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Vasomotor Center? A Possible Role in the Treatment of Hypertension

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Abstract

The global burden of hypertension and associated co-morbidities (cardiac failure, renal failure), is constantly rising despite the availability of newer drugs. Therefore, this study was planned to review the role of VMC (Vasomotor Center) in hypertension along with adding stress-relieving methods in lifestyle measures to prevent an epidemic of hypertension. For this purpose textbook of physiology, and various reference studies were used. The text-book of physiology suggests the location of VMC (Lower pons and medulla) and its functioning related to blood pressure regulation. It receives a signal from baroreceptors and produces either a decrease or an increase in blood pressure. The VMC is influenced by the cerebral cortex and hypothalamus. The pathophysiology suggests that possibly chronic stress, mental overwork disturbs the cortical influences to hypothalamus and shifts VMC to a higher level and that results in high basal sympathetic discharge and increased LV ejection force along with shifting of baroreceptors and renal mechanism to a new higher level which brings the blood pressure or whole body vasculature to the same high level resulting in hypertension. The repetition of the same process shifts BP even higher. The centrally acting drugs, mental rest, sound sleep and stress relieving methods like yoga, Vipassana, etc. may help to reduce cortical impulses and to bring VMC back to normal. VMC will automatically correct various BP control mechanisms and bring back BP to normal. Thus continuous efforts are needed to remove precipitating factors of hypertension. The methods to relieve stress and exhaustion must be employed in lifestyle for hypertension besides JNC guidelines.

Keywords: Vasomotor Center, Hypertension, Cardiac failure, Renal failure and Cardiovascular disease.

Abbreviations: VMC-Vasomotor Center, RAAS-Renin-Angiotensin-Aldosterone System, OSA-Obstructive Sleep Apnea, $LVEF_O$-LV-Ejection Force, EEG-Electroencephalography, ACE-Angiotensin-Converting Enzyme, ARB-Angiotensin II Receptor Blocker, CCBs-Calcium Channel Blockers, CKD-Chronic Kidney Disease, CVD-Cardiovascular Disease, ASCVD-Atherosclerotic Cardiovascular Disease, IHD-Ischemic Heart Disease.

Introduction

The global burden of essential hypertension and associated co-morbidities (cardiac failure, renal failure) is rising continuously [1]. Despite the availability of newer drugs for hypertension, the epidemic is not under control especially in developing countries [2,3]. Hypertension is a state of vascular system where the whole body vasculature is set at a particular level for a particular person [4]. BP>140/90 according to JNC7 is hypertension [5]. Lifestyle modification and the use of 2-4 antihypertensive agents are recommended at various stages of hypertension (JNC8) [6]. Despite triple-drug therapy, blood pressure control is only mild to moderate especially in the elderly [7]. This review emphasizes primarily the physiologic aspect of blood pressure control; possible role of VMC and its connections with the hypothalamus and cortex (indirectly) in the development of high blood pressure and secondarily role of adding stress-relieving (stress and mental exhaustion) methods in lifestyle measures to prevent an epidemic of hypertension [8-10].

Review of Literature

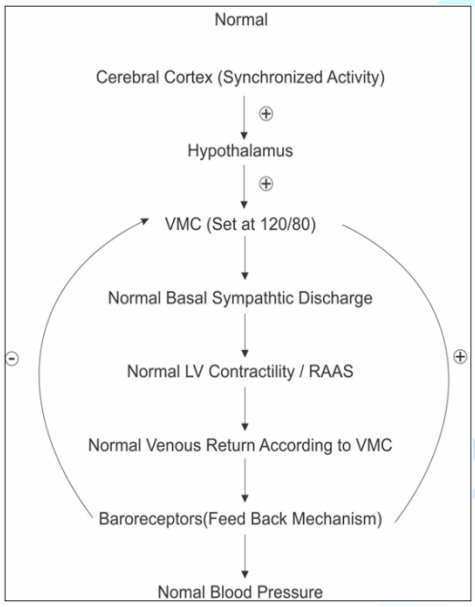
Textbook of physiology and various reference studies have been reviewed [8-35]. We will discuss the review in the following sections.

Physiology of Blood Pressure Control-Role of Vasomotor Center

The vasomotor center is located bilaterally in the reticular substance of the medulla and lower third of pons. This center has a vasoconstrictor area that sends sympathetic impulses to reach via the spinal cord to arterioles, arteries and virtually all organs. A vasodilator area sends an impulse via vagus nerve is less predominant and a sensory area, nucleus of tractus solitaries which receives signals from baroreceptors and send it to vasoconstrictor or vasodilator area. Under normal conditions, the vasoconstrictor area transmits signals continuously to the sympathetic nerve fibers releasing a small amount of noradrenaline at nerve endings maintaining basal sympathetic tone. This vasomotor center sets blood pressure at a particular level.

This message is conveyed to each vessel and heart via sympathetic discharge. The vasomotor center is influenced by many parts of the cerebral cortex has an excitatory or inhibitory effect on the vasomotor center. Stimulation of anterior temporal lobe, the orbital areas of the frontal cortex, and the anterior part of the cingulate gyrus, the amygdala, the septum, and the hippocampus can excite or inhibit the vasomotor center. The hypothalamus exerts a powerful excitatory or inhibitory effect on the vasomotor center.

Thus it plays an important role in controlling the vasoconstrictor system. The basal sympathetic tone decides the cardiac contractility, arteriolar resistance in resting state. For example, at blood pressure 120/80 mm Hg the VMC is set at 120/80 whole body vasculature and cardiac contractility is maintained at that level to produce B.P. at this level. The RAAS (RAAS-Renin Angiotensin Aldosterone System) also is set accordingly. VMC has a dual relationship in maintaining blood pressure, on one hand, it has self-tone influenced by the hypothalamus and various cortical areas, on the other hand, it is connected to baroreceptors and adjusts blood pressure according to their signals **(Flow chart 1)** [4,8].



Flow chart 1: Normal physiology-Normal Blood Pressure.

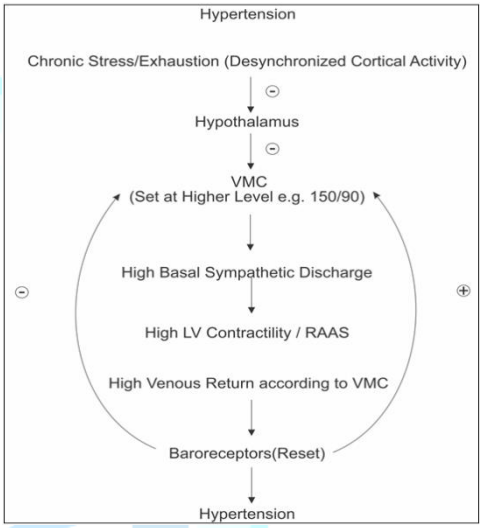
Pathophysiology of High Blood Pressure

The pathophysiology of hypertension is still not clear. Various mechanisms including sympathetic nervous system over activity genetics, excess salt intake and pressure natriuresis, obesity, OSA (Obstructive Sleep Apnea), insulin resistance, nitric oxide pathway, and hypertension and its association with increased basal sympathetic discharge-cortical connections have been mentioned [9,11-19]. The maximum association of essential hypertension is found with sympathetic over activity directly or indirectly involved in different mechanisms of hypertension including OSA, insulin resistance, obesity, endothelial dysfunction RAAS etc. [20-23]. It is the increased basal sympathetic discharge and not overt discharge. Overt discharge is mainly present in white coat hypertension.

At the beginning (normotensive state), there is an elevation in basal sympathetic discharge which increases LV Ejection Force ($LVEF_O$) shifts blood pressure from normotensive to stage 1 and then to stage 2 and further shifts from one value to further higher values into stage 2 [24]. There is a resetting of the whole body system including cardiac output according to that new blood pressure level. Though sympathetic discharge may come down to normal after shifting, now the whole-body system, all receptors are set to a newer level so even if sympathetic activity comes back to normal, B.P. does not return to normal. There is a certain adaptation of the baroreceptor and renal mechanism to a newer level.

Reasons for Elevated Basal Sympathetic Discharge

It is clear from previous studies that this discharge is central in origin. How basal rhythm is disturbed? Possibly persistent-stress, mental overwork, fast mental speed disturbs cortical influences (desynchronization; associated with low voltage fast Beta activity in Electroencephalography-EEG) to hypothalamus and shifts VMC to a higher level (possible resetting of VMC) and therefore basal discharge increases. So there are two situations one if blood pressure is high VMC tries to bring back to normal (normal physiology) two is that if VMC is set at a higher level it will give more basal sympathetic discharge and bring the blood pressure or whole body vasculature to the same higher level of VMC **(Flow chart 2)** [8,9,24].



Flow chart 2: Hypertension? Shift of VMC.

Consequences of Resetting of VMC at Different Levels

Once VMC is set at a particular level blood pressure is set at that level, to achieve blood pressure at that level cardiac contractility, stroke volume, venous return, Renin-Angiotensin level, vascular tone, etc. are set accordingly. For example, systolic blood pressure 120 mmHg has lesser values for all these parameters as compared to 140 mmHg systolic blood pressure and further less if blood pressure is 160 mmHg. One may find high LV (Left Ventricular) contractility (ejection force)/$LVEF_O$, high renin levels at a high blood pressure level. So the whole body system operates according to the VMC level.

Conclusion (Pathophysiology)

For the development of hypertension, there is a possible resetting of VMC at a higher level. Starting from cortical impulses to the hypothalamus there is a shift of VMC at a higher level followed by high basal sympathetic discharge and increased LV ejection force there is shifting of baroreceptors and renal mechanism to a new higher level along with BP. Repetition of the same process shifts BP even higher.

Available Antihypertensive Treatment

(Joint National Committee) JNC 7: According to JNC 7 guidelines for Hypertension, two or more antihypertensive drugs will be required to control hypertension to goal in most patients i.e. to under 140/90 mm of Hg, or less than 130/80 mm of Hg for patients with diabetes or chronic kidney disease. It was suggested that a blood pressure goal of less than 140/90 mm Hg, lifestyle modification, and polytherapy, e.g. a thiazide diuretic for stage 1 hypertension (<160/100 mmHg) and

combination therapy with a thiazide diuretic and an Angiotensin-Converting Enzyme (ACE) inhibitor, Angiotensin II Receptor Blocker (ARB), or calcium channel blocker for stage 2 hypertension (≥ 160/100 mmHg) [5].

JNC 8-Lifestyle Changes: According to JNC 8-various lifestyle changes have been suggested including cessation of smoking, control of blood glucose and lipids, healthy diet, moderate alcohol consumption, reduced sodium intake, that is, less than 2400 mg per day and, moderate to vigorous physical activity 3-4 times a week. Drug Therapy in JNC 8-First-line drugs for Hypertension is Thiazide diuretics, ACE inhibitors, ARBs and Calcium Channel Blockers (CCBs). Beta-blockers are no longer considered as first-line drugs. ACE inhibitors/ARBs are the first choice drugs in patients with Chronic Kidney Disease (CKD) irrespective of ethnic backgrounds. For African descent patients without CKD, calcium channel blockers or thiazides are preferred. The goal for all patients<60 years, BP should be<140/90 mmHg, irrespective of presence or absence of diabetes DM (Diabetes Mellitus) or CKD. The goal for the elderly>60 years without CKD or DM or both, BP is targeted at<150/90 mm/Hg. The goal for elderly>60 years with CKD or DM or both, BP is targeted at<140/90 mmHg.

ACC 2017 Guidelines/Recommendations for Hypertension Management: According to American College of Cardiology (ACC) 2017 patients are categorized into normal (<120 mmHg SBP), elevated (120-129 mmHg SBP), stage-1 (130-139 mmHg SBP) and stage-2 (>140 mmHg SBP) hypertension. Detection of white coat hypertension and masked hypertension is required. Regular follow-up is also mandatory. Non pharmacologic intervention includes weight loss (at least 1 kg for overweight), Healthy diet (rich in fruits/vegetables/whole grains), reduced intake of dietary sodium (1000 mg reduction in a day) increase potassium intake, enhance physical activity (aerobic/dynamic resistance/isometric resistance) 3 sessions per week, moderate alcohol intake (men<2 drinks daily/women<1 drink daily). Oral antihypertensive therapy categorizes into three

- Primary agents-Thiazide type diuretics (Chlorthalidone, Hydrochlorthiazide)/ACE inhibitors (Ramipril, Lisinopril)/ARBs (Azilsartan, Candesartan)/CCB-dihydropyridine (Amlodipine, Nifedipine)/CCB-nondihydropyridine (Diltiazem).
- Secondary agents-loop diuretics (Torsemide), Potassium-sparing diuretics, Beta-blockers (cardioselective-atenolol, along with vasodilatory property Nebivolol), Renin inhibitors and alpha-1 blockers. Centrally Alpha2-agonists (Clonidine, Moxonidine) and other centrally acting drugs are reserve drugs as the last line due to side effects.
- CVD (Cardiovascular Disease) risk and hypertension goal-A) Clinical CVD or 10 year (Atherosclerotic Cardiovascular Disease) ASCVD risk>10% (BP goal<130/80), B) No clinical CVD or 10 year ASCVD risk<10% (BP goal<130/80) [25].

ESC 2018 Guidelines for Hypertension: It includes 10 point strategy to:
Define: (>140/90 mmHg office BP) and
Screen BP: (office and home readings)
Considering drug treatment of hypertension: Adults with Grade 1 hypertension (office BP 140-159/90-99) aged up 80 years, should receive drug treatment if their BP is not controlled after a period of lifestyle intervention alone. For high-risk patients with Grade 1 hypertension, or patients with higher grades of hypertension (e.g., Grade 2 hypertension; ≥ 160/100 mmHg), drug treatment should be initiated alongside lifestyle interventions.

Special considerations in older patients: For people over the age of 80 years, who have not yet received treatment for their BP, BP treatment should be considered when office systolic BP is ≥ 160 mmHg.
How low should BP is lowered? 'A target range' for treated BP has been introduced. Office systolic BP should be lowered to<140 mmHg in all treated patients, including independent older patients who can tolerate treatment. The aim should be to target systolic BP to 130 mmHg for most patients if tolerated.

Treatment of hypertension-lifestyle interventions is important: The treatment of hypertension involves lifestyle interventions and drug therapy. Lifestyle interventions such as sodium restriction, alcohol moderation, healthy eating, regular exercise, weight control, and smoking cessation are important.

Start treatment in most patients with two drugs, not one: Monotherapy is usually inadequate therapy for most people with hypertension Initial therapy with a combination of two drugs should now be considered usual care for hypertension.

A single pill strategy to treat hypertension: For better compliance single pill combination therapy is now the preferred strategy for initial two-drug combination.

A simplified drug treatment algorithm: A combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic is the preferred initial therapy for most patients. For those requiring three drugs, a combination of an ACE-inhibitor or ARB with a CCB and a thiazide/thiazide-like diuretic should be used. Beta blockers should be used when there is a specific indication for their use, e.g. angina, post myocardial infarction, heart failure with reduced ejection fraction, or when heart rate control is required.

Managing cardiovascular disease risk in hypertensive patients-going beyond BP: Hypertensive patients frequently have concomitant cardiovascular risk factors. Statin therapy should be more commonly used in hypertensive patients with established cardiovascular disease Benefit from statin therapy has also been observed in hypertensive patients at the border between low and moderate risk. Antiplatelet therapy, especially low dose aspirin is also indicated for secondary prevention in hypertensive patients but is not recommended for primary prevention, i.e. in patients without cardiovascular disease [26].

Mechanism of action of various drugs: These drugs reduce cardiac contractility, inhibit ACE activity, or promote diuresis. None of these drugs focuses upon restoring cortical-hypothalamic signals or bringing back VMC to a previous normotensive level. Centrally acting drugs are not the first line in any guidelines. Centrally acting antihypertensive drugs such as clonidine induce peripheral sympathoinhibition and a fall in blood pressure as a result of alpha-2 adrenergic receptor agonist action in the brain stem. Newer centrally acting drug Moxonidine in addition to alpha2 agonist has an affinity for imidazoline receptor subtype 1, which reduces sympathetic activity and blood pressure. It is suggested to be effective in cases where other agents such as thiazides, beta-blockers, ACE inhibitors, and calcium channel blockers are not appropriate or irresponsive [27].

Long term side effects of antihypertensive therapy: Beta-blockers can cause bronchoconstriction, reduced cardiac output, fatigue, heart block, dizziness, depression, bradycardia (decreased heartbeat and function), cold extremities, poor circulation in the hands and feet), claudication, etc. CCBs are associated with pedal edema, postural hypotension, headache, etc. Common side effects of ACE inhibitors/ARBs are cough and angioneurotic edema and diuretics are electrolyte imbalance and arrhythmia [28].

Results of Antihypertensive Treatment from a Few Previous Studies

Trends in Prevalence and Control of Hypertension, 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline: The age-standardized proportion of controlled hypertension among adults receiving antihypertensive pharmacologic treatment increased from 1999-2000 (25.6%) to 2015-2016 (43.5%). There was no consistent improvement in control throughout the full period among

non-Hispanic blacks, individuals aged>60, or those with diabetes mellitus, chronic kidney disease or high cardiovascular disease risk [7]. **The global burden of hypertension** analysis suggested that the number of adults with hypertension in 2025 was predicted to increase by 60%. Hypertension is an important public health challenge worldwide. Prevention detection, treatment, and control of this condition should receive high priority [29].

Low dose triple pill (TRIUMPH Trial) lowers blood pressure more than usual care triple therapy reduces blood pressure by 8.7 mmHg systolic v/s 4.5 for usual care [30].
In the United States, about 77.9 million (1 out of every 3) adults have high blood pressure, Data from NHANES 2007-2010 showed that of those with high blood pressure. 81.5 percent are aware they have high BP. 74.9 percent are under current treatment. 52.5 percent are under control and 47.5 percent are not under control [31,32].

Principal Results of the (JATOS trial) Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients-In this trial, the primary end point was the combined incidence of cardiovascular disease and renal failure, and the secondary endpoints were total deaths and any safety problems. Although final blood pressures (systolic/diastolic) were significantly lower in the strict-treatment group compared with the mild-treatment group (135.9/74.8 vs. 145.6/78.1 mmHg; p<0.001), the incidence of the primary endpoint was similar in the two groups (86 patients in each group; p=0.99). Total deaths were 54 in the strict-treatment group vs. 42 in the mild-treatment group (p=0.22), and treatment was withdrawn because of adverse events in 36 patients in each group (p=0.99). An interaction between age and treatment for the primary endpoints (p=0.03) was seen. Further studies are needed to assess the optimal treatment strategy for hypertension in the elderly. There was also no significant group difference in the secondary endpoints [33].

In clinical trials of patients with untreated hypertension and an average blood pressure of 155/100 mmHg, treatment with 5 mg/80 mg per day of Nebivolol/valsartan for four weeks resulted in an average reduction in systolic and diastolic blood pressures of 8.3 mmHg and 7.2 mmHg, respectively. Higher doses did not typically improve blood pressure control [34,35].

Conclusions of various studies:

- Inadequate blood pressure control (mild to moderate control with 3-4 drugs i.e. 8-10 mmHg in the long term in systolic blood pressure, especially in elderly
- No significant difference in endpoints
- Continuous rise in the incidence of hypertension along with other comorbidities like diabetes, Dyslipidaemia, IHD (Ischemic Heart Disease), etc.
- Trials recommend the need for further studies to assess the optimal treatment strategy for hypertension in the elderly.

Side effects of therapy: After observing these facts do we need some other measures in lifestyle management besides available measures? To achieve better smooth control over hypertension. Possibly at all stages of hypertension with or without drug treatment, it must be directed to stress-relieving methods that reduce cortical influences; this, in turn, will help VMC to back to normal again. VMC will automatically correct various BP control mechanisms and bring back BP to normal. Drugs are, the primary way to control blood pressure at individual levels, but to control a global epidemic of hypertension; the better way is to improve lifestyle measures by reducing stress and mental exhaustion at a community level. There should be a bigger role and further work upon centrally acting drugs.

How to Bring Back VMC-Reset Cortical-Hypothalamic Signals-Is it Possible?

No clear answer/prospective results are available. This possibly requires continuous reduction/removal in mental stress/exhaustion. All efforts (relaxation methods given below) must be employed to relieve stress and exhaustion in lifestyle for hypertension besides JNC suggestions.

For mental exhaustion (burn out) from early childhood; the following must be done-An adequate balance between mental work and mental rest, avoid excess use of the laptop, mobile, computers and television. Take good sound sleep for around 7 hours daily to rejuvenate neurotransmitters and reduce exhaustion. Practice mental relaxation/Vipassana which helps to replenish the neurotransmitters (Vipassana-state of complete mental silence i.e., no active writing, reading, no speaking), it must be quantitative more the mental exhaustion much the\duration of Vipassana. Spend some time in the garden to have tranquillity of mind. Practice sports/yogic exercises daily.

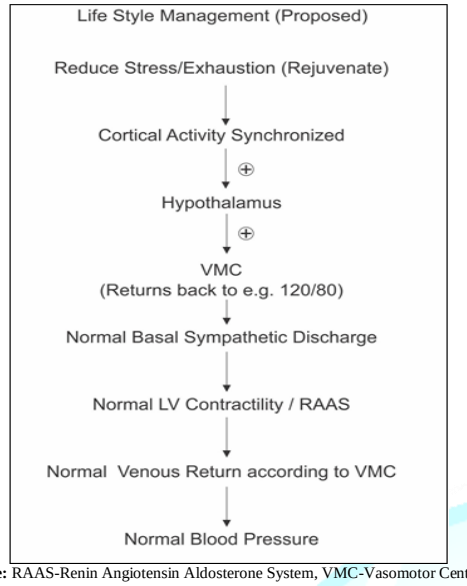
How relaxation techniques help-Relaxation (No active concentration) techniques, such as Shavasana, Makrasana, Vipassana (relaxation postures where body and mind are allowed to relax) and sound sleep relaxes the prefrontal network/lobe helps in replenishment of neurotransmitters and helps in the integration/control of the other parts of the brain. Fatigue of the prefrontal lobe/network increases distractibility by irrelevant stimuli there is a reduced attention span and increased sympathetic activity.
For chronic stress and fast mental speed following must be done Try to avoid hurriedness in completing work, avoid competitiveness, jealousy and high expectations in life. Practice meditation, spend some time in nature; it reduces stress and fast mental speed. Practice yogic exercises daily (Shavasana, Makrasana, few breathing exercises). Try to divert the mind from stress thoughts by listening to soft music, light sports, etc. Meditation is effective in reducing stress and fast mental speed.

How meditation acts-During meditation, the person is asked to keep his concentration/attention at particular point (mostly breath). The more the person can concentrate the less will he be disturbed by external/ internal stimuli? Attention/concentration is an important function of the prefrontal network (lobe) which acts as an integrator for other networks (lobes) and helps in keeping attention. Meditation possibly improves overall control of the prefrontal network (lobe) over other parts of the brain including the hypothalamus thereby reducing sympathetic discharge to various stimuli. All such above measures rejuvenate the brain and help in the replenishment of neurotransmitters, synchronize cortical-hypothalamic signals, decrease basal sympathetic discharge and help in the control of blood pressure **(Flow chart 3)** [10, 36-38].

Conclusions and Suggestions

High blood pressure is a state of vascular system where whole body vasculature is set at a higher level due to a higher setting of vasomotor center. This occurs due to desynchronized cortical-hypothalamic signals to the vasomotor center (stress, fast mental speed, and mental exhaustion). The outcome is increased basal sympathetic tone and hypertension. There is no substitute for a healthy lifestyle in preventing blood pressure mainly mental health (try to prevent to rise in sympathetic tone).

This can be achieved by the prevention of stress, mental exhaustion and fast mental speed in daily life. Stress relaxation methods/adequate mental rest at regular intervals may also help. Dietary/drug therapy aimed at the use of nutritional supplements providing choline (helps in synthesis of acetylcholine in brain prevents mental exhaustion) and various alternate substances (supposed to reduce stress) like Brahmi (Bacopa monnieri) Shankhpushpi (Convolvulus pluricaulis) can also be used. More work is required for centrally acting drugs to be included as a regular part of therapy for hypertension [36].



Note: RAAS-Renin Angiotensin Aldosterone System, VMC-Vasomotor Center.

Flow chart 3: Stress relaxation-VMC back to normal-Normal blood Pressure.

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