Review Article
Medical Therapy of Heart Failure: Harnessing the Recent Research and Concepts
Dr. Vinod Nikhra

Review Article
Pathogenesis, Classification and Primary Prevention of Atrial Fibrillation
Dr. Pranab Jyoti Bhattacharyya

Review Article
Best Practices in Hypertension-2017
Dr. PC Manoria, Dr. Pankaj Manoria, Dr. SK Parashar, Dr. RK Jha

ECG of the Month
Low Voltage Electrocardiogram
Dr. SR Mittal

Editor in Chief | Dr. O. P. Yadava

cimsasia.com
get connected | get addicted
THE MOST POWERFUL DRUG SEARCH
Rational Prescription - Don’t shoot (....hic) - prescribe off the hips!  

OP YADAVA  

Medical Therapy of Heart Failure: Harnessing the Recent Research and Concepts  

VINOD NIKHRA  

Pathogenesis, Classification and Primary Prevention of Atrial Fibrillation  

PRANAB JYOTI BHATTACHARYYA  

Best Practices in Hypertension-2017  

P C MANORIA, PANKAJ MANORIA, S K PARASHAR, R K JHA
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Doppler Imaging in Evaluation of Diastolic Dysfunction</td>
<td>157</td>
</tr>
<tr>
<td>Low Voltage Electrocardiogram</td>
<td>160</td>
</tr>
<tr>
<td>Valvular Vegetations</td>
<td>166</td>
</tr>
</tbody>
</table>
Rational Prescription - Don’t shoot (….hic) - prescribe off the hips !

On a random audit, most prescriptions would throw up irrational prescribing of certain default medicines like multi vitamins, anxiolytics, hypnotics, sedatives, laxatives and antacid/gas tablets’. Most of these are inconsequential and, even though a huge national waste of resources and money, are at least harmless. However, of the so called antacids, proton pump inhibitors (PPI) have long been under scrutiny and have been known to interact with other medicines. They have also been implicated in chronic kidney disease, infections and bone fractures in presence of osteoporosis. To cap it all, a recent study1 has shown that long duration use of PPIs is associated with ‘Mortality’ (Hazard ratio-HR-1.25). In a longitudinal observational Cohort Study conducted at the US department of Veteran Affairs,1 at a mean follow up of nearly six years, PPI use was associated with 25% increased mortality as compared to the H2 receptor blockers. This mortality risk was also observed when PPI users were compared with non users (HR 1.15, CI 1.14 to 1.15). In fact the mortality risk of PPI was magnified if the users did not have any gastrointestinal condition, thereby challenging the indiscriminate and default prescription of these group of drugs.

These findings are in contradiction to previous studies like the COGENT Trial, where no safety issues or mortality was observed in high risk coronary artery disease patients with PPI use versus placebo. However, this study was limited due to its short follow up of only six months and the results of the ongoing COMPASS Trial, with a much longer follow up, are keenly awaited to address the issue.

Even though not proven, the signals are quite significant enough to be taken cognizence of, and even intuitively, it makes no sense to prescribe a drug indiscriminately when its benefit has not been conclusively demonstrated. This is more so relevant in our country, where we the Indians are so ‘Gut obsessed’ that unless we move the heavens through the bottom end, at least once a day if not twice, and that too heartedly, we do not feel satisfied. Sour eructations and burping too are a national pastime and ubiquitous complaints and constituent of all diseases and syndromes that are Indian. We as doctors will be served well, treating them verbally rather than pharmacologically, even if it means spending a few moments extra with our patients.

Medical Therapy of Heart Failure: Harnessing the Recent Research and Concepts

VINOD NIKHRA

Abstract
The HF is a complex clinical syndrome associated with significant morbidity and potential loss of work days, hospitalization and substantial cost of treatment. Furthermore, its clinical course is gradually progressive, affecting quality of life (QOL) especially during later years of life, with significant mortality. The HF is attended by cardiovascular alterations in form of arterial stiffening and left ventricular hypertrophy. The myocardial metabolism is relatively normal during the early stages of HF, but with the advancing stages, alterations occur at cellular and molecular levels. There occurs a depletion of myocardial enzymes and cofactors responsible for downregulation of fatty acid oxidation, increased glycolysis and glucose oxidation, reduced respiratory chain activity, and an impaired reserve for mitochondrial oxidative flux leading to alterations in myocardial energetics. During recent years, there has been substantial progress in understanding and treatment of HF as well as improvement in treatment modalities. In a nutshell, the medical therapy for HF envisages to relieve symptoms of HF and improve quality of life, and retard the progression of HF. Further, it aims to reduce episodes of acute decompensation and need for hospitalization, and finally to reduce the mortality in HF and help the patients to live longer by harnessing the recent research for improving the myocardial contractile dysfunction and modulation and manipulation of myocardial substrate metabolism having therapeutic potential.
There is a rising incidence of HF worldwide affecting around 25 million people. In general, the HF prevalence is 6–10 percent, with an annual incidence of 1 percent in adults over the age of 65. One-year mortality due to HF is about 20 percent and 5-year mortality is as much as 50 percent. Currently, HF is a major health concern carrying an increased morbidity and potential loss of work days, hospitalization and substantial cost of treatment. Furthermore, the clinical course is gradually progressive, which affects QOL especially during later years of life. The untreated HF fare clinically worse over time and treatment outcome is often suboptimal. However, with optimal treatment, which is challenging but holds promise, the progression of HF can be contained or reversed with improvement in QOL.

HF, a complex clinical syndrome, is initiated after either damage to myocardium following an acute coronary event or because of left ventricular (LV) remodeling as in hypertensive heart disease, or because of a gene defect as in a hereditary cardiomyopathy. Further, the clinical courses of HF is influenced by aetiology, duration, underlying coronary artery disease (CAD), endothelial dysfunction and ischemic injury, and presence of comorbidities such as diabetes, hypertension, and obesity. The affliction adversely affects the cardiac pumping capacity, and in most cases is asymptomatic for a variable period. HF presents as both diastolic and systolic LV dysfunction, and there occurs decreased exercise capacity, fluid retention and pulmonary congestion. The symptomatic HF patients represent the visible part of an iceberg and best defined as the acute decompensation of chronic HF.

At the cellular and subcellular levels, the HF is associated with defects in mitochondrial function. The alterations in substrate metabolism contribute to contractile dysfunction and LV remodelling. At the advanced stages of HF, the myocardium has low ATP content due to a decreased ability to generate ATP by oxidative metabolism and loss of contractile strength. There is a progressively reduced myocardial performance, mainly due to the loss of myocardial tissue and dysfunctional viable myocytes, or a combination of both. Myocardial metabolism is altered and the substrate utilization switches from mostly fatty acids to glucose. In addition to metabolic derangements, there is increased adrenergic tone which adds further to metabolic dysregulation and the progression of myocardial dysfunction.

The incidence of HF is directly related to age and the ageing affects cardiac contractile properties and LV size, myocardial flow reserve and mitochondrial function. A hallmark of HF is the re-expression of fetal form of genes altering mitochondrial energetics. In the fetal and immediate new-born period, the heart is very reliant on glycolysis as a source of energy. Post-birth, there is a dramatic 10-fold increase in fatty acid oxidation accompanied by a parallel decrease in glycolytic rates. Various key enzymes including malonyl-CoA involved in fatty acid oxidation are altered in transition from fetal to adult metabolism. With ageing (~69 vs. 29 years of age), there occurs a reversal, expressed as a decrease in myocardial fatty acid uptake and oxidation, with no change in glucose uptake under resting conditions.

As compared to sympathetic nervous system, components of renin angiotensin system (RAS) come into play comparatively later in HF. The AT1 receptor activation, leads to vasodilatation, inhibition of cell growth, natriuresis and bradykinin release; whereas the activation of AT2 receptors leads to vasodilatation, inhibition of cell growth, natriuresis and bradykinin release. The sustained expression of Aldosterone provokes endothelial dysfunction, oxidative stress and inflammation, and...
provokes hypertrophy and fibrosis within vasculature and myocardium, resulting in reduced vascular compliance and increased ventricular stiffness.\(^7\)

The myocardial metabolism is relatively normal during the early stages of HF, but with the advancing stages metabolic alterations occur at cellular and molecular levels.\(^8\) There occurs a depletion of myocardial adenosine triphosphate, phosphocreatine, and creatinine kinase, and downregulation of fatty acid oxidation, increased glycolysis and glucose oxidation, reduced respiratory chain activity, and an impaired reserve for mitochondrial oxidative flux affecting myocardial energetics adversely.

Arterial stiffening is a sign of cardiovascular ageing. Arteries nearer the heart are elastic, whereas the smaller peripheral arteries are muscular. With arterial stiffening, there occurs a progressive increase in stiffness from the ascending aorta to the peripheral arteries. This leads to arterial hypertension and remodelling of arteries, which is further complicated by atherosclerosis, characterized by presence of plaques and further arterial narrowing.\(^9\)

Central aortic stiffening has a major influence on central blood pressure (CBP), and directly relates to coronary perfusion. Aortic stiffness contributes to CV risk through influences on LV afterload and hypertrophy. The increased stiffening is associated with inappropriate CBP and blood flow to the organs. The increased aortic stiffness is an independent predictor of CV events. Hypertension is associated with a number of structural and functional changes in the vascular tree. At the level of the large arteries, there is a gradual stiffening and loss of endothelial function. At the level of small arteries, there is also a loss of endothelial function in hypertension, contributing to an augmented vasopressor sensitivity leading to arteriolar narrowing and rarefaction of the number of arterioles and capillaries. Thus, the macro- and microcirculation are affected in hypertension and contribute to target-organ damage at the level of the brain, the eyes, and the kidneys, and potentially, contributes to myocardial ischemia.

The cardio-ankle vascular index (CAVI) is an important predictor of CV diseases and a stiffness index of the systemic arteries from the origin of the aorta to the ankle.\(^10\) It indicates the severity of narrowing due to arteriosclerosis and atherosclerosis, and also the vascular tone. The CAVI is elevated with ageing, and in hypertension, CAD, diabetes mellitus, renal disease, smoking and stress. In middle-aged hypertensives with metabolic syndrome, higher CAVI values were associated with subclinical inflammation, oxidative stress, LVH, and diastolic dysfunction. In HF, there is a negative correlation between the CAVI and LV ejection fraction. This has important implications for the pharmacological treatment of hypertension. An ideal antihypertensive regimen should abolish the vicious cycle between the increased resistance in the microcirculation and the increased stiffness of the larger arteries. An optimal antihypertensive therapy improves large arterial stiffness by decreasing arterial wall tension and central aortic BP.

The CAVI decreases with the administration of statins, angiotensin converting enzyme (ACE) inhibiting and angiotensin receptor blocking (ARB) agents, and calcium channel blockers (CCBs). The combination of an ACEI/ARB and a CCB has a synergistic effect on BP lowering, arterial function and structure. There are important differences between the various types of antihypertensive drugs regarding their effects on parameters of large arterial stiffness depending on the differential effects of drugs on arterial wall properties and the autonomic nervous system. There is a negative effect of older beta-blockers (BBs), mainly atenolol on central BP, attributable to the lowering of heart rate, which leads to augmentation of aortic systolic BP. The newer BBs with vasodilating properties, such as nebivolol, are devoid of these effects. Indapamide, ACEIs and CCBs appear to have a beneficial effect on arterial stiffness and vascular function. The ASCOT study showed beneficial effects of statin therapy on carotid artery stiffness in patients receiving perindopril or amlopidine.\(^11\)

LVH is a cardinal manifestation of subclinical organ damage in a variety of settings including hypertension, CAD and heart failure.\(^12\) LVH is the result of a combined effect on the cardiac structure of deranged hemodynamic and non-hemodynamic factors and the interplay between HT, and/or volume overload with genetic, humoral, and hormonal factors as major determinants of LVH.\(^13\) LVH is a marker for increased CV risk and is typically characterized by cardiomyocyte hypertrophy and interstitial fibrosis due to an imbalance between stimulatory (i.e., angiotensin II, endothelin I, catecholamines, aldosterone, basic fibroblast growth factor, insulin like growth factor) and inhibitory factors (prostaglandins, NO, natriuretic peptides) controlling myocardial texture and growth.\(^14\)

Clinically, HF can develop in the absence of coronary artery disease in patients with a history of LVH due to hypertension or aortic stenosis, though unlike HF in patients with a history of ischemic heart disease, LV dilatation develops relatively late in hypertensive patients who progress to HF. The mechanisms that precipitate
HF have been related to neuro-hormonal activation secondary to poor cardiac function, presumably due to poor diastolic filling and increased metabolic stress and decreased phosphorylation potential.

The heart has a high level of architectural efficiency maintained by a constant turnover and rebuilding from a steady supply of nutrients. But, the heart is designed to pump against volume, not against pressure. In case of a higher pressure gradient, that is, high afterload, there is a compensatory LVH, and higher oxygen consumption and greater expenditure of energy, which has implications on myocardial energetics.

The heart is an aerobic organ and efficient volume pump with variable oxygen consumption depending upon work. The heart propels ~5 l/min of blood, >7000 l/day and >2.6 million l/year, and to perform its work, the myocardium hydrolyses >6 kg of adenosine triphosphate (ATP) daily, which is produced by transferring chemical energy from nutrients taken up into the myocytes from the bloodstream. The myocardium can oxidize fatty acids and glucose simultaneously and in variable ratios according to substrate availability and physiological state.  

About 95 percent ATP generation in the normal myocardium is from oxidative phosphorylation in the mitochondria. About 60–70 percent of ATP hydrolysis fuels contractile shortening, and the remaining 30–40 percent is used for the sarcoplasmic reticulum Ca²⁺-ATPase and other ion pumps. The regulation of myocardial metabolism is linked to arterial carbon substrate concentration, hormone concentrations, coronary flow, inotropic state, and the nutritional status, whereas the metabolic pathways are controlled by regulatory enzymes, changes in the concentration of metabolites and metabolic proteins.

In the normal heart, ~60–90 percent of the acetyl-CoA is from β-oxidation of fatty acids, and 10–40 percent from the oxidation of pyruvate derived from glycolysis and lactate oxidation. The glycogen pool in the heart is relatively small. The oxidation of glucose and pyruvate and the activity of PDH in the heart are decreased by elevated rates of fatty acid oxidation, such as occur if plasma levels of free fatty acids (FFA) are elevated, and the pyruvate oxidation is enhanced by suppression of fatty acid oxidation. The primary substrates utilized by the myocardium are free fatty acids (FFAs); and glucose, and lactate, with amino acids and ketones, play a minor role. Three interconnected pathways regulate FFA breakdown, ATP synthesis, and energy transfer from the mitochondria to the contractile myocardial apparatus. A notable aspect of FFA oxidation is its higher myocardial oxygen consumption, lower thermodynamic yield and decreased mechanical efficiency, as compared with glucose.

The rate of fatty acid uptake by the heart is primarily determined by the concentration of non-esterified fatty acids in the plasma. FFAs are associated with proteins or covalently bound to coenzyme A or carnitine, and their plasma concentration is regulated by the net release from triglycerides in adipocytes, chylomicrons and VLDL hydrolysed by lipoprotein lipase. Hormone-sensitive lipase is activated by catecholamines and inhibited by insulin. Once transported across the sarcolemma, the non-esterified fatty acids bind to FA binding proteins (FABPs) and are then activated by esterification to fatty acyl-CoA by fatty acyl-CoA synthase (FACS). In the normal heart 70–90 percent of the fatty acids entering the cell are converted to acylcarnitine and immediately oxidized, and 10–30 percent enter the intracellular triglyceride pool. Fatty acid β-oxidation occurs primarily in the mitochondria and to a small extent in peroxisomes.

Carnitine palmitoyl transferase (CPT-I) serves the key regulatory role in controlling the rate of fatty acid uptake by the mitochondria. The activity of CPT-I is in turn regulated by malonyl-CoA, formed by carboxylation of acetyl-CoA. The activity of acetyl-CoA (ACC) is inhibited by phosphorylation by AMP activated protein Kinase (AMPK). Thus, activation of AMPK reduces malonyl-CoA formation and accelerates of fatty acid oxidation. The AMPK activation in the heart also stimulates glucose transporter translocation and glucose uptake; thus activation of AMPK can cause an increase in both carbohydrate and fatty acid metabolism. Thus, when the metabolic rate of the heart is increased, as occurs during exercise, increased AMPK activity would increase ACC production from both carbohydrates and lipids, and thus ensure an adequate supply of substrate to the mitochondria. An important nuclear gene transcription control that regulates the capacity for myocardial mitochondrial fatty acid oxidation is regulated by the peroxisome proliferator-activated receptors, or PPARs.

The NO also plays an important role in the regulation of myocardial substrate metabolism. Its activity, in turn, is regulated by a possible feedback mechanism involving AMPK. Because NO is a main regulator of vascular tone and cardiac function, the regulatory effect exerted by AMPK on eNOS represents a link between metabolic adaptations and cardiovascular function under conditions of stress.

With LVH and In HF states, there are significant changes in the myocardial energetics. The myocardial architecture remains relatively intact and certain myocytes are viable, but dysfunctional. This heralds various metabolic imbalance and abnormalities. There occur altered substrate utilization (increased dependence on glucose), decreased oxidative phosphorylation, decreased high-energy phosphate content, generation of reactive oxygen species, and mitochondrial dysfunction. There is decreased activity of fatty acid β-oxidation, tricarboxylic acid (TCA) cycle enzymes, and complexes involved
in the electron transport chain (ETC). This is further exacerbated by the increasing metabolic demands triggered by the excessive and continuous activation of the sympathetic nervous system typical of HF.

In the HF myocardial energy metabolism is altered initially as the physiologically adaptive response. The myocardial adaptation aims to maximize efficiency by:
- A preferential use of glucose metabolism, mediated by a down-regulation of pyruvate dehydrogenase isoforms (PDKs) - which exerts a negative control on glucose oxidation;
- Lower expression of the PPARα/ RXR2 complex and of the enzymes CPT-1 and medium chain acyl-CoA dehydrogenase, leading to a decline in FFA metabolism; and
- Down-regulation of uncoupling proteins.

The metabolic adaptations come early, whereas the changes in substrate use are a late-stage phenomenon. In advanced HF, there is a downregulation of myocardial fatty acid oxidation enzymes, which is consistent with the switch in substrate metabolism away from fatty acid oxidation towards greater glucose oxidation. In the early stages of HF there is a normal rate of fatty acid oxidation, but in advanced or end-stage HF there is downregulation of fatty acid oxidation. Results from animal models of HF by Recchia et al, support the concept that there is relatively normal myocardial substrate metabolism in the early and middle stages of the development of HF, but a sharp switch away from fatty acid towards carbohydrate oxidation in end-stage HF. The metabolic changes in HF are accompanied by a fall in cardiac NO, which exerts an effect on cardiac substrate utilization. The lack of NO in HF also leads to excessive mitochondrial O2 consumption and contributes to coronary microcirculatory dysfunction and myocardial ischemia. The failing heart has significantly reduced mRNA for the fatty acid oxidation enzymes long-chain acyl-CoA dehydrogenase (LCAD) and medium-chain acyl-CoA dehydrogenase (MCAD), as well as protein levels of MCAD, with no downregulation of the mRNA for the glycolytic enzyme GAPDH. Thus in the early stages of HF, as in the normal heart, the myocardium primarily relies on fatty acid as an oxidative substrate. The increase in glycolytic flux and glucose oxidation with HF is perhaps due to alterations in pathway regulation that are secondary to suppression of fatty acid oxidation, and are not due to upregulation of proteins involved in glucose uptake, glycolysis, or pyruvate oxidation.

Later with the progression of HF, the compensatory hyperadrenergic state leads to elevation of blood FFA levels and insulin resistance, which lead to up-regulation of FFA metabolism, increased oxygen consumption, and decreased cardiac efficiency. With the progression of the HF, a steady decline in utilization of both FFAs and glucose occurs, leading to impaired energy delivery to the myocytes leading to further LV dysfunction. In HF various metabolic changes occur including a reduction in total cellular ATP levels, resulting in an increase in the AMP: ATP ratio leading to low energy states and hypoxia. The AMPK plays an important role in the myocardial response to ischemia and the development of post-ischemic LV dysfunction and in the development and progression of HF.

There occur altered expression of both glycolytic and mitochondrial enzymes, both nuclear and mitochondrial transcription alterations, and ETC and oxidative phosphorylation defects in HF. In addition, HF impairs the capacity for the creatine kinase system to transfer mitochondrial ATP to the myofibril. In the failing heart, there are mitochondrial membrane disruptions and matrix depletion, a lower capacity for respiration with a variety of substrates, and decreased
capacity for oxidative phosphorylation. There results in a reduced ability to generate ATP, a fall in myocardial ATP content, a rise in ADP, and an impairment of the kinetics of cardiac contraction and relaxation.

During recent years, there has been substantial progress in understanding and treatment of HF as well as improvement in treatment modalities available for CVD and other causative disorders leading to HF. The aims and goals of medical therapy for HF (Figure 3) are to:

- Relieve symptoms of HF and improve quality of life
- Slow down the progression of HF
- Reduce episodes of acute decompensation and need for hospitalization
- Reduce the Mortality in HF and Help the patients live longer.

The standard medical therapy is aimed at improving clinical symptoms and slowing the progression of contractile dysfunction and LVH. The treatment aims to correct fluid volume overload by diuretic, improve hemodynamic derangements by digoxin and other inotropic agents, and suppress neuro- hormonal over-activity and imbalance by drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonist (MRA).

There are some novel therapies for HF, introduced in recent years, which modulate the metabolic function of the heart and appear to be promising to improve the performance of viable myocardium.

1. **Trimetazidine**: As a partial inhibitor of 3-ketoacyl CoA thiolase, the terminal enzyme of β-oxidation, it improves glucose oxidation, reduces Ca²⁺ current, and prevents Ca²⁺ overload. By preserving the ATP pool, reducing lipid peroxidation, inhibiting the catecholamine-mediated increase of intracellular diastolic Ca²⁺ concentration, and preventing reductions in sarcoplasmic reticulum Ca²⁺ content, it appears to protect myocardial damage. It increases LVEF, myocardial perfusion, oxidative metabolism, and work efficiency in HF. Trimetazidine plus standard therapy show improvement of symptoms, clinical complications and QOL in elderly patients with IHD and reduced ventricular function.

   Chronic inhibition of myocardial FFA oxidation has been investigated with trimetazidine in HF patients and rodent models. Trimetazidine is an effective antianginal drug. In addition, it alters myocardial phospholipid metabolism, stimulating the turnover and accumulation of long-chain fatty acids into phospholipids, decreasing the fraction of phospholipids containing linoleic acid, and increasing the content of phospholipids comprising oleic and stearic acids. In animal HF models, it significantly decreased PDH activity and chronic treatment with trimetazidine extended the average survival.

   A small clinical trial, treatment with trimetazidine resulted in significant improvement in LV ejection fraction at rest and enhanced LV wall motion during a dobutamine stress test in NYHA classes II and III HF patients. In other clinical studies, trimetazidine improved systolic LV function in patients with diabetes and ischemic cardiomyopathy compared with placebo. Treatment with trimetazidine for 6 months also improved diastolic function. Trimetazidine has not been evaluated in patients with HF from other than an ischemic origin, nor have large-scale clinical trials were conducted.

2. **Ranolazine**: It bears a structural similarity to trimetazidine. In myocytes, it inhibits the late inward sodium (Na⁺) channel. The Na⁺-mediated Ca²⁺ overload plays a role in the mismatch between excitation/contraction coupling and oxidative phosphorylation in the failing myocardium. Thus, ranolazine has positive haemodynamic effects documented after 3 months of oral treatment with ranolazine. Further, it also exerts beneficial effects on myocardial hypertrophy, fibrosis, and capillary density. As in vitro evidence, in a dog model of HF, infusion of ranolazine improved LVEF and mechanical efficiency without increasing MVO₂. However, in the TIMI-36 trial, treatment with ranolazine did not affect the rates of hospitalization for HF in patients with non ST-elevation acute coronary syndromes.

3. **Ivabradine**: The elevated heart rate (HR) in HF reflects over-activity of the sympathetic nervous system and is associated with adverse CV outcomes. The high HR is an
independent risk factor in HF and lowering HR is known to improve outcome. The beta-blockers reduce HR in HF treatment, but the up-titration of beta-blockers is associated with an increased risk of adverse reactions including negative inotropic effect and vasoconstriction in the bronchi. Ivabradine acts directly and selectively inhibits the If current in the SA node without affecting the myocardial contractility or relaxation, ventricular repolarization, or intracardiac conduction. This mechanism of action has potential benefits of decreased HR in HF and ivabradine is useful in patients with symptomatic LV systolic dysfunction, elevated HR, and intolerance to beta-blockers. The BEAUTIFUL (Morbidity-Mortality Evaluation of the If inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Systolic Dysfunction) trial established that ivabradine reduced HR without any effect on the primary endpoint of cardiovascular death or admission to a hospital for new-onset or worsening HF. Further, in a subgroup of patients with an HR of at least 70 bpm, ivabradine revealed a clear benefit with respect to the secondary endpoints of admission to a hospital for a fatal or non-fatal ACS or myocardial infarction. Another study, the SHIFT (Systolic HF Treatment with If Inhibitor Ivabradine) trial having patients with stable symptomatic HF, LVEF of 35 percent or less and in sinus rhythm with an HR of 70 or more, ivabradine significantly reduced hospital admission for worsening HF and deaths due to HF. The effect was consistent across all subgroups, including the elderly.

4. **Sacubitril/valsartan:** The combination of RAAS blockade with inhibition of neprilysin, is potentially superior to blockade of the renin-angiotensin-aldosterone system alone by ACE inhibitors or ARBs, for treatment of chronic and symptomatic HF, in patients having LVEF of less than 40 percent. The agent combines a neprilysin inhibitor, sacubitril and an ARB, valsartan. Neprilysin is responsible for the degradation of vasoactive peptides such as NPs, bradykinin, and adrenomedullin and contributes to the breakdown of angiotensin II. As NPs act to promote natriuresis, diuresis, and vasodilation, neprilysin inhibition counteracts the neuro-hormonal activation and inhibits the RAAS. This agent can be used in conjunction with other HF therapies. The PARAMOUNT - Prospective Comparison of ARNi (angiotensin receptor-neprilysin inhibitor) with ARB on Management of Heart Failure with Preserved Ejection Fraction (HFpEF) - trial and PARAGON-HF have examined the long-term outcome of Sacubitril/valsartan compared with valsartan in patients with HFrEF. The PARADIGM-HF (Prospective Comparison of ARNi with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) Trial was conducted in patients who had NYHA class II–IV HF and an LVEF of not more than 40 percent, who were randomly assigned to Sacubitril/valsartan or enalapril. The trial outlined a benefit with ARNi therapy and was associated with significant reductions in all-cause mortality, CV mortality, and hospitalization for worsening HF. This trial provided strong evidence for superiority of the ARNi in patients with HF with reduced ejection fraction (HFrEF).

These observations reflect the lack of effective therapies, targeted to the underlying pathophysiological processes within ischemic cardiomyocytes. There is, thus, a need for novel therapies for HF to improve cardiac performance and prevent the progression of LV dysfunction and reverse LVH, and improve the prognosis. The novel therapies should act through optimization of myocardial substrate metabolism, shifting that away from fatty acids towards carbohydrate oxidation to improve pump function and retard the progression of HF, and favourably modulate the myocardial metabolic function of the heart and have potential to improve the performance of viable myocardium. Further, the novel therapies should be able to target and improve damaged cardiac architecture and functional derangement due to CVD and other disorders responsible for HF.

A promising approach to metabolic therapy in HF is to modulate substrate utilization and shift the energy substrate preference from fatty acid to glucose. The evidence from various clinical and animal studies supports the concept that stimulating myocardial carbohydrate oxidation and downregulating myocardial fatty acid oxidation can optimize LV function and improve mechanical efficiency.

(1) **Dichloroacetate (DCA)/Sodium Pyruvate intravenous infusion:** In theory, glucose metabolism can be augmented by inhibiting pyruvate dehydrogenase kinase (PDK) and mitochondrial fatty acid uptake in HF. The compound, DCA inhibits FFA oxidation by inhibiting of PDK. This leads to increased activity of the mitochondrial pyruvate...
dehydrogenase complex and increased glucose utilization. DCA, thus, increases pyruvate oxidation and switches the heart towards glucose, the more efficient fuel. In a small study, there was a significant increase in stroke volume and improvement in LV contractile function in NYHA classes III and IV HF patients treated with intravenous DCA to inhibit PDH kinase, activate PDH, and increase pyruvate oxidation.31

In vitro studies also demonstrate that pyruvate infusion increased contractile function and potentiated the contractile effects of β-adrenergic stimulation in normal myocardium and in isolated samples of failing human myocardium. During pyruvate infusion there was an increased ejection fraction and cardiac output that immediately reversed upon cessation of the infusion. However, from a practical standpoint, it is not clinically feasible to intravenously infuse sodium pyruvate to attain high arterial pyruvate concentrations. Further studies are needed to characterize the therapeutic potential and safety profile of these modalities.

(2) Glucose–insulin–potassium (GIK) therapy: In theory, the infusion of insulin during the peri-myocardial infarction period may decrease adverse cardiac events and improve mortality by increasing myocardial glucose uptake and oxidation, and by increasing pro-survival signalling mechanisms. But, clinically the GIK therapy has shown mixed results. The lack of benefit may be due to differences in revascularization, other signalling cascades involved in ischemia and that cardiac glucose transport and metabolism is also regulated by factors like glucagon-like peptide 1 (GLP-1) in addition to insulin. Cottin et al., observed an improved wall motion score and LV ejection fraction in patients with ischemic heart disease and LV dysfunction when treated with an infusion of insulin under normoglycemic conditions. Nikolaidis et al., demonstrated that an infusion of GLP-1 over a 2-day period improved LV function and increased myocardial glucose uptake in dogs with experimental HF.

(3) CPT Inhibitors - Etomoxir and Perhexiline: The CPT-I results in increased expression of PPAR-α regulated genes and prevents the HF-induced fall in the mRNA for metabolic enzymes. It stimulates the PPARα/RXRα complex through the build-up of long-chain fatty acyl-CoA in the cytosol. This results in a paradoxical stimulation of the expression of the enzymes of fatty acid oxidation but decreases flux through the pathway. Etomoxir irreversibly inhibits mitochondrial Carnitine palmitoyl transferase-1 (CPT-1) and long chain FA oxidation resulting in a shift in myocardial energy metabolism from FFA to glucose utilization. In an initial studies, etomoxir appeared to improve myocardial function and clinical status in patients with HF. However, its use was associated with an elevation in liver enzymes. Rupp et al have demonstrated that chronic treatment with etomoxir in rats with LV hypertrophy improved LV function and sarcoplasmic Ca2+ handling, increased expression of SERCA2, and attenuated the transition from compensated to failing cardiac hypertrophy.

Perhexiline is a potent inhibitor of CPT-1 and CPT-2. In a small study in HF patients, it improved HF symptoms, MVO2max, and LVEF. The inhibition of malonyl-CoA decarboxylase (MCD) can also be a means to modulate myocardial metabolism in HF. It decreases FFA oxidation with a parallel increase in pyruvate oxidation by increasing myocardial levels of malonyl-CoA. In animal studies the MCD inhibition exerts positive effects on cardiac function and cardiac efficiency. Another CPT-I, oxifenicine can prevent ventricular remodelling and slow the progression of HF in dogs. In the study, it significantly attenuated LV wall thinning, prevented LV dilation and hemodynamic dysfunction, and delayed the terminal failure.

(4) The AMPK-modulating drugs: The AMPK regulates fatty acid uptake and oxidative phosphorylation. By inhibiting ACC, it increases CPT-1-dependent fatty acid oxidation to increase energy production in cardiomyocytes. It also stimulates glucose uptake by the translocation of GLUT4 transporters. In addition, it regulates intracellular pathways that promote normal endothelial function. The AMPK is an emerging therapeutic target. The currently available AMPK-modulating drugs act indirectly. Metformin is known to activate AMPK and is associated with reduced coronary events and CV death in diabetics. In mouse models of ischemia-induced HF, metformin treatment significantly improved survival and post-infarct LV systolic function. It also reduces cardiomyocyte apoptosis in cell culture models and blunts the LV dysfunction associated with tachycardia-mediated HF in dogs. Thiazolidinediones and statins also activate AMPK indirectly.

1. Trimetazidine and Ranolazine are already available and have been shown to be beneficial in treatment of HF. These therapies modulate the myocardial metabolic function and appear to improve the performance of viable myocardium.

2. The β-adrenergic receptor antagonists: Their long-term use improves LV function and reduces mortality in HF patients. This improvement is associated with a switch in myocardial metabolism away from fatty acid uptake and oxidation towards more glucose uptake and carbohydrate oxidation, and greater lactate uptake. In a 3 month of study in dogs with heart failure, metoprolol improved LV function and a significantly decreased in CPT-I activity, suggesting the shift in substrate metabolism due to

PERHAPSE....
3. **Mineralocorticoid receptor antagonist:** Aldosterone is one of the most important neuro-hormones in the pathophysiology of HF affecting salt and water retention, endothelial dysfunction, ventricular hypertrophy, and myocardial fibrosis. In the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study, eplerenone reduced the primary composite outcome of risk of death from cardiovascular causes and first hospitalization for HF by 37 percent in comparison with placebo. Based on the results of RALES (Randomized Aldactone Evaluation Study) and EPHESEUS (Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), the guidelines recommend the addition of low-dose MRA like, spironolactone or eplerenone, to optimize therapy in all patients with moderate to severe chronic HF (NYHA class III and IV) patients with HFrEF in addition to ACE inhibitors or ARBs, in the absence of hyperkalemia and/or significant renal dysfunction.

4. **Patiromer and Zirconium cyclosilicate:** With the use of RAAS inhibitors and MRAs in patients with HF, hyperkalemia is a common electrolyte disturbance in clinical practice and a major limiting factor for their use. The two novel potassium absorbents, patiromer calcium and zirconium silicate increase potassium loss via gastrointestinal tract (GIT) and have demonstrated efficacy and safety in recent trials. Patiromer is an orally administered non-absorbable polymer that binds potassium in exchange for calcium in the GIT. It increases fecal excretion of potassium and consequently decreases plasma potassium levels. In the PEARL-HF study tested the combined use of patiromer with spironolactone significantly lowered serum potassium levels from baseline relative to placebo and prevented the development of hyperkalemia for more than 4 weeks in patients with HF. Zirconium cyclosilicate is an inorganic crystal that entraps potassium in the intestinal tract. It exchanges sodium and hydrogen ions for potassium. A dose-dependent excretion of potassium occurs in the feces. The HARMONIZE study was an RCT evaluating long-term efficacy and safety in patients with hyperkalemia.

5. **Relaxin:** It is a naturally occurring hormone that is produced by the failing myocardium. Relaxin interacts with a G protein-coupled receptor, leads to increased cyclic adenosine monophosphate (cAMP) and increased nitric oxide production through increased activity of inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) expression. Additionally, relaxin upregulates the activity of vascular matrix metalloproteinase-2 (MMP-2), which activates endothelin-1, leading to endothelin-B receptor activation and subsequent nitric oxide production. Thus, relaxin increases cardiac output, arterial compliance, and renal blood flow. Because of its potent vasodilator properties as well as its ability to increase renal perfusion, relaxin of interest as a potential therapy for acute HF. Serelaxin is a recombinant form of the human hormone relaxin. The Pre-RELAX-AHF (Relaxin in Acute Heart Failure) study evaluated the effects of relaxin in patients with acute decompensated heart failure (ADHF). The key findings were dyspnea relief, reduced readmission due to HF or renal failure as well as a decrease in CV mortality at 180 days. However, in 14% cases, there was significant fall in blood pressure. The RELAX-AHF study also enrolled ADHF patients who have a systolic blood pressure of more than 125 mmHg and renal dysfunction. Here too, serelaxin significantly improved dyspnea, shortened the length of hospital stay, and decreased the incidence of worsening HF as compared with placebo. There was also an improvement in the 6-month mortality outcomes.

6. **Ularitide:** Retention of fluid and sodium play an important role and decongestive treatment is required in both acute and chronic HF. NPs are activated in HF and inhibit the RAAS and induce vasodilation and natriuresis. NPs consist of atrial NP (ANP), BNP, C-type NP (CNP), D-type NP (DNP), and urodilatin. They act as diuretic, natriuretic, vasodilating agents without any inotropic or chronotrophic effects and offer an attractive strategy for HF treatment.

Urodilatin is a modified version of pro-ANP, produced mainly by distal renal tubule cells and is involved in renal sodium handling. Ularitide, a synthetically produced urodilatin, has shown hemodynamic and clinical benefits in patients with ADHF. Other synthetic NPs such as carperitide (a recombinant form of ANP) and nesiritide (a recombinant form of BNP) have shown benefit in congestive HF. The SIRIUS II study utilized ularitide in Patients with Symptomatic, Decompensated Chronic Heart Failure and reported similar findings.

Despite multipronged existing therapies, HF as a disease has a suboptimal QOL, poor prognosis and a high mortality rate. The recent research is focussed on identifying novel strategies to recover the damaged and the dysfunctional yet viable myocardium, improve symptomatology and QOL, and prolong survival. There are needed a new class of drugs which activates specific protective biomolecules and reduces damage to the heart and vasculature. These drugs will potentially preserve the pumping ability of the heart and delay the onset of heart failure, and reduce CV mortality.

1. **Carnitine and L-carnitine:** Acute and chronic administration of carnitine can increase glucose oxidation in the isolated perfused rat heart.
by increasing the acetyl-carnitine concentration and decreasing the acetyl-CoA concentration, and thus relieving acetyl-CoA inhibition on PDH. A randomized double-blind trial in 472 myocardial infarction patients showed that oral carnitine therapy (6 g/day) initiated within 24 h after the onset of chest pain failed to affect clinical outcome or LV injection fraction over the course of 1 year of treatment; however, it did significantly reduce the rate of increase in the LV end-diastolic volume.

Some small studies suggest that people who take L-carnitine supplements soon after a myocardial infarction may be less likely to have another episode, die of heart disease, or develop heart failure. However, few other studies show no benefit. Controlled trials in HF patients relating to carnitine have not been reported.

2. Coenzyme Q10 (CoQ10):

The CoQ10, endogenously synthesised and diet-supplied lipidsoluble cofactor, is a key component in the mitochondrial ETC for ATP generation, and exists in abundance in the normal myocardium. It functions in the mitochondrial inner membrane to transfer electrons from complexes I and II to complex III. In addition, its redox activity enables CoQ10 to act as a membrane antioxidant. The myocardial CoQ10 content tends to decline with worsening of HF and the myocardial CoQ10 depletion has been postulated as a mechanism in development and progression of congestive HF.

A number of controlled trials with supplemental CoQ10 in HF have shown improvements in functional parameters such as ejection fraction, stroke volume and cardiac output. Recently, long-term therapy with CoQ10 has been shown to improve HF symptoms, reduce major adverse cardiovascular events (MACE), and safe and well tolerated. Subsequent meta-analyses have also confirmed these findings.

CoQ10 appears in the plasma circulation as ubiquinol. Nausea is the most common symptom, followed by an allergic maculopapular rash. Caution should be taken in the patients who are on oral anticoagulant therapy, given the similarities of CoQ10 with vitamin K. There may occur a reduction in blood pressure and heart rate, without any significant ECG changes. Theophylline is also affected by cytochrome p450 enzymes and animal studies have demonstrated altered pharmacokinetics of theophylline with co-administration of CoQ10. Statin therapy appears to deplete CoQ10 levels. Here, CoQ10 supplementation will help.

3. Resveratrol: Resveratrol (3,5,4, trihydroxystilbene), is a polyphenol, found predominantly in grapes and berries, and a major component of red wine. Resveratrol has multiple beneficial cardiovascular effects and though its recommendation for use in the treatment of HF as a drug remains unclear, its use as a nutraceutical for CVD and HF has been highlighted. Current research has suggested its potential in preventing or regressing defects in cardiac structure and function in experimental models of heart disease. There are strong indications about its potential in preventing or retarding the development of HF55 and it has an efficacy of in humans with CVD and HF.

In experiments, administration of resveratrol has been shown to prevent and/or retard the progression of HF in animal models of HF induced by myocardial infarction, pressure overload, myocarditis, and chemotherapy-induced cardiotoxicity. In addition, some animal studies have shown that resveratrol improves cardiac function and survival when administered as a treatment for established HF. Resveratrol acts on the peripheral tissues to improve skeletal muscle and endothelial/vascular function and thus reverse the changes induced by HF. Resveratrol treatment of
mice with established HF lessens the severity of the HF phenotype by lessening cardiac fibrosis, improving molecular and structural remodelling of the heart, and enhancing diastolic function, vascular function, and energy metabolism.\cite{13}

4. HSP20: The myocardium makes certain peptides including various heat-shock proteins (HSPs) to counteract apoptosis following physical and oxidative stress. In the heart, transient ischemia followed by reperfusion (ischemia/reperfusion, I/R) induces necrosis and apoptosis, leading to myocardial dysfunction. Preservation of myocardial function after I/R depends on critical adaptive responses, some of which are believed to involve the heat-shock proteins (HSPs). The HSPs synthesis arises transiently as a tool to protect cellular homeostasis after exposure to stressful and potentially deleterious stimuli. Thus, HSPs are mediators of myocardial protection, particularly in ischemia and reperfusion injury. The HSP20 lies dormant in heart and is activated under stressful conditions by phosphorylation. It regulates activities of vasodilation and platelet aggregation. The increased expression of HSP20 in cardiomyocytes is associated with an improved contraction and protection against β-agonist–induced apoptosis. The cardio-protective effects of HSP70 have been shown in isolated animal hearts after global or regional ischemia. Recently, protection during myocardial ischemia has also been shown for the small heat-shock proteins HSP27 and αB-crystallin. The HSP20 shares considerable sequence homology with HSP27 and αB-crystallin, and appears important in cardioprotection against ischemic injury.\cite{14}

The increased expression of HSP20 in the heart protects against I/R injury, resulting in an improved recovery of cardiac function and reduced infarction. Thus, HSP20 may constitute a new therapeutic target and the idea to develop medicines that would ‘switch on’ HSP20 in CVD patients and those with a high risk, and possibility that this new class of drugs would provide protection against heart diseases such as CAD and LVH and HF.

The HSP20 regulates vasodilation and suppress platelet aggregation, and improves contractile function and protects against β-agonist–mediated apoptosis. In studies, the increased HSP20 expression in the heart protects against IR injury, resulting in full functional recovery and reduced infarction. Thus, outlining the significance of HSP20 in contractile function of heart and cardioprotection.\cite{15} The findings in animal models and human patients, endorse HSP20 as a potential therapeutic target for ischemic heart disease.\cite{16}

\begin{thebibliography}{100}
c


Pathogenesis, Classification and Primary Prevention of Atrial Fibrillation

PRANAB J YOTI BHATTACHARYYA

Abstract

The prevalence of atrial fibrillation (AF), already the most common sustained cardiac arrhythmia, is constantly rising, even after adjusting for age and presence of structural heart disease. AF increases the risk of stroke six-fold and is associated with a two-fold increase in mortality, predominantly caused by cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. The electrophysiological mechanisms and classification of AF are well described. Although AF may be asymptomatic, up to two thirds of patients report that the arrhythmia is disruptive to their lives. Finally, the treatment of AF and its associated complications creates a significant and increasing economic burden. This article focuses predominantly on the pathophysiology of the arrhythmia and primary preventive strategies of atrial fibrillation.

Keywords
- atrial fibrillation
- Omega-3 polyunsaturated fatty acids (PUFAs)
- angiotensin receptor blocker
- VKAs

Review Article

Atrial fibrillation (AF) is a progressive disease evolving from paroxysmal through persistent to ‘permanent’ forms, a process attributed to electrical and structural remodelling related to both the underlying disease and AF itself. Despite extensive research, the understanding of the aetiology and pathogenesis of AF is still incomplete. As a result, there are no set primary preventive strategies in place apart from general cardiology risk factor prevention goals. Medical treatment has yet to demonstrate clinical efficacy in preventing progression. This brief review will discuss the pathogenesis, classification and primary prevention strategies of AF.

Several mutations that predispose to AF have been identified. These mutations cause a gain of function of repolarization potassium currents that result in shortening of atrial refractoriness and facilitate...
atrial reentry. Multiple polymorphisms have been identified that are associated with idiopathic AF, structural heart disease, or postoperative AF. These polymorphisms are in genes that affect potassium and sodium channels, sarcosine, the renin-angiotensin system, connxin 40, endothelial nitric oxide synthase, and interleukin-10. The end results are changes in calcium handling, fibrosis, conduction, and inflammation that predispose to AF. \(^1\)

Remodelling of atrial structure and ion channel function:
Various aetiological factors (Diabetes, Heart failure, Obesity, Coronary artery disease, Hypertension, Ageing, Genetic predisposition) cause a complex array of pathophysiological changes in the atria, including stretch-induced atrial fibrosis, hypocoagulability, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion channel dysfunction, and \(\text{Ca}^{2+}\) -instability. These changes enhance both ectopy and conduction disturbances, increasing the propensity of the atria to develop or maintain AF. Atrial Fibrillation in itself can aggravate many of the mechanisms, which may explain the progressive nature of the arrhythmia. \(^2\)

The mechanisms responsible for AF are complex. Triggering events may differ from maintenance mechanisms. Also, the clinical phenotypes of paroxysmal, persistent, and long-standing persistent AF have different electrophysiologic characteristics because of remodelling and different cardiac modulators that affect the substrate, such as heart failure, atrial stretch and ischaemia, sympathetic-vagal influences, inflammation, and fibrosis.

There are probably two electrophysiological mechanisms of AF:
1) Focal initiation and maintenance of atrial fibrillation and
2) The multiple wavelet hypothesis and rotors as sources of atrial fibrillation

One or more automatic, triggered, or microreentrant foci, so-called drivers, which fire at rapid rates and cause fibrillation-like activity, and multiple reentrant circuits meandering throughout the atria that annihilate and reform wavelets, thereby perpetuating the fibrillation. The left atrium contains the site of dominant frequency discharge, with a left-to-right gradient. Both mechanisms may be present simultaneously.

Rapid discharges from the pulmonary veins are the most common triggers of AF and may also play a perpetuating role, more so in paroxysmal AF than in persistent AF. This explains why pulmonary vein isolation is more effective in eliminating paroxysmal AF. In persistent AF, changes in the atrial substrate (fibrosis) usually warrant additional ablation of the atrial substrate. \(^2,3\)

Triggering foci for AF may include sleeve of atrial myocyte extending into pulmonary veins – these foci manifest delayed after depolarizations and triggered activity in response to catecholamine activity, rapid atrial pacing and stretch. Other foci may include foci within the pulmonary vein, within superior vena cava, ligament of Marshall, musculature of coronary sinus, left atrial wall and along the crista terminalis in RA. Factors perpetuating AF may include – Multiple wavelet hypothesis (fractionation of wavefronts traversing the atria into daughter wavelets), Rotors and interstitial fibrosis (predispose to intra atrial re-entry and AF).

Most common cardiac abnormalities associated with AF are Hypertension, Ischemic heart disease, mitral valve disease, Hypertrophic cardiomyopathy, and Dilated cardiomyopathy. Less common causes include restrictive cardiomyopathies (amyloidosis), constrictive pericarditis, cardiac tumours and severe pulmonary hypertension.

Apart from these, Obstructive sleep apnoea (OSA) increases the risk of AF. Temporary or reversible causes of AF are excessive alcohol intake (holiday heart), open heart or thoracic surgery, myocardial infarction, pericarditis, myocarditis and pulmonary embolism. Hyperthyroidism is the most common correctable cause of AF. Tachycardia can sometimes induce AF. These patients usually have AV nodal re-entrant tachycardia or a tachycardia related to WPW syndrome that degenerates into AF. In addition to long-established risk factors, newer etiologies, such as excessive physical activity, elevated vitamin D levels (>100 ng/mL), excessive niacin intake (>500 mg/d), and, possibly, high doses of N3-PUFAs, are being discovered.

Based on the presentation, duration, and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing, and permanent AF. First diagnosed AF is defined as AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms. AF that terminates spontaneously within 7 days is termed paroxysmal, and AF present continuously for more than 7 days is called persistent. AF that is persistent for longer than 1 year is termed long-standing, whereas long-standing AF refractory to cardioversion is termed permanent. \(^3\)

Lone AF refers to AF that occurs in patients younger than 60 years who do not have hypertension or any evidence of structural heart disease. It is clinically relevant because patients with lone AF are at lower risk for thromboembolic complications, thus eliminating the necessity for anticoagulation with warfarin. Also, because of the absence of structural heart disease rhythm-control drugs such as flecainide can be safely used in such patients. \(^3\)

In the context of non-vitamin K antagonist oral anticoagulants (NOACs) use in AF, the distinction between "valvular" and "non-valvular" AF has gained focus although it remains a matter of debate. Currently, "valvular AF" refers
to patients with mitral stenosis or artificial heart valves (and valve repair), and should be treated with VKAs (Warfarin). Valvular heart diseases, such as mitral regurgitation, aortic stenosis (AS) and aortic insufficiency, do not result in conditions of low flow in the left atrium, and do not apparently increase the risk of thromboembolism brought by AF.5

The role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) in the prevention of AF is currently controversial, with some studies suggesting benefits and some disputing this. At present, the evidence is insufficient to support the use of ACE inhibitors and ARBs for the sole purpose of preventing AF.3,4

β-Blockers (BBs) also have been shown to decrease the incidence of new onset AF in various settings including heart failure, after CABG and myocardial infarction.6,7,8

There is evidence to suggest that aldosterone antagonists may be beneficial in the primary and secondary prevention of AF. Spirolactone and eplerenone have been shown to be beneficial in this setting.9,10

Statins do not prevent AF, except after open heart surgery. Therefore, the data available do not support the use of statins for the prevention of AF.11

Omega-3 polyunsaturated fatty acids (PUFAs) have an anti-inflammatory effect and can also have direct ion channel effects. Pretreatment with omega-3 PUFAs in combination with an antiarrhythmic drug (amiodarone or sotalol) may be helpful in preventing recurrent AF after cardioversion of persistent AF.12,13

Potential risk factors associated with AF development have been discussed. A proper understanding and acknowledgement of these risk factors may allow primary care physicians and cardiologists to initiate preventive strategies and, thereby, potentially decrease the risk of AF. Potential Strategies for the Prevention of Atrial Fibrillation may include: Weight loss (maintaining a BMI of 18-25), Tight glucose control (hemoglobin A1c < 7.0% of total hemoglobin), Blood pressure control, Maintain normal HDL-C levels, Close supervision and management of patients with OSA, Limit alcohol consumption to 2-3 drinks per day, Avoid strenuous exercise routines, Consume moderate amounts of caffeine, Consume omega-3 fatty acids or a diet rich in these polyunsaturated fatty acids. There is a large body of scientific evidence to suggest that drinking moderate amounts of coffee and tea does not cause AF and may even decrease its occurrence.14

Atrial fibrillation is the most common arrhythmia worldwide, and it has a significant effect on morbidity and mortality. Although our current understanding of the pathogenesis of AF is incomplete, the last few decades have seen dramatic progress in this field. Despite continued improvements in the treatment of AF, effective methods for preventing AF remain elusive. Important targets for preventive therapy include both the processes underlying the development of triggers for AF and the substrate susceptible to AF. We need to better evaluate the impact of early treatment of known AF risk factors.

Best Practices in Hypertension-2017

P C MANORIA, PANKAJ MANORIA, S K PARASHAR, R K JHA

Abstract
Change is the way of life. Everything in this universe changes, so also the best practices for hypertension keep on changing to further optimize the results. It is important to bear in mind that the mortality in a controlled hypertensive is not similar to a normotensive and is at least two times greater. This occurs due to 2 reasons, atherosclerosis which continues unabated even in controlled hypertensive and fibrosis in the left ventricle, left atrium, aorta and small vessels which contribute to increased morbidity and mortality. Therefore, the treatment of hypertension should not be BP centric, but a disease centric approach should be employed. It is important to bear in mind that the office based readings of BP represents only a snapshot in time with low reproducibility. The ambulatory blood pressure monitoring provides an idea about the 24 hr BP profile. Besides this, it also gives an idea about the dipping patterns of blood pressure, the morning surges and the BP variability which has substantial prognostic and therapeutic implications. The goals of BP control are 140/90 mm Hg. but the SPRINT trial created flutter by showing benefits of lowering of BP to 120 mm Hg compared to 140. It is important to bear in mind that BP measurement in this trial was unique and never done before, i.e., unattended, automated, nonobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Therefore it seems the reading of SPRINT 120 mm Hg is equivalent to 130 mm Hg, if we record BP of the same patient in the conventional manner in the clinic. Among drugs used for hypertension, CTD and indapamide are preferred over hydrochlorothiazide, Azilsartan the new sartan, has additional advantages of producing greater fall in blood pressure with vasculoprotective properties and new CCBs Cilnidipine and Benedipine have additional advantage over amlodipine in that they provide renoprotection and have minimal chances of edema. Atenolol is out and currently, vasodilatory

Keywords
- BP goal
- ACCORD
- SPRINT
- dippers
- resistant hypertension
- interventional therapy
betablockers like nebivolol are used for treatment of hypertension particularly when it is associated with coronary heart disease and heart failure. Spironolactone is the fourth preferred drug in resistant hypertension. Angiotensin Receptor Neprilysin inhibitor is undergoing evaluation in hypertension with lot of excitement. A panoply of interventional techniques including renal denervation have been evaluated for treatment of hypertension, but none of them have been approved for clinical use.

The last couple of years have witnessed spectacular advances in the field of hypertension, both in terms of enhanced understanding and in the availability of rich panoply of therapeutic options. Due to this, the best practices for hypertension keep on changing.

Hypertension is the biggest global cause of mortality. It is important to bear in mind that control of hypertension is not self sufficient to improve outcome of the disease because the mortality in a controlled hypertensive is at least two times that of normotensive. This occurs due to two reasons:

1. **Atherosclerosis:** Hypertension is self sufficient to initiate and perpetuate atherosclerosis and this continues unabated even after control of blood pressure. This is classically illustrated in specimen of aorta of coarctation in children who usually do not have risk factors for atherosclerosis. The aorta below the coarc segment is normal but there is extensive atherosclerosis above it. Interestingly, the HOPE-31 trial has shown that when candesartan + hydrochlorothiazide is used with rosuvastatin in patients with hypertension who did not have cardiovascular disease and were at intermediate risk, there is a statistically significant reduction of 24% in the primary end points of cardiovascular death, MI and stroke compared to the group receiving candesartan + hydrochlorothiazide alone.

Gadolinium Enhancement (LGE) on Cardiac Magnetic Resonance (CMR). This makes the ventricle vulnerable for development of heart failure and is also a risk factor for development of ventricular arrhythmias and sudden cardiac death.

b. **Fibrosis in the left atrium:** This predisposes for development of atrial fibrillation (AF) and stroke. This can be visualized by LGE on CMR and is also utilized in conjunction with CHA2DS2-VASc score for prediction of stroke in AF. Moreover, in those patients who have marked left atrial fibrosis, the recurrence after Radio Frequency Ablation (RFA) for atrial fibrillation for restoring sinus rhythm is high. In fact, most of the electrophysiologists, before attempting RFA in AF, visualize fibrosis in left atrium by CMR.

c. **Fibrosis in the Aorta:** In normal young individuals, the aorta is compliant and the aortic Pulse Wave Velocity (PWV) is about 8 meters / sec. But if there is fibrosis in the aorta, this results in decreased compliance and the aortic PWV is increased. In normal individuals the pulse wave after travelling from aorta to periphery comes back to aorta in diastole and this result in augmentation of diastolic blood pressure and increase in coronary filling, but in aortopathy, because of increase in aortic PWV, the pulse wave traverses fast from aorta to periphery and comes back to aorta in systole itself. This exerts several deleterious effects on the aorta.

i. Increase in central aortic systolic pressure.

ii. Increased LV after load.

iii. Increased pulsatile strain with chances of plaque rupture.

iv. No diastolic augmentation of pressure.

v. Decreased coronary perfusion.

Aortopathy is a very important predictor of future cardiovascular events in hypertension.

There are betablockers like nebivolol are used for treatment of hypertension particularly when it is associated with coronary heart disease and heart failure. Spironolactone is the fourth preferred drug in resistant hypertension. Angiotensin Receptor Neprilysin inhibitor is undergoing evaluation in hypertension with lot of excitement. A panoply of interventional techniques including renal denervation have been evaluated for treatment of hypertension, but none of them have been approved for clinical use.

The Ambulatory Blood Pressure Monitoring (ABPM) provides an idea about the 24 hour BP profile. Besides this, it also gives vital information regarding several parameters mentioned below.

a. Nocturnal blood pressure: Normally the blood pressure falls in the night by 10%. If it does not dip in night than it is called non dipper pattern and this is associated with increased morbidity and mortality. There are

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP Criteria</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>Ambulatory BP Criteria</td>
<td>135</td>
<td>85</td>
</tr>
<tr>
<td>Daytime</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>Nighttime</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>24-H</td>
<td>130</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 1: Criteria for diagnosing hypertension
several types of nocturnal BP patterns as mentioned in (Table 2).
The important causes of non dippers include obesity, obstructive sleep apnoea (OSA), high salt intake in salt sensitive subjects, orthostatic hypotension, autonomic dysfunction, chronic kidney disease (CKD), old age, diabetic neuropathy, etc.

b. Morning surges of blood pressure: Normally the BP starts rising 90 minutes before the expected arousal, the maximum rise being less than 35 mm Hg. If the surge is more, this is associated with increased incidence of cardiovascular events.10-12

c. Blood pressure variability: The BP variability (BPV) is defined as the average variation of BP throughout 24 hrs. quantitated as the SD of ABPM readings and is usually around 10-15 mm Hg for the day and 5-10 mm Hg for the night time. If the BP variability is increased, this is associated with increased incidence of cardiovascular events. Interestingly, the use of calcium channel blockers like amlodipine decreases BPV and is associated with decreased cardiovascular events.

Moreover the effect of BP lowering medicines is best assessed by 24 hour ABPM13-14

Table 2: Criteria for different types of dippers

<table>
<thead>
<tr>
<th>Subset</th>
<th>Nocturnal BP fall</th>
<th>Night to day time BP ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dippers</td>
<td>10-20%</td>
<td>0.8 to 1</td>
</tr>
<tr>
<td>Extreme dippers</td>
<td>&gt;20%</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Non dippers</td>
<td>No fall</td>
<td>1.0</td>
</tr>
<tr>
<td>Reverse dippers</td>
<td>↑ BP during night</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

Table 3: BP goals for treatment of hypertension in general patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>General adults age &lt;60</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Elderly</td>
<td>140-150/90</td>
<td>&gt;150/90</td>
<td>&gt;150/90</td>
<td>&gt;150/90</td>
<td>&gt;150/90</td>
</tr>
<tr>
<td>Diabetic non proteinuric</td>
<td>&lt;140/85</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>CKD non proteinuric</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>CKD proteinuric</td>
<td>&lt;130</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
</tbody>
</table>

Currently, most of the guidelines recommend goal of 140/90 mm Hg for general patients (Table 3). For elderly (JNC 2014 >60 years and for ESH/ESC 2013,ASH/ISH 2014/80 years) goals of <150/90 may be acceptable.

b. Diabetics: The JNC-7 guidelines in 2003 endorsed a target of 130/80 mm Hg and lower was considered better. The concept of lower is better was prevalent based on observational data from MRFIT and other trials showing increasing levels of SBP to be associated with higher risk of macrovascular events but there is no evidence from observational or RCTs that achieving SBP lower than 130 with drugs is associated with decreased risk of cardiovascular events. The UKPDS 38,15 ADVANCE16 and HOT17 trials were also used in support of this recommendation but in UKPDS the BP achieved in the intensive arm was only 144/82 and the SBP during follow up in ADVANCE trial was 134.7. The hot trial subgroup which was targeted to achieve DBP <80 actually achieved a reading of 81.1 mm Hg. Therefore the recommendation to lower BP <130/80 was not based on solid evidence. Moreover, several trials like ONTARGET,18 PROFESS,19 TRANSCEND,20 INVEST, ACCORD BP trials
reported no benefit, or even harm, when lower BP target was achieved. The ACCORD BP trial\(^1\) carried out in diabetic hypertensive patients showed that tight BP control is not beneficial. The ACCORDION trial\(^2\) also did not favour tight BP control. This is an extended study of 3957 patients of ACCORD trial who were followed for an additional 54-60 months. During this time, patients who had been in the intensive BP arm in the main trial were no longer aiming for the lower BP goals, so the difference in BP between the two groups narrowed from 14.5 mmHg at the end of the main trial to 4.2 mmHg at the end of the follow-up period. Results from the follow-up period showed a 9% non-significant reduction in the primary end point of major CV events over a median follow-up of 8.8 years from randomization. During the long-term follow-up, an interaction between BP and glycaemia interventions became significant (P for interaction 0.037), with evidence of benefit for intensive BP lowering in participants randomized to standard glycaemic therapy (HR = 0.79, 95% CI 0.65–0.96).

The INVEST trial\(^3\) showed that tight control of BP (<130) in diabetics with CAD is associated with a trends towards increase in all cause mortality compared to usual control (130-140). The extended follow up of INVEST trial\(^4\) showed that in hypertensive patients with coronary artery disease, achieving a systolic BP of 130–140 mmHg seems to be associated with lower all-cause mortality after approximately 11.6 years of follow-up.

Due to above mentioned trials, the professional bodies were compelled to recommend less stringent targets (Table 4). The SPRINT trial\(^5\) however, created a flutter by showing that 120 SBP was better than 140 mm Hg (Figure 1,2).

The SPRINT trial showed a 25% reduction in the primary end points of MI, ACS (non-MI), stroke, heart failure or CV death, the all cause mortality and CV mortality decreased by 27 and 43 % respectively. The hospitalization for heart failure was decreased by 38%.

The SPRINT trial did show benefits of additional lowering of SBP to 120 mm Hg but it is important to bear in mind that the technique of BP measurement in this trial was unique and never done before, i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Due to this a lower reading of blood pressure by 8-10 mm is recorded. Therefore the reading of SPRINT 120 mm Hg is equivalent to about 130 mm Hg, if we record BP in a conventional manner in the clinic.

The SPRINT trial also has several limitations:
1. It is an open label study.

<table>
<thead>
<tr>
<th>Table 4: BP targets in diabetics as per various guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.No.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

7. CHEP-2017 <130/80

The trial showed a 25% reduction in the primary end points of MI, ACS (non-MI), stroke, heart failure or CV death, the all cause mortality and CV mortality decreased by 27 and 43 % respectively. The hospitalization for heart failure was decreased by 38%.

The SPRINT trial did show benefits of additional lowering of SBP to 120 mm Hg but it is important to bear in mind that the technique of BP measurement in this trial was unique and never done before, i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Due to this a lower reading of blood pressure by 8-10 mm is recorded. Therefore the reading of SPRINT 120 mm Hg is equivalent to about 130 mm Hg, if we record BP in a conventional manner in the clinic.

The SPRINT trial also has several limitations:
1. It is an open label study.

Table 5: Comparison between ACCORD and SPRINT trials

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ACCORD</th>
<th>SPRINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Complex factorial study design could have prevented a statistically significant difference</td>
<td>Randomized, controlled, open-label</td>
</tr>
<tr>
<td>Age</td>
<td>Mean age 62. Individual with age &gt;80 excluded and this led to younger group of patients</td>
<td>Older, mean age 68</td>
</tr>
<tr>
<td>CV risk</td>
<td>Lower risk patients because of lower age and dyslipidemic patients were assigned to lipid arm and excluded from BP arm</td>
<td>Higher risk patients</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Only diabetics enrolled</td>
<td>Excluded</td>
</tr>
<tr>
<td>Diuretics</td>
<td>HCTZ often used</td>
<td>CTD often used</td>
</tr>
<tr>
<td>Intensive BP lowering</td>
<td>No effect on CV events</td>
<td>↓ CV events</td>
</tr>
<tr>
<td>Event rates</td>
<td>Lower than predicted because of lower CV risk profile</td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>Common in diabetics and greater BP lowering may decrease perfusion pressure and increase CV events</td>
<td>Less common in non-diabetics</td>
</tr>
</tbody>
</table>

![Figure 1. SPRINT Trial primary end point and all cause mortality](image-url)
2. It represents only 20% of total hypertensive population as patients with diabetes, congestive heart failure, proteinuria >1 gm/day, eGFR < 20 were excluded.

3. The SPRINT trial cannot be applied to diabetics as the ACCORD BP and ACCORDION trial carried out in diabetic patients were negative.

4. It cannot be applied to frail elderly.

However, SPRINT and the ACCORD trial had several differences and this may perhaps account for failure of ACCORD BP trial to show benefits of intensive BP lowering (Table 5).

The 2016 European Guidelines on CVD prevention in clinical practice did not endorse SPRINT trial but said that based on current data, it may still be prudent to recommend lowering SBP/DBP to values within the range 130-139/80-85 mm Hg, and possibly close to the lower values in this range, in all hypertensives.

The Canadian blood pressure guidelines recommend 130/80 mm Hg for diabetics and were the first to endorse sprint trial in 2016 as well as in 2017 (Table 6) by recommending a target of 120/80 mm Hg for the high risk group, although this is not recommended by any other guidelines.

The AACE/ACE Consensus statement released in 2017 has recommended a target of 130/80 mm Hg for diabetic patients.

To solve the discrepancy between various studies and to detect an appropriate target several meta-analyses were examined. These showed that the target for BP control in general should be, 140/90 mm Hg but for those at high risk of stroke or those with diabetic kidney disease and proteinuria a target of 130/80 is acceptable. Stringent BP goal does not benefit other endpoints like CV mortality, all cause mortality and myocardial infarction.

The ADA 2017 has issued a consensus for BP targets in diabetics and seems most acceptable at present time. There is irrefutable evidence that SBP > 140 mm Hg is harmful. Therefore the goal of systolic BP should be <140 mm Hg. in most patients. A goal closure to 130 mm Hg is recommended for subset of patients who are at high risk of stroke or have albuminuria. Lowering BP below 130 does not improve outcome (except stroke) and may be detrimental. There is strong evidence that DBP > 90 mm Hg. is associated with harm. The goal of DBP in diabetics should be <90 but a goal closer to 80 mm Hg. may be recommended for patients at high risk of stroke or those who have proteinuria. Targeting BP to <70 mm Hg. is harmful.

In the recent Heart Outcomes Prevention Evaluation (HOPE)–3 trial 12,705 participants at intermediate risk who did not have CV disease were randomized to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo and were followed for 5.6 years. The first co-primary outcome was the composite of death from CV causes, nonfatal

<table>
<thead>
<tr>
<th>Table 6: Hypertension Canada’s 2017 guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subset</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>High risk*</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>All others</td>
</tr>
<tr>
<td>Elderly</td>
</tr>
</tbody>
</table>

*Clinical or sub-clinical cardiovascular disease, Chronic kidney disease (non-diabetic nephropathy, proteinuria <1 g/d, or estimated glomerular filtration rate 20-59 ml/min/1.73m²). Estimated 10-year global cardiovascular risk>15%, Age ≥75 years.

<table>
<thead>
<tr>
<th>Table 7: Targets for blood pressure in chronic kidney disease and hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S.No.</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
myocardial infarction, or nonfatal stroke; the second co-primary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. Therapy with candesartan plus hydrochlorothiazide was not associated with a lower rate of major CV events than placebo despite a BP decrease of 6.0/3.0 mmHg in the active treatment group. Addition of rosuvastatin showed a statistically significant reduction of 24% in the primary endpoint. The only subgroup who benefited from BP lowering was the subgroup of participants with initial systolic BP > 143.5 mmHg36.

Commonly four groups of drugs are used for the treatment of hypertension.

a) **Diuretics:** Chlorthalidone (CTD) is preferred over hydrochlorothiazide (HCTZ) which we have been using for several decades. This is because CTD produces a greater reduction in BP including nocturnal BP and is associated with a decrease in the cardiovascular events (CVE). HCTZ has never been shown to reduce CVE. Indapamide is also a good diuretic and has no metabolic side effects.

b) **RAAS Blockers:**

There are 3 types of RAAS blockers as mentioned below:

i. **Angiotensin Converting Enzyme Inhibitors (ACEIs):** These agents, although they produce incomplete RAAS inhibition, but have excellent outcome data.

ii. **Angiotensin Receptor Blockers (ARBs):** Telmisartan in the OMTARGET trial was found equivalent to ACE inhibitor Ramipril and is approved for clinical use like the ACEI Ramipril.

Azilsartan is a new sartan and has the advantage over other sartans that besides blocking AT1 receptors, it also activates ACE2, Angiotensin (1-7), mass pathways and provides vasculoprotective and vasodilatory effects. In terms of blood pressure reduction it is therefore more potent than the other sartans and provides good blood pressure control.

iii. **Direct Renin Inhibitors (DRI):** These drugs despite a sound theoretical basis failed to produce outcome data in various trials and therefore they are not preferred.

**Amlodipine** is a time tested CCB for treatment of hypertension and has been tested in several large scale trials with beneficial results. But the main problem with amlodipine is pedal edema. Of late the fourth generation, CCB cilnidipine is now commercially available. It has the advantage that it not only acts on the L-type calcium channel blockers but also blocks the N-type calcium channels which suppresses excess norepinephrine release from the sympathetic nerve endings. This provides cardio-protection37 as it does not increase heart rate and cardiac contraction and also provides renal protection by decreasing proteinuria.38 It also produces venodilation and decreases chances of pedal edema.39 Of late, a new CCB benidipine is available which blocks the L,N and T type calcium channels. It follows the membrane approach which leads to long duration of action even after short half life of 2 hours. It provides better BP control than other CCB like amlodipine and cilnidipine and because of T-type calcium channel blockage, it significantly improves the urinary protein excretion and provides better kidney protection than amlodipine and Cilnindipine. Besides this benidipine also provides cardiovascular benefit by improving nitrous oxide and cGMP (vasodilution) and reducing oxLDL (anti-atherosclerotic action), aldosterone levels.40

**The Conclusion**

For several years beta blockers like atenolol have been commonly used for treatment of hypertension but the meta-analysis by Carlberg41 showed that it increases all cause mortality and CV mortality by 13% and 16% respectively. It increased MI by 17% and curiously enough the strokes were increased by 30%. As a result the NICE guidelines for hypertension in 2011 degraded beta blockers to number four. Currently, vasodilatory beta blockers like Nebivolol and carvedilol are used for treatment of hypertension. These have minimal side effects but long terms trials are lacking.

Most patients of hypertension in the long run require combination therapy.42 The desirable combinations are ACEI / ARB + Diuretics, ACEI / ARB + CCB, CCB + Diuretics, ACE / ARB + CCB + Diuretics.

**Conclusion**

Hypertension uncontrolled (>140/90 mm hg) with triple combination i.e., ACEI/ARB + CCB + diuretics is categorized as resistant hypertension. Currently the most potent combination is Azilsartan + Benidipine + Chlorthalidone.

Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence. Resistant hypertension is associated with a high risk of CV and renal events.43-46

But before labeling somebody as resistant hypertension, one should rule out the possibility of apparently difficult to control hypertension due to inappropriate cuff size, pseudohypertension, non-adherence to drug therapy, unknowingly consuming large amount of salt, inadequately prescribed dosage or improper combinations, white coat hypertension, drug induced hypertension etc. If true resistant hypertension is present, one should exclude obstructive sleep apnoea (OSA), hypothyroidism, renovascular hypertension, primary aldosteronism, aortoarteritis, endocrinal hypertension etc.
alpha blockers, like prazosin, direct vasodilators like hydralazine, minoxidil, centrally acting drugs like clonidine, moxonidine etc. This drug has already been approved for clinical use in patients with heart failure with reduced ejection fraction as Class-I (B) recommendation in various guidelines. The valsartan in ARNI produces RAAS blockade and the neprilysin inhibition with sacubitril results in increased bioavailability of natriuretic peptides, bradykinin and substance P, which produces natriuretic, vasodilatory and anti-proliferative effects.

ARNI is now being evaluated for treatment of hypertension. The PARAMETER study showed favourable effects. This 52-week multi-center study randomized 454 patients with hypertension aged ≥60 years with a mean sitting systolic blood pressure (SBP) of ≥150 to <180 and a pulse pressure of >60 mm Hg to once daily ARNI (200 mg) or olmesartan (20 mg) for four weeks, followed by a forced titration to double the initial doses for the next eight weeks. At 12–24 weeks, if the BP target had not been attained, amlopidine (2.5–5 mg) and subsequently hydrochlorothiazide (6.25–25 mg) were added. The primary and secondary endpoints were changes from baseline in central aortic systolic pressure and central aortic pulse pressure at week 12, respectively.

Results showed that after 12 weeks, patients treated with ARNI had a 3.77 mm Hg greater reduction in central aortic systolic pressure and a 2.4 mm Hg greater reduction in central aortic pulse pressure from baseline compared to patients treated with olmesartan. Additionally, the 24 hour ambulatory brachial and central SBPs were significantly reduced from baseline to 12 weeks in both treatment arms, with ARNI lowering brachial SBP by an additional 4.1 mm Hg and central SBP by an additional 3.3 mm Hg compared to olmesartan. This finding was most pronounced during the night time.

In other findings, a greater percentage of patients treated with olmesartan (47 percent) required additional hypertension medication at weeks 12–24 compared to patients in the ARNI group (32 percent). Investigators also noted that an exploratory analysis of the carotid-to-femoral pulse wave velocity indicated a trend toward a greater improvement in a subgroup of ARNI treated patients with the stiffest arteries at baseline.

Table 8: Ongoing trials of LCZ696 in hypertension

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Patient population</th>
<th>Brief title</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01785472</td>
<td>Essential hypertension</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients With Essential Hypertension</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>NCT01599104</td>
<td>Essential hypertension</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>NCT01870739</td>
<td>Essential hypertension</td>
<td>A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects With Hypertension</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>NCT01615198</td>
<td>Essential hypertension</td>
<td>Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients With Essential Hypertension</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>NCT01681576</td>
<td>Salt-sensitive hypertension</td>
<td>Assessment of LCZ696 and Valsartan in Asian Patients With Salt-sensitive Hypertension</td>
<td>Valsartan</td>
</tr>
<tr>
<td>NCT01256411</td>
<td>Essential hypertension</td>
<td>A Long-term (12 Months) Safety, Tolerability and Efficacy Study of LCZ696 in Patients With Essential Hypertension</td>
<td>NA</td>
</tr>
<tr>
<td>NCT01601470</td>
<td>Mild-to-moderate hypertension</td>
<td>Evaluation of Drug-drug Interaction Between LCZ696 and Sildenafil in Subjects With Mild to Moderate Hypertension</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>NCT01353508</td>
<td>Hypertension; heart failure and healthy volunteers</td>
<td>Sodium Excretion of LCZ696 in Patients With Hypertension; Heart Failure and Healthy Volunteers</td>
<td>Valsartan</td>
</tr>
<tr>
<td>NCT01692301</td>
<td>Hypertension</td>
<td>Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients With Hypertension</td>
<td>Olmesartan, Amlodipine, HCTZ</td>
</tr>
<tr>
<td>NCT01663233</td>
<td>Essential hypertension</td>
<td>Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Comparison With Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>NCT01646671</td>
<td>Severe hypertension</td>
<td>Safety and Tolerability and Efficacy of LCZ696 in Japanese Severe Hypertensive Patients</td>
<td>NA</td>
</tr>
<tr>
<td>NCT01631864</td>
<td>Hypertension, concurrent obesity</td>
<td>Evaluation of the Metabolic Effects of LCZ696 and Amlodipine in Obese Hypertensive Subjects</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>ISRCTN11958993</td>
<td>Chronic kidney disease</td>
<td>Randomized multicentre pilot study of LCZ696 vs. Irbesartan in patients with chronic kidney disease: UK Heart And Renal Protection (HARP)-III</td>
<td>Irbesartan</td>
</tr>
</tbody>
</table>
PARAMETER is the first randomized study demonstrating the ability of ARNI to significantly reduce central blood pressure and pulse pressure compared to an ARB in high-risk older patients with systolic hypertension and a wide pulse pressure. These data are important because lowering systolic and pulse pressure in older people with stiffened arteries is an unmet need in our endeavour to reduce the risk of cardiovascular disease and heart failure in older people. The results suggest that ARNI has been able to achieve more in this regard than existing treatments and indeed this is an exciting advance.

The holy grail of systolic hypertension therapy is to achieve a ‘destiffening’ effect. The fact that release of BNP was reduced for ARNI provides indirect evidence that this may be occurring. Currently, studies are under way using MRI to directly measure changes in arterial distensibility following ARNI treatment.

Although ARNI has shown an impressive reduction in systolic and diastolic blood pressure, the long-term antihypertensive efficacy of ARNI has not been fully evaluated. Moreover, the effect of ARNI on cardiovascular outcomes in patients with hypertension is unknown. It is also to be seen whether ARNI also confers long-term prognostic benefits in patients with hypertension. Further studies need to be conducted to elucidate the role of ARNI in hypertensive patients with (i) diabetes, (ii) chronic kidney disease (iii) elderly (iv) resistant hypertension. Since blacks were underrepresented in the published hypertension trials, future trials should also include adequate black population. Most importantly, studies need to be conducted comparing antihypertensive efficacy and outcome of ARNI with other drug classes such as ARBs, calcium-channel blockers and diuretics.

Besides PARAMETER trial, several other clinical trials are ongoing (Table 8).

Several interventions have been used for the treatment of hypertension like arterial baroreflex activation, Iliac AV anastomosis and renal sympathetic denervation.

a. Baroreflex activation: It decrease blood pressure by vagal stimulation but the problem with this technique is that carotid stenosis is seen in about 60% of patients and we do not know how to prevent it?

b. Iliac AV anastomosis: In this external iliac artery connected to external iliac vein by a device. It decreases blood pressure by decreasing vascular resistance. This is associated with venous stenosis in 25% of patients but this can be treated by venodilatation.

c. Renal sympathetic Denervation: This was a very promising technique and the initial results with SYMPLICITY-1 and 2 were exciting but distressingly enough the SYMPLICITY HTN-3 trial, though it met the safety end point, it failed to show any reduction in blood pressure compared to the sham control group. Therefore it has not been approved for clinical use. The failure of the trials was attributed to several reasons like operator inexperience/failure, fault with the catheter and patient in the late stage of disease with burnt out sympathetic activity. The problem with the technique is that there is no parameter to document the success of renal denervation / technical failure immediately after the procedure. Newly improved catheters for the procedure are being designed with circumferential denervation of renal artery and its branches and the initial results are exciting. It seems renal sympathetic denervation is still alive and not dead and may bounce back in future.

But we should not forget that the major battle for hypertension is to be fought outside the clinics and hospitals because the major chunk of hypertensive patients is still out of reach. This can never be done merely by the medical fraternity but requires cohesive efforts by the government, voluntary agencies, para-medical workers, electronic and print media etc.

Hypertension is the commonest cause of cardiovascular morbidity and mortality throughout the globe including our country. Prevention should be the goal and indeed it is possible. For hypertensive patients, we have a panoply of powerful antihypertensive drugs to control it. But for optimum treatment, a disease centric approach should be employed rather than merely a BP centric approach.


Tissue Doppler Imaging in Evaluation of Diastolic Dysfunction

SR MITTAL

Abstract
Tissue Doppler imaging is a novel echocardiographic technique that directly measures myocardial velocities. Our review focuses on the clinical use of echocardiography in the evaluation of left ventricular diastolic function.

In tissue Doppler imaging, Doppler echocardiography is used to record velocities of myocardial tissue. Routinely longitudinal velocities of medial and lateral mitral annulus and lateral tricuspid annulus are evaluated in apical four chamber view. During diastole, annuli move away from apex due to filling of the ventricles. Normally two diastolic waves are recorded. First wave is recorded during early filling of ventricles due to active relaxation. It is termed Ea or e'. The second wave is recorded during ventricular filling due to atrial contraction. This is termed Aa or a'. Normally Ea velocity is more than Aa velocity (Figure 1 to 3). Normal values of Ea velocity are more than 15 cm/sec for lateral mitral annulus and more than 10 cm/sec for medial mitral annulus.1 Diastolic dysfunction of the ventricles affect the absolute and relative velocities of these waves.

In stage of impaired relaxation early filling

Dr. SR Mittal is Head, Department of Cardiology at Mittal Hospital and Research Centre, Ajmer, Rajasthan
Figure 3. Tissue Doppler imaging of lateral tricuspid annulus showing normal pattern.

Figure 4. Tissue Doppler imaging of lateral mitral annulus showing stage 1 diastolic dysfunction. Aa velocity was more than Ea velocity.

Figure 5. Tissue Doppler imaging of medial mitral annulus showing stage 1 diastolic dysfunction. Aa velocity was more than Ea velocity.

Figure 6. Tissue Doppler imaging of lateral tricuspid annulus showing stage 1 diastolic dysfunction. Aa velocity was more than Ea velocity.

Figure 7. Tissue Doppler imaging of lateral tricuspid annulus showing stage 2 diastolic dysfunction. There was significant decrease in Ea velocity and increase in Aa velocity.

Figure 8. Tissue Doppler imaging of lateral tricuspid annulus from another patient showing stage 2 diastolic dysfunction. There is significant decrease in Ea velocity and increase in Aa velocity.

Figure 9. Tissue Doppler imaging of lateral mitral annulus showing stage 3 diastolic dysfunction. Velocities of both Ea and Aa waves are reduced.

Figure 10. Tissue Doppler imaging of medial tricuspid annulus showing stage 3 diastolic dysfunction. Velocities of both Ea and Aa wave are reduced.
of the ventricles is reduced resulting in blunting of Ea wave. Diminished filling during early diastole is compensated by increased filling by forceful atrial contraction. This results in increased velocity of Aa wave. Aa wave, therefore velocity less than 8cm/sec suggests pseudo normalization.

In stage of restrictive filling, atrial contraction is reduced due to decreased compliance (increased stiffness) of ventricles. Therefore, both Ea and Aa velocities are reduced (figure 9, 10). As restrictive filling deteriorates from reversible to irreversible stage (stage 4) velocity of Ea and Aa waves further declines. By this time most of the patients also have gross systolic dysfunction. Sa velocity is, therefore, also significantly reduced. (Figure 11 & 12).

References
Low Voltage Electrocardiogram

SR MITTAL

Abstract
Low voltage electrocardiogram is defined as QRS complexes <0.5 mv in limb leads and <1.0 mv in precordial leads. In nearly 50% of cases only limb leads are affected. Attenuation on correctly standardized sequential ECGs carries same significance even if it does not fulfill the definition. It can be a normal variant in some persons free of cardiovascular disease. Low voltage electrocardiogram can be due to decreased electric potentials generated by the myocardium e.g. in multiple infarcts, cardial amyloidosis, fulminant myocarditis, dilated cardiomyopathy, hypothyroidism etc. Impaired conduction of electric potentials to the recording electrodes is another possibility. It occurs in pericardial effusion, chronic constrictive pericarditis, chronic obstructive airway disease and anasarca. More than one factor is usually contributory in a given patient. Correction of underlying pathology can normalize the QRS voltage.

Keywords
- amyloidosis
- cardiomyopathy
- chronic constrictive pericarditis
- chronic obstructive airway disease
- coronary artery disease
- myocarditis
- pericardial effusion

It is defined as QRS complexes of less than 0.5 mv in frontal plane leads and less than 1.0 mv in precordial leads. In nearly 50% of patients only limb leads are affected and chest leads have normal voltage resulting in electrocardiogram voltage discordance. Attenuation of QRS voltage on correctly standardized sequential ECG is important even if it does not fulfill the definition.

For the sake of understanding, causes have been divided into different groups. However, in a given case, more than one factor may be contributory.

Standard ECG is calibrated to a voltage sensitivity of 10 mm/mv on vertical axis. Incorrect standardization at 5 mm/mv produces low voltage ECG. All waves (P, QRS and T) and all leads (limb leads as...
Extensive loss of viable myocardium is responsible for decreased QRS voltage. Heart failure, pulmonary congestion and oedema may also contribute to low voltage.

Low QRS voltage can occur in apparently healthy individuals without any apparent explanation. Low QRS is associated with increased risk of mortality even in patients free of cardiovascular disease.4,5 Placing left precordial leads over the breast (rather than under the breast) can produce low voltage in these leads in females with heavy breasts.

Reduced voltage is due to underlying myocardial oedema.8 QRS amplitude attenuation is transient and improves as the clinical and echocardiographic parameters improve.9 This is in contrast to acute coronary syndrome in which QRS voltage remains substantially unchanged from admission onward.9,10 Other usual ECG findings are T wave inversion in leads V1 to V3. Lead aVR may show ST depression with upright T wave as this leads is diagonally opposite to left ventricular apex.10

Sinus tachycardia is invariable. In addition to myocardial injury, peripheral oedema may also contribute to low QRS voltage.13 Other ECG findings include increased ventricular activation time due to slow conduction through injured tissue, small notching and slurring due to multiple foci of myocardial necrosis, pathologic Q waves, ST segment depression, T wave inversion and atrial and ventricular extrasystoles.14

Low amplitude with notched and wide QRS is seen particularly in the frontal plane leads.15,16 Low amplitude in limb leads with high voltage in precordial leads meeting voltage criteria of LVH is strongly associated with adverse outcome.12
suggestive. Biatrial enlargement is common due to elevated end diastolic pressure and associated mitral and tricuspid regurgitation. Left axis deviation is common due to left antero-superior fascicular block. LBBB is common. Combination of LBBB with right axis deviation is strongly suggestive.

Myocardial oedema per se, lung congestion, pleural effusion and oedema contribute to low voltage QRS. Significant decrease in QRS voltage has been observed in cardiomyopathy after adriamycin chemotherapy.

Low QRS voltage, RBBB and ST segment elevation in lead V1 are significant predictors of cardiogenic shock in acute pulmonary embolism.

(i) Hypothyroidism

Electrocardiogram is characterized by low voltage of all wave forms, sinus bradycardia and low to inverted T waves without significant ST segment deviation in many or all leads. Low voltage is related to serum free T4 and serum albumin. There is no significant relation to pericardial effusion.

All electrocardiographic deflections have low voltage. T wave shows shallow inversion in all leads except lead aVR. As cardiac tamponade develops, sinus tachycardia appears. Some patients with massive effusion may show electrical alternans (Figure 7, 8) due to swinging motion of heart. Uncommonly alternans may affect all wave forms i.e. P, QRS and T. Electrical alternans disappears after aspiration of pericardial fluid. If acute pericarditis coexists, coved upwards ST
Segment elevation may be present in all leads except lead aVR (Figure 9).\textsuperscript{27} As opposed to myocardial infarction, there are no reciprocal ST depression.

Thickened pericardium prevents transmission of electric potentials to surface. However, pericardectomy only partially restores the QRS amplitude suggesting that fibrosis of underlying myocardium contributes to low voltage QRS.\textsuperscript{28} Sinus tachycardia is present.\textsuperscript{26} Some cases develop atrial fibrillation. It is due to atrial dilation due to impaired atrial emptying.

Signs of left atrial enlargement may be present in sinus rhythm (Figure 10, 11). QRS shows low amplitude. T waves are of low amplitude or inverted. Inverted T waves are usually associated with involvement of underlying myocardium.\textsuperscript{28} Low voltage affects QRS specially in lead I (Figure 12) and left precordial leads (Figure 13).\textsuperscript{24,31} With development of pulmonary artery hypertension, P waves become tall and peaked in leads II, III, aVF and frontal plane QRS axis shifts to right (Figure 14).

Figure 10. Electrocardiogram from a case of pericardial constriction showing low voltage QRS, T wave inversion in most of the leads and left atrial overload (negative P wave in lead V\textsubscript{1}).

Figure 11. Electrocardiogram from a case of pericardial constriction showing low voltage QRS, T wave inversion in most of the leads and evidence of biatrial overload (Tall P wave in leads II, III, aVF and prominent negative deflection of P wave in lead V\textsubscript{1}).

Figure 12. Electrocardiogram from a case of emphysema showing significantly decreased QRS voltage in lead I.

Figure 13. Electrocardiogram from a patient with chronic obstructive airway disease showing markedly diminished QRS amplitude in limb leads and leads V\textsubscript{5} to V\textsubscript{6}.

Figure 14. Electrocardiogram from a patient with cor pulmonale showing low QRS voltage in limb leads and leads V\textsubscript{5}, V\textsubscript{6}, right axis deviation, right ventricular hypertrophy (prominent R wave in lead V\textsubscript{1}) and right atrial overload (tall P waves in leads II, III, aVF and qR in V\textsubscript{1}).

Figure 15. Electrocardiogram from an obese person showing low amplitude of QRS. P and T waves are normal.
Although obesity is frequently enumerated as one of the causes of low QRS voltage, only a small number of obese patients have low voltage QRS.\(^3\) Other electrocardiographic findings include leftward shift of frontal plane QRS axis and prominent q waves in inferior leads presumably because of diaphragmatic elevation.

**ECG OF THE MONTH**

**Precordial Low Voltage**

Precordial low voltage is seen in patients with asci.\(^5\) It is hypothesized that increased intra-abdominal pressure influences the anatomical position and electrical axis of heart. Cranial placement of precordial electrodes increases QRS voltage in leads V\(_1\)-V\(_3\). It is considered as one of the causes of low voltage QRS in cirrhosis.\(^36\) Oedema and hypoalbuminemia could be contributory. Removal of ascites significantly increases the voltage.\(^36\)

**In a patient with anasarca, multiple factors e.g. concomitant pericardial effusion, pleural effusion and ascites could contribute to low voltage. Periphera oedema also affects the voltage of P and T waves. Changes are reversible. Peripheral oedema secondary to nonsteroidal anti-inflammatory drugs,\(^39\) thiazolidinediones, chronic renal failure, cirrhosis and hypoalbuminemia has been shown to be associated with reversible reduction in QRS amplitude.\(^9\)

---

MCQs

Low Voltage ECG

Q1. Low voltage QRS is defined as
(A) <0.5 mv in limb leads
(B) <1 mv in limb leads
(C) <1 mv in precordial leads
(D) <2 mv in precordial leads.

Q2. Low voltage QRS mostly affects
(A) Limb leads
(B) Leads V1 to V3
(C) Leads V4 to V6
(D) Leads V7 to V9.

Q3. Low voltage QRS can be due to
(A) Standardization at 5 mm/mv
(B) Normal variation
(C) Inferior infarction
(D) Acute pericarditis without effusion.

Q4. Acute phase of Takotsubo cardiomyopathy produces
(A) Transient attenuation of QRS
(B) Permanent attenuation of QRS
(C) T wave inversion in leads II, III, aVF
(D) ST depression with upright T wave in lead aVR.

Q5. Cardiac amyloidosis produces
(A) LVH by voltage criteria
(B) LVH on echocardiography
(C) Hypokinesia on echocardiography
(D) 1st degree AV block.

Q6. Myocarditis produces
(A) A-V block
(B) Sinus bradycardia
(C) Increased ventricular activation time
(D) Pathologic Q waves.

Q7. Dilated cardiomyopathy produces
(A) Attenuation of QRS in limb leads
(B) Tall QRS in precordial leads
(C) Tall QRS in limb leads
(D) Attenuation of QRS in precordial leads.

Q8. Which of the following strongly suggest dilated cardiomyopathy?
(A) RBBB+ LASFB
(B) RBBB + LPIFB
(C) LBBB + RAD
(D) Biatrial enlargement.

Q9. Adriamycin cardiomyopathy produces
(A) Bradycardia
(B) LVH by voltage criteria
(C) Pleural effusion
(D) Pericardial effusion.

Q10. Attenuation of QRS voltage can result from
(A) Pulmonary congestion
(B) Right sided pleural effusion
(C) Myocardial oedema
(D) Pneumomediastinum.

Q11. Massive pulmonary embolism produces
(A) RBBB
(B) ST depression in lead V1
(C) Tall T wave in leads V1 to V3
(D) Q waves in leads II, III, aVF.

Q12. Hypothyroidism is characterized by
(A) Low voltage T waves
(B) ST segment depression in limb leads
(C) ST segment elevation in precordial leads
(D) Sinus bradycardia.

Q13. In hypothyroidism, QRS voltage correlates with
(A) Serum T4
(B) Serum albumin
(C) Pericardial effusion
(D) Myocardial oedema.

Q14. Acute pericarditis produces
(A) Coved upward ST elevation in most leads
(B) Reciprocal ST segment depressions
(C) Left atrial enlargement
(D) T wave inversions.

Q15. Which ECG finding is specific of cardiac tamponade
(A) Sinus tachycardia
(B) Electrical alternans
(C) Attenuation of QRS voltage
(D) T wave flattening.

Q16. Chronic constrictive pericarditis produces attenuation of QRS voltage due to
(A) Thick pericardium
(B) Myocardial fibrosis
(C) Pericardial effusion
(D) Right sided pleural effusion.

Q17. In context of pericardial constriction T wave inversion correlates with
(A) Pericardial inflammation
(B) Pericardial effusion
(C) Thickness of pericardium
(D) Myocardial fibrosis.

Q18. Which factors can contribute to low voltage QRS
(A) Oedema
(B) Hypoalbuminemia
(C) Pulmonary congestion
(D) All.

Q19. Most sensitive ECG finding in emphysema is
(A) Low voltage QRS in lead I
(B) P- Pulmonale
(C) RVH
(D) RAD.

Q20. Which conditions can produce low voltage QRS
(A) Asthenia
(B) Ascites
(C) Anasarca
(D) All.

Valvular Vegetations

MONIKA MAHESHWARI

Figure 1. Trans thoracic echocardiogram (apical four chamber view) showing vegetation on mitral valve.

Figure 2. Trans thoracic echocardiogram (parasternal short axis view) showing vegetation on pulmonary valve.

Figure 3. Trans thoracic echocardiogram (apical five chamber view) showing vegetation on aortic valve.

Figure 4. Trans thoracic echocardiogram (apical four chamber view) showing vegetation on tricuspid valve.

Dr. Monika Maheshwari is Associate Professor at Jawahar Lal Nehru Medical College, Ajmer, Rajasthan.
CARDIOLOGY TODAY
INSTRUCTIONS TO AUTHORS

MANUSCRIPT

Manuscripts must be neatly typed in double space typing throughout on one side of the sheet of good quality bond paper of the size 28 x 22cm with 3cm margins on both sides. Words should not be hyphenated at the end of a line. Authors are requested to send the article on e-mail arun.kharkwal@cims.co.in or CD with one origial copy of the type script should be submitted alongwith to the Publisher, CIMS Medica India Pvt Ltd, 709, Devika Tower, Nehru Place, New Delhi-110019.

Material received for publication will be acknowledged and the decision regarding publication will be communicated to the “Author for correspondence”.

The manuscript of case reports/studies and original articles should be arranged in the following sequence: Title page, Abstract, Key Words, Introduction, Material and Methods, Results, Discussion, Acknowledgments, References, Tables and legends to figures.

Article title: Title should be concise, easier to read and should include all information in the title that will make electronic retrieval of the article both sensitive and specific.

Authors’ names and institutional affiliations: The name of the department(s) and institution(s) to which the work should be attributed.

Disclaimers, if any, Source(s) of support in the form of grants, equipment, drugs, or all of these. Declaration of Conflict of Interest.

Contact information for corresponding authors: The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript (‘corresponding author-may or may not be the “guarantor” for the integrity of the study). The name and address of the author to whom requests for reprints should be addressed or a statement that reprints are not available from the authors.

Abstract: Structured abstracts are preferred for all original research, systematic reviews and case studies. The abstract should provide the background for the study or the article. In case of original research article abstract should state the study’s purpose, basic procedures, main findings, principal conclusions, and funding sources.

Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be clear, and any unspecified subgroup analyses should be described. Provide only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods and Material: Methods should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

Selection and Description of Participants: Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report—for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

Technical Information: Identify the methods, apparatus (give the manufacturer’s name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarised in the abstract.

Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantitatively present and interpret the results in the Results section (e.g., means ± SEM) or as a measure of effect size. References for the design of the study and statistical methods should be to standard works when available, and statistical methods should be stated in the methods section. Editors may request that authors provide color photographs, positive transparencies, or color negatives, and all data be stored in both hard copy and electronic form.

DISCUSSION: Emphasise the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence. Do not repeat in detail data or other information given in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by summarising the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

UNITs OF MEASUREMENT

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius/Fahrenheit.

Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal. Journals that want the units they use for reporting hemotologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratortory information in both local and International System of Units (SI). Editors may request that authors use alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

ABBREVIATIONS AND SYMBOLS

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Address submissions to: The Publisher

CARDIOLOGY TODAY
CIMS Medica India Pvt Ltd, 709, 7th Floor, Devika Tower, Nehru Place, New Delhi-110 019
Tel: 011-4285 4300, Fax: 011-4285 4310
E-mail: arun.kharkwal@cims.co.in
ABOUT MYSELF

Name ___________________________ Qualification ___________________________
Speciality ________________________ Occupation ____________________________
Postal address ______________________________________________________________
City ____________________________ PIN __________________ State ________________
Phone ___________________________ E-mail _______________________________

I am interested in subscription of your following journals

<table>
<thead>
<tr>
<th>Publication</th>
<th>Periodicity</th>
<th>Rate per issue (INR)</th>
<th>1 Yr (INR)</th>
<th>2 Yrs (INR)</th>
<th>Overseas (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMS</td>
<td>Quarterly</td>
<td>390</td>
<td>1400</td>
<td>2600</td>
<td>50</td>
</tr>
<tr>
<td>IDR - Tripe i</td>
<td>Bimonthly</td>
<td>220</td>
<td>1200</td>
<td>2200</td>
<td>50</td>
</tr>
<tr>
<td>JPOG</td>
<td>Bimonthly</td>
<td>1700</td>
<td>9500</td>
<td>18000</td>
<td>250</td>
</tr>
<tr>
<td>Cardiology Today</td>
<td>Bimonthly</td>
<td>1700</td>
<td>9500</td>
<td>18000</td>
<td>250</td>
</tr>
<tr>
<td>CIMS Annual</td>
<td>Yearly</td>
<td>550</td>
<td>550</td>
<td>1000</td>
<td>50</td>
</tr>
</tbody>
</table>

Note: All remittances only by DD payable at Mumbai in the name of "CIMS Medica India Pvt. Ltd."

The above published rates are subject to change by the publishers at any point without any prior notice or assigning any reason. In the event of any price change, intimation will be sent after receipt of the order.

CIMS Medica India Pvt. Ltd.
(Previously known as UBM Medica India Pvt Ltd.)

- Registered Office: Margosa Building, No. 2, 3rd Floor, 13th Cross, Margosa Road, Malleshwaram, Bengaluru - 560 003, Karnataka, India.
  Tel: +91-80-4346 4500, Fax: +91-80-4346 4530
- Corporate Office: Boomerang (Kanakia Spaces), Wing-B1, #403, 4th Floor, Chandiwali Farm Road, Chandiwali, Powai, Mumbai - 400 072, Maharashtra, India.
  Tel: +91-22-6612 2600, Fax: +91-22-6612 2626
- Regional Office: #709, 7th Floor, Devika Tower, Nehru Place, New Dehi - 110019, India.
  Tel: +91-11-4285 4300, Fax: +91-11-4285 4310