Role of Sympathovagal Imbalance in Gestational Hypertension: A Mini-Review

Kuzhanthaivelu Karthiga¹, Gopal Krushna Pal¹*, Subramaniyam Velkumary¹, Dasari Papa², Nivedita Nanda³

¹Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, INDIA.
²Department of Obstetrics and Gynaecology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, INDIA.
³Department of Biochemistry, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, INDIA.

*Correspondence
Dr. Gopal Krushna Pal
Senior Professor of Physiology, Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry-605 006, INDIA.
Phone: +91-9344291160
Email: drgkpal@gmail.com

ABSTRACT
Hypertension is one of the most common medical problem encountered in about 15% of pregnancies and it contributes to 12% of maternal morbidity and mortality especially in developing countries of south-east Asia. The Autonomic Nervous System (ANS) has a prominent role in the cardiovascular system adaptation to pregnancy. However, in gestational hypertension, sympathetic overactivity leads to intense vasoconstriction that results in hypertension. Current evidence suggests that sympathovagal imbalance is highly prevalent in women with Gestational Hypertension (GHT). The sympathovagal imbalance is a major cardiovascular risk in hypertensive disorders including the hypertensive disorders of pregnancy. Thus, sympathovagal imbalance is not only the physiological mechanism for genesis of hypertension in GHT, but also a major contributor to cardiovascular risk in GHT.

Key words: Gestational hypertension, Sympathovagal imbalance, Baroreflex sensitivity, Cardiovascular risks, Autonomic dysregulation.

GESTATIONAL HYPERTENSION:
Definition, Types, Disease Burden
Hypertension is one of the most common medical problem encountered in about 15% of pregnancies and it contributes to 12% of maternal morbidity and mortality especially in developing countries of south-east Asia. Gestational hypertension (GHT) is defined as a systolic BP of at least 140 mm Hg and/or a diastolic blood pressure of at least 90 mm Hg on at least two occasions at least 6 hr apart after the 20th week of gestation in women known to be normotensive before pregnancy. Hypertensive Disorders of Pregnancy (HDP) complicate 5% to 10% of pregnancies and are increasing the prevalence of cardiometabolic diseases in younger women. Normal pregnancy is marked by an initial drop in mean arterial pressure, with an eventual rise in Blood Pressure (BP) to pre-pregnancy levels. The development of HDP involves a number of factors that result in volume and hemodynamic alterations that fail to adapt to the changes accompanying pregnancy.

Classification and Epidemiology of HDP
The American College of Obstetricians and Gynecologists (ACOG) classifies 4 categories of HDP. In 2017, the American College of Cardiology and American Heart Association (ACC/AHA) issued a clinical practice guideline on hypertension that reclassified the previous category of prehypertension into elevated BP (systolic BP 120–129 mm Hg) and stage 1 hypertension (systolic BP 130–139 mm Hg or diastolic BP 80–89 mm Hg). The ACOG guidelines do not incorporate the most recent hypertension definitions and this is an area in which new evidences are essential. A recent re-examination of the high-risk aspirin trial data during pregnancy reported that the newly identified stage 1 hypertension in pregnancy was associated with increased risk of preeclampsia compared with normotensive women (39% versus 15%) and that randomization to aspirin reduced this risk (24% versus 39%).

Prevalence and Disease Risk Burden
There are well established associations between HDP and the development of maternal Cardiovascular Disease (CVD) later in life. Although the associations between preeclampsia and future CVD have long been known, newer evidence suggests that there are also long-term CVD risks associated with Gestational Hypertension (GHT), although the etiology of GHT is thought to be distinct from that of preeclampsia. Whether preeclampsia and GH result as manifestations of already preexisting CVD risk or whether they contribute to the pathogenesis of later CVD development is unclear.

PATHOPHYSIOLOGY OF GHT
Uteroplacental insufficiency and a susceptible maternal vascular and metabolic phenotype are the underlying etiology of gestational hypertension. It is well established, however, that the condition is heterogeneous, with multiple pathways leading to vasoconstriction and end-organ ischemia. Preeclampsia aggregates in families and new evidence suggests that fetal genetic variants near FLT1 (fms-related tyrosine kinase
1), a gene involved in angiogenesis, may contribute to risk. Precise causes of preeclampsia are still unknown, but the factors that contribute for preeclampsia includes impaired angiogenesis, systemic endothelial dysfunction, and decreased vascular compliance resulting in impaired accommodation of the volume expansion required for healthy gestation. Importantly, preeclampsia involves multisystem dysfunction. There is evidence of structural and functional cardiac impairments in women during pregnancies complicated by gestational hypertension. Cardiometabolic risk factors are also elevated during these pregnancies.

It is unclear if GHT has a different etiology from preeclampsia or whether is an early stage of a shared phenomenon. GHT and preeclampsia have similar risk factors, such as obesity, parity and history of preeclampsia in previous pregnancies. There are race disparities in the risk factors and prevalence of both GHT and preeclampsia, with black women carrying a higher burden of disease. The risk of adverse newborn outcomes is higher with preeclampsia when compared to GHT. In one study, the risk of preterm delivery was found in to be 7.2% in normotensive women, 12.5% in women with GHT and 39.2% in those with preeclampsia. Studies report that the level of inflammatory markers may be distinct in women with GHT compared with preeclampsia, with the possibility that women with GHT can compensate more successfully. In contrast, preeclampsia is more often associated with placental disease characterized by impaired markers of angiogenesis. Progression to chronic hypertension after delivery may help further elucidate whether GHT and preeclampsia have different etiologies. Specifically, 42% of women with preeclampsia and 39% of women with GHT progress to hypertension after mean follow-up of 2.5 years compared with rates as low as 1% among the women with normotensive pregnancies.

**SYMPATHOVAGAL IMBALANCE Concept and its Role in Hypertension**

The major pathophysiology of primary hypertension (HTN) is vasoconstriction induced by increased sympathetic tone. Pal et al. have reported that there is contribution of vagal withdrawal in addition to the sympathetic over activity in the genesis of HTN. Recently, sympathovagal imbalance (the autonomic dysfunction due to inequality between sympathetic and parasympathetic activities) has emerged as the main physiological support for the development of hypertension.

Emotional responses of the body and responses to the environment occur without conscious effort of the individual. These responses are called autonomic responses and are executed through the autonomic part of the nervous system, known as the Autonomic Nervous System (ANS). Through its innervation to all visceral organs, the ANS controls all major functions of the body, such as circulation, respiration, digestion, excretion, reproduction, immunity and metabolism. The ANS executes its functions through its two major subdivisions: the sympathetic and the parasympathetic systems. Broadly, the sympathetic system is involved in energy mobilization and utilization and the parasympathetic system in energy restoration and storage. Although these divisions of the ANS are physiologically opposite, they are reciprocal to each other in their outflow and functions. Normally, the body tries to maintain a balance between the storage and utilization of energy by balancing the parasympathetic and sympathetic activities. In a healthy individual, sympathetic and parasympathetic (vagal) systems are in dynamic balance, known as sympathovagal balance, which contributes to effective internal homeostasis.

As blood vessels of systemic vasculature are stimulated exclusively by sympathetic vasoconstrictor fibers, sympathetic overactivity was suggested to be the primary pathophysiological mechanism for essential HTN. Earlier it was documented that the initial phase of HTN is characterized by increased cardiac output and normal peripheral resistance, whereas in established HTN, cardiac output remains normal with increased peripheral vascular resistance. It was observed that in patients with chronic HTN, vascular resistance remains elevated even after a complete blockade of the ANS suggesting that vascular tone in established HTN is not dependent on autonomic tone for its maintenance. Also, it was observed that the level of plasma norepinephrine, the index of sympathetic activity that remains high in the early phase of HTN, normalizes in established HTN. These observations indicate the transformation from hyperkinetic circulation in early borderline HTN to a high vascular resistance in established HTN with the normalization of markers of enhanced sympathetic tone. However, the reports of recent studies reveals that the sympathetic drive remains elevated in established HTN. Thus, it appears that a decline in the hemodynamic response to sympathetic drive, not the decrease in sympathetic tone itself and also down-regulation of cardiac β-adrenergic receptors in response to sustained elevation in sympathetic tone normalize cardiac output in established HTN. The progressive increase in vascular resistance in established HTN is explained by Folkow’s theory, which explains that adaptive vascular hypertrophy of the resistance blood vessels with progressive thickening of smooth muscle of the tunica media results in an increase in the wall-lumen ratio in chronically elevated BP. The structural changes in the vessel wall in chronic HTN render blood vessels hyper-responsive to circulating endogenous vasoconstrictors, which amplifies the already existing increased vascular resistance. There are also reports that increase in sympathetic tone causes thickening of the vessel wall and increases the vascular reactivity. Thus, increased vascular resistance in HTN is a neural–vascular–humoral mechanism, in which autonomic modulation plays an important role in determining the vasomotor tone.

**SYMPATHOVAGAL IMBALANCE in GHT**

The Autonomic Nervous System (ANS) has a prominent role in the cardiovascular system adaptation to pregnancy. Normal pregnancy is associated with a decrease of parasympathetic and increase of sympathetic activity at rest and upon cardiovascular reflexes stimulation which returns to baseline after delivery. These changes maintain optimal uteroplacental blood flow. The factors that largely contribute to the development of hypertension are decreased size of the vascular compartment (vasoconstriction) and increase volume of the compartment (increased blood volume). However, in this dysfunction, hypertension develops in spite of low blood volume, which clearly indicates that the primary contributor to GHT is increased vasoconstriction induced by sympathetic over-reactivity. Recent reports from our laboratory confirmed that there is increase in sympathetic tone by spectral HRV analysis in the first trimester of pregnancy in women with high risks for GHT predicts the development of GHT in these women that clinically manifests in third trimester of pregnancy.

**Assessment of Autonomic Functions in GHT**

Heart Rate Variability (HRV) is a widely used non-invasive clinical tool that provides a valuable measure of sympathetic and parasympathetic function. The derived HRV indices are determined in two domains, time domain and frequency domain. The majority of HRV parameters indicate parasympathetic influences, while only low frequency (LF) power is influenced by the sympathetic nervous system. LF-HF ratio, the index of sympathovagal homeostasis represents the balance between sympathetic and parasympathetic activities of the individual at any given time in resting supine conditions. Lesser values of this ratio indicate there is more parasympathetic activity and greater values indicate sympathetic overactivity.

---


Karthiga, et al.: Sympathovagal Imbalance in Gestational Hypertension
The autonomic nervous system activity can also be evaluated by measuring the sensitivity of baroreceptors embedded in the carotid sinus and aortic arch walls. Baroreceptor reflex serves as “buffering” mechanism to control sudden fluctuations in blood pressure.

Another tool that provides an estimate of sympathetic activity is measuring plasma and urinary catecholamines in addition to other blood markers e.g., neuropeptide Y.[23] All biomarkers of sympathetic activity has the limitation of being affected by numerous confounding factors that can make interpretation difficult.[24]

CONCLUSION

Pregnancy Induced Hypertension (PIH) is currently referred to as Gestational Hypertension (GHT). PIH is a state of volume contraction (decreased ECF volume and blood volume). Generally, in a state of volume contraction blood pressure decreases, as ECF volume is a major contributor to cardiovascular risk in GHT. Therefore, lifestyle modifications especially practice of yoga may be encouraged to pregnant women with risk factors for pregnancy to ensure sympathetic vagal homeostasis, prevent the genesis of hypertension in pregnancy, as there are reports of attainment of sympathovagal balance by practice of yoga such slow pranayamas.[25] From diagnosis to therapy. Hypertension. 2016;67(6):1072-9.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ANS: Autonomic Nervous System; GHT: Gestational Hypertension; HDP: Hypertensive Disorders of Pregnancy; BP: Blood Pressure; ACOG: American College of Obstetricians and Gynecologists; ACC: American College of Cardiology; AHA: American Heart Association; CVD: Cardiovascular Disease; FLT1: fms-related tyrosine kinase 1; HRV: Heart Rate Variability; PIH: Pregnancy Induced Hypertension; LF: Low Frequency.

REFERENCES

34. Pal GK. Role of sympathovagal balance in achieving effective homeostasis.
Karthiga, et al.: Sympathovagal Imbalance in Gestational Hypertension


