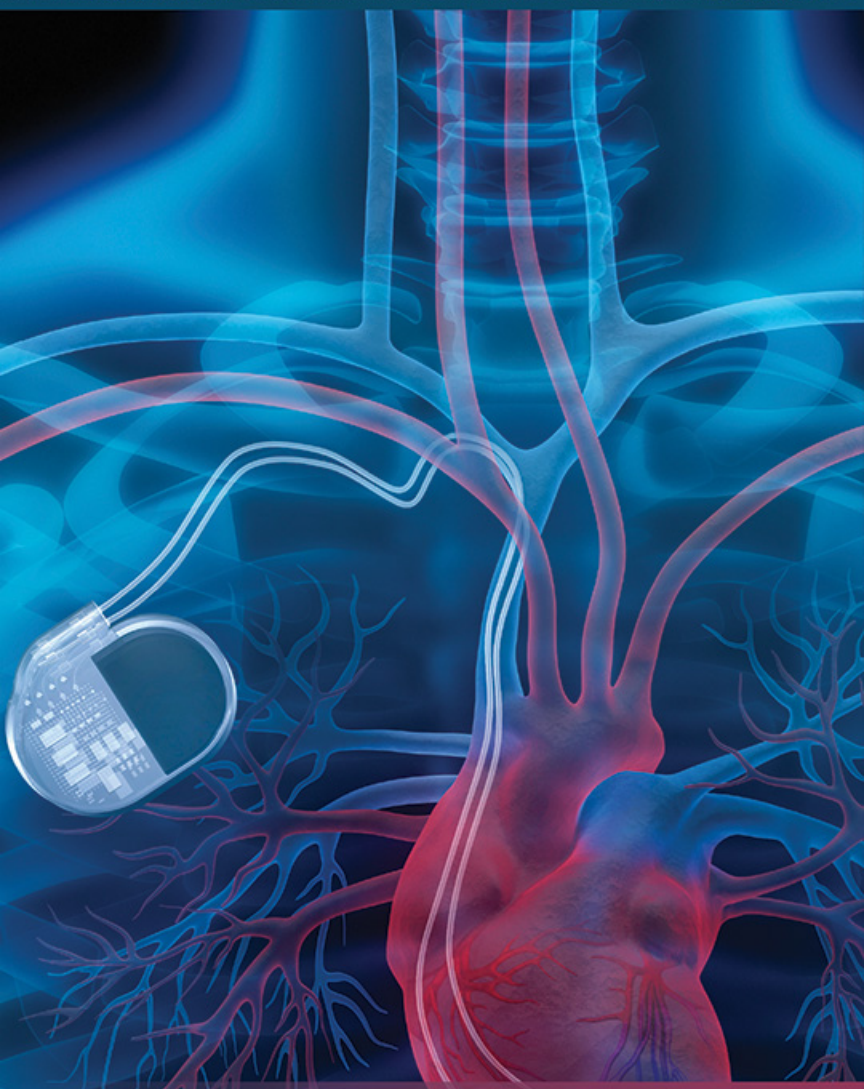


CARDIAC PACING

A Physiological Approach

Asit Das

JAYPEE

Contents

CHAPTER 2

Introduction to Physiological Pacing

INTRODUCTION

From its first human implantation (October 8th, 1958 by Swidish Surgeon Ake Senning) the right ventricular apical pacing has saved millions of lives. But, within one decade it was proved to be nonphysiological as it causes several deleterious hemodynamic effects. Right ventricular apical pacing alters left ventricular electrical and mechanical activation. Chronic right ventricular apical pacing causes left ventricular dilatation and reduction in left ventricular ejection fraction by a process called 'remodeling'. It causes some cellular and subcellular changes which persist for long-time even in absence of continued pacing. These changes have been related to increased mortality and morbidity in patients with ventricular pacemakers.

ADVERSE EFFECTS OF RV APICAL PACING

In general, the negative effects of right ventricular (RV) apical pacing have been attributed to the abnormal electrical and mechanical activation pattern of the ventricles. During RV apical pacing, the conduction of the electrical wave front propagates through the myocardium, rather than through the His-Purkinje conduction system. As a result, the electrical wave front propagates more slowly and induces heterogeneity in electrical activation of the myocardium, comparable to left bundle branch block. This is characterized by a single breakthrough at the interventricular septum and the latest activation at the inferoposterior base of the left ventricular (LV). Various acute and long-term deleterious effects of right ventricular apical pacing are summarized in Table 2.1.

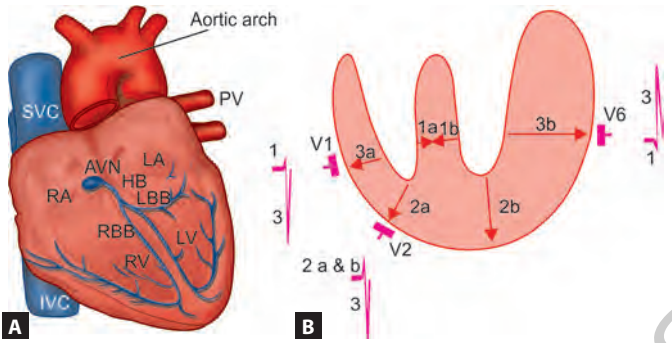
ELECTROCARDIOGRAPHIC CHANGES

Normal activation of the ventricles starts with conduction of the electrical impulse from the atrioventricular (AV) node to the His bundle. From the His bundle, at the superior margin of the muscular interventricular septum, the right bundle branch

Table 2.1 Short- and long-term effects of right ventricular (RV) apical pacing

Metabolic changes: • Changes in regional perfusion • Changes in oxygen demand
Remodeling: • Asymmetric septal hypertrophy • Left ventricular and left atrial dilatation • Functional mitral regurgitation • Histopathological changes
Hemodynamics: • Decreased cardiac output • Increased left ventricular (LV) filling pressures
Mechanical function: • Changes in myocardial strain • Interventricular mechanical dyssynchrony • Intraventricular mechanical dyssynchrony
Miscellaneous: • Increased risk of atrial fibrillation • Promotion of ventricular arrhythmia • Activation of sympathetic nervous system

proceeds intramyocardially as a thin, unbranched extension of the His bundle along the right side of the interventricular septum and terminates in the Purkinje plexuses of the right ventricular (RV) apex, at the base of the anterior papillary muscle. The left bundle branch also has a short intramyocardial route in the interventricular septum before giving rise to its two branches: anterior and posterior fascicle. A third fascicle is also described recently, known as centroseptal fascicle, supplies the mid-septal area of the LV and arises either from the main left bundle branch or from its anterior or posterior subdivision, or from both. The anterior subdivision is longer and thinner than the posterior one. For this reason it is more vulnerable to damage, so that conduction disturbances along this fascicle are much more common than the ones involving the posterior fascicle. The three subdivisions continue in a network of Purkinje fibers, located subendocardially in the lower third of the septum and in the anterior free wall, and extending to the papillary muscles. The Purkinje fibers are long and large. The numbers of gap junctions in these fibers are very high resulting in their very fast conduction velocity. During normal antegrade excitation, fast propagation over these long fibers, together with the wide distribution of Purkinje—myocardial junctions, induces a high degree of electrical coordination between distant regions of the myocardium. His bundle as well as the right and the left bundle branches are electrically isolated from the adjacent working myocardium. The only sites where the Purkinje system and the normal working cells are electrically

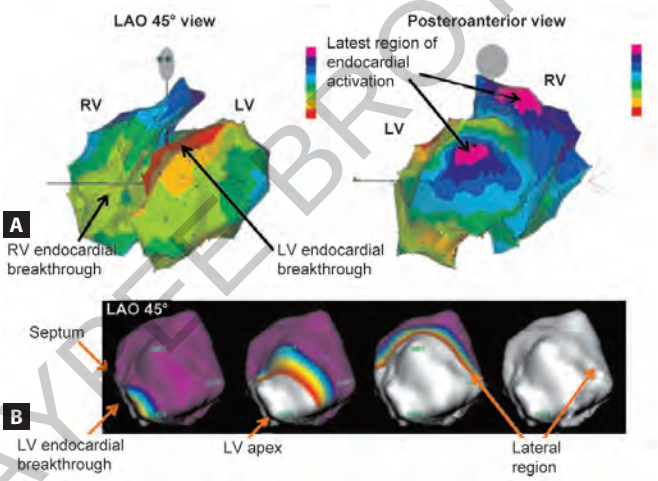


Figs 2.1A and B (A) Normal AV node and infranodal conduction system, (B) Diagram illustrating the mechanism of normal intraventricular conduction. With normal intraventricular conduction, activation of the ventricles begins in the left lower third of the interventricular septum and spreads transversely from left to right through the septum. This left-to-right vector, however, is opposed by the smaller right-to-left septal vector which originates from the right bundle branch, and which arises in the right side of the interventricular septum (vector 1). Paraseptal activation occurs next, spreading transversely from endocardial to epicardial surfaces (vector 2). This is followed by endocardial-epicardial activation of the free walls both in right and left side.
Abbreviations: SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; AVN, AV node; HB, common bundle of His; RBB, right bundle branch; LBB, left bundle branch; RV, right ventricle; LV, left ventricle.

coupled are the so-called Purkinje—myocardial junctions, located subendocardially both in the RV and in the LV. Impulse conduction in the Purkinje system is from base to apex and occurs quickly (3–4 m/s).[1] The activation of the myocardial muscular tissue in the septum occurs mainly from apex to base.[2] In the LV and RV free wall, impulse conduction also occurs from apex to base and from endocardium to epicardium. As a consequence of this impulse conduction, the posterobasal area is the last activated part of the ventricles. The electrical impulse is conducted approximately four times slower (0.3–1 m/s) in the normal myocardium than in the Purkinje system. In humans, total ventricular activation lasts 60–80 ms, corresponding with a QRS duration of 70–80 ms.[2]

Three-dimensional electroanatomical mapping data suggests that in the normal heart, the first site of endocardial ventricular activation (endocardial breakthrough site) is usually in the LV, at the interventricular septum or in the anterior region. Within approximately 10 ms the activation begins in the RV endocardium, near the insertion of the anterior papillary muscle, i.e. the exit of the right bundle branch.[7] After activation of these regions, depolarization wave fronts proceed simultaneously in the LV and RV, predominantly from apex

to base and from septum to lateral wall in both ventricles (Figs 2.2A and B). The latest activated endocardial region of the RV is the basal area near the AV sulcus and the pulmonary conus. Overall, the posterolateral/basal area of the LV is the last part of the heart to be depolarized. Simultaneous depolarization wave front occurs centrifugally from the endocardium to the epicardium. However, the earliest ventricular epicardial activation site (epicardial breakthrough site) occurs usually at the pretrabecular area of the RV from where there is a radial spread towards the apex and the base, within the subepicardial layers.[7] In a normal heart, the duration of total ventricular electrical activation is 50–80 ms. The short ventricular activation time stresses the important role of the Purkinje fibers system in the synchronization of electrical myocardial activity. So, pacing in the right ventricular outflow tract (RVOT) septal region seems to produces a more physiological electrical activation sequence and endocardial-epicardial breakthrough pattern.



Figs 2.2A and B (A) Color-coded (red indicating the earliest and purple the latest activation site) 10 ms isochronal maps, obtained with contact electroanatomical mapping system, of biventricular activation in a normal heart. The earliest endocardial ventricular activation site (breakthrough site) is recorded in the LV anterior septal region (red spot). The latest activated regions are the posterolateral walls of both RV and LV; (B) Unipolar isopotential maps, recorded with noncontact mapping system of LV activation sequence in a normal heart. The LV endocardial breakthrough is recorded in the septum. The activation wave front (white spot) proceeds fast toward the anterior, then to the lateral region and finally to the posterior region.
(*Courtesy:* Cecilia Fantoni, Angelo Auricchio. Electrical activation sequence in 'Cardiac Resynchronization Therapy' 2nd edition, editor: Cheuk-Man Yu, David L. Hayes, Angelo Auricchio, pub. Blackwell Futura, 2008 with permission)
Abbreviation: LAO, left anterior oblique

Normally, the right ventricle (RV) contraction is a complicated peristaltic movement beginning in the inflow region and extending to the outflow tract.[3] The RV is largely silent during conventional electrocardiography because it generates weak electrical forces completed early in the QRS complex and mostly concealed by left ventricle (LV) depolarization. In patients with left bundle branch block (LBBB), surface electrocardiographic recordings demonstrated rapid initial myocardial activation (short rS duration) suggestive of intact right bundle branch (RBB) conduction despite the presence of LV conduction abnormalities.[4,5] The activation pattern likely reflects the course of the RBB, which passes down the septum to the base of the anterior papillary muscle and then fans out into multiple free-running false tendons terminating in the free wall as a profuse subendocardial Purkinje network. This generates nearly simultaneous activation of the free wall in a radial manner, likely responsible for initiation of RV contraction from the inflow tract to outflow tract.[6] In contrast, the LV free wall depolarizes from apex to base (Fig 2.3).

The electrical effects of RV pacing are similar to left bundle branch block (LBBB). The QRS configurations are similar. LV activation occurs transseptally after RV depolarization in both. The RV-paced wave-fronts propagated slowly from apex to base, in contrast to rapid and radial spread during intrinsic activation. The prolongation of the duration of global RV activation by RV pacing is driven by slow conduction areas generated locally around the stimulus site. Delay permits intrinsic right bundle branch-mediated conduction to contribute to RV free wall depolarization, resulting in varying degrees of wave-front fusion (Fig. 2.4). The pattern and duration of RV free wall activation are the outcome of the balance of intrinsic **(centrifugal)** and RV-paced **(centripetal)** wave-fronts. When RV-paced delays are less, global RV activation duration is not delayed (although direction of depolarization is different from intrinsic conduction). In contrast, when intrinsic AV conduction is absent or poor, the RV is committed to activation by the RV pacing and RV activation duration is longer. RV pacing also disturb septal depolarization.

Data from the literature indicate that the extent of synchrony and sequence of activation during ventricular pacing are determined by at least four myocardial properties: (1) the poor coupling of the ectopically generated impulse to the rapid conduction system. The impulses coming from the normal myocardium can enter the Purkinje system only at the apical part, the sites where during normal conduction the impulse exits this system. Therefore, in most cases the sequence of activation during ventricular pacing is governed

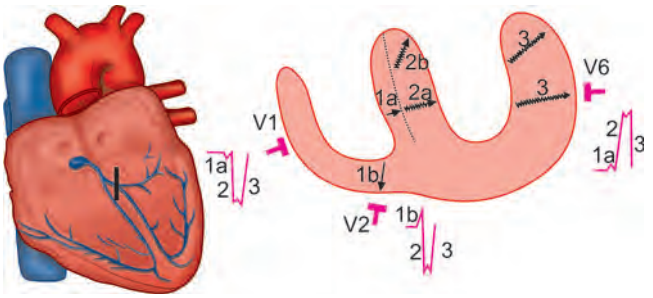
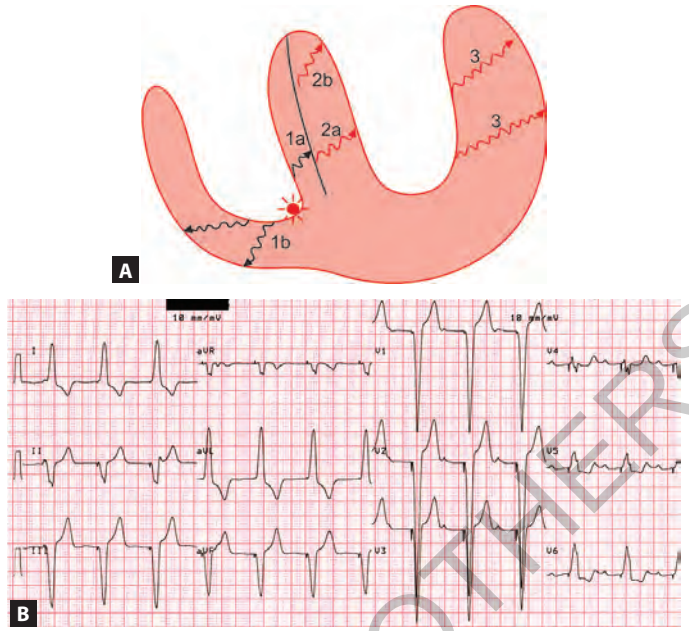


Fig. 2.3 *The mechanism of left bundle branch block:* Right septal activation—ventricular activation begins in the right side of the interventricular septum and proceeds from right to left through the septum. This results in a small right-to-left vector which is the normal right septal vector (vector 1a). Unlike normal intraventricular conduction, this is not opposed by a concomitant greater left-to-right force of the left septal mass. This unopposed vector will results in a small initial positive deflection in leads oriented to the left side of the interventricular septum (lead V6) and a small negative deflection in leads oriented to the right side of the interventricular septum (lead V1). This component is very small and needs sensitive ECG machine to record. *Delayed and anomalous left septal activation:* Following right septal activation, the activation process "jumps", the intraseptal physiological barrier (dotted line) and activates the left side of the septum in a delayed and anomalous fashion. This results in vectors of large magnitude which are directed to the left and posteriorly (vector 2). This results in a tall R wave in leads oriented to the left side of the septum (lead V6) and a deep S wave in the leads oriented to the right side of the septum (lead V1). Further delay in the activation of the superior region of the interventricular septum (vector 2b) may result in a slurred or notched plateau at the apex of the bizarre QRS complex recorded by left-oriented leads (lead V6), and a slurred or notched nadir in the right-oriented leads (lead V1). *Delayed and anomalous activation of the free left ventricular wall*: Septal activation is followed by delayed and anomalous activation of the free left ventricular wall. This results in a vector of large magnitude which is directed to the left and posteriorly as well as somewhat superiorly (vector 3) which is reflected by a tall R′ deflection in left-oriented leads (lead V6) and a deep secondary S wave in right-oriented leads (lead V1)

by the slow conduction through the normal myocardium, away from the pacing site,[7] (2) because the conduction through the myocardium is up to four times slower than conduction through the Purkinje system, activation of the entire ventricular wall is more asynchronous than during normal sinus rhythm and atrial pacing, (3) the conduction velocity is approximately two times faster in the direction parallel to muscle fiber length (isotropic conduction) than in the direction perpendicular to them (anisotropic conduction).[8] Therefore, in a particular layer, the wave-front has an elliptic shape. Because fiber-orientation changes by more than 90° across the LV wall,



Figs 2.4A and B The mechanism of electrical dyssynchrony in right ventricular apical pacing: (A) Different vectors: blue arrow indicates the balanced vector of intrinsic (centrifugal) and RV-paced (centripetal) wave-fronts stimulating RV free wall and RV septum, red arrow indicates slow propagation of wave front though the myocardium activating LV septum and LV free wall, star indicates pacing site; (B) Resultant 12 lead surface ECG

and because impulses are also conducted in transmural direction, a complex three-dimensional helical wave-front is present in the LV wall during pacing,[9] (4) the most endocardial fibers, even though not part of the Purkinje system, conduct impulses faster than the fibers in the major part of the LV wall.[10]

To summarize, normal physiological activation of the ventricles is characterized by minimal asynchrony, monotonic activation, earlier LV than RV activation, and earlier apical than basal activation. During LBBB and RV apex pacing, the activation sequence deviates significantly from the physiological one.

MORPHOLOGICAL CHANGES

Normal cardiac contraction efficiently uses the geometric spiral arrangement of ventricular myocardial fibers. Activation of the specialized His-Purkinje system enables depolarization to occur in an established fashion with nearly simultaneous

biventricular activation. However, cellular and molecular structures are not constant and are influenced and molded by electrical and hemodynamic forces. Therefore, alternative stimulus initiation can produce abnormal contraction patterns that affect ventricular synchrony changing regional myocardial blood flow with a redistribution of fiber strain.[11] This ultimately produces altered segmental wall shortening, abnormal metabolism, and inefficient work. The findings of more adverse cellular and subcellular alterations in patients with chronic RV apical pacing favors the concept that altered contractile stresses associated with chronic right ventricular apical pacing may adversely effect myocardial cellular growth.

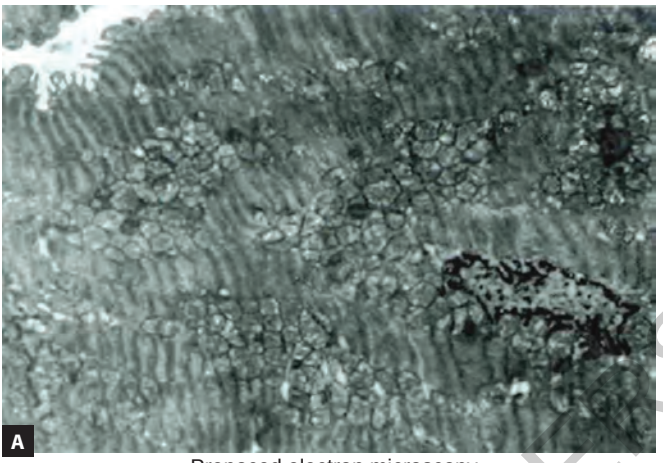
Varying combination of the following various abnormal histopathological changes (Figs 2.5A and B) are noted in patients with prolonged right ventricular apical pacing:[12]

- Myofiber hypertrophy,
- Myofiber variation,
- Endocardial sclerosis,
- Fat infiltration,
- Interstitial fibrosis,
- Altered mitochondrial size, number, or histologies.

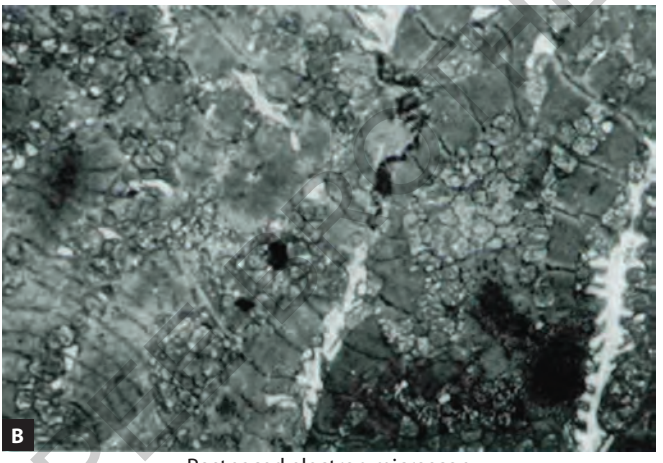
Studies have shown that these ultrastructural changes indicate that the site of origin of ventricular stimulation, *per se*, and not artificial electrical stimulation or loss of atrioventricular (AV) synchrony, appears to be responsible for the observed compensatory cellular remodeling as changes are not seen in patients with right ventricular septal pacing.[13]

Three important morphological alterations are noted in patients with chronic right ventricular apical pacing: **ventricular dilatation, asymmetric septal hypertrophy, and septal hypoperfusion**. These structural adaptations in the left ventricle are the results of asynchronous electrical activation from right ventricular apical pacing.

Left ventricular dilatation and dyssynchrony leading to deterioration of left ventricular function in chronic right ventricular apical pacing is secondary to a process also known as '**remodeling**'. Pacing at right ventricular apex disturbs the natural pattern of activation and contraction because conduction of the electrical wave front takes place slowly through ventricular myocardium rather than through the His-Purkinje system (electrical dyssynchrony). The mechanical effect of asynchronous electrical activation is dramatic because the various regions differ not only in the time of onset of contraction, but also in the pattern of contraction. Early contracting regions close to the pacing site stretch not-yet activated remote regions. This stretching further delays shortening of these late-activation regions and increases



Prepaced electron microscopy



Postpaced electron microscopy

Figs 2.5A and B (A) Prepaced electron micrograph (EM) illustrating clumping of an increased number of relatively normal-appearing mitochondria but with preservation of the normal myofiber arrangement; (B) Postpaced EM compared with A, mitochondrial aggregates appear abnormal with variable sizes and shapes, distorting and thinning the surrounding myofibers. (Original magnification X12.500)
(*Courtesy:* Peter P Karpawich, Raja Rabah, and Joel E. Haas: Altered Cardiac Histology Following Apical Right Ventricular Pacing in Patients with Congenital Atrioventricular Block. PACE 1999; 22:1372-1377 with permission).

their force of local contraction by virtue of the (local) Frank-Starling mechanism. Because of their vigorous contraction, the late-activated regions impose loading on the earlier activated territories, which now undergo systolic paradoxical stretch. This reciprocated stretching of regions within the LV wall causes a less effective and energetically less efficient contraction.[14] The local differences in contraction pattern in the paced ventricle

imply a redistribution of mechanical work, perfusion, and oxygen demand within the LV wall.[11] All these in long-term give rise to gradual dilatation of the left ventricle.

Asymmetrical hypertrophy in patients with RV apical pacing is most likely due to the redistribution of workload, as evidenced by the regional differences in circumferential shortening in systole (CSsys) and external work.[15] Regional differences in macroscopic hypertrophy are related to regional differences in myocyte diameter without differences in regional collagen content, indicating that the hypertrophy is due to a proportional increase of myocyte and collagen volume (discussed later).

Most interestingly, the mechanical dyssynchrony induced by RV apical pacing can persist even when the pacing is withdrawn (i.e. in absence of electrical asynchrony) probably because of cellular derangements, such as, myofibrillar cellular disarray, dystrophic calcification, disorganized mitochondria and down-regulation of proteins involved in calcium homeostasis and impulse conduction, in late-activated regions. Increased sympathetic stimulation, resulting in elevated myocardial catecholamine levels, also contributes to the development of asymmetric hypertrophy. The late-activated, most-hypertrophied regions show the most pronounced cellular derangements, such as down-regulation of proteins involved in calcium homeostasis and impulse conduction leading to dystrophic calcifications and disorganized mitochondria and myofibrillar cellular disarray.

METABOLIC CHANGES

Total myocardial work is reduced by 50% in early-activated regions and is increased by 50% in late-activated regions, as compared with the situation during normal electrical activation, as during atrial pacing.[16] Several studies report regional differences in myocardial blood flow, glucose uptake, and oxygen consumption during ventricular pacing, which are similar to the differences in mechanical workload. [17-19] As compared to sinus rhythm myocardial blood flow and oxygen consumption are approximately 30% lower in early-activated regions and approximately 30% higher in late-activated regions. Several observations support the idea that the regional differences in myocardial blood flow and oxygen consumption are caused by the regional differences in workload. Lactate extraction decreases and oxygen extraction increases when perfusion becomes insufficient. Regional perfusion adapts well to an altered mechanical load. Interestingly, the regional differences in blood flow during pacing disappear during total

CARDIAC PACING
A Physiological Approach

Salient Features

- It is a comprehensive book focused on the technical issues of selective site cardiac pacing
- Contains enormous illustrations and examples, which make it easy to understand and friendly for the cardiology students and practitioners
- Describes small history of pacemaker
- Involves chapter on adverse outcomes of conventional pacing
- Comprehensive coverage of different techniques of atrial and ventricular selective site pacing
- Different methods of left ventricular (LV) lead placement in difficult situations during CRT implantation
- Plenty of illustrations, examples offer unique opportunity to easily understand the difficult techniques.

Asit Das MD (General Medicine) DNB (Cardiology) is Clinical Tutor, Department of Cardiology, Institute of Postgraduate Medical Education and Research (IPGMER) and SSKM Hospital, Kolkata, West Bengal, India. He has completed his graduation (1998) from RG Kar Medical College, Kolkata, West Bengal. Subsequently, he has completed his MD (General Medicine) (2005) and DNB (Cardiology) (2011), respectively. He is actively involved in pacemaker and device implantation since last 8 years.

Shelving Recommendation
CARDIOLOGY

ISBN 978-93-5250-182-3

9 789352 501823