Sympathetic Nervous System Regulation in Human Normotensive and Hypertensive Pregnancies

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The progression from conception through to the postpartum period represents an extraordinary period of physiological adaptation in the mother to support the growth and development of the fetus. Cardiometabolic dysregulation during this period is associated with the future development of cardiovascular morbidity.[1] In particular, hypertensive pregnancy disorders, including gestational hypertension (GH) and preeclampsia, are the leading causes of maternal–fetal morbidity and mortality in the developed world, including North America.[2] In the 10 to 14 years after pregnancy, women who have had preeclampsia also demonstrate an elevated risk for hypertension (risk ratio, 3.70), ischemic heart disease (risk ratio, 2.26), stroke (risk ratio, 1.8),[3] and end-stage renal disease (risk ratio, 4.7)[4] compared with women who had normotensive pregnancies. However, the most sobering statistic identifies preeclampsia as an independent risk factor for cardiovascular disease death (hazard ratio, 2.14) that is further elevated with earlier onset of preeclampsia (hazard ratio, 9.54 for diagnosis by 34 weeks gestation).[5] The 30-year survival rate for these women at a median age of 56 years is only 86%.[5] This elevated risk is believed to be related to persistent cardiovascular dysfunction.

Currently, the pathogenesis of hypertensive pregnancy disorders remains unclear, and as a result, there exist few effective strategies to mitigate the development of GH and preeclampsia in women who are known to be at increased risk. We need to consider that pregnant women are an understudied population in clinical research because of their supposed vulnerability.[6] Therefore, studies during pregnancy often involve the use of either cross-sectional studies or the use of data during the postpartum phase as a control for a prepregnant state. Thus, there is a lack of evidence-based knowledge on the physiology of blood pressure regulation during pregnancy. In particular, an understudied link between pregnancy and the development of maternal hypertension may lie in the sympathetic nervous system regulation of the peripheral vascular smooth muscle, an important determinant of systemic vascular resistance, blood pressure, and tissue blood flow.[7]

In nonpregnant populations, hyperactivity of sympathetic outflow to the peripheral vasculature has been associated with hypertension[8] and heart failure.[9] As such, the hypothesis that excessive sympathoexcitation contributes to the development of pregnancy-related hypertensive disorders has been examined.[10–14] However, few studies have been designed explicitly to examine sympathetic regulation during normotensive pregnancy.[13–19]

Although the importance of research into the mechanisms contributing to the development of GH and preeclampsia is clear, the understanding of cardiovascular regulatory mechanisms as they pertain to normal, healthy pregnancy remains a necessary platform on which our understanding of complex disorders must be based. As such, an improved understanding of the changes in cardiovascular function which occur during normotensive pregnancies is likely to aid in the subsequent prevention and treatment of hypertensive pregnancy disorders. Therefore, the primary purpose of this paper is to summarize our current understanding of the cardiovascular adaptations to normal healthy pregnancy, with specific emphasis on the role of the sympathetic nervous system. We will then identify known sites of sympathetic dysregulation which are associated with GH or preeclampsia, highlighting areas requiring further research in normal or hypertensive pregnancies. We have cited literature on animal models of pregnancy to attempt to explain potential mechanisms for altered regulation. However, we have limited these citations to areas of research where no human data exist or could not be plausibly be studied in humans (eg, central brain stem alterations). Although this paper is focused on the role of the sympathetic nervous system in determining cardiovascular health during pregnancy, we acknowledge that multiple factors have been identified which are likely to contribute to hypertension during pregnancy. We direct the reader to several excellent reviews, which detail these possibilities, including the associated alterations to vascular function,[20] angiogenesis,[21] innate immunity,[22] oxidative stress,[23] and the central integration of the neural control of blood pressure.[24] Interestingly, most of the primary pharmacological therapies that are currently used to treat preeclampsia target the influence of the sympathetic nervous system even though the role of the sympathetic nervous system in the control of blood pressure is poorly understood.

Throughout this review, normal is defined by singleton pregnancy in the absence of hypertension as well as other nonhypertensive pregnancy-induced morbidities (eg, gestational diabetes mellitus). It is worth noting that our focus on singleton pregnancy is because of the absence of research in this area. In our review, GH is defined by de novo hypertension (>140/90 mm Hg) that manifests no earlier than 20 weeks' gestation.[25]

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According to the American College of Obstetricians and Gynecologist, preeclampsia is defined by de novo hypertension (>140/90 mm Hg) that manifests no earlier than 20 weeks' gestation and proteinuria (>0.3 g/d protein in a 24-hour urine or protein/creatinine ratio ≥0.3). In the absence of proteinuria, preeclampsia is defined by the new-onset hypertension and any of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms.[26] For the purpose of this review, however, the definition of preeclampsia given by all of the authors cited was the new-onset of hypertension (>140/90 mm Hg) and proteinuria (>0.3 g/d protein in a 24-hour urine) after the 20th week of gestation. The studies that included women with preeclampsia do not mention the severity or onset of the disease.

Hemodynamic Adaptations to Pregnancy

In a normal healthy pregnancy, an early rise in cardiac output is thought to be because of a reduction in after-load (peripheral vascular resistance) in conjunction with an increase in heart rate.[27] Concurrently, there is an increase in shear stress on the arterial endothelium, which in turn evokes nitric oxide release and contributes to a reduction in peripheral vascular resistance.[28] This is manifest as a reduction in arterial pressure within the first 8 weeks of gestation, which reaches a nadir late in the second trimester before rising to prepregnant levels in the third trimester.[29] The systemic vasodilation and an increase in arterial compliance[30] also accommodate the significant plasma volume expansion (up to 150% of prepregnancy values),[31] which peaks in the third trimester.[29]

To date, many studies have examined changes in vascular function which occur over the course of normal pregnancy. A thorough analysis of the effect of pregnancy on endothelial and vascular smooth muscle responses to mechanical and pharmacological stimuli lies beyond the scope of this review and has been the subject of a meta-analysis.[32] For the purpose of this review, we will emphasize the changes in sympathetic nervous system activity (SNA) throughout pregnancy.

Direct Measurements of the SNA in Normotensive Pregnancies

Sympathetic hyperactivity is a hallmark of many clinical disorders. As in nonpregnant populations, the microneurographic technique is an important tool for the direct measurement of SNA. It consists of the percutaneous insertion of a tungsten microelectrode (100–200 µm) into a nerve bundle in a superficial nerve (peroneal, median, or radial nerves). This electrode is used to record the activity of postganglionic efferent sympathetic neurons innervating the vascular smooth muscle within skeletal muscle.[33] The muscle sympathetic nerve activity (MSNA) signal is most commonly represented as individual bursts of activity (ie, integrated MSNA), each of which is the product of a neural volley from ≥1 sympathetic neurons. In addition to measures of integrated MSNA, a relatively recent application of microneurography has been the development of recordings from distinct, individual sympathetic neurons.[34] This modified technique provides information about the firing patterns of individual neurons, which may provide more quantitative information about efferent sympathetic outflow than integrated measures alone.[34] Although technically challenging and limited to experimental settings, microneurography in both of these forms provides direct mechanistic insight into sympathetic nervous system regulation of the peripheral muscle vasculature. The role of the sympathetic nervous system in the control of blood pressure throughout pregnancy, however, remains poorly understood. To date, only 12 studies have used microneurography to investigate sympathetic regulation during pregnancy.

Normal pregnancy is associated with a significant increase in SNA, from 50% to 150% above nonpregnant levels. Specifically, pregnancy-induced sympathoexcitation occurs within the first 6 weeks of gestation[15,16] and remains elevated through the second[10,18,35] and third trimesters[10,13,14,17,18,35–37] before returning to baseline levels by 6 weeks post-partum[10,12,13] (Figure 1).

Greenwood et al[12,13] have reported that single unit MSNA firing frequency is increased during the third trimester, and the magnitude of this increase exceeds the ≈1.5-fold increase in integrated MSNA burst frequency in the same trimester. This finding indicates that a given sympathetic burst during the third trimester of pregnancy contains a greater number of impulses (ie, action potentials) than a given burst in the nonpregnant state. Recently, Schmidt et al[19] using a custom action potential detection software found that the number of action potentials per burst, and number of active amplitude-based clusters of action potentials in pregnant women in their third trimester, was comparable to nonpregnant women.[19] Nevertheless, the total number of sympathetic action potentials per minute was higher in pregnant women relative to nonpregnant women at rest.[19]

Sympathetic Neurotransmitter Release

The increase in neural activity during pregnancy is likely manifest as an increase in neurotransmitter release.[38] Sympathetic nerve firing results in the release of neurotransmitters, including norepinephrine and neuropeptide Y, which are stored in vesicles in nerve terminals.[39] Concentrations of circulating plasma norepinephrine have long been used as a surrogate, indirect marker of global SNA because of the proportional relationship between nerve activity and plasma norepinephrine concentrations which exists under many,[40,41] albeit not all,[42] experimental conditions. To date, baseline circulating norepinephrine has been found to be elevated[15,43] or unchanged[44] during healthy pregnancy. These conflicting reports may be reflective of the limitations inherent to plasma norepinephrine sampling, which is directly dependent on the rate at which norepinephrine is released, taken up by sympathetic neurons, or degraded. Blood flow through the tissue from which plasma is being sampled, and total plasma volume will also influence the measurement of norepinephrine.[45] With respect to the latter, the well-established hypervolemia that occurs during pregnancy[31] would be expected to dilute circulating plasma norepinephrine levels relative to nonpregnant subjects. Therefore, overall plasma norepinephrine data seem to support an increase in neurotransmitter release during healthy pregnancy.

Neurovascular Transduction

Neurovascular transduction is the functional effect of a given amount of sympathetic activity (burst or group of bursts) on vascular diameter, stiffness, and or resistance. Because pregnancy

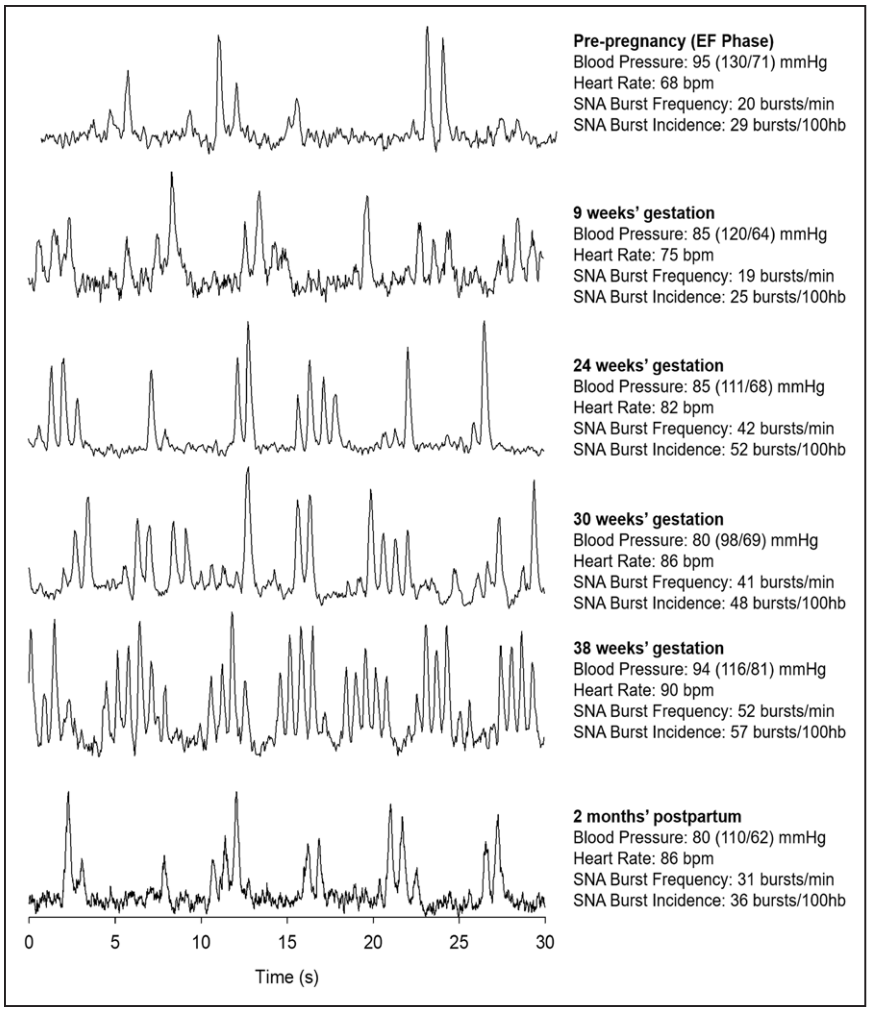

Figure 1. Sympathetic nervous activity (SNA; raw neurograms) and cardiovascular data from one participant before, throughout, and after pregnancy. Data represent the longitudinal assessment of mean arterial blood pressure (systolic/diastolic blood pressure), heart rate and SNA, burst frequency, and burst incidence (raw neurograms) before pregnant (early follicular [EF] phase), during (9, 24, 30, and 38 wk gestation), and after 2-mo post-partum. These data highlight the significant increase in sympathetic nerve activity observed during normotensive pregnancy. Figure adapted from Reyes et al[35] with permission. Copyright © 2018, The Authors.

is a state of sympathoexcitation, it is important to consider peripheral vascular resistance as the primary outcome of the MSNA input. Although an increase in sympathetic neural outflow induces vasoconstriction, vasoactive circulating factors may concomitantly induce vasodilation, potentially disrupting the association between MSNA and peripheral resistance. The extent to which SNA is transduced into vascular resistance is of particular relevance with respect to pregnancy, given that direct correlations between MSNA and total peripheral resistance exist in young healthy men[46] but not in young healthy nonpregnant women.[47] It has been found that uterine arteries from normotensive pregnant women in their third trimester have increase α-1 receptor sensitivity.[48] However, this might be offset by a concurrent increase in β-2 adrenergic sensitivity[49] and the progressive loss of uterine sympathetic nerves.[50] These data suggest that sympathetic neurovascular transduction is offset or blunted in normotensive pregnant women.

During normotensive pregnancy, total peripheral resistance is reduced as early as the first trimester[15] although no change in forearm vascular resistance has been observed across first,[15] second,[10] and third trimesters.[10,13] This disparity between limb skeletal muscle vascular resistance and systemic vascular resistance indicates that vasodilation in other vascular beds is the primary site of action, perhaps as an early adaptation to accommodate plasma volume expansion. Regardless, the lack of increase in skeletal muscle resistance concurrent with a marked increase in MSNA demonstrates a blunting of sympathetic vascular transduction. Jarvis et al[15] quantified this finding by normalizing measures of forearm vascular resistance to either MSNA burst frequency or total MSNA. In both cases, basal neurovascular transduction was reduced in early pregnancy relative to prepregnancy values.[15] A reduction in basal neurovascular transduction has also been observed by our laboratory in the second[35] and third trimesters of pregnancy.[35,37] Thus, normotensive pregnancy seems to be associated with lower sympathetic vascular transduction compared with the nonpregnant state.

The study of nonpregnant populations has shown that neurovascular transduction is affected by menopause[51] and phases of hormonal contraceptive use,[52] indicating that sex hormones may exert an influence over neurovascular transduction. Among the myriad hormonal changes that occur during pregnancy are large increases in sex hormones estradiol and progesterone, and modest increases in testosterone,[53] each of which has been hypothesized to affect sympathetic neurovascular regulation. Thus, it may be that the sex hormones account for some of the decreased in neurovascular transduction during pregnancy. Indeed, the vasodilatory properties of estradiol are well documented and have been described in several reviews.[54]

Potential Mechanisms Associated With an Increase in MSNA During Pregnancy

Sex Hormones

Several research groups have attempted to determine the underlying mechanisms associated with an increase in MSNA during pregnancy. Changes in circulating hormone levels are thought to be primary contributors to the systemic vasodilation of pregnancy, given that peripheral vasodilation occurs before full placentation.[29] The vasodilatatory properties of estradiol have been hypothesized to contribute to a general vasodilation, which in turn manifests as a curvilinear adaptation in peripheral vascular resistance and arterial stiffness, such that both reach a nadir in second trimester during normotensive pregnancy. It has also been suggested that estradiol also plays a role in sympathetic activity modulation. Bilateral injection of estradiol into the insular cortex of male Sprague Dawley rats resulted in a significant increase in renal SNA.[55] However, a similar relationship has not yet been clearly demonstrated in human pregnancy. Although changes in estradiol early in pregnancy do not correlate with changes in MSNA,[15] we have observed in a longitudinal assessment of 2 pregnant women (before, during, and after pregnancy) that estradiol have a positive correlation with MSNA (r^2=0.93; P=0.01).[35] The relationship between progesterone and MSNA is also of interest. A positive association between progesterone and MSNA has been observed previously in a nonpregnant population, as measured across the regular menstrual cycle.[56] Jarvis et al[15] suggested an association between the increase in circulating progesterone and the magnitude of sympathoexcitation in early pregnancy (R=0.56; P=0.08). Our longitudinal data of 2 pregnant women also supported this association (r^2=0.81; P=0.03).[35] In addition, higher progesterone concentrations have been also associated with an attenuation of the baroreflex-mediated sympathoexcitatory response in virgin rats[57] and with blunting of the carotid vasomotor baroreflex gain in nonpregnant women.[58] This may be one mechanism contributing to the observed reduction in sympathetic baroreflex gain observed during pregnancy.[17] In nonpregnant women with polycystic ovary syndrome, chronic elevations in circulating testosterone levels seem to be correlated to the magnitude of sympathoexcitation[59]; this has led to the suggestion that an increase in testosterone levels during pregnancy could also contribute to the increase in MSNA activity during pregnancy.[60] This has not been studied directly, and our limited longitudinal data (n=2) do not suggest an association between testosterone levels and MSNA activity.[35] Therefore, to date there remains limited data supporting an influence of sex hormones on sympathetic control. Although nonpregnant and animal models have demonstrated a clearer relationship between sex hormones and MSNA, larger longitudinal assessments are required to determine the extent to which pregnancy-induced sympathoexcitation is attributable to changes in sex hormones.

Central Sympathetic Activation

An alteration in the excitatory and inhibitory inputs within central autonomic pathways may also contribute to changes in the regulation of sympathetic outflow in pregnancy. It has been demonstrated that acute inhibition of the paraventricular nucleus of the hypothalamus decreased lumbar SNA while acute inhibition of the arcuate nuclei decreased lumbar, renal, and splanchnic SNA to a greater extent in pregnant rats compared with nonpregnant rats.[61]

At brain stem level, it has been shown that increases in renal SNA in response to bilateral GABA (gamma-aminobutyric acid) receptor blockade in the rostral ventrolateral medulla were greater in near-term pregnant Sprague Dawley rats compared with nonpregnant rats. In addition, the authors found that there was a transient increase in renal SNA after the blocking of the angiotensin receptors in the rostral ventrolateral medulla, which was greater in pregnant rats compared with nonpregnant rats. This supports the concept that there is a greater central sympathetic drive during pregnancy localized within the rostral ventrolateral medulla or other innervating structures.[62]

Modulation of sympathetic activity during pregnancy could also be altered by different hormones within the hypothalamus and brain stem areas responsible for sympathetic tone. Certainly, relaxin is known to increase vasopressin secretion contributing to plasma volume expansion during pregnancy.[63] Recently, it was shown that exogenous relaxin increased lumbar sympathetic activity in nonpregnant Sprague Dawley rats but not in pregnant Sprague Dawley rats.[64] Authors proposed that the relaxin receptors in the subfornical organ from pregnant rats could have become desensitized as a result of long-term exposure to increased relaxin during pregnancy.[64] Other circulating factors, such as leptin[65,66] and insulin, have been shown to increase SNA in nonpregnant rats by increasing melanocyte-stimulating hormone and glutamatergic of the paraventricular nucleus [66] and in the case of insulin by suppressing tonic paraventricular nucleus neuropeptide Y inhibition in the arcuate nuclei.[67] Interestingly, these factors are associated with pregnancy-related complications, such as preeclampsia.[68] Their role during pregnancy, however, has not been specifically assessed. There is an increasing body of evidence suggesting that hormones implicated in blood volume regulation may also play a role in increased MSNA activity during pregnancy. It has been established that in male rats, intracerebral infusion of aldosterone is associated with an increase in sympathetic outflow.[69] In early pregnancy, an increase in MSNA was positively correlated with aldosterone concentrations.[15] Moreover, Reyes et al[35] in a longitudinal case series report found that changes in vasopressin and aldosterone were strongly correlated with changes in MSNA during human pregnancy. Furthermore, compared with nonpregnant rats, there is a downregulation of the protein expression and activity of neuronal nitric oxide synthase in the hypothalamus in near-term pregnant rats. A decrease in nitric oxide concentrations in the paraventricular nucleus could be associated with a decreased nitric oxide inhibition of vasopressin neurons leading to normal/augmented vasopressin levels in pregnant rats and increased MSNA.[70] Interestingly, Charkoudian et al[36] recently demonstrated that vasopressin is associated with the biological variability in MSNA in pregnant but not in nonpregnant healthy women. These data suggest that during pregnancy, a complex mechanism underlying central sympathetic activation could be responsible for the parallel increases in MSNA and changes in plasma volume regulation.

Currently, the brain stem centers associated with the observed blunting of sympathetic baroreflex gain in normotensive pregnancy have not been identified. Nor have potential alterations in central neural control during hypertensive pregnancies.

Response of the Autonomic Nervous System During Stress

Just as important as basal neurovascular function is the responsiveness of the sympathetic and vascular systems to stress. To date, few studies have investigated whether reflex sympathetic regulation is affected over the course of pregnancy. The sum of evidence available in this area suggests that reflex control of MSNA is maintained during normal pregnancy but can be affected by the onset of GH or preeclampsia.

Baroreceptor Control of MSNA

The baroreflex is an important mechanism regulating arterial blood pressure. The discrepancy between increased MSNA and decreased blood pressure during pregnancy suggests that there is a reduced contribution of the autonomic nervous system to blood pressure regulation during pregnancy. Indeed, animal studies have demonstrated that during pregnancy there is a suppression of baroreflex function, characterized by either (1) an attenuation of the set point of mean arterial pressure[71]; (2) an attenuation of the maximal level of heart rate achieved when arterial pressure is lowered[72]; or (3) an attenuation of the gain of the cardiovagal and sympathetic baroreflex.[73,74] In humans, it has been shown commonly (but not universally[16,17,75]) that there is an attenuation of cardiovagal baroreflex gain during pregnancy[13,76–78] and specifically in the third trimester relative to nonpregnant women.[13] Using beat-to-beat blood pressure and MSNA signals, our laboratory recently showed that pregnant women during their third trimester also have a decreased sympathetic baroreflex gain relative to nonpregnant women.[17] This is consistent with work performed in animal models.[74] However, there is likely some variation in the adaptation of the sympathetic baroreflex with gestation. A recent longitudinal case study indicated that sympathetic baroreflex gain was enhanced throughout a normotensive pregnancy[16] while Reyes et al[35] found the opposite. Therefore, although there remains some controversy between studies, it seems as though normal healthy pregnancy is associated with a reduction in sympathetic baroreflex gain and either no change or a reduction in cardiovagal baroreflex gain. This may be due in part to differing methodologies used across studies.

Sympathetic activation induced through maneuvers designed to unload the baroreceptors (head-up tilting[18]; Valsalva maneuver) has been elicited in normotensive pregnant women in both the first[15] and third trimesters.[11] In contrast to other forms of analysis, head-up tilting was associated with similar increases in MSNA burst frequency, incidence, and total MSNA in the first,[15,18] second, and third trimesters.[18] Likewise, execution of Valsalva's maneuver caused a similar increase in MSNA burst frequency between the third trimester of pregnancy and nonpregnant normotensive controls.[11] Together these data indicate that the baroreceptor-related range of sympathetic outflow during acute hypotensive or hypertensive maneuvers may be unaffected by pregnancy. It is also important to note that these maneuvers act to unload/load both cardiopulmonary and arterial baroreceptors. It is unclear whether there may be a differential adaptation in cardiopulmonary versus arterial baroreceptors because of a significant blood volume expansion and increase in pre-load, concurrent with a decreased arterial resistance and decrease in pressure. The mechanisms leading to a reduced baroreflex gain during pregnancy are not clear. There is evidence that baroreceptor afferent signaling in response to changes in pressure may be depressed[79] or that brain stem centers associated with the baroreflex arc may be affected (see section above).

From a functional perspective, unloading of the baroreceptors through orthostatic stress has been associated with smaller increases in peripheral vasoconstriction in pregnant women relative to nonpregnant controls.[80] Within the context of similar reflex increases in MSNA during baroreceptor unloading, a smaller vasoconstrictor response is indicative of a reduction in sympathetic vascular transduction during pregnancy. This is important as Jarvis et al[15] also noted that prolonged head-up tilt was associated with the development of presyncope in early pregnancy more often than pre-pregnancy.

MSNA Responses to Cold Pressor Test

The cold pressor test, which involves the immersion of a limb (usually the hand) into ice water for a set period of time, evokes a large, nonspecific stress-mediated increase in MSNA.[81] It has been used extensively in pregnancy, and its safety is established in both healthy and complicated pregnancies.[11,37,82] Similar increases in integrated MSNA burst frequency responses (+12±4 versus +13±4 bursts/min, pregnant versus nonpregnant) and mean arterial pressure are observed between normotensive women in their third trimester of pregnancy and normotensive nonpregnant controls.[11] Whereas Usselman et al[37] found that pregnant women in their third trimester had greater increases in burst frequency and total MSNA relative to nonpregnant participants during a cold pressor test, with no changes in neurovascular transduction. Interestingly, basal neurovascular transduction in these pregnant women was reduced. These data highlight the evident dissociation between sympathetic activity and hemodynamic outcomes during pregnancy.

MSNA Responses to Isometric Exercise

Isometric exercise stretches or deforms the working skeletal muscle and tendons and increases metabolite production and accumulation (eg, H^+, lactate). This stimulates sympathetic control centers in the brain stem, leading to increased MSNA and vasoconstriction.[83] Concurrently, conscious effort activates brain stem centers that increase heart rate and in turn cardiac output. Thus, the blood pressure response to exercise is the product of increases in peripheral resistance (vasoconstriction) and cardiac output.[84] Although the MSNA response to isometric handgrip has been investigated in normotensive (and hypertensive, see section MSNA Responses to Isometric Exercise) pregnant women, this study did not include a nonpregnant control group.[12] Thus, it remains unknown whether pregnancy augments the responsiveness to exercise. However, in healthy pregnant women, cardiovascular responses to isometric contraction are similar to those of nonpregnant women.[85,86]

SNA and Reactivity in Pregnancies Complicated With GH or Preeclampsia

In 1996, Schobel et al[11] performed the first study to compare sympathetic outflow between normotensive nonpregnant, normotensive pregnant, and women with preeclampsia. The authors observed that preeclampsia (33±3 bursts/min) was associated with elevated MSNA burst frequency compared with both healthy pregnancy (10±1 bursts/min) and the nonpregnant state (12±2 bursts/min).[11] However, it is interesting to note that the authors did not observe an increase in resting MSNA in normotensive pregnant women relative to nonpregnant women, in contrast to the body of literature outlined above. Subsequent to the Schobel et al[11] study, MSNA has been compared between preeclamptic and normotensive pregnancies in only one study, which corroborated a relative elevation in baseline sympathetic activity in women with preeclampsia.[14] Conversely, several studies have compared sympathetic activity between normotensive pregnant women and women with GH, observing elevated MSNA in women with GH.[12–14] The Figure 2 summarizes the SNA before and during pregnancy, and post-partum in normotensive pregnancies and pregnancies complicated by either GH or preeclampsia. The figure highlights the variability of the data when comparing women with GH and preeclampsia and women with normotensive pregnancies. It is likely that the endothelial damage generated by the multiple factors acting together in the developing of preeclampsia may predispose these women to other vascular dysfunction in addition to the hypertension noted in GH. Among the aforementioned studies, increases in MSNA in GH and preeclampsia range from 150% to 300% above nonpregnant levels. Concomitant with the requisite return to normal blood pressure which occurs in GH and preeclampsia during the postpartum period, MSNA is also reduced to levels similar to nonpregnant normotensive controls, as assessed at a minimum of 6 weeks post-partum.[12,13] Together, studies of integrated MSNA in normal pregnancy, GH, and preeclampsia indicate that pregnancy per se is associated with an increase in sympathetic outflow, such that sympathoexcitation relative to the prepregnant state is not specific to pregnancy-induced hypertensive disorders. The difference between normal and hypertensive pregnancies seems to be the magnitude of increase in sympathetic outflow, particularly during the third trimester of gestation. To date, only one study has made direct comparisons of SNA between women with GH and preeclampsia.[14] In this study, integrated MSNA burst incidence was not significantly different between women with GH (62±4 bursts/100 hb) and women with preeclampsia (51±7 bursts/100 hb; mean±SEM). However, the incidence of single unit sympathetic activity was significantly elevated in GH relative to preeclampsia (128±23 impulses/100 hb versus 62±11 impulses/100 hb; $P<0.01$). This large discrepancy in single unit firing patterns between GH and preeclampsia may be indicative of a different, central pathogenesis of sympathetic activity in GH versus preeclampsia.

Alterations in Neurotransmitter Release in GH and Preeclampsia

Elevated concentrations of both norepinephrine[87] and neuropeptide Y[88] have been observed in women with preeclampsia relative to normotensive pregnant women. However, despite the differences in baseline MSNA that exist between GH and normotensive pregnancy, similar concentrations of circulating norepinephrine have been observed.[89] Acknowledging the limitations in interpreting norepinephrine data as outlined above, these data emphasize the importance of considering neurotransmitter and vascular outcomes of sympathetic outflow

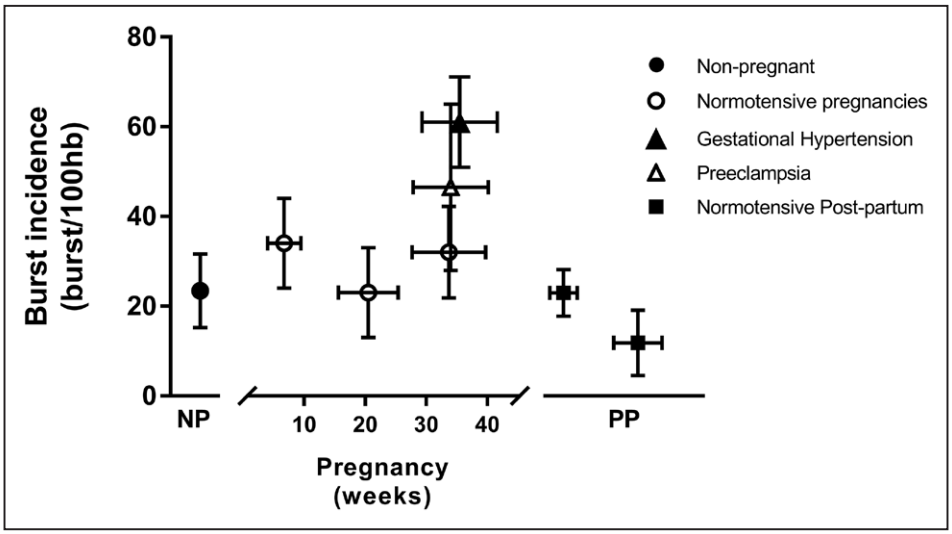

Figure 2. Summary data demonstrating sympathetic nervous system activity (SNA; burst incidence) at rest before, during, and after normotensive and hypertensive pregnancy. An increase in SNA during the first trimester of pregnancy compared with nonpregnant (NP) state is observed. During the second trimester of pregnancy, there seems to be a modest decline of SNA followed by a further increase in SNA during the third trimester. During post-partum (PP), there is a progressive decrease of SNA to NP values. Available data in women with gestational hypertension and preeclampsia suggest significant sympathetic hyperactivity. Presented data were extracted (from figures when necessary) and summarized from original articles. Data source: references [10–18, 35]. Closed circle: NP women (n=62). ○: women with normotensive pregnancies (first trimester n=12; second trimester n=23; third trimester n=109). ▲: women with gestational hypertension (n=42). Δ: women with preeclampsia (n=20). ■: women with normotensive pregnancies during PP (early postpartum [6–16 wk; n=15]; late postpartum [26 wk; n=22]). Data presented as weighted mean±weighted SD.

in concert with direct measures of MSNA obtained through microneurography to obtain a complete picture of sympathetic neurovascular regulation in pregnancy.

Neurovascular Transduction in GH and Preeclampsia

It has been suggested that preeclampsia/GH-related hypertension occur because of an inability of vasodilatory factors to sufficiently oppose the vasoconstrictive influence of elevated MSNA.[10] In normotensive pregnancy, the factors that induce vasodilation effectively counterbalance MSNA and even exceed the vasoconstrictory influence of MSNA to reduce neurovascular transduction.[15,89,90] These vasodilatory mechanisms so effectively counteract the vasoconstrictory influence of MSNA that mean arterial blood pressure is slightly reduced during pregnancy, rather than being maintained at nonpregnant levels.[13,15,29] Conversely, baseline calf vascular resistance is elevated relative to normotensive pregnant controls in GH[13,14] and preeclampsia.[14] Furthermore, women with GH exhibit augmented vascular resistance[89] and pressor responses[91] to norepinephrine infusion compared with normal pregnant women, and isolated vessels from women with preeclampsia may[92] or may not[93] exhibit an increased tension in response to norepinephrine exposure. Women who develop preeclampsia have consistently greater vascular stiffness throughout pregnancy.[94] Importantly, the peripheral vascular stiffening and resistance occurring during preeclampsia are greater than that observed with chronic hypertension, highlighting the severity of abrupt de novo vascular dysfunction in these women.[95,96] Aside from the documented increase in sympathetic neural outflow, which occurs in hypertensive pregnancies,[10–13] evidence exists to suggest that impaired endothelial-dependent vasodilatory capacity may also contribute to the increased vascular resistance observed in preeclampsia.[97,98] Direct comparisons in vascular resistance between GH and preeclampsia have shown that calf vascular resistance is similar between GH and preeclampsia.[14] Interestingly, single unit MSNA was higher in the women with GH in comparison with preeclampsia,[14] indicating that a relatively higher transduction of the sympathetic signal into vascular resistance may occur in preeclampsia relative to GH.

Response of the Autonomic Nervous System During Stress in GH and Preeclampsia

Laboratory stress tests are trustworthy diagnostic tools to elicit dysfunctional responses to identify populations at risk of hypertension.[99] Recently, Greaney et al[100] demonstrated that young normotensive women with a family history of hypertension have an exaggerated blood pressure and MSNA response in the cold pressor test compared with counterparts with no family history of hypertension. Thus, similar tests have been proposed to predict the development of pregnancy-related hypertension.[101] However, direct research investigating their use in pregnancy is limited.[101]

Baroreceptor Control of MSNA

Although information on the influence of GH on sympathetic responses to acute baroreceptor unloading is lacking, in women with preeclampsia, relative increases in MSNA in response to Valsalva's maneuver seem similar to normotensive women during the third trimester of pregnancy.[11] However, the prevailing hypertension and elevated basal sympathetic activity that characterize preeclampsia are at odds with one another and, as such, suggest baroreflex resetting. This is supported by an observed blunting of the sympathetic baroreflex in the reduced uterine perfusion pressure model of preeclampsia.[102] However, there are no data that specifically evaluate sympathetic baroreflex gain in human hypertensive pregnancies, an important area for understanding the regulation of blood pressure in these women.

MSNA Responses to Cold Pressor Test

The data accumulated thus far indicate that cold pressor test–mediated increases in MSNA burst characteristics[11,12] and single unit MSNA[12] are similar in women with GH or preeclampsia compared with normotensive pregnant women. However, an exaggerated increase in both diastolic and systolic blood pressures has been observed at 16 to 20 weeks' gestation in women who subsequently developed preeclampsia compared with normotensive pregnant women (diastolic blood pressure: 7.3±4.9 versus 3.9±4.7 mm Hg, P=0.03; systolic blood pressure: 14.2±5.5 versus 8.5±7.2 mm Hg, P=0.02).[82] Further research is needed to study the potential of the cold pressor test to identify underlying cardiovascular disease risk (aberrant sympathetic and vascular function) in otherwise healthy women as well as the potential mechanisms contributing to an augmented pressor response in those predisposed to hypertension during pregnancy.

MSNA Responses to Isometric Exercise

It is known that women with GH exhibit similar increases in MSNA in response to isometric hand-grip exercise as healthy pregnant women.[12] In women with preeclampsia, augmented blood pressure responses to isometric hand-grip[103] have also been observed relative to normotensive pregnant women, but it is not yet known whether this is because of an elevated sympathoexcitatory response, an elevated vasoconstrictory response, or both. In addition, a study in pregnant women (28–32 weeks gestation) found that isometric hand-grip held for 3 minutes had a sensitivity of 81% and specificity of 96.5% in identifying GH with assessment of diastolic blood pressure alone.[104] However, whether this same hypersensitivity exists before preeclampsia has not been determined, and the underlying mechanisms of this hyper-responsiveness have not been identified.

Perspectives and Future Directions

Understanding the mechanisms of blood pressure regulation during pregnancy is key to develop new diagnostic tools and therapeutic options to treat common pregnancy complications, such as GH and preeclampsia. Although the past 2 decades have marked a large increase in our knowledge about sympathetic regulation in normotensive pregnancy and hypertensive pregnancy disorders, there still remains much to elucidate (Figure 3). A discrepancy between the increase in SNA and a decrease in total peripheral resistance has been attributed to an increase in the vasodilatory mechanisms from both endothelium-dependent and independent pathways. We identify the following knowledge gaps that should be addressed. In doing so, this will offer the opportunity to develop better

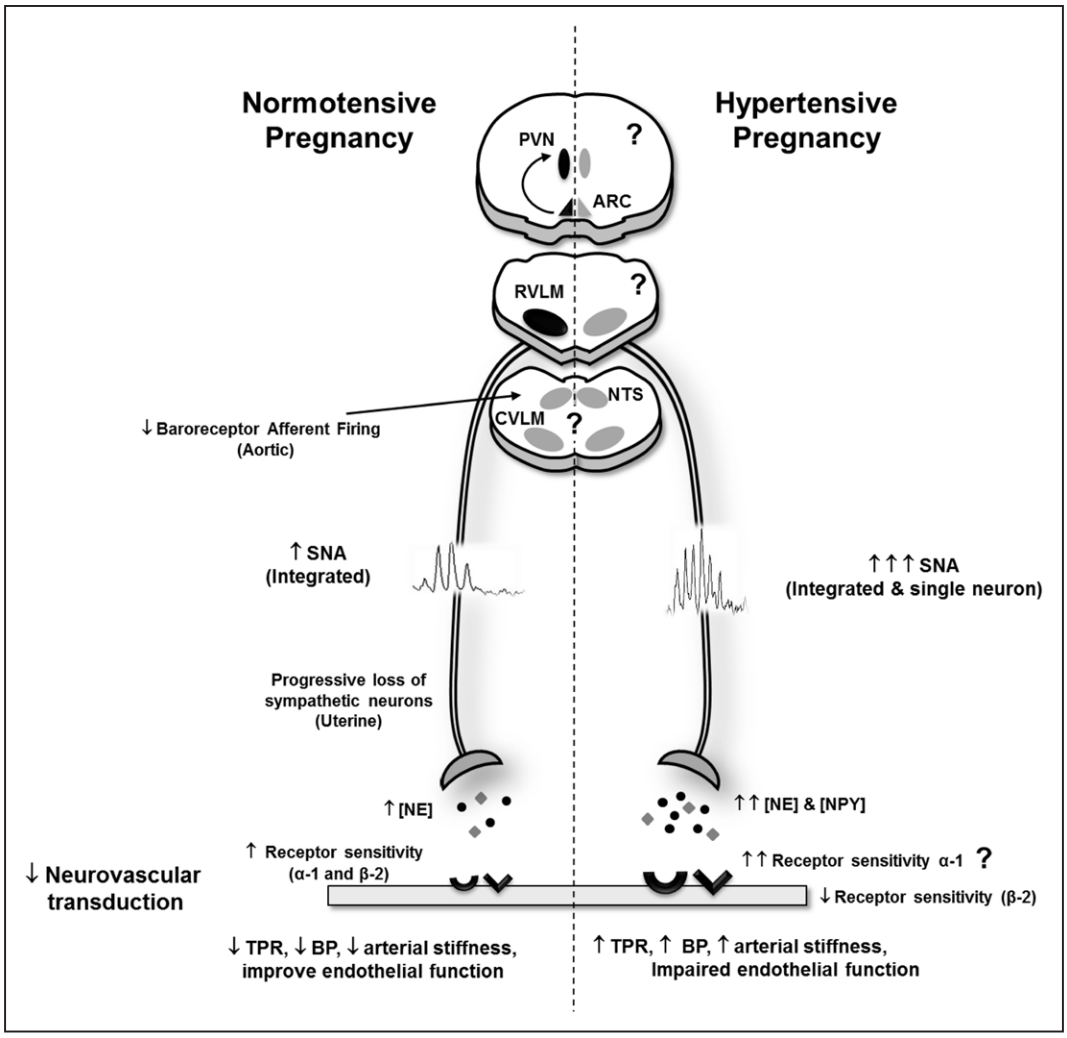

Figure 3. Schematic representation of the pathways involved in changes of autonomic nervous system activity during pregnancy. **Left**, Data represent the physiology of the autonomic nervous system during a normotensive pregnancy. **Right**, Data represent the physiology of the autonomic nervous system during a hypertensive pregnancy. Question marks indicate current knowledge gaps. The upwards arrows indicate an increase in the variable mentioned; while the downwards arrows indicate the opposite. The arrows in the normotensive panel represent a change compared with nonpregnant state. The arrows in the hypertensive panel represent a change compared with normotensive pregnancies. Pregnancy is associated with an increased paraventricular nucleus of the hypothalamus (PVN) activity secondary to an increased α-melanocyte–stimulating hormone activity from the arcuate nucleus (ARC) and a decreased inhibition of neuropeptide Y (NPY) neurons. Rostral ventrolateral medulla (RVLM) activity has also been demonstrated to be increased during pregnancy. The overall effect of these changes lead to an increase in basal muscle sympathetic nerve activity (MSNA) activity and an increase in norepinephrine (NE) concentrations. The neurovascular transduction of the MSNA signal is offset. There is evidence of a progressive loss of uterine sympathetic nerves (guinea pig), which could explain the decreased neurovascular transduction observed during pregnancy. It has been demonstrated that compared with normotensive pregnancies, there is a further increased MSNA in hypertensive pregnancies. There are no data available to demonstrate changes in the brain stem that could lead to an exaggerated MSNA activity during a hypertensive pregnancy. There has been demonstrated, however, that NE and NPY concentrations in women with preeclampsia are elevated compared with normotensive pregnant women. Data from brain stem and afferent inputs have been derived from animal studies and remain to be studied in human populations. BP indicates blood pressure; CVLM, caudal ventral lateral medulla; NTS, nucleus tractus solitarius; and SNA, sympathetic nervous activity.

understand pressure regulation during pregnancy and develop diagnostic tools and therapeutic options to women with GH and preeclampsia.

1. Alterations in the plasticity of the sympathetic nerves in the uterus[50] and the mesenteric vascular bed[105] in animal models have suggested (but not yet investigated) that there is a complex mechanism by which neurovascular transduction is altered differently during normotensive and hypertensive pregnancy. Thus, research that integrates SNA, vascular function, hemodynamics, and neurotransmitter release is needed.Basal MSNA is only one aspect of vascular control, and understanding neurovascular reactivity to various stressors is likely to be as or more relevant and important for understanding blood pressure control.
2. Increasing our knowledge in pregnancy vascular physiology relies on the implementation of longitudinal studies recruiting women at different times during gestation and controlling for different variables, such as age, weight, and ethnicity among others. Simply, there remains a significant lack of information on the influence of these factors in regulating neurovascular control in normal pregnancy, much less in pregnancy-related hypertensive disorders.

Conclusions

Taken together, baseline MSNA data collected during normotensive, human pregnancies support a pregnancy-induced sympathoexcitation,[10,12–14,17,18,36,37] which manifest early in gestation[15,16] but which seems to be offset by reduced transduction of the sympathetic signal into vascular outcomes.[12,13,15] This change in neurovascular transduction suggests a mechanism by which mean arterial pressure is reduced in normal pregnancy relative to pre- or nonpregnant controls. Likewise, disproportionate increases in baseline MSNA associated with GH[12–14] and preeclampsia[11,14] compared with normotensive pregnant and nonpregnant women likely contribute to the hypertension that is quintessential to the diseases, in conjunction with changes in neurovascular communication and vasodilatory function.[94,95,97]

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Disclosures

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