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Hypertension and Pregnancy

Siddharth N Shah

ABSTRACT

• Hypertensive disorders involve 15% of pregnancies and are increasing due to late pregnancies and excess weight, which makes it a public health problem.
• Chronic arterial hypertension increases the risk of preeclampsia, intra-uterine growth retardation and placental detachment.
• Prophylactic doses of aspirin must be envisaged from the first trimester of pregnancy in patients at risk.

INTRODUCTION

The theory of fetal programming has taught us that the occurrence of chronic and cardiovascular diseases at an adult age would already, in part, be determined and influenced by intra-uterine life. Placenta is considered as a simple anatomical waste. In the present-day context, once delivery is carried out, the placenta does not present any clinical significance and is only analysed in some cases (suspicion of infection, delay in growth...). However, on integrating the genetic and epigenetic factors, pre-existing maternal diseases and environmental factors, the placenta depicts changes via intra-uterine life, holding the potential of throwing light on certain pathogenic mechanisms. Far from being an inert organ, the placenta dynamically interacts with the mother and the fetus all through its growth. Emerging from the interactions and reciprocal influences between these three players, the materno-placento-fetal physiology is a complex process, and a determining one for the life of the future adult.

Arterial hypertension in women is one of the principal causes of morbidity and involves 15% of pregnant women. However, the risk scores and the strategies for cardiovascular risk reduction, used in clinical practice in adults, does not apply to young women who are in the procreating age. Hypertensive disorder in pregnancy shows signs of vascular disease and remodeling which entirely mimic atherosclerosis and which are similar to the

1Editor-in-Chief: Clinical Journal of Hypertension; Hon. Physician and Diabetologist, Bhatia Hospital, Saifee Hospital, S.L. Raheja Hospital, Mumbai; Executive Editor: JAPI
lesions observed in the coronaries and the great vessels. Being the first indicator of arterial damage due to hypertension, the study of placental vascularisation offers a survey of future vascular health of the woman and an opportunity for an early implementation of risk reduction measures.

It is estimated that hypertensive disorders complicate 15% of pregnancies. This number is expected to rise with pregnancies occurring at a later age and the observed increase in the BMI in the general population. Complicated pregnancies of chronic arterial hypertension are strained with an increased risk of preeclampsia, intrauterine growth retardation (IUGR) and placental detachment. Indeed, the rate of preeclampsia in hypertensive patients varies between 25-50%, according to the duration of progress of hypertension, personal history of preeclampsia in an earlier pregnancy and the presence of diastolic arterial hypertension between 100-110 mmHg. The risk of low birth weight is more than double and perinatal mortality is three to four times greater than that of the general population.

The risk of placental detachment is also doubled in case of chronic arterial hypertension, and this association is much stronger in case of preeclampsia added on to a concomitant IUGR. These three conditions are linked to a placental ischemic disease, which makes one suppose a common pathophysiological mechanism in association with an abnormality of placental vascularisation and exacerbated in case of chronic arterial hypertension.

During its nine months of intra-uterine life, the fetus depends entirely on the placenta for its development and its protection. This transitory organ has an extraordinary capacity of assuming the function of several organs, whilst ensuring the transport of respiratory gases and nutrients, the elimination of metabolic waste, the synthesis of growth and pregnancy hormones, which guarantee immune interactions between the mother and the fetus. Thus, a healthy and functional vascularisation is essential to fetal growth and to a good progress of the pregnancy.

In its normal development, the placenta puts into place a uteroplacental circulation which comprises a maternal circulation and a fetal circulation (Figure 1). The two blood networks develop in parallel, without however ever coming into contact. A part of the embryonic tissue, called the trophoblast and initially made up of cytotrophoblast and syncytiotrophoblast, is responsible for the process of implantation in the endometrium and the development of the placenta. The cells of the trophoblast are organised in placental villosities with the fetal capillary network in their center. On the maternal side, the spiral arteries, emerging from uterine circulation, are subjected to lysis activity of the syncytiotrophoblast, and are transformed into lacunae of maternal blood which flows between these villosities, the inter-villous space.

In this encounter, a fundamental stage of development of placental vascularisation consists of the migration of a sub-population of cells of the trophoblast in the endometrium, leading to an essential physiological remodeling of the spiral arteries. The latter will lose their smooth muscle bed which will be replaced by
fibrous tissue. This significant modification releases the arteries of their tonus control through neuro-hormonal mediators, which enable an increase in the blood flow towards the placenta and configures it as an organ with low resistance. The abnormal invasion of the trophoblast and the incomplete remodeling of the spiral arteries are partly at the origin of placental dysfunctions and abnormalities of fetal development (Figure 2).9

Chronic arterial hypertension is traditionally a silent disease, whose first signs of attack of the organ are sometimes only detectable after several years of progression. However, some abnormalities of utero-placental circulation are already evident in hypertensive patients within a few weeks of pregnancy itself. Investigation of the uterine arteries by Doppler enables the detection of the first signs of vascular insufficiency, by revealing a raised resistance index or protodiastolic incisures (notch). The isolated presence of a uterine notch in the second trimester is difficult to interpret, since it can occur in a physiological situation or disappear in the third trimester. The predictive value of the parameters of the uterine Doppler combined with other markers, have especially been studied in the preeclampsia. Particularly in the case of chronic arterial hypertension, the anomalies of uterine Doppler in the second trimester in hypertensive patients are often associated with the augmentation of preeclampsia, IUGR, low birth weight. This requires a close clinical and echographic follow-up throughout the pregnancy.

On macroscopic examination of placenta, signs of circulatory insufficiency could already be present in the form of a hypotrophic placenta, placental infarction and placental detachment. On histological examination, maternal vasculopathy as well as ischemic and inflammatory modifications of the placenta have been described. Among the lesions observed, one could count an incomplete remodeling of the spiral arteries, with retention of the muscular bed, and acute atherosis, a fibrinoid necrosis, placental infarction and a chronic villitis of indeterminate origin.

**Acute atherosclerosis and lack of remodeling of spiral arteries**

Acute atherosis, described in spiral arteries of hypertensive pregnancies, makes a reference to its similarity with the first stages of development of atherosclerotic lesions observed in the coronary arteries and other big vessels. Acute atherosis is characterised by the sub-endothelial accumulation of lipid-laden spumous cells, a fibrinoid vascular necrosis and a perivascular lymphocytic infiltrate. In good preeclampsia studies, the presence of acute placental atherosis has been described in the case of chronic arterial hypertension, disseminated erythematous lupus, antiphospholipids antibody syndrome, diabetes, IUGR and even in normal pregnancy.
The causes and consequences of acute atherosis of the placenta are not well known. They could be the reflection of an increased inflammatory state, found in all the above-mentioned diseases, and a disturbed lipid metabolism. These acute atheromatous changes induce a narrowing of the arterial lumen, and facilitate vascular occlusion, thrombi, thus reducing the blood flow and contributing to placental dysfunction and to delayed growth of the fetus. The incomplete remodeling of the maternal spiral arteries are not however limited to acute atherosis. Arteries have too much of vasoreactivity, due to the retention of smooth musculature, leading to lesion of the hypoxia-reoxygenation type and could be responsible for oxidative stress. A high speed maternal blood flow disturbs the network of fetal villosities and thus contributes to thrombotic events and accumulation of fibrin.

The preliminary results of a Netherlands cohort study concerning the correlation between placental vascular abnormalities and post-partum maternal cardiovascular risk markers were published this year. Considering the glycemic and lipid profiles which were carried out on the first day after-delivery in patients with preeclampsia or IUGR, and comparing them with normal pregnancies, the authors suggest an association between higher levels of triglycerides and LDL cholesterol and the presence of acute placental lesions of atherosis. The future work announced by this team will consolidate this first observation.

PREVENTION AND PERSPECTIVES

At the present moment, the prevention of obstetrical complications linked to chronic arterial hypertension rests on the administration of prophylactic doses of aspirin from the first trimester. Nevertheless, in the absence of strong evidence, the American College of Obstetricians and Gynecologists remains cautious and suggests that aspirin be reserved for hypertensive patients with high risk of obstetrical complications (women with a history of early preeclampsia, prematurity or having presented with more than one episode of preeclampsia). The association between the abnormalities of placental vascularisation and future vascular health of the mother and child and the establishment of a cardiovascular risk score taking into consideration the histological aspects seems promising, in order to target women who could benefit from strategies for risk reduction, specially for a subsequent pregnancy.

CONCLUSION

Chronic arterial hypertension could affect the physiological development of utero-placental circulation and is associated with an increased risk of ischemic placental diseases. Placental pathology enables the detection of atheromatous changes in arterial vascularisation whose clinical significance ought to be specified. As in any other target organ of hypertension, pregnancy should have its place in the decision on a preventive strategy.

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7. Burton GJ, Fowden AL. The placenta: A multifaceted


ABSTRACT

Background: Coronary artery disease remains the dominating cause of death in the world. Despite understanding & controlling the known risk factors for coronary artery disease, it remains the worldwide epidemic. This raises the possibility of the presence of unknown or underestimated risk factors. The role of uric acid as a prognostic factor in patients with acute coronary syndrome is controversial. The aim of the present study is to estimate serum uric acid levels in acute coronary syndrome and its correlation with Killip’s classification of heart failure & in hospital mortality.

Methods: A total of 100 patients with acute coronary syndrome meeting the inclusion and exclusion criteria, with an equal number of age and sex matched controls were selected for study during the period 1st July 2016 - 30th June 2017. Serum uric acid level was estimated on day 0 and 7 of acute coronary syndrome.

Results and observations: A statistically significant higher level of serum uric acid concentration in patients of acute coronary syndrome (5.80±1.53) was observed on the day of admission as compared to controls (3.8±0.85). There was no statistically significant difference observed in relation with diabetes and hypertensive status and gender. Higher serum uric acid (>7mg/dl) level along with higher Killip’s class (III, IV) was associated with higher mortality and major adverse cardiac events.

Conclusion: Patients with elevated serum uric acid levels belonged to higher Killip’s classification and were associated with higher in hospital mortality. Hence serum uric acid can be used as a short term prognostic marker in patients with acute coronary syndrome.

INTRODUCTION

Cardiovascular disease is responsible for 30% of all deaths in the world. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years. About 80% of the global burden of cardiovascular
disease occurs in low and middle income countries. In India cardiovascular diseases (CVD) have become the leading cause of mortality.¹ CVD affects Indians at least a decade earlier and in their most productive midlife years when compared to the people of European ancestry. India carries a significant portion of this global burden. In addition, case fatality attributable to CVD in low-income countries, including India, and appears to be much higher than in middle and high income countries.² Reasons for the high propensity to develop CVD, the high case fatality, and the high premature mortality include biological mechanisms, social determinants, and their interactions.³

Until now various bio-markers have been studied in patients of acute coronary syndrome (ACS). However, no single marker gives definite prognostic information during the course of the disease. While there is no doubt that multiple factors play different roles in the development of acute coronary syndrome, recent studies have revealed the potential role of hyperuricemia as a novel prognostic marker. Uric acid is the final product of purine metabolism in humans, and its level is determined by dietary intake, rate of cell turn-over in the body, and renal excretion. Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular pH and negative membrane potential.⁴ Under ischemic conditions the activity of xanthine oxidase and uric acid synthesis are increased in vivo, and therefore we can consider elevated serum uric acid as a marker of underlying tissue ischaemia.⁵ Epidemiological studies have recently shown that uric acid may be a risk factor for cardiovascular diseases and a negative prognostic marker for mortality in subjects with heart failure and coronary artery disease.

The aim of the present study was to note levels of serum uric acid in acute coronary syndrome, to correlate serum uric acid levels with Killip class and to observe any relationship between serum uric acid level and mortality following acute coronary syndrome.

**MATERIALS AND MEHODS**

The present study was a single centered observational prospective study conducted from July 2016 to June 2017 for a period of one year in the Department of General Medicine at Silchar Medical College & Hospital, Silchar. A total of 100 patients with acute coronary syndrome meeting the inclusion and exclusion criteria, with an equal number of age and sex matched controls were selected for the study. All patients who were of age greater than 18 years and diagnosed as ACS with at least 2 of the following criteria: a) Presence of typical symptoms like chest pain, palpitation etc on admission b) ECG changes consistent with acute MI in at least 2 contiguous leads c) Elevation of the cardiac enzymes (Troponin T & I, CK-MB) were considered for study. All the patients diagnosed with ACS presented within 12 hours. All acute STEMI patients who presented within 12 hours of onset, and were eligible for fibrinolytic therapy received fibrinolytic therapy using intravenous streptokinase with the dose of 1.5 million units, and given over 30 to 60 minutes. Patients diagnosed with gout and with other recognized risk factors known to increase serum uric acid levels like renal failure, multiple myeloma, leukemia, lymphoma, hemolytic anemia, psoriasis, hypoparathyroidism, chronic alcoholism and patients taking drugs that are known to raise serum uric acid levels like diuretics, chemotherapeutic agents, nicotinic acid, ACE inhibitors like Losartan, salicylates, ethambutol and pyrazinamide were excluded from the study.

A detailed history and physical examination with special reference to Killip class was carried out. All patients underwent routine investigations including complete hemogram, renal function tests, liver function tests, ECG, chest x-ray and echocardiography. Patients were followed up till hospital stay i.e. 7 days. Serum uric acid level was measured on day 1 & 7 of ACS.
A detailed statistical analysis was carried out. Basal serum uric acid levels were compared with controls with unpaired ‘t’ test. The levels of serum uric acid on day 1 and 7 were compared by paired ‘t’ test. Uric acid levels and Killip class was compared with coefficient of correlation. The study was approved by the Ethics committee of the hospital.

RESULTS AND OBSERVATIONS

In the present study, 100 patients with ACS with an equal number of age and sex matched healthy controls were studied. The age of the cases varied from 36 to 85 years, the mean age being 58.13±10.08 years. Maximum number of cases (36%) was in the age group of 50-59 years. Majority of the cases were male (68%) and the male: female ratio was 2.12: 1. In the present study, the highest numbers of patients were non smoker (67%), and only 33% of patients were smoker. Out of 100 cases, only 7 had family history of IHD as against 2 in the control group. Obesity was found in only 24% of the patients and 36% were overweight. Echocardiogram showed mild LV dysfunction in 32 patients, moderate LV dysfunction in 38 patients, severe in 18 patients and normal LV function in 12 patients. Only 43% of the patients were hypertensive. Type 2 Diabetes mellitus was found in 47% of the patients.

In the present study, majority of the cases were having STEMI (80%), followed by NSTEMI (15%) and Unstable Angina (5%). In the present study the most common presenting symptom was chest pain (92%) followed by increased sweating (52%), nausea and vomiting (28%). Four patients presented with altered mental status. Mean serum uric acid levels on day 1 was 5.80±1.53 and on day 7 was 4.93±1.26. There is a significant reduction of uric acid levels on Day 7 on comparing with day 0 (P = 0.034). The mean serum uric acid level of controls on day 1 was 3.8±0.85. The baseline characteristics of both the groups are shown in Table 1.

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Serum uric acid level on the day of admission was positively correlated with Troponin T.
levels (Pearson correlation 0.807, P value <0.00001) and CK-MB levels (Pearson correlation 0.768, P value <0.00001) (Figures 1, 2).

Negative correlation was found between the serum uric acid level on the day of admission and ejection fraction obtained (Pearson correlation -0.827, P value <0.00001) (Figure 3).

On day of admission out of 100 patients, 18 patients had serum uric acid >7 mg/dl, in which 14 patients were in Killip class IV and 2 each in class II and III (P value <0.0001) (Table 3).

Out of the 22 patients who died, 17 had serum uric acid level > 7.0 mg/dl and 5 patients had serum uric acid < 7 mg/dl. Of these 22 patients, 12 died on the day of admission and 10 patients died over next 7 days. Out of 22 patients who died 14 patients were in Killip class IV (Table 4, 5, 6).

DISCUSSION
Elevated SUA levels have been associated with an increased risk for Cardio-vascular disease. The potential mechanisms by which SUA may directly cause cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium. Previous studies have shown that serum uric acid increases in cardiac failure. In a study done in Japan in 2005 by Kojima et al it was shown that serum uric acid levels correlate with Killip classification. Combination of Killip class and serum uric acid level after AMI is a good predictor of mortality in patients who have AMI.

Present study was conducted in 100 patients of ACS, who presented to hospital with in 12 hrs of onset of symptoms. All the patients with acute STEMI were thrombolysed in our study. One hundred age and sex matched healthy controls were also evaluated for comparison of uric acid levels. Out of 100 patients, 80 had STEMI, while 15 patients were of NSTEMI and 5 patients had unstable angina (UA).

In the present study, mean age of cases was 58.13±10.08 years and of controls were 58.16±10.18 years. According to study by MY Nadkar et al the mean age of patients was

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<td>6</td>
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58.29±11.31 years and the mean age in control group was 56.84±8.98 years. Similar findings were also observed in the study conducted by **LS Patil et al** and **Gandiah P et al**.

There was a statistically significant higher level of serum uric acid concentration in patients with ACS on day of admission as compared to controls (P=<0.00001). This finding of the present study correlated with studies done by **Gandiah P et al** and **MY Nadkar et al**. Similar findings were also observed in the study conducted by **LS Patil et al** and **Gandiah P et al**.

There was a statistically significant higher level of serum uric acid concentration in patients with ACS on day of admission as compared to controls (P=<0.00001). This finding of the present study correlated with studies done by **Gandiah P et al** and **MY Nadkar et al**. Similar findings were also observed in the study conducted by **LS Patil et al** and **Gandiah P et al**.

There was no significant difference in uric acid levels between male and female patients (P=0.375). Similar finding was observed by **Gandiah P et al** and **MY Nadkar et al**. However in the study by **Kojima S et al** males had higher uric acid level as compared to females.

There was no significant difference in uric acid levels between hypertensive and non hypertensive patients (P=0.183). This finding of the present study correlated well with the studies by **LS Patil et al**, **MY Nadkar et al** and **Qureshi et al**. In contrast to finding of present series **Harris P et al** and **Kojima S et al** noted that serum uric acid level was significantly correlated with hypertension. In another study by **Chen L et al** serum uric acid was significantly associated with hypertension in patients aged <40 years.

There was no significant difference in uric acid levels between diabetic and non diabetic patients (P= 0.1910). This finding was in concordance with the study by **LS Patil et al**, **MY Nadkar et al** and **Toumilheto et al** in which there was no significant association between serum uric acid and diabetic status. However this finding is in contrast to other study by **Safi et al** and **Harris P et al** where hyperuricemia was significantly associated with type 2 diabetes mellitus. There was no significant difference in uric acid levels between smokers and non smokers which was similar to the study by **Qureshi et al**.

Serum uric acid level on the day of admission was correlated with Troponin T value a strong positive correlation was obtained (Pearson correlation 0.807, P value <0.00001), that is, as the value of one increases the other also increases. **Hasic et al** in their study found the similar positive correlation. In the study of **Lippi et al** significantly higher SUA levels in patients with Troponin T values above decisional threshold was revealed.

Serum uric acid level on the day of admission was correlated with CK-MB value a strong positive correlation was obtained (Pearson correlation 0.768, P value <0.00001). Similarly **Amrut A Dambal et al** and **Harris P et al** also found statistically significant positive correlation between CK-MB and uric acid on day of admission.

In the present study when serum uric acid level on the day of admission was correlated with ejection fraction (%) a strong negative correlation was obtained (Pearson correlation -0.827, P value <0.00001). **Chen L et al** showed a significantly lower LVEF in patients with high serum uric acid. **Yoshiro et al** and **Pinelli M et al** clarified in his study that high UA levels reduced LVEF independently of the severity of Ischemic heart disease (IHD). In contrast **Nozari Y et al** there was no correlation between uric acid and LVEF (Correlation coefficient= -0.111, P=0.129).

In the present study, out of 100 patients, 18 patients had serum uric acid >7 mg/dl, in which 14 patients were in Killip class IV and 2 each in class II and III (P value <0.0001, highly significant). Thus patients of Killip class IV had higher levels of uric acid as compared to other Killip classes. In a study done in Japan in 2005 by **Kojima S et al** it was shown that serum uric acid levels correlate with Killip classification. **MY Nadkar et al** also found that there was a positive correlation between serum uric acid level and Killip class on day of admission. Similar findings were also observed by **LS Patil et al** and **Gandiah P et al**.

In the present study, there was significant relation between uric acid level and in-hospital mortality. High serum uric acid levels on admission were strongly associated with increased mortality. In the present study
out of 100 cases, 22 patients (22%) died. More than half of the patients (12) died on the day of admission and 10 patients died over next 7 days. Out of the 22 patients who died, 17 had serum uric acid level more than 7.0 mg/dl and 5 patients had serum uric acid less than 7.0 mg/dl.

Bickel C et al reported that one mg/dl increase in serum uric acid levels was associated with a 26% increase in mortality. Siniša Carl et al and MY Nadkar et al concluded in their study that serum uric acid level after acute myocardial infarction is a good predictor of mortality.

Out of 12 patients died on the day of admission (day 1), 8 patients were in Killip class IV, 3 patients in Killip class III and 1 patient in Killip class I. Over next 7 days another 10 patients died, out of which 6 were in Killip class IV, 3 in Killip class III and 1 in Killip class II. In the study by MY Nadkar et al 83% of patients who died were in higher class i.e. class III and IV at time of admission. Similar observations were found in the study by by LS Patil et al and Gandiah P et al.

CONCLUSION

It is concluded from the present study that serum uric acid levels were higher in patients of ACS as compared to healthy controls. Patients with elevated serum uric acid levels belonged to higher Killip’s classification and had higher mortality. It can be inferred from this study that serum uric acid can be regarded as an inexpensive independent risk factor and prognostic marker of short term mortality in patients with ACS.

Although, conduction of this study in a sole institution with paucity of time and resource highlighted the role of serum uric acid in influencing the course of ACS, a more elaborate multi centric study would have been desirable to precisely establish the role of serum uric acid in ACS. It is hoped that the present study will encourage new studies related to the above subject with a broader spectrum and for longer durations.

REFERENCES


ABSTRACT
Left ventricular hypertrophy is an important complication of long standing hypertension and valvular heart diseases and is proven to be associated with target organ damage. Left ventricular hypertrophy refers to be an increase in the size of the myocardial fibres in the main cardiac pumping chamber. Such hypertrophy is usually the response to the chronic volume or pressure overload. Hypertension is the leading causes of left ventricular hypertrophy followed by aortic stenosis, aortic regurgitation and mitral regurgitation. The present study is done to compare various electrocardiographic criteria’s for left ventricular hypertrophy using echocardiography as gold standard.

Materials and Methods: The present study included 110 patients with history and clinical profile suggestive of cardiac morbidities such as hypertension, aortic stenosis, aortic regurgitation, and mitral regurgitation having the evidence of left ventricular hypertrophy in echocardiography and as well as fulfilling the criteria’s of electrocardiography. Electrocardiographic criteria’s used for diagnosis of left ventricular hypertrophy were Sokolov-Lyon index, Romhilt-Estes scoring system, Total QRS voltage criteria. Diagnostic validity tests such as specificity, sensitivity and Kappa’s measure of agreement were performed.

Results: Using Sokolov-Lyon index criteria could diagnose left ventricular hypertrophy in 29 (38%) of patients with 82% specificity. Using Romhilt-Estes scoring system electrocardiography could diagnose left ventricular hypertrophy in 43 (56%) of patients with 79% specificity. Using Total QRS voltage criteria electrocardiograph could diagnose left ventricular hypertrophy in 46 (60%) patients with 91% specificity. The present study found sensitivity 38% for

1Junior Resident-3, 2Professor, 3Associate Professor, 4Junior Resident-2, Dr. D.Y. Patil Medical College & Hospital, Pune, Maharashtra
**INTRODUCTION**

Left ventricular hypertrophy is the condition that severely affects the morbidity and mortality from cardiovascular diseases including myocardial infarction, congestive cardiac failure, and stroke. In developing countries like India the prevalence of left ventricular hypertrophy is increasing.\(^1\) Left ventricular hypertrophy is no longer to be considered as an adaptive process that compensates the pressure imposed on the heart, but has been considered as an independent and significant risk factor for sudden death, acute myocardial infarction, and congestive cardiac failure.\(^2\)

The increase in the left ventricular mass represents the final pathway towards the adverse effects on the cardiovascular system leading to the serious complications.\(^3\) The electrocardiographic assessment of cardiac dimensions has lost its prominence in the favour of imaging techniques that provide a multi-dimensional display of the heart but secondary ST-T changes due to left ventricular hypertrophy which are uniquely determined from the electrocardiography and are known to increase the risk of cardiovascular morbidity and mortality.\(^4\)

Today two dimensional echocardiogram still demands considerably more time, lack of technical skill of the operator and complexity of processing than routine 12-lead electrocardiograph.

Electrocardiographic criteria used in left ventricular hypertrophy are

1. **Sokolow-Lyon index:**\(^5\) In 1949, Sokolow and Lyon pointed out that the presence of ventricular hypertrophy in adult is suggested when the sum of S wave in VI and R wave in V5 or V6 totals more than 35 mm.

2. **Romhilt and Estes scoring system for left ventricular hypertrophy:**\(^6\) Romhilt and Estes in 1968 developed a point scoring system. A score of five or more points on ECG is diagnostic of left ventricular hypertrophy. A score of 4 points indicates that there is probably left ventricular hypertrophy.

3. **Total QRS voltage criteria:**\(^7\) The total QRS voltage is obtained by adding the QRS amplitude in each lead in a 12-lead electrocardiogram. The amplitude of the QRS complex is measured from the peak of the R wave to the dip of the S wave according to the method of Siegel and Roberts. The total QRS voltage of 174 mm is taken as normal. Any value 175 mm or more will be taken as significant indicating left ventricular hypertrophy. Considering the magnitude of left ventricular hypertrophy study designed to co-relate between three different electrocardiographic criteria’s of left ventricular hypertrophy using echocardiography as gold standard.

**MATERIALS AND METHODS**

The present study included 110 patients with history and clinical profile suggestive of cardiac morbidities such as hypertension, aortic stenosis, aortic regurgitation, and

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**Conclusion:** The sensitivity for Total QRS criteria was 60% to 38% for Sokolov-Lyon criteria. The different electrocardiographic criteria used for the diagnosis of left ventricular hypertrophy, Total QRS voltage criteria showed better sensitivity compared to other criterias. So for the diagnosis of left ventricular hypertrophy, the role of electrocardiographic criteria is of limited value and thus echocardiography is the choice for the diagnosis of left ventricular hypertrophy.

**Key words:** Electrocardiography, Echocardiography, Sokolov-Lyon index, Romhilt-Estes score system, Total QRS voltage criteria
mitral regurgitation having the evidence of left ventricular hypertrophy in echocardiography and as well as fulfilling the criteria’s of electrocardiography. This study was cross sectional analytical study. Institute Ethics Committee approvals will be obtained before start of the study.

The electrocardiographic variables recorded were Voltage of R, S or Q waves in all the leads, ST-T changes, Axis, Duration of QRS complexes in limb leads, Intrinsicoid deflexion in V5, V6, ‘P’ terminale in VI (Tables 1, 2).

The study group: comprised of patients who have echocardiographic evidence of left ventricular hypertrophy.

The control group: comprised of patients who had no echocardiographic evidence of left ventricular hypertrophy.

Electrocardiographic criteria’s used in this study are:

I. Sokolov - Lyon Index5: S in VI, + R in V5 or V6 > 35 mm

II. Romhilt - Estes point score system6 (Table 1)

III. Total QRS voltage criteria7: The total QRS voltage was obtained by adding the QRS amplitude in each lead in a 12-lead electrocardiogram. The amplitude of the QRS complex was measured from the peak of the R wave to the dip of the S and Q-wave, whichever was greater, according to the method of Siegel and Roberts. A total QRS voltage of 174 mm was taken as normal. Any value 175 mm or above was taken as significant indicating left ventricular hypertrophy. These three criteria are most widely used and hence present study was done on these three criteria.

After obtaining results of electrocardiogram and echocardiography diagnostic validity tests (specificity and sensitivity) and Kappa measure of agreement were performed (Table 3).

RESULTS

In this study 110 patients were enrolled. Out of 110 patients 67 were male and 43 were female. Among the study subjects 64 were hypertensive, 13 patients were having mitral regurgitation (MR), 8 were suffering from aortic regurgitation (AR), 10 had aortic stenosis (AS) and 15 were having combined lesions (MR, AR, AS and AR).
The patients were divided into two groups, the study group and the control group.

Clinical profile of the patients with left ventricular hypertrophy included the shifting of apical impulse in 50 patients, chest pain (unstable angina) in 6 patients, palpitations in 37 patients, shortness of breath (exertional dyspnoea) in 7 patients, and headache was only seen in 10 patients who were having hypertension (Table 4).

The study group patients had echocardiographic evidence of left ventricular hypertrophy i.e., the average of septal and posterior wall thickness > 1.2 cm. This study group comprised of 76 patients out of which 48 were males and 28 females. The control group patients had no echocardiographic evidence of left ventricular hypertrophy i.e., the average of sums of septal and posterior wall thickness was < 1.1 cm.

The control group consisted of 34 patients out of whom 19 were males and 15 females. Using Sokolov-Lyon index criteria could diagnose left ventricular hypertrophy in 29 (38%) of patients with 82% specificity. But the Kappa’s measure of agreement is 0.14 which suggests that there is poor measure of agreement between electrocardiography and echocardiography in diagnosing left ventricular hypertrophy.

Using Romhilt-Estes scoring system electrocardiography could diagnose left ventricular hypertrophy in 43 (56%) of patients with 79% specificity. Using Total QRS voltage criteria electrocardiograph could diagnose left ventricular hypertrophy in 46 (60%) patients with 91% specificity.

The present study found sensitivity 38% for Sokolov-Lyon index, 56% sensitivity for Romhilt-Estes point score system and 60% sensitivity and 91% specificity for Total QRS voltage criteria (Table 5).

SOKOLOV - LYON INDEX
The sensitivity shown by Sokolov-Lyon index is 38%, with specificity of 83%. The diagnostic accuracy being 51%. But the Kappa’s measure of agreement is 0.14 which suggests that there is poor measure of agreement between electrocardiography and echocardiography in diagnosing left ventricular hypertrophy.

ROMHILT - ESTES POINT SCORE SYSTEM
The study shows a better sensitivity compared to Sokolov-Lyon index (Table 6). The study showed 49% sensitivity when 5 points were used and 56% sensitivity when 4 points were used, whereas the diagnostic accuracy being 63% by using 4 point score and 59% by using 5 point score Kappa measure of agreement is 0.29 suggesting a poor measure of agreement between echocardiogram and electrocardiogram in diagnosing left ventricular hypertrophy.

TOTAL QRS VOLTAGE CRITERIA
This study showed the highest sensitivity of 60% as compared to the other electrocardiogram.
graphic criteria used which was used for this study. The Kappa measure of agreement is 0.4 which suggests that there is a fair measure of agreement between electrocardiogram and echo diagnosing left ventricular hypertrophy.

**DISCUSSION**

The present study was conducted with an aim to study the clinical profile and electrocardiography criteria in patients with left ventricular hypertrophy and then co-relating them with two dimensional echocardiography. As two dimensional echocardiography being the gold standard to diagnose left ventricular hypertrophy we compared three important electrocardiographic criteria for diagnosing left ventricular hypertrophy.

The electrocardiographic (ECG) diagnostics of left ventricular hypertrophy (LVH) currently is based primarily on the QRS voltage criteria. However, increased QRS voltage in the setting of actual anatomical left ventricular hypertrophy (LVH) is not a consistent finding, as reflected in a wide range of both sensitivities and specificities of ECG criteria for LVH.\(^9,10\) Nevertheless, ECG criteria for LVH have been shown to be a strong independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension and in the general population.\(^11,12\)

**Table 7: Single Table Analysis of Total QRS voltage**

<table>
<thead>
<tr>
<th>ECG</th>
<th>Echo Positive</th>
<th>Echo Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>46</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>Negative</td>
<td>31</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>77</strong></td>
<td><strong>33</strong></td>
<td><strong>110</strong></td>
</tr>
</tbody>
</table>

**Sokolov - Lyon criteria**\(^5\) is the oldest, simplest and quickest method for the diagnosis of left ventricular hypertrophy which was described in 1949 by Sokolow M and Lyon TP.\(^14\) The Kappa measure of agreement was found to be 0.14 by Sokolow Lyon criteria, suggesting that there was a poor measure of agreement between electrocardiography and echocardiography in diagnosing left ventricular hypertrophy. The present study found sensitivity 38% and specificity 82% of Sokolov-Lyon index. Reichek et al\(^13\) reported sensitivity 21% and specificity 95%. Murphy et al\(^14\) reported sensitivity 60% and specificity 80%. Jaggy et al\(^15\) reported sensitivity 61% and specificity 68%. Martin et al\(^16\) reported sensitivity 31% and specificity 75%.

**Romhilt and Estes point score system**\(^6\) involves complicated data acquisition for scoring. In the present study Kappa measure of agreement is 0.24 suggesting a poor measure of agreement between echocardiogram and electrocardiogram in diagnosing left ventricular hypertrophy. However, a better sensitivity compared to Sokolov-Lyon index was found. The present study found sensitivity 49% and specificity 82% by Romhilt and Estes point score system. Reichek et al\(^13\) reported sensitivity 50% and specificity 95%. Kansal et al\(^17\) reported sensitivity 57% and specificity 81%. Murphy et al\(^14\) reported sensitivity 60% and specificity 90%. Hameed et.al\(^18\) reported sensitivity 35% and specificity 90%.

**Total QRS voltage criteria**\(^7\) with the normal upper limit for total QRS amplitude of 175 mm was first determined by Roberts and Day\(^19\) and later validated by Odom et al.\(^20,21\) Odom et al\(^20\) found that the upper limit of 175 mm yielded specificity of 100% for diagnosing LVH in

**Table 8: Sensitivity, Specificity, Accuracy, Positive Predictive value, Negative Predictive Value and Kappa Measure of agreement of Different Electrocardiographic Criteria for Left Ventricular Hypertrophy**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>ECG criteria</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Accuracy %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>Kappa measure of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S.L. Criteria</td>
<td>38</td>
<td>82</td>
<td>51</td>
<td>83</td>
<td>36</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>R.E point score 4 point</td>
<td>56</td>
<td>79</td>
<td>63</td>
<td>86</td>
<td>43</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>5 point</td>
<td>49</td>
<td>82</td>
<td>59</td>
<td>86</td>
<td>41</td>
<td>0.24</td>
</tr>
<tr>
<td>3</td>
<td>Total QRS</td>
<td>60</td>
<td>92</td>
<td>69</td>
<td>94</td>
<td>49</td>
<td>0.47</td>
</tr>
</tbody>
</table>
subjects with heart weight less than 400 g.\textsuperscript{21} Compared to Sokolov-Lyon and Romhilt-Estes criteria the total QRS criteria showed better sensitivity, specificity, accuracy and a fair Kappa measure of agreement. The Kappa measure of agreement was found to be 0.40 which suggests that there is a fair measure of agreement between electrocardiogram and echo diagnosing left ventricular hypertrophy (Tables 7, 8, 9, 10). The present study found sensitivity 60% and specificity 91% by total QRS voltage criteria. Odom et al\textsuperscript{20} reported sensitivity 70% and specificity 90%. Jaggy et al\textsuperscript{15} reported sensitivity 42% and specificity 78%. Martin et al\textsuperscript{16} reported sensitivity 30% and specificity 86%.

**CONCLUSION**

Hypertension is one of the leading causes of left ventricular hypertrophy. The other causes of left ventricular hypertrophy are aortic stenosis, aortic regurgitation, and mitral regurgitation. In this study, 60% were patients of hypertension, 12% patients were of aortic stenosis and combined valvular diseases (MR, AR, AS & AR).

The sensitivity was in the range of 60% for total QRS voltage criteria to 38% for Sokolov Lyon criteria. Among the different criteria used Total QRS criteria showed better sensitivity compared to others. In the evaluation of patients for left ventricular hypertrophy, the role of electrocardiography with all the commonly used criteria is of limited value and echocardiography is the method of choice. Electrocardiogram showed a better sensitivity in detecting left ventricular hypertrophy only when it is severe.

**REFERENCES**


Resistant Hypertension: Management Guidelines

Ashok K Taneja¹, Akshat Taneja²

INTRODUCTION
Resistant hypertension defined as blood pressure that remains above the target level in spite of concurrent use of three antihypertensive agents of different classes. Out of three classes one class must be a diuretic. Identifying resistant hypertension is of paramount importance as there is tremendous increase in morbidity & mortality. Moreover, it identifies patients having reversible causes of hypertension and/or patients may benefit from special diagnostic and therapeutic procedures. Patients whose blood pressure is controlled with four or more medications should be considered to have resistant hypertension.¹ Points to remember is:

a. One of the three agents should be a diuretic.
b. All agents should be prescribed at optimal doses (ie, 50 percent or more of the maximum recommended antihypertensive dose)
c. Although patients with resistant hypertension may have elevations in both systolic and diastolic pressures, isolated systolic hypertension is common.
d. Resistant hypertension is not synonymous with uncontrolled hypertension, since resistant hypertension is not the only cause of uncontrolled hypertension.
e. Other causes include inadequate treatment regimens and pseudo resistance or inappropriate BP measurements.²

Terminologies

a. Apparent Resistant hypertension
b. Pseudoresistant hypertension
c. True resistant hypertension

a. Apparent resistant hypertension: Patients have uncontrolled clinic blood pressure (ie, greater than or equal to 140/90 mmHg) despite being prescribed three or more antihypertensive medications, or require prescriptions of four or more drugs to control their blood pressure. There is apparent lack of control on > or =3 medications.
b. Pseudoresistant Hypertension: Pseudo resistance refers to poorly controlled hypertension that appears resistant to treatment but is actually attributable to other factors. The five most common causes of pseudo resistance are:

1. Inaccurate measurement of blood pressure
2. Poor adherence to antihypertensive therapy

¹Sr. Consultant Diabeto-Cardiologist, ²Jr. Resident, Tanjena Heart-Diabetes Centre, New Colony, Gurgaon 122001, Haryana
3. Suboptimal antihypertensive therapy
4. Poor adherence to lifestyle and dietary approaches
5. White coat hypertension: Also called isolated clinic or office hypertension. It refers to patients who have office readings that average more than 140/90 mmHg and reliable out of office readings that average less than 140/90 mmHg. The office BP is usually taken by a nurse or technician rather by a physician. Clue to the diagnosis is patients with white coat hypertension have less severe target organ damage and appear to be at less cardiovascular risk, compared to those patients with persistent hypertension during ambulatory monitoring.

c. True resistant hypertension

Patients with true resistant hypertension are those who have uncontrolled clinic blood pressure despite being compliant with an antihypertensive regimen that includes three or more drugs (including a diuretic, and each at optimal doses) and who also have uncontrolled blood pressure confirmed by 24-hour ambulatory blood pressure monitoring. It represents higher risk of morbidity & mortality.³

PREVALENCE

The true prevalence of resistant hypertension is not known. A major problem is that not all patients with uncontrolled hypertension have resistant hypertension as defined above; many are uncontrolled because of poor adherence or inadequate treatment regimens. Pooled analysis shows prevalence rates of 10.1% and 7.9% for uncontrolled resistant hypertension among individuals treated for hypertension and all hypertensive individuals, respectively. Whereas, data from North America and Europe with a combined sample size of >600,000 hypertensive participants, the prevalence of resistant hypertension is 14.8% of treated patients and 12.5% of all hypertensives. Framingham Heart Study reported only 48% of treated participants were controlled to <140/90 mm Hg and less than 40% of elderly participants (>75 years of age). Among higherrisk populations and in patients with diabetes mellitus or chronic kidney disease (CKD), with application of the lower goal blood pressures as recommended in JNC 7 for, the proportion of uncontrolled patients is even higher. Of NHANES participants with chronic kidney disease, only 37% were controlled to <130/80 mm Hg and only 25% of participants with diabetes were controlled to <130/85 mm Hg.⁴

ETIOLOGY

A. Primary causes

B. Secondary causes

C. Factors contributing to resistant hypertension

A. Primary causes:-

- Older age; especially >75 years
- High baseline blood pressure and chronicity of uncontrolled hypertension
- Target organ damage (left ventricular hypertrophy, chronic kidney disease)
- Diabetes
- Obesity
- Atherosclerotic vascular disease
- Aortic stiffening
- Sex (women)
- Ethnicity (black)
- Excessive dietary salt intake.

B. Secondary causes:

- Primary hyperaldosteronism
- Renal artery stenosis
- Renal parenchymal disease
- Obstructive sleep apnoea
- Phaeochromocytoma
• Thyroid diseases
• Cushing’s syndrome
• Coarctation of the aorta
• Intracranial tumours

C. Factors contributing to resistant hypertension:
   i. Lifestyle factors:-
   • Obesity
   • Excess alcohol intake
   • Excess dietary sodium
   • Cocaine and amphetamines misuse
   ii. Drug related causes:
       • Non-steroidal anti-inflammatory drugs
       • Contraceptive hormones—Combined oral contraceptives are more often associated with elevated blood pressure, whereas menopausal hormone therapy has minimal effects.
       • Adrenal steroid hormones
       • Sympathomimetic agents (nasal decongestants, diet pills)
       • Erythropoeitin, cyclosporin, and tacrolimus use
       • Liquorice (suppresses the metabolism of cortisol)
       • Herbal supplements (ephedra, bitter orange, etc)
   iii. Volume overload:
       • Progressive renal insufficiency
       • High salt intake
       • Inadequate diuretic therapy.

Treatment of resistant Hypertension is a diagnosis of exclusion requiring a systematic approach to Evaluation & management.6,8

EVALUATION
A. Medical history: The medical history should document age of onset, duration, severity, and progression of the hypertension. Particular emphasis should be given to concurrent medication use (including herbal and over-the-counter medications). Mention must be made regarding the response to prior medications used. Patient adherence to the treatment must be established. The patient should also be questioned about possible manifestations of secondary causes of hypertension, such as Renal artery stenosis, Co-arctation of aorta, Pheochromocytoma and Cushing’s syndrome.

B. Physical examination — The physical examination should include careful measurement of the blood pressure, detailed cardio-vascular exam including peripheral pulses and murmurs in carotids/subclavian/femoral or abdominal aorta. Detailed fundoscopic examination looking for retinopathy must be done. Diminished femoral pulses and/or a discrepancy between arm and thigh blood pressures which may suggest aortic coarctation or significant aortoiliac disease should be carefully noted.6

C. Investigations
   • Urea and electrolytes. KFT
   • Estimate glomerular filtration rate, 24-hr creatinine clearance.
   • Plasma glucose
   • Plasma renin or aldosterone levels
   • 24 hour urinary metanephrines or normetanephrines (for phaeochromocytoma) and sodium excretion to check salt sentivity.
   • Urine analysis—microalbuminuria and macroalbuminuria, haematuria, VMA (R/O Pheochromocytoma).
   • Electrocardiography: Look for LVH
and pre-existing ischemic heart disease or arrhythmias.

- Screening for primary aldosteronism begins with a paired, morning measurement of the plasma aldosterone concentration (PAC) and plasma renin activity (PRA) to PAC/PRA ratio.

- Non-invasive imaging — Most patients with resistant hypertension should undergo noninvasive imaging for renal artery stenosis, atherosclerotic disease in other vascular beds, coronary artery disease, cerebrovascular disease. Get a whole abdomen USG done to rule out structural renal disease, Aortic aneurysm etc.

- Echocardiography: Transthoracic (TTE) & Transesophageal (TEE). Look for LV mass (LVH); systolic & diastolic functions, any structural disorder of heart including aorta. Particular attention should be paid to coarctation of aorta. Look carefully peripheral arteries to rule out any stenosis.

- CT Scan/MRI: where secondary causes are suspected.

- Renal imaging: including CT renal angiogram to rule out renal artery stenosis or mass or structural renal/adrenal disease.

- Confirm Accuracy of BP measurement by 24 hr ABPM (ambulatory BP measurement) to check for Pseudo Resistance and White Coat effect.

- Renal Biopsy: A renal biopsy is required for undiagnosed glomerulonephritis.

**MANAGEMENT**

1. Confirm Accuracy of BP measurement
2. Non-Pharmacological
3. Pharmacological
4. Device Therapy

1. **Confirm Accuracy of Measurement:** Utilize correct BP measurement technique and rule out white coat hypertension. Tips for obtaining accurate BP in your clinic/office:-
   - Allow the patient to sit quietly or relaxed for at least 5 min.
   - Remove clothing that constricts upper arm.
   - Average of 3 or minimum 2 readings 1 minute apart. If different in both arms, take the higher value.
   - Cuff should be of appropriate size covering 80% of arm circumference.
   - Nicotine intake, smoking, caffeine intake should be avoided before taking BP.
   - Automated BP apparatus may have advantage, but calibration necessary.
   - Home BP measurement is a good tool but take average of 4-5 reading to minimize error.
   - To confirm white coat effect compare home/office BP readings and do ambulatory BP Measurements (ABPM).

2. **Non-pharmacologic intervention:** A vast epidemiological data suggests an apparent relationship between resistant hypertension and lifestyle choices and habits. For example, observational studies have shown that people with raised blood pressure tend also to have low dietary calcium, higher sodium intake, salt resistant, dyslipidemic, dysglycemic and obesity. The role of diet, exercise, alcohol, caffeine, potassium and magnesium supplements, sodium (table) salt and use of rock salt have been widely studied and all have shown beneficial effects. The music therapy, yoga, meditation & relaxation therapies have shown good benefits in lowering calcitrant BP. However, there are certain lifestyle barriers to control BP which are:-
A. Interfering substances

B. Dietary salt Intake

C. Alcohol consumption

D. Obesity

A. Interfering substances: Certain drugs may elevate BP or may inhibit the effects of antihypertensives, e.g.

• NSAIDS & Cox 2 inhibitors.
• Sympathomimetic drugs like ephedra, phenylelepherins, amphetamines etc.
• Herbal supplements
• Anabolic steroids
• Appetite suppressants
• Erythropoitin
• Oral Contraceptives.

If possible, discontinue the offending drug or modify it.

B. Dietary Salt Intake: First ascertain whether patient is salt sensitive or salt resistant. Excessive dietary Salt ingestion is a risk factor for developing resistant BP. Calculate urinary sodium excretion, if it is >150 mmol/day, patient need to reduce salt intake to urinary excretion of<100mmol/day. Practically it amounts to 2.4mg per day i.e.half tea spoon fill in 24 hrs.No table salt or snacks to be used. Elderly/blacks/Indians & patients with CKD are very salt sensitive. Instead of using table salt,add lemon or soup toppings to salads or cut fruits.6

C. Alcohol intake: More than 3-4 drinks (120ml) per day also contributes to resistance. Moderate alcohol consumption i.e. Men=60-70ml/day; Women=30-40ml/day (of 42% proof i.e. whisky, rum, vodka) or less should be ensured. For 12 % proofs like wine or beer-more than 1 pint should not be allowed.7

D. Obesity is associated with more severe hypertension & resistance. The target should be reduction of weight by increasing physical exercise and adopting high fibre-protein diet e.g DASH, Mediterranean etc.

3. Pharmacotherapy

The choice of agents should be individualized and may depend upon consideration of prior benefit, history of adverse events, financial limitations and the presence of concomitant diseases such as chronic kidney disease or diabetes. However as per JNC 7 & subsequently by 8 the broad guidelines are:-

A. The triple combination of an ACE inhibitor or ARB, a long-acting dihydropyridine calcium channel blocker (usually amlodipine), and a long-acting thiazide diuretic (preferably chlorthalidone) is often effective and generally well tolerated. (A+C+D).

B. If the patient is still hypertensive, additional medications are added sequentially. Other possible agents that may be used include:

i. Beta blockers preferably with vasodilator properties (labetalol, carvedilol, or nebivolol) or combined beta & alpha blockers (Prazocin)

ii. Centrally acting agents (clonidine or guanfacine).

iii. Direct vasodilators (hydralazine or minoxidil).

If beta blockers are used, a vasodilating beta blocker, such as labetalol, carvedilol or nebivolol, may provide more antihypertensive benefit with fewer side effects compared to traditional beta blockers, particularly when high doses are used.6,8

iv. Direct Renin Inhibitors: Aliskiren, the only available direct renin inhibitor, is at least as effective as ARBs in reducing end target organ damage but has not
been directly tested in resistant hypertension.

v. Endothelin receptor antagonists are a new family of antihypertensive medications that are currently being evaluated.

a. Darusentan has demonstrated significant dose-dependent reductions in both systolic and diastolic blood pressures and has been positively evaluated in resistant hypertension.

b. Atrasentan is another highly selective endothelin receptor antagonist that has shown positive results in blood pressure reduction for 72 patients.

c. Omapatrilat- is medication that combines inhibitors of vasoconstrictive mediators with drugs that potentiate vasodilating mediators by inhibiting their breakdown by neutral endopeptidases (NEPs) [OCTAVE trial].

4. Device therapy: In the pathophysiology of hypertension the role of activity of sympathetic nervous system (SNS) is amply established. In resistant Hypertension, there is increased SNS activity with inhibition of Parasympathetic nervous system (PSNS) causing tachycardia & vaso-constriction. On the other hand, subdued SNS activity with increased parasympathetic activity results in bradycardia & vaso-dilatation. Thus, understanding of this pathophysiology has allowed the exploration of (physical) sympathectomy to treat human hypertension in the middle of last century. Nonselective crude surgical lumbar sympathectomy gave significant relief from severe hypertension but unfortunately increased the incidence of bothersome side-effects such as symptomatic postural hypertension. Hence, the procedure did not find a place in the therapy of hypertension and was abandoned. In the last decade, technological and safety advances have led to the refined techniques to selectively ablate renal sympathetic activity, so-called renal denervation (RDN) therapy. Similarly, baroreceptor activation therapy (BAT) has
also been developed simultaneously as a method of sympathetic deactivation to treat hypertension. Following techniques have recently been evaluated:

A. Percutaneous transluminal radiofrequency sympathetic denervation of the renal arteries (RDN).

B. Carotid Baroreflex Activation Therapy (BAT).

C. Median Nerve Modulation.

D. Central Arterio-venous Coupler Therapy (CAVCT)

A. RDN: In the last decade this procedure has gained recognition. Many devices have been developed to cause selective RDN. A catheter is inserted in the renal arteries which delivers thermal injury to disrupt the local afferent and efferent nerve fibers. Radiofrequency ablation is the preferred mode of energy. Symplicity HTN-3 trial\(^{11}\) showed promising results. Radiofrequency ablation of the renal sympathetic nerves should be reserved for patients who meet all of the following criteria.\(^{10,11}\) Figure 1.

- Resistant hypertension
- Pseudoresistant hypertension has been excluded (e.g., white coat effect, non-adherence to Optimal dose & type of treatment etc).
- Identifiable secondary causes of resistant hypertension, such as primary aldosteronism, have been excluded.
- Renal function is preserved (estimated glomerular filtration rate greater than or equal to 45 mL/min/1.73 m).
- The renal artery anatomy is eligible (i.e., there are no accessory renal arteries and no renal artery stenosis or renal artery revascularization)

B. Carotid Baroreceptor Stimulation Therapy (BTA): Activation of baroreceptors results in decrease in the SNS activity via central mechanism (Figure 2). Affrent reflexes originating from the carotid body inhibit the cardiovascular efferents from the brain resulting in sympathetic deactivation which leads to vaso-dilatation (reduced systemic vascular resistance) and bradycardia. Long-term observations with baroreflex activation therapy (BAT) are not yet available but the short term results are encouraging.\(^{10,11}\) A device (Rheos BAT system), similar to pacemaker, is implanted which electrically stimulates carotid baroreceptors. The results evaluated at 3 months BAT device showed an office BP reduction of 21/12 mm Hg and ABP was reduced by 6/4 mm Hg. At 2 years followup, the office BP was reduced by 33/22 mm Hg and ABP was reduced by 24/13 mm Hg.\(^{12}\)

C. Median Nerve Modulation (MNM): Median nerve modulation is done by a small coin which gently stimulates the median nerve. The Ecoin is implanted under the forearm skin to activate the median nerve. The low powered electrical stimulus, communicates with the multiple pathways in the brain which control the blood pressure (Figure 3). The procedure takes only 20 minutes to perform in the office setting. Ecoin showed a significant improvement in the office and ABP levels.\(^{15}\) SBP fell 10.31 ± 20.93 mm Hg and ABP fell by 4.68 ± 11.05 mm Hg (Figure 4) at 6 months. No significant procedure related adverse effects were noted.\(^{13}\)

D. Central Arterio-venous Coupler Therapy (CAVCT): In resistant hypertension increased peripheral vascular resistance (due to arterial wall thickening) is the hallmark. A new technique—the Rox coupler creates a small A-V fistula (AVF) between the iliac artery and vein with a controlled shunt flow creating a low resistance
vascular bed and the system vascular resistance table. A large study of 80 persons (40 patients & 40 controls) showed that at 6 months the AVF group showed a significant reduction in office BP and ABP levels. Figure 4. The novel technique was shown to be effective but a third of AVF patients developed ipsilateral venous stenosis which resolved after stenting or venoplasty. This unique promising procedure awaits further testing and additional research.¹⁴

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Introduction

Thiazide type diuretics are the first line drug for the treatment of hypertension. However, its use is limited by potential complications of hyponatremia especially in elderly population. Hyponatremia is an occasional but severe cases can lead to severe symptoms and rarely death. Practically all the cases of severe diuretic induced hyponatremia are due to a thiazide-type diuretic.¹⁻⁷ A loop diuretic is much less likely to induce this problem unless the diuretic has induced volume depletion⁸ or water intake is very high (since loop diuretics partially impair urinary diluting capacity).

Incidence

The exact incidence is uncertain.¹⁹⁻²¹ One of the 10 years of retrospective cohort study on 2613 patients showed a incidence of hyponatremia (defined as serum sodium of 130 meg/l or less) was 30% in patients who received thiazide uretic (66 of 220 patients). In comparison to these incidence was 18% (422 of 2393 patients) in patients who received alternate therapy. The highest incidence occurred in the first three months after the initiation of thiazide diuretic but the risk continued to remain for 10 years of follow up period. The median time to diagnosis of hyponatremia was 1.7 years, hence it is important to regularly monitor these patients.

The incidence also increases with increasing age. This study showed a slightly higher incidence (37 vs 24%) in patients greater than 60 years. However, this difference was not statistically significant. This association has also been shown in various other studies. Each 10-year increment of age was associated with a twofold increase in risk, and every 5 kg increment in body mass decreased the odds ratio by 27 percent.¹⁻⁵,¹²,²²,²³

Pathogenesis

Lower incidence of hyponatremia with loop diuretics is probably because of the different mechanism of action as compared to the thiazide type diuretics.

Loop diuretics act by interfering with accumulation of NaCl in the medulla. Although the loop diuretic can increase ADH levels by inducing volume depletion, responsiveness to ADH is reduced because of the impairment in the medullary gradient.⁹ As a result, water retention and the development of hyponatremia will be limited, unless distal delivery is very low or water intake is very high.

The thiazides, in comparison, act in the cortex in the distal tubule; as a result, they do not interfere with medullary function or with ADH-induced water retention. In addition, in vitro data indicate that thiazides increase...
water permeability and water reabsorption in the inner medullary collecting duct, an effect that is independent of ADH.\(^9\) In addition to water retention, the combination of increased sodium and potassium excretion (due to the diuretic) and enhanced water reabsorption (due to ADH) can result in the excretion of urine with a sodium plus potassium concentration higher than that of the plasma.\(^3\) Loss of this fluid can directly promote the development of hyponatremia independent of the degree of water intake.

To summarize, various mechanisms which can lead to diuretic induced hyponatremia are:

1. Volume depletion can stimulate the release of ADH, leading to the production of a concentrated urine.\(^1,3,8\)
2. Enhanced ADH release may be a secondary event induced by nausea and other neurologic symptoms.
3. Thiazide diuretics may be associated with water retention that is independent of ADH.\(^10\)
4. Patients treated with diuretics may have a reduced glomerular filtration rate, which is a common contributor to hyponatremia in older adults
5. Decreased dietary protein intake, due to dietary preferences or acute illness, may limit electrolyte-free water excretion and predispose to hyponatremia in patients treated to thiazides.

In most patients, the combination of sodium plus potassium loss and water retention accounts for essentially all of the fall in the plasma sodium concentration.\(^2,4\) However, there are patients in whom this does not appear to be the case, raising the possibility that the hyponatremia is due in part to osmotic inactivation of sodium in the cells or perhaps bone.\(^16\) How or if this actually occurs is not clear. A similar hypothesis was proposed in the syndrome of inappropriate ADH and then seemingly excluded by careful balance studies.\(^17,18\)

**CLINICAL MANIFESTATIONS**

The clinical manifestations of diuretic-induced hyponatremia are similar to those of other causes of hyponatremia. The hyponatremia typically begins soon after the onset of thiazide therapy and corrects over a period of days to two weeks after the cessation of therapy.\(^2,3\) Most patients do not exhibit signs of volume depletion.\(^2,6\)

Diuretic-induced hyponatremia is rarely, if ever, associated with cerebral edema severe enough to cause herniation of the brain. This was illustrated in a series of 223 patients hospitalized for symptomatic hyponatremia due to thiazide diuretics; the mean plasma sodium was 115 meq/L.\(^6\) The major symptoms were malaise, lethargy, dizzy spells, and vomiting, all of which are well described manifestations of severe hyponatremia. There was only a 1 percent incidence of seizures and no cases of herniation.\(^6\)

The older literature includes reports of brain damage in outpatients with thiazide-induced hyponatremia.\(^3,7\) However, at the time of these studies, the consequences of overly rapid correction were unknown. The reported patients were all treated with hypertonic saline, increasing the plasma sodium concentration by more than 25 meq/L in 48 hours, a rate of correction now known to be associated with osmotic demyelination in the brain.

**TREATMENT**

Treatment of diuretic-induced hyponatremia consists of discontinuing the diuretic and administering either isotonic saline or, if the hyponatremia is severe or symptomatic, hypertonic saline. There is a potential risk of overly rapid correction of the hyponatremia with either regimen. Once the diuretic has been cleared and the patient becomes euvoletic, antidiuretic hormone (ADH) release will be appropriately suppressed, resulting in the excretion of a dilute urine, which can lead to rapid excretion of the excess water. Thus, patients with moderate to severe hyponatremia must be monitored carefully during
treatment to minimize the risk of osmotic demyelination.¹

Prevention

There is no proven way to identify patients at risk of developing hyponatremia after diuretic therapy, making prevention difficult. A regular course follow up of the patient for serum sodium levels should be done especially in elderly individuals and patients with less body weight. Also, patient and family should be thought about the signs and symptoms of the disease for an early diagnosis and prompt treatment. A thiazide diuretic should generally not be used in patients who have had a previous episode of hyponatremia.

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Non-Pharmacological Management of Hypertension - Beyond Controversy

Bhupendra Chaudhary¹, Rajeev Aggarwala², Puneet Bhasin³

ABSTRACT

Traditional approaches to control the epidemic of blood pressure-related atherosclerotic cardiovascular disease (ASCVD) have largely focused on drug therapy in persons with hypertension. Still, non-pharmacologic therapy, also termed lifestyle modification, has an important and expanding role that complements drug therapy. Specifically, non-pharmacologic therapies can serve as initial therapy in Stage 1 hypertensive patients, facilitate medication step down or withdrawal in patients with well-controlled hypertension, prevent hypertension in high-risk populations, and reduce blood pressure in normotensive individuals and thereby lower their risk of ASCVD.

It particularly refers to life-style modifications i.e. therapeutic lifestyle changes (TLC) which include reducing dietary sodium, exercise for at least 30 min per day, five days per week; to have Dietary Approach to stop Hypertension (DASH) diet protocol and to achieve a weight loss goal of 4.5 kg or more by non-pharmacological measures such as increased physical activity, reduced salt intake, reduced fat intake, alcohol abstinence, smoking cessation, behavioural changes, yoga, meditation etc.

In fact, when we talk about controlling of hypertension, lifestyle modifications is always the first step of foremost importance.

INTRODUCTION

Non-pharmacologic approaches have enormous potential as a means to reduce blood pressure and control hypertension, thereby preventing the occurrence of ASCVD. The current challenge to health care providers, government officials, and the general public is to develop and implement effective clinical and public health strategies that lead to desirable lifestyle modifications.

High blood pressure is an independent risk factor for cardiac as well as cerebro-vascular diseases. At the cut off of 140/90 mmHg, 28 to 44% of the world population has hypertension, with ethnic variations. The lifetime risk of developing hypertension is estimated to be
90%. Indeed, blood pressure is a continued process and any increase above optimal levels, confer additional independent risk of coronary heart disease, stroke, congestive heart failure, end-stage renal disease, peripheral vascular disease and others.

All over the globe, hypertension is poorly controlled. About one third of patients have achieved the National High Blood Pressure Education Programme goal of 140/90 mmHg or lower. The mainstay of hypertension is pharmacotherapy. However, the non-pharmacological aspects are important, but often overlooked. Although, some lifestyle modifications may seem to have only minimal blood pressure lowering effect, these should not be discounted, but rather should be given top priority.

A reduction of systolic blood pressure of 5 mmHg has been associated with 14% reduction in mortality caused by stroke, 9% in mortality caused by heart disease and 7% in all cause mortality. In addition, a weight loss 4.5 kg, a realistic goal for most individuals who are overweight, can reduce or prevent hypertension. Multiple mechanisms appear to contribute to BP reduction by dietary intervention (reduced weight and sodium, alcohol abstinence and increased calcium, potassium and magnesium). For exercise, these include improvements in arterial endothelial function and compliance, left ventricular structure as well as function and perhaps vascular blood supply with increased cardiorespiratory endurance. The available evidence is excessively in support of TLC (therapeutic lifestyle changes) for management of elevated BP and for the primary prevention of hypertension.

While antihypertensive agents have been used, it is imperative that reduction of blood pressure to optimal levels and prevention of age-related increase in BP be pursued actively. There has been increasing emphasis on the prevention and treatment of hypertension by non-pharmacological means, termed lifestyle modifications. Lifestyle modifications that effectively lower BP are reduced sodium intake, increased physical activity, weight loss, smoking cessation, alcohol abstinence in alcoholics and the Dietary Approaches to Stop Hypertension (DASH) diet eating plan.

**STRONGLY RECOMMENDED LIFESTYLE MODIFICATIONS**

**Sodium Reduction**

There is a strong & consistent evidence that reducing sodium intake reduces blood pressure. Dietary salt (sodium chloride) intake has a linear association with blood pressure. Reduced sodium intake to approximately 2 gm/day can prevent hypertension, can facilitate blood pressure control in elderly patients on medication and can potentially prevent cardiovascular events in overweight individuals.

In a Trial of Non-pharmacologic intervention in the Elderly (TONE) study, patients were randomized to a low sodium diet (5 gm of sodium chloride or 2 gm of sodium), a usual care (i.e. no study related counselling in lifestyle change). The intervention group had a 2.8 mmHg more reduction in systolic blood pressure than the control group. A study done later on, assessed the impact on blood pressure of three levels of daily sodium intake i.e. 3.6, 2.0 and 1.2 gm per day, representing a typical American diet. Results demonstrated a graded blood pressure response, with a correlation between greater reduction in blood pressure with lower sodium consumption. The message is as follows:

- Reduce salt intake to (5 gm of sodium chloride or 2.0 gm of sodium/day).
- Reduce amount of salt in food preparations.
- Avoid foods having high salt content.

**Some foods with a high sodium content**

- Potato chips, salted crackers/biscuits
- Fast foods, tomato juice (canned)
- Commercially prepared soups and stews
- Pastries or cakes, processed cheese

It should be noted that in the elderly (and
in Black patients), sodium restriction may be more effective than in Whites and young people.

A lower sodium level of 1,500 mg a day or less is appropriate for people 51 years of age or older and individuals of any age, who have high blood pressure, diabetes or chronic kidney disease. 

Tips for decreasing sodium in diet:

- **Trace how much salt is to be in daily diet**: To keep a food diary to estimate how much sodium is in food and drinks on daily basis.

- **To read food labels**: To choose low-sodium alternatives of the foods and beverages purchased daily.

- **To eat fewer processed foods**: To avoid potato chips, frozen dinners and processed lunch.

- **To avoid extra salt**: To add spices, rather than salt, to add more flavour to your foods.

- **To go slow**: If it is not possible to reduce the sodium drastically, it may be done gradually.

**EXERCISE/INCREASED PHYSICAL ACTIVITY**

Aerobic exercise has positive effects on blood pressure, whether or not a person has hypertension. It reduces, on an average, systolic blood pressure by 4.0 mmHg and diastolic blood pressure by 3.0 mmHg. Additional benefits of aerobic exercise are increased insulin sensitivity and increasing high density lipoprotein cholesterol (HDLC) level.

Since low-calorie diets are challenging, one must also increase energy expenditure with aerobic exercise to have a decent chance for successful weight reduction, which will help in achieving the goal blood pressure. Physicians should help patients find an activity that they enjoy, because enjoyment will increase their adherence. Patients may listen to music while walking, which may help to maintain interest level. If one has pre-hypertension (systolic blood pressure between 120 and 139, diastolic BP between 80 and 89), exercise can help avoid developing full blown hypertension. Regular physical exercise can bring blood pressure down to safer levels.

Avoid being a ‘Weekend Warrior’. It is not a good strategy to limit all exercise on the weekends to make up for weekday inactivity. Those sudden bursts of activity could actually be harmful.

**Recommendation**: Brisk walking for 30 minutes per day, ideally on most days of the week but at least on five days per week. Most health benefits occur with at least 150 minutes per week of moderate-intensity physical activity, such as brisk walking. Some physical activity is better than none, and more activity results in greater benefits. Health benefits of exercise include reduced rates of all-cause mortality, coronary heart disease, hypertension, stroke, type 2 diabetes, metabolic syndrome, colon cancer, breast cancer and depression.

A programme can be structured, so that someone could burn up to 200 extra calories or more a day, over and above the basic calories used for sedentary living etc.

**WEIGHT LOSS**

Weight loss is an important lifestyle modification in reducing blood pressure. A reduction of 5 kg can help reduce blood pressure or prevent hypertension. A reduction of 10 kg may produce a reduction in systolic blood pressure of 5 to 20 mmHg. Weight reduction is more effective than a low salt diet in young adults. However, in middle aged and elderly subjects, there is a significant additive effect of weight reduction and salt restriction on lowering blood pressure.

Besides shedding kilos, one should also keep an eye on one’s waistline. Carrying too much weight around the waist, one can have greater risk of high blood pressure, in general.

- Men are at risk, if their waist measurement is greater than 102 cm (40 inches).
• Women are at risk, if their waist circumference is greater than 88 cm (35 inches).
• Asian men are at risk, if their waist measurement is greater than 90 cm.
• Asian women are at risk, if their waist measurement is greater than 80 cm.

ALCOHOL CONSUMPTION
In view of bad effects of alcohol as well as because of availability of other health benefit programmes, alcohol consumption is not recommended at all for non-drinkers or drinkers.

As part of a comprehensive lifestyle program, alcohol consumption should be limited to two drinks per day (about 1 oz or 30 ml of ethenol) for most men and 1 drink per day women and lighter weight men. If somebody does not normally drink alcohol, the physician should not advocate drinking, as a way to lower blood pressure. There are more potential harms than any benefit to drinking alcohol. Drinking more than the suggested amounts should be cut back.

DIETARY MODIFICATION AND SUPPLEMENTATION
The Dietary Approaches to Stop Hypertension (DASH) Eating Plan study showed that an even lower intake of sodium further reduces BP in both normotensives and hypertensives. However, palatability concerns are important and the fact should be kept in mind that other nutrients intake would suffer, whilst trying to stick to such an intensive regimen (5 gm of salt/day).

The DASH eating plan outlines a diet rich in fruits and vegetables, high in low fat dairy products, potassium, magnesium as well as calcium and low in saturated fats. This can produce a mean reduction of 6 mmHg in systolic blood pressure and 3 mmHg in diastolic blood pressure.

Premier Trial: In this trial, the impact of comprehensive lifestyle changes on blood pressure was assessed. Participants in the lifestyle changes had a greater reduction in blood pressure than those in the usual care group and this was further enhanced with addition of the DASH eating plan.

Garlic is commonly used as a dietary supplement to lower blood pressure. Data from two randomized controlled trials comparing the use of garlic vs. placebo in patients with hypertension showed that garlic may have some blood pressure-lowering effect. However, compared with dietary changes, reduced sodium intake, and physical activity, there is insufficient evidence to support the use of garlic in reducing morbidity or mortality associated with cardiovascular events.

Cocoa has a small but statistically significant blood pressure-lowering effect (average of 2 to 3 mm Hg) in adults with hypertension, but there is no evidence that it improves patient-oriented outcomes in the long term.

Although vitamin C, coenzyme Q10, omega-3 fatty acids, and magnesium have been used for lowering blood pressure, there is no evidence to support their use in the management of hypertension due to lack of data on well-designed randomized controlled trials.

SODIUM, POTASSIUM & BLOOD PRESSURE
Sodium (Na) and potassium (K) fluctuate antagonistically. A decrease in potassium leads to sodium retention, whereas an increase in potassium leads to sodium excretion, thereby promoting diuresis and natriuresis.

In persons with essential hypertension, a diet low in potassium results in a systolic increase of 7 mmHg because of increased sodium retention. Increased potassium resulted in a reduction of 2.42 mmHg in systolic blood pressure and a drop of 1.57 mmHg in diastolic blood pressure. However, current recommendations are to obtain adequate potassium intake through a healthy diet.

SMOKING CESSATION
Cigarette smoking causes 4 mmHg increase in systolic blood pressure and 3 mmHg increase
in diastolic blood pressure. Compared with placebo, nicotine released during cigarette smoking increases sympathetic nervous activity which in turn increases myocardial oxygen demand through increased blood pressure, heart rate and myocardial contractility.

Hypertensive patients, those who smoke have increased risk of total, ischemic as well as hemorrhagic stroke and this rise is related to the number of cigarettes smoked. Smoking cessation should be part of any comprehensive lifestyle modification plan to reduce the risk of high blood pressure and cardiovascular disease.

**YOGA, MEDITATION & OTHER RELAXATION TECHNIQUES**

Yoga and meditation include a variety of techniques, such as repetition of a word or phrase (mantra) and careful attention to the process of breathing, to achieve a state of inner calm, detachment and focus. Transcendental meditation may even reduce blood pressure modestly and also reduces mortality in patients with hypertension. Meditation may have other benefits and does not appear to be harmful, except in patients with psychosis. Biofeedback techniques have been proven effective and may be considered in clinical practice to lower blood pressure.

The mechanism by which relaxation techniques lower blood pressure is unclear. One theory suggests that they may help lower the stress and physiologic arousal produced by the autonomic nervous system, thereby reducing blood pressure.

**CLINICAL FOCUS**

- Lifestyle modifications have definite role in all categories of hypertension and is especially advised in pre-hypertensive stage.
- Lifestyle modifications should be the first-line of therapeutic approach in all patients with mild hypertension.
- Regular exercise, sodium restriction, weight loss measures etc. should be strictly adhered to by hypertensives to maintain a better quality of life.
- Therapeutic lifestyle modifications minimize the cost of pharmacological intervention and the untoward effects of various drugs.
- Daily exercise, as per recommendation, is always better than weekend vigorous exercise, which may actually be harmful.
- Dietary modification, as per DASH protocol, is ideal and may be gradually attained.
- Alcohol can never be recommended and should not be initiated in non-drinkers.
- Meditation helps in achieving the goal BP and at the same time helps in having physical and mental well-being.
- Pharmacological intervention in a timely fashion is desirable in all patients having BP, who are not optimally controlled with therapeutic lifestyle modifications.

**SUMMARY**

Non-pharmacologic measures should be part of routine management of hypertension. It is emphasized that simple advice from physicians can have positive influence on patient’s motivation to make positive lifestyle changes. Lifestyle recommendations’ should not be given as lip service but instituted with adequate behavioural and expert support and reinforced periodically. Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients undergoing non-pharmacological treatment should be followed up closely to start drug treatment when needed and in a timely fashion.

Non-pharmacologic approaches to reduce BP have enormous potential as a means for preventing hypertension and controlling BP, thereby reducing the occurrence of ASCVD. Now, the greatest challenge is developing and implementing strategies that lead to a reduced salt intake, reduced weight,
increased physical activity, moderate alcohol intake among those who drink, and an overall healthy dietary pattern.

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CASE REPORT

Robotic Adrenalectomy: An Emerging option in the treatment of Pheochromocytoma

Ameya Tirodkar¹, Nihar Mehta², AB Mehta³

ABSTRACT
Pheochromocytoma is a rare catecholamine secreting tumor originating usually from adrenal medulla and produces signs and symptoms due to excessive catecholamine secretion from tumour. A 50 year old lady, hypertensive since 20 years was admitted at our center with recent history of three episodes of accelerated hypertension in the last two months; despite being on three anti hypertensive drugs. Clinical suspicion of pheochromocytoma was confirmed with transabdominal USG, CT scan of abdomen & by 24 hour urinary catecholamine level. After three weeks of pre-operative preparation with labetalol and propanolol, she was re-admitted for Adrenalectomy. Robot assisted Adrenalectomy was performed using the da Vinci Robotic system. Patient had an uneventful perioperative course and was discharged on day 3 of the procedure.

Pheochromocytoma is a rare cause of hypertension. Adrenlectomy offers complete cure from this condition. Intraoperative handling the tumour and excision is technically challenging. Robotic Surgery provides an efficient alternative to conventional Laproscopic adrenalectomy, minimizing the overall complications of the procedure.

INTRODUCTION
Pheochromocytoma is a rare tumor originating from catecholamine secreting chromaffin cells that are derived from the ectodermic neural system and mostly situated within the adrenal medulla.¹ It is estimated that the annual incidence of pheochromocytoma is approximately 0.8 per 100,000 person-years.² Catecholamine-secreting tumors are rare neoplasms, probably occurring in less than 0.2 percent of the patients with hypertension.¹² We present a case of adrenal pheochromocytoma in a 52 year aged female patient presenting with paroxysmal attacks of hypertension who was treated successfully by Robotic Adrenalectomy.

CASE REPORT
A 52 years female was admitted with complaints of paroxysmal attacks of dizziness and headache for last 6 months. She required 3
anti-hypertensive medications, Telmisartan 40 mg, Nebivolol 5 mg and Amlodipine 10mg for her blood pressure control. She was admitted in emergency with Hypertensive crisis at an outside hospital. She was diagnosed to have hypertensive left ventricular failure for which she required treatment with i.v. Nitroglycerine and ICU stay for few days. Patient was stabilized and discharged with increased doses of anti hypertensive medicines to optimize her blood pressure. Recurrent hospitalizations and labile blood pressure with headaches had increased morbidity in the last 6 months for which she had frequent consultations at different centers with no relief.

On physical examination patient had a Pulse of 70/min, Blood Pressure of 160/90mm hg. Complete blood count, Random Blood Sugar, Blood urea, Chest X-rays and ECG reports were within normal limit. Thyroid, chest and cardiovascular system examination were unremarkable. There was no abdominal bruit or lower extremity oedema. Serum creatinine, Serum Potassium and other electrolytes were normal. Plasma Renin levels were within normal levels.

Apart from the routine investigations, Plasma Metanephrine level were slightly raised 73.2 pg/ml (normal <65 pg/ml). Her 24 hours Urine metanephrine levels were normal.

She underwent a CT Scan of Abdomen with contrast which revealed a 14 mm x 8 mm well defined enhancing lesion in the medial limb of the right adrenal with Hounsfield unit (HU) of – 3 units (Figures 1, 2).

In view of her clinical and laboratory findings, it was decided to prepare the patient for elective Right Adrenalectomy. She was started on Tablet Prazosin 2.5 mg 12 hourly and gradually stepped up to 5 mg 12 hourly. Tab Labetalol was added to the treatment regimen for the next 3 weeks. She underwent Robotic right Adrenalectomy under General Anaesthesia. Patient had minor intra operative Blood pressure fluctuations during the procedure. She tolerated the procedure well. Her blood pressure normalized to 110/70 mm hg on first post operative day.

Her post operative course was uneventful. Her blood pressure medications requirement had decreased and patient was discharged on third post operative day with Tablet prazosin 2.5 mg and Tablet Labetelol 25 mg once a day. The excised Adrenal gland mass was sent for Histopathology analysis which showed hyperplasia of Adrenal Medulla with oncolytic changes (Figure 3). Immunohistochemistry study of the sample demonstrated all cells of Medulla to be strongly positive for...
Chromogranin and Synaptophysis, which are markers of Neuroendocrine tumours (Figures 4, 5).

The patient had clinical improvement with decrease in the dosage of her anti hypertensive medications. There were no further episode of paroxysmal headaches on following up of the patient for 6 months.

DISCUSSION
Pheochromocytomas are rare neuroendocrine tumors originating from chromaffin tissue. They are found in 0.2-0.6 % of subjects with hypertension. The cost-effectiveness of diagnostic workup of pheochromocytoma is markedly restricted by low specificity of clinical symptoms together with symptoms overlapping within a wide variety of other conditions, including idiopathic hypertension, hyperthyroidism, heart failure, migraines, and anxiety. The most common sign of pheochromocytoma is hypertension, found in approximately 95% of patients and related to catecholamine excess. Upto two-thirds of patients with hypertension who have pheochromocytoma, may have paroxysmal elevation of blood pressure. Our patient had underlying essential hypertension with paroxysms of accelerated hypertension.

The clinical manifestations of a pheochromocytoma result from excessive catecholamine secretion by the tumor. The first step in the diagnosis is the biochemical confirmation of catecholamine excess. Plasma metanephrine testing has the highest sensitivity (96%) for detecting a pheochromocytoma, but it has a lower specificity. In comparison, 24 hour urinary catecholamines and metanephrines have a sensitivity of 87.5% and a specificity of 99.7%. In our case plasma metanephrine levels were high.

The biochemical diagnosis is then followed by the localization of the pheochromocytoma and / or metastases. Computed Tomography (CT) scanning with contrast or Magnetic Resonance Imaging (MRI) is carried out to locate and determine the size of the tumour. In this case a 14 mm x 8 mm mass was detected in the medial limb of the Right Adrenal
gland. Surgical resection of the tumour is the treatment of choice and usually results in cure of hypertension. It is also important to remember that tumor manipulations during surgery may be associated with the release of tremendous amounts of catecholamines into circulation, which might be capable of overpowering the pharmacological blockade.

In order to control hypertension levels prior to an operation, even in preoperative normotensive patients, it is recommended that patients undergo preoperative pharmacological treatment. Careful preoperative preparation requires combined alpha and beta blockade to control blood pressure and to prevent intraoperative hypertensive crisis. Alpha-adrenergic blockade, in particular, is required to control blood pressure and prevent a hypertensive crisis. Our patient was put on labetalol and prazosin prior to the Robotic Adrenalectomy surgery.

Robotic Adrenalectomy is found to be at par with Laproscopic Adrenalectomy in terms of success rates, complications and conversion to open resection. In addition, current use of this modality is limited by higher cost, which precludes its routine use. However it provides potential advantages of a shorter hospital stay, less blood loss, and lower occurrence of postoperative complications.13

It is challenging to maintain normal haemodynamics during Pheochromocytoma resection, in the face of catecholamine surges (especially at laryngoscopy, peritoneal insufflation, surgical stimulation, and tumor handling) followed by the opposite scenario following tumor ligation. It requires aggressively utilizing potent, short acting, intravenous, anti-hypertensive agents – sodium nitroprusside and nitroglycerin - to control sudden changes in blood pressure during surgery. If adequately primed for the surgery, the chances of wide blood pressure fluctuations are minimized.

Our patient underwent Robotic excision of the Right Adrenal Gland and with 3 days of post operative stay in the hospital. On three months of post surgery follow up, patient was weaned off her hypertension medications and had no further episode of accelerated hypertension.

**CONCLUSION**

Pheochromocytoma is an important cause of Secondary Hypertension, which has a definite surgical cure. In addition to being a great mimicker; pheochromocytoma represents one of the most challenging diagnosis. This case emphasizes the importance of appropriate preoperative conditioning of the patient to minimize the intraoperative haemodynamic instability. Robot assisted adrenalectomy is a novel surgical approach the post operative stay, and minimize complications and morbidity in such patients.

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HSICON 2018

31st August - 2nd September 2018 • Thiruvananthapuram (Trivandrum)

Organising Chairman
Dr. P. K. Sasidharan
e-mail: sasidharanpk@gmail.com

Organising Secretary
Dr. R. Chandni
Mobile: 9447202748
e-mail: chandnisajeevan@gmail.com
Rosuvastatin range
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Roseday® 5/10/20/40
Rosuvastatin 5/10/20/40 mg

Roseday® F5/F10/F20
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