens EG, Peeters LL, Gommer ED, et al. The visually-evoked cerebral blood flow response in women with a recent history of preeclampsia and/or eclampsia. *Ultrasound Med Biol* 2009;35(01):1–7 [PubMed: 18845379]
142. Janzarik WG, Ehmann R, Ehlers E, et al. Neurovascular coupling in pregnancy and the risk of preeclampsia. *Stroke* 2014;45(09): 2792–2794 [PubMed: 25034711]
143. Kim YJ, Lee BE, Lee HY, et al. Uterine artery notch is associated with increased placental endothelial nitric oxide synthase and heat shock protein. *J Matern Fetal Neonatal Med* 2010;23(02): 153–157 [PubMed: 20017704]
144. Kaufmann C, Elbel GK, Gössl C, Pütz B, Auer DP. Frequency dependence and gender effects in visual cortical regions involved in temporal frequency dependent pattern processing. *Hum Brain Mapp* 2001;14(01):28–38 [PubMed: 11500988]
145. Kaufmann C, Elbel GK, Gössl C, Pütz B, Auer DP. Frequency dependence and gender effects in visual cortical regions involved in temporal frequency dependent pattern processing. *Hum Brain Mapp* 2001;14(01):28–38 [PubMed: 11500988]
146. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9(01):63–75.e2 [PubMed: 23305823]
147. Derreberry TM, Holroyd S. Dementia in women. *Psychiatr Clin North Am* 2017;40(02):299–307 [PubMed: 28477654]
148. Luckhaus C, Flüß MO, Wittsack HJ, et al. Detection of changed regional cerebral blood flow in mild cognitive impairment and early Alzheimer's dementia by perfusion-weighted magnetic resonance imaging. *Neuroimage* 2008;40(02): 495–503 [PubMed: 18207425]
149. Malojcic B, Giannakopoulos P, Sorond FA, et al. Ultrasound and dynamic functional imaging in vascular cognitive impairment and Alzheimer's disease. *BMC Med* 2017;15(01):27 [PubMed: 28178960]
150. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging* 2002;23(03):421–431 [PubMed: 11959405]
151. Sorond FA, Hurwitz S, Salat DH, Greve DN, Fisher ND. Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people. *Neurology* 2013;81(10): 904–909 [PubMed: 23925758]
152. Evans HM, Howe PR, Wong RH. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised Placebo-controlled intervention trial. *Nutrients* 2017;9(01):E27 [PubMed: 28054939]
153. Mudrovic N, Arefin S, Van Craenenbroeck AH, Kublickiene K. Endothelial maintenance in health and disease: importance of sex differences. *Pharmacol Res* 2017;119:48–60 [PubMed: 28108363]