The Deleterious Effect of Right Ventricular Apical Pacing on Atrial Function in Patients with Preserved Systolic Function

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ABSTRACT

Abstract of thesis entitled:

The Deleterious Effect of Right Ventricular Apical Pacing on Atrial Function in Patients with Preserved Systolic Function

Submitted by Xie Jun Min

Supervisor: Yu Cheuk Man

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Cardiac pacing has been the only effective treatment in the management of patients with symptomatic bradycardia caused by sinus node dysfunction or atrioventricular block for decades. Conventional dual-chamber pacing is performed by implanting two leads in right atrial (RA) appendage and right ventricular (RV) apex separately. RV apex is the most commonly applied pacing site because it can be easily reached and allows a chronically stable position and stimulation thresholds. However, large randomized clinical trials have suggested that right ventricular apical (RVA) pacing may cause abnormal ventricular contraction and reduce pump function and lead to myocardial hypertrophy, in particular in patients with impaired left ventricular (LV) function. Recent studies have also reported a reduced LV systolic function in patients with pacing indications and preserved ejection fraction. The deleterious effects of RVA pacing on LV function may be related to the abnormal electrical and mechanical activation pattern or ventricular dyssynchrony. During RVA pacing,

conduction of the electrical wave front propagates slowly through ventricular myocardium rather than through the His-Purkinje conduction system, comparable to left bundle branch block (LBBB). In addition, RVA pacing alters ventricular synchrony and loading conditions which may result in diastolic heart failure with abnormal LV relaxation, high filling pressure and low cardiac output state. Furthermore, it is possible that left atrial (LA) remodeling and reduction of atrial function may occur during RVA pacing. However, it is not been carefully studied.

Echocardiography is a convenient, non-invasive and established tool to assess cardiac function in clinical practice. Conventional two-dimensional echocardiography is useful to assess cardiac chamber size, volume and function. With the development of real time three-dimensional echocardiography (RT3DE) and color tissue Doppler imaging (TDI), echocardiography provides further valuable information and more accurate measurements which include myocardial velocity and parameters of dyssynchrony. In the present study, the main echocardiographic parameters including the maximal left atrial volume (LAVmax), pre-atrial contraction volume (LAVpre) and the minimal left atrial volume (LAVmin) were assessed by two-dimensional echocardiography. Peak systolic (Sm-la), peak early diastolic (Em-la), peak late diastolic (Am-la) velocities of left atrium (LA) and atrial conduction time (from onset of P wave on electrocardiogram to onset of atrial velocity) were measured by TDI.

In a cross-sectional study, ninety-eight patients who had been implanted with RVA-based dual-chamber pacemakers were enrolled. Four patients with pacing dependent were excluded. Eventually 94 patients were included in the final analysis. Echocardiography was performed (iE33, Philips) during intrinsic ventricular conduction (V-sense) and RVA pacing (V-pace) modes with 15 minutes between switching modes. We aimed to investigate if RVA pacing has any acute effects on atrial remodeling and function in patients with preserved ejection fraction (LV ejection fraction > 45 %). The result showed that during V-pace, LA volumes increased significantly when compared with V-sense (LAVmax: 52.0 ± 18.8 vs. 55.2 ± 21.1 ml, p = 0.005; LAVpre: 39.8 ± 16.4 vs. 41.3 ± 16.6 ml, p = 0.014; LAVmin: 27.4 ± 14.0 vs. 29.1 ± 15.1 ml, p = 0.001). TDI parameters showed significant reduction in Sm-la (3.0 ± 1.1 vs. 2.7 ± 0.9 cm/s, p < 0.01), Em-la (2.7 ± 1.1 vs. 2.4 ± 1.0 cm/s, p = 0.001). However, there was no change in Am-la.

In a prospective study, patients with symptomatic bradycardia, preserved ejection fraction, and received RVA pacing were recruited. Echocardiography was performed at both baseline and one year follow up through a standard protocol by experienced echocardiographers. LA volumes and velocities as well as intra- and interatrial dyssynchrony were measured offline with the use of dedicated software. The objectives of this study were to investigate: (1) if RVA pacing has any deleterious effects on LA remodeling and function during long-term follow up; (2) if RA appendage pacing has separate effects on atrial pump function, intra- and interatrial

dyssynchrony; (3) if atrial dysfunction and dyssynchrony can predict atrial high rate episodes (AHREs) burden in the first year of RVA pacing. The main findings of this study were: (a) at one year follow up, LA volumes and indexes were increased with reduction in passive emptying fraction and total emptying fraction. Atrial velocities showed significant reduction when compared with baseline; (b) in multivariate regression analysis, the ratio of transmitral early diastolic filling velocity to mitral annular early diastolic velocity (E/e') > 15 at one year and reduction of LV ejection fraction $\geq$ 5% were independent predictors of reduction of Am-la > 30%; (c) high percent of RA appendage pacing prolonged atrial conduction and induced intra- and interatrial dyssynchrony. (d) Am-la < 5.3 cm/s can predict AHREs burden which had a sensitivity of 71% and specificity of 75%.

In conclusion, our studies suggest even short-term RVA pacing induces LA dilatation and impaired passive atrial function, though it did not have direct effect on active atrial contractility. However, chronic RVA pacing results in LA remodeling and reduces atrial function with decreased contractility. This was more likely to occur in those with impaired LV ejection fraction and evidence of diastolic dysfunction. Atrial dysfunction and interatrial dyssynchrony can predict AHREs burden after chronic RVA pacing. Therefore, measures that may minimize such adverse effect of pacing on atrial function need to considered for patients receiving RVA pacing, such as the use of new pacing modalities.

摘要

心臟起搏器的植入是治療由竇房結功能異常或房室傳導阻滯引起的有癥狀的慢性心律失常的唯一的，有效的方法。傳統的雙腔起搏器有兩個電極，一個電極置於右心耳，另一個電極置於右心室心尖部。右心室心尖起搏最常見，因為電極放置於右心室心尖部，位置穩定且易達到電刺激閾值。但是，大型臨床試驗已經證明右心室心尖起搏可以引起心室收縮異常以及泵功能受損，導致心肌肥厚，特別是起搏器植入前已有心功能受損者。近期研究發現，對於有植入起搏器指征且左心室射血分數正常的患者，右心室心尖起搏也能引起左心室收縮功能減低。右心室心尖起搏對左心室功能的影響可能與心臟電激動順序異常或者心室舒縮不同步有關。右心室心尖起搏時，電激動時靠心肌細胞間的慢性傳導而不是靠心室浦肯野纖維，這種情況類似于左束支傳導阻滯。

此外，右心室心尖起搏改變了心室收縮的同步性以及負荷的情況，可能導致舒張性心力衰竭，呈現左心室舒張異常，充盈壓力增高以及低心輸出量的狀態。在左心室功能受損的同時，左心房也可能發生重構及功能的減低。但是，右心室心尖起搏對心房功能的研究甚少。

在臨床上，超聲心動圖是一種便捷，無創且價值肯定的評價心臟功能的方法。傳統的二維超聲可以準確評估心腔大小，容積以及功能。隨著三維超聲以及彩色組織多普勒超聲的出現和發展，新的測量指標如心肌運動速度，不同步指數等為全面評估心臟提供了更有價值和更準確的方法。此論文共包括了兩項研究：橫斷面研究和前瞻性研究。主要探討急性（短期）和慢性（長期）右心室心尖起搏對左心房結構和功能的影響。研究中主要的參數包括：心房最大容積，心房收縮前容積，心房最小容積，心房肌運動速度，竇房傳導時間等。

在横斷面研究中，研究對象為已經植入雙腔起搏器（右心室心尖起搏）者，在右心室起搏和感知兩種模式間隔 15 分鐘分別採集超聲心動圖（包括二維，三維及彩色組織多普勒超聲）圖像。此研究目的是觀察急性右心室心尖起搏對左心房大小及功能的影響。我們發現，左心房顯著擴大，心房肌在心室收縮前及舒張早期運動速度減低，但是在心室舒張晚期，心房肌運動速度沒有明顯變化。

在前瞻性研究中，納入的研究對象為有病癥的慢性心律失常，有植入雙腔起搏器指征且左心室射血分數正常的患者。在植入右心室心尖起搏的雙腔起搏器后隨訪一年，觀察左心房的結構及功能的變化，右心耳起搏對左心房和心房間同步性的影響，以及左心房功能和同步性的變化是否能夠預測快速心房率的發生。我們發現，在植入右心室心尖起搏的雙腔起搏器一年後，左心房容積在主動收縮前及收縮晚期比植入前明顯變大，而左心房被動射血分數及總射血分數變小。 通過對彩色組織多普勒超聲圖像的分析，我們發現心房肌運動速度在心室收縮和舒張不同時相都有不同程度地減低。除了右心室心尖起搏對左心房功能的影響外，右心耳起搏頻繁可以使竇房傳導時間延長，加速左心房內及心房間運動不同步，降低心房肌的運動速度。用心房間運動不同步及左心房主動收縮速度（發生在心室舒張晚期）可以預測快速心房率的發生，這對於心房纖顫的發生及預防具有很重要的臨床意義。

通過這兩項研究，可以得到這樣的結論：急性右心室心尖起搏可以使心房擴大以及被動收縮功能受損，并沒有影響左心房的主動收縮性。但是，慢性右心室心尖起搏可以導致左心房重構及功能異常，這種情況更易於出現在那些左心室收縮及舒張功能受損者。因此，在研究新的起搏方式時，應考慮減少不必要的右心室起搏對心房功能的損傷。

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PUBLICATIONS

I. Full Papers Published in International Journals

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LIST OF ABBREVIATIONS

A = transmitral atrial filling velocity

ACT = atrial conduction time

AF = atrial fibrillation

AHREs = atrial high rate episodes

Am-la = peak late diastolic velocity of left atrium

AUC = area under curve

AV = atrioventricular

BSA = body surface area

CI = confidence interval

CRT = cardiac resynchronization therapy

CT = computed tomography

Cum%AP = cumulative percentage of right atrial appendage pacing

Cum%VP = cumulative percent ventricular pacing

CW = continuous wave

DT = deceleration time

E = transmitral early diastolic filling velocity

ECG = electrocardiogram

E/e' = ratio of transmitral early diastolic filling velocity to mitral annular early diastolic velocity

Em-la = peak early diastolic velocity of left atrium

HCM = hypertrophic cardiomyopathy

HR = hazard ratio

IAS = interatrial septum

IVC = inferior vena cava

IVRT = isovolumic relaxation time

LA = left atrial / left atrium

LAVmax = maximal left atrial volume

LAVmin = minimal left atrial volume

LAVpre = pre-atrial contraction volume of left atrium

LBBB = left bundle branch block

LV = left ventricular / left ventricle

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVOT = left ventricular outflow tract

MBF = myocardial blood flow

MR = mitral regurgitation

MRI = magnetic resonance imaging

OR = odds ratio

P-ALA = time interval from onset of P wave on electrocardiogram to onset of peak late diastolic velocity of left atrial anterior wall

P-IAS = time interval from onset of P wave on electrocardiogram to onset of peak late diastolic velocity of interatrial septum

P-ILA = time interval from onset of P wave on electrocardiogram to onset of peak late diastolic velocity of left atrial inferior wall

P-LA = time interval from onset of P wave on electrocardiogram to onset of peak late diastolic velocity of left atrial lateral wall

P-RA= time interval from onset of wave P on electrocardiogram to onset of peak late diastolic velocity of right atrial free wall

PW = pulsed wave

RA = right atrial / right atrium

ROC = receiver operating characteristics

RT3DE = real time three-dimensional echocardiography

RV = right ventricular / right ventricle

RVA = right ventricular apical

RVOT = right ventricular outflow tract

SA = sinoatrial

Sm-la = peak systolic velocity of left atrium

TDI = tissue Doppler imaging

Tmsv-16SD = standard deviation of time to minimum regional volume for 16 segments of LV

TR = tricuspid regurgitation

Ts-SD = standard deviation of time to peak systolic velocity during ejection phase of the 12 LV segments by TDI

SECTION I
INTRODUCTION

CHAPTER 1 RIGHT VENTRICULAR APICAL (RVA) PACING

1.1 Cardiac Conduction System in Normal Heart

There is a specialized conduction system, which is responsible for rapid conduction of electrical impulses in order to create coordinated contraction of the whole heart (Figure 1.1). The specialized conduction system consists of the sinoatrial node, conduction pathways through the atria, the atrioventricular node, the conduction pathways through the ventricles including His bundle, the right bundle branch, the left bundle branch and the Purkinje fibers (1).

1.1.1 Sinoatrial Node

The sinoatrial node is the major generator of cardiac impulses which locates at the junction of the right atrium (RA) and superior vena cava. However, the location of the sinoatrial node is variable in adults. In a small number of cases, the sinoatrial node is found to slung over the crest of the right atrial (RA) appendage (2).The sinoatrial node contains of a variety of cells which initiate electrical impulse and extend the activity between pacemaker cells and regular atrial myocardial cells (3).The cells have the most rapid inherent rhythm in the normal heart with 60-100 beats per minute at rest. It has been suggested that multiple pacemakers were responsible for impulse initiation within the node, and more superior the position, the faster is the heart rate. The heart rate is also controlled by the autonomic nervous system. The extranodal pacemakers are potentially important pathologically leading to ectopic sites and resulting in atrial tachycardia (4,5). Therefore, in human heart,

the sinoatrial node takes on two essential functions: it irritates a steady repetitive signal that generates the normal heart beat named "sinus rhythm"; and the normal sinus rhythm fluctuates to provide an optimal heart rate to maintain the most effective cardiac output (6).

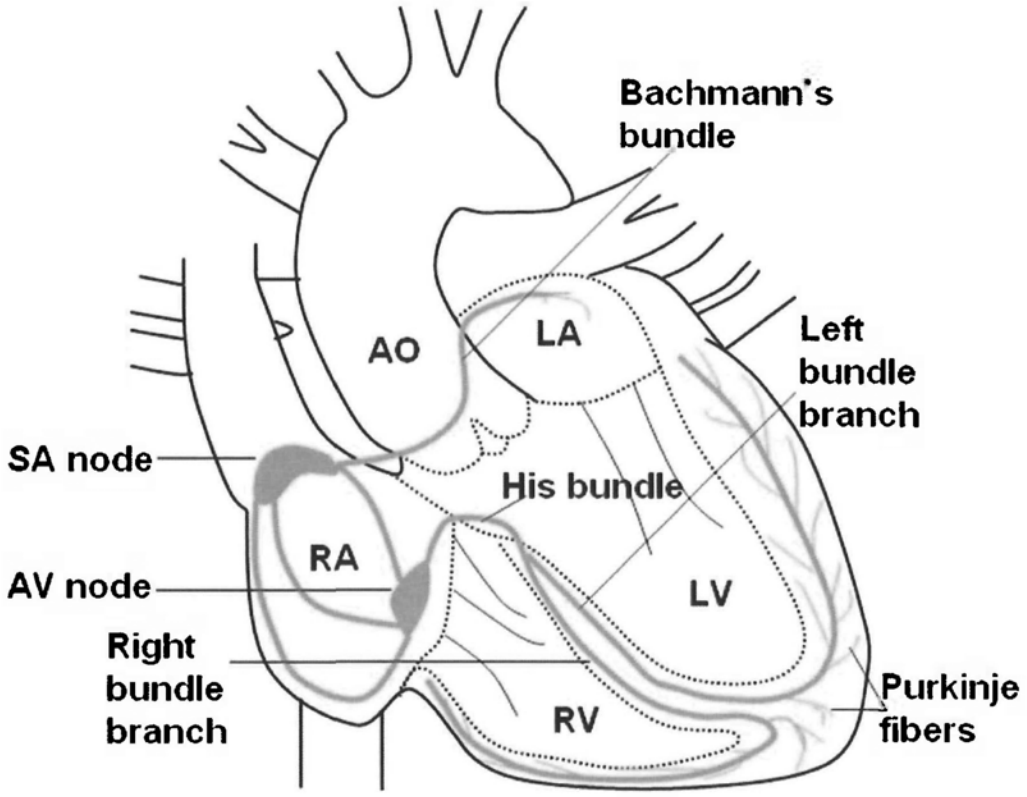


Figure 1.1 Cardiac conduction system. Normal impulses generate from the sinoatrial (SA) node, travel through the atria, converging on the atrioventricular (AV) node, and then conduct through His bundle, right and left bundle branches and Purkinje system and rapidly depolarize the ventricles, as shown in blue-green line.

1.1.2 Atrioventricular Node

The atrioventricular node is connected to the sinoatrial node by several specialized fiber tracts, which is a complex histological structure (7). The conduction of electrical impulses is rapid. Impulses to left atrial (LA) are through Bachmann's bundle which locates in anteroseptal portion of the interatrial septum (IAS) and finally reach the atrioventricular node through three pathways (6). However, the conduction through the atrioventricular node is relatively slow. It takes 80 milliseconds or more for impulse signals to propagate through the atrioventricular node (8). There are three important functions in the atrioventricular node: (1) It delays the passing impulse (approximately 40 milliseconds) and allows time for complete atrial contraction; (2) it also operates as an electrical impulse generator like the sinoatrial node; (3) it serves as a cardio-protective filter for limiting ventricular rate during atrial tachyarrhythmias. In addition, the atrioventricular node has an abundant arterial blood supply and response to the autonomic nervous system or humoral signals.

1.1.3 His Bundle and Bundle Branches

The electrical impulses travel through the His bundle (atrioventricular bundle) and then deliver to left and right bundle branches for distribution to the ventricular myocardium. His bundle is a narrow tubular structure that runs through the membranous septum to the crest of the muscular septum. It is quickly subdivided into a left bundle branch and a right bundle branch. His bundle acts as a "transfer

station" for receiving the electrical signals from the atrioventricular node and transmits to left and right bundle branches and then terminates in a Purkinje network. Because of having the specialized conduction system, the electrical impulses are rapidly conducted to each area of the ventricles and responsible for the almost simultaneous activation of the ventricles. Besides the conduction system, it is also possible to transmit electrical signal through ordinary myocardial cells to cells. However, the process is so slow (8).

Thus, in the heart, the myocytes must be activated by electrical signals. The process is so called electromechanical coupling. The sinoatrial node is the natural pacemaker. The electrical signals fired from the sinoatrial node travel through the atria, transmit to the atrioventricular node, and then propagate through the His bundle and bundle branches and finally to the Purkinje fibers. The process of conduction is rapid in order to simultaneously stimulate contraction of the cardiac chambers. In left ventricle (LV) and right ventricle (RV), the electrical wave front propagates transmurally from the endocardium to the epicardium.

1.2 Indications for RVA Pacing — Bradycardia

1.2.1 Conduction Disorders in Sinus Node Dysfunction

Bradyarrhythmia disorders occur when failure of adequate impulse initiation or propagation. Sinus node dysfunction or sick sinus syndrome and atrioventricular block are most common conduction disorders in the heart. Sinus node dysfunction is

a heterogeneous clinical syndrome of diverse etiologies, which includes sinus arrest, sinoatrial block, sinus bradycardia (heart rate slower than 60 beats per minute), chronotropic incompetence and various supraventricular tachycardias such as atrial tachycardia, atrial flutter and atrial fibrillation (AF). The incidence of sinus node dysfunction is increased with advancing age (9,10).

1.2.2 Conduction Disorders in Atrioventricular Block

Electrical impulses may be normally generated by the sinoatrial node and successfully propagated through the atria, but blocks at any level of atrioventricular conduction system. Atrioventricular block is classified as first-, second-, and third-degree atrioventricular block. First-degree atrioventricular block is defined as a PR interval greater than 0.20 seconds with one-to-one relationship between atrial and ventricular activation. Second-degree atrioventricular block is including two patterns: Mobitz type I (Wenckebach) and type II. Mobitz type I atrioventricular block is the pattern characterized by progressive prolongation of the PR interval until a blocked beat occurs. Mobitz type II atrioventricular block is characterized by fixed PR interval before and after blocked beats. Third-degree atrioventricular block or complete heart block is present with absence of atrioventricular conduction, which may be acquired, congenital, or iatrogenic.

1.2.3 Permanent RVA Pacing

Cardiac pacing has been the only effective treatment for symptomatic bradycardia

caused by sinus node dysfunction or atrioventricular block for decades (11). However, first-degree atrioventricular block is not the indication for permanent cardiac pacing. Appendix I outlines the current used guideline, which is recommended by the American College of Cardiology / American Heart Association / Heart Rhythm Society (ACC/AHA/HRS) in 2008. Conventional RVA pacing is common, effective and well-tolerated. There are two leads in conventional RVA pacing, one at RA and the other at right ventricular (RV) apex to achieve physiological pacing. The applied lead in RV apex is easy for the implanter to reach with stable position and stimulation thresholds chronically. However, the detrimental effects of RVA pacing on cardiac structure, LV function and dyssynchrony have been reported recently. The pathophysiological basis of RVA pacing and evidence of detrimental effects will be reviewed in following section.

1.3 Detrimental Effects of RVA Pacing on Ventricles

1.3.1 Asynchronous Electrical Activation and Mechanical Contraction

Optimal LV contraction and efficient pump function need normal electrical cardiac activation sequence. During RVA pacing, pacing impulse disturbs the natural pattern of activation and contraction. The conduction of the electrical wave front propagates slowly through ventricular myocardium, rather than through the His-Purkinje system, which is semblable to left bundle branch block (LBBB) (12-15). However, in patients with LBBB, the left ventricular (LV) endocardial activation sequence is heterogenous and right-to-left transseptal activation, but without AV dyssynchrony

(12,16).

1.3.2 RVA Pacing in Animal Models

Animal studies have suggested that ventricular asynchronous electrical activation is the main cause of impaired LV pump function (13,17,18). The effects of asynchronous activation on mechanical contraction are pronounced. Regions closed to the pacing site have an earlier and more vigorous shortening clockwisely during the early phase of systole because of low afterload. In remote regions from pacing site the stretch are delayed. When all regions are activated and LV pressure rises, remote regions with longer fiber length shorten more during the ejection time by virtue of "Frank-Starling" mechanism. The delayed but increased systolic shortening will impose systolic stretch to the early activated regions exhibiting premature relaxation. Therefore, the paradoxical contraction pattern will cause a redistribution of myocardial work load and less efficient contraction (14,18).

It has been also demonstrated that RVA pacing causes reduction of stroke volume, LV function, and regional myocardial perfusion and oxygen consumption in animal models (17-20). In addition hypofunctioning regions surrounding the pacing site are larger than LV-based pacing by use of magnetic resonance imaging (MRI) tagging, which is associated with reduced myocardial pump function in canine hearts (18). Similar results are observed in human studies (21-24). The harmful effects of RVA pacing on cardiac function in human studies will be reviewed in subsequent section.

1.3.3 RVA Pacing in Human Studies

1.3.3.1 Mechanisms of Ventricular Remodeling and Dysfunction

The mechanisms of ventricular remodeling and dysfunction during RVA pacing are shown in Figure 1.2. It has been demonstrated that RVA pacing results in abnormal electrical activation sequence and leads to ventricular dyssynchrony. The asynchronous activation is manifested as prolonged QRS duration resembling LBBB due to slow myocardial conduction. In recent years, large clinical trials reported the detrimental effects of RVA pacing on ventricles in patients with bradycardia due to sinus node dysfunction and atrioventricular block. The adverse effects include ventricular remodeling, dilatation and asymmetric hypertrophy (25), elevated diastolic filling pressure (26), increased functional mitral regurgitation and presence of myocardial perfusion defect and reduced left ventricular ejection fraction (LVEF).

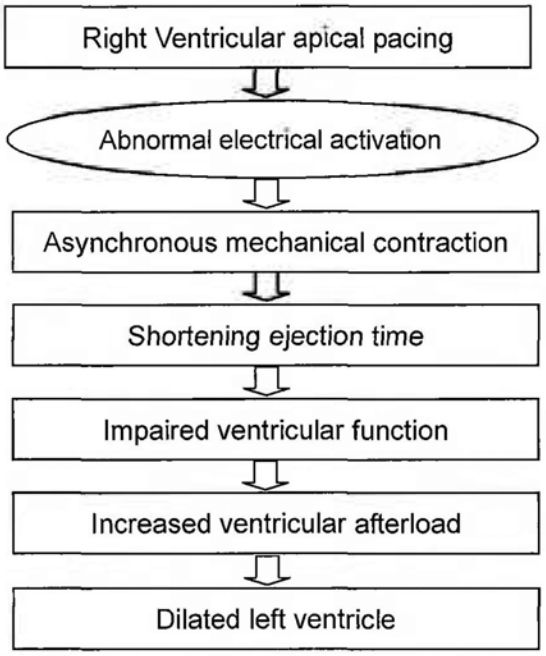


Figure 1.2 Mechanisms of ventricular remodeling and dysfunction during RVA pacing.

1.3.3.2 Long-term Effects of RVA Pacing on Left Ventricle

(I) Systolic Function

The strong association between ventricular pacing in the dual-chamber pacing (DDDR) mode and heart failure was first established in MOde Selection Trial (MOST) (22), which was a 6-year, randomized trial of DDDR versus single-chamber pacing (VVIR) in 2010 patients with symptomatic sinus node dysfunction. The researchers found that cumulative percent ventricular pacing (Cum%VP) was a strong predictor of heart failure hospitalization in DDDR (Cum%VP > 40%) and VVIR (Cum%VP > 80%) and the risk of AF increased linearly with Cum%VP form 0% to 85%. It indicates that ventricular dyssynchrony induced by ventricular pacing increases the risk of heart failure hospitalization and AF in sinus node dysfunction and mitigates the benefit of atrioventricular synchrony in dual-chamber pacing. It was reported later that nearly 20% of patients with sinus node dysfunction treated with VVIR pacing had severe pacemaker syndrome. Patients with lower resting sinus rates and a higher percentage of paced beats were more likely to develop pacemaker syndrome, which defined as either congestive signs or symptoms associated with retrograde conduction during VVIR pacing or a more than 20 mmHg reduction of systolic blood pressure associated with symptoms of dizziness, weakness, presyncope or syncope. This study also concluded that the only way to prevent pacemaker syndrome is to implant atrial-based pacemakers (27). Their results were consistent with previous Canadian Trial of Physiological Pacing (CTOPP) study (28).

(II) Myocardial Perfusion

Long-term RVA pacing also affects myocardial perfusion mainly over the inferior and apical segments of LV, where was close to pacing lead (29). Tse et al (29) demonstrated that up to 65% of patients (a total of 43 patients had complete heart block and DDDR pacing) with ventricular pacing had perfusion defects when using Thallium-201 exercise myocardial scintigraphy after at least 3-year follow up. Only 19% of patients with perfusion defects had coronary artery disease confirmed by coronary angiogram. Similar results were reported in a larger study in the same year (30).

(III) Myocardial Blood Flow

Ventricular pacing may reduce myocardial blood flow (MBF) in the earliest activated region of LV and the reduction of MBF is reversible when normal ventricular activation and contraction restored in patients with sick sinus syndrome (31). However, in a study compared the myocardial thickness in dog with LV pacing and patients with LBBB and found that the early-activated septum was thinner in LBBB than late-activated posterior LV wall. The study indicates that asymmetry of LV wall thickness can be induced by asynchronous electric activation, which may be explained by local adaptation of myocardial mass to local differences in mechanical load (32).

1.3.3.3 Acute Effects of RVA Pacing on Left Ventricle

(i) Systolic function

Pacing sites and atrioventricular delay modulate the acute effect of pacemaker therapy for patients with severe heart failure. QRS width is the most important variable for prediction of acute pacing benefit (33,34). Nahlawi et al (23) demonstrated that LV systolic function was reversible but only part of the adverse changes associated with RVA pacing. In the study, 12 patients with intact atrioventricular conduction (short atrioventricular delay of 100 ms) and normal LVEF received dual-chamber pacemakers. LVEF was significantly reduced after short-term (2 hours) and mid-term (one week) RVA pacing. LVEF did not completely recover immediately after disconnection of short-term or mid-term RVA pacing despite restoration of a normal activation sequence. However, LVEF was similar to baseline AAI at 32 hours after cessation of mid-term ventricular pacing. In addition to the role of abnormal sequence of activation, the changes of myocardial perfusion, sympathetic nerve activity and myofibrillar disarray might also explain the acute effect of RVA pacing on ventricular systolic function.

(ii) Diastolic Function

Lieberman et al (26) demonstrated that RVA pacing may acutely elevate LV end-diastolic pressure and impair diastolic relaxation in patients with or without preexisting systolic dysfunction using pressure-volume analysis. It was further noted that LV and biventricular pacing improved hemodynamics and function compared to

RV pacing in patients with preexisting LV dysfunction with LVEF < 40%. Another study also reported that LV diastolic function has impaired immediately in patients with preserved LV contractility after shifting pacing mode from ventricular sensing to pacing (35). Yu et al (36) compared acute changes of LV systolic and diastolic function as well as systolic and diastolic dyssynchrony in RVA pacing and biventricular pacing. They noted that systolic function was not improved and mitral regurgitation (MR) remained persistent in patients with RVA pacing. However, they found that transmitral early diastolic filling velocity (E), and mean peak myocardial early diastolic velocity by tissue Doppler imaging (TDI) from 6 basal segments were significant reduced during both RVA pacing and biventricular pacing. This indicates that LV early diastolic function is invariably and adversely affected by RVA pacing.

(iii) Left Ventricular Transverse Motion

Acute RVA pacing impairs LV twist due to basal rotation delay and both basal and apical rotation depressed (37). Delgado et al (38) reported the development of decreased LV shortening and twist as well as dyssynchrony after acute RVA pacing when compared to normal controls using two-dimensional speckle tracking echocardiography. Regional systolic longitudinal and radial function reduces in the wall near the RV pacing lead and intramural (within the LV wall) dyssynchrony is also noted (39). LV dyssynchrony was also demonstrated by real time three-dimensional echocardiography (RT3DE) in patients with intrinsic ventricular conduction (V-sense) compared with RVA pacing (V-pace) with 15 minutes interval

(40). Nearly 50% (46 / 93) of patients developed LV dyssynchrony, as defined by standard deviation of time to minimum regional volume for 16 segments of LV, Tmsv-16SD > 16 ms.

1.3.3.4 Effects of RVA Pacing on Right Heart

In contrast to adult, pacing-induced electromechanical dyssynchrony did not acutely affect LV and RV function in children with normal cardiac function (41,42). Vaturi et al (43) investigated that tricuspid regurgitation (TR) severity after active RVA pacing in patients without preexisting heart failure and tricuspid diseases. The results showed that TR increased significantly but without significant change in RV area due to possible interference with tricuspid valve closure by the presence of an endovascular electrode.

1.3.3.5 Summary of the Detrimental Effects of RVA Pacing

Previous studies showed that dual-chamber pacing was superior to single site ventricular pacing for patients with sinus node dysfunction (10,44). However, the potential harmful effects of dual-chamber pacing were gradually recognized due to abnormal electrical activation and ventricular dyssynchrony (22,24,40,45,46). Ventricular dyssynchrony induced by RVA pacing may be relevant in resulting LV dysfunction and AF directly. The detrimental effects of RVA pacing are summarized in Table 1.1.

Table 1.1 Detrimental effects of right ventricular apical pacing

Abnormal electrical activation
Asynchronous electrical activation
intra ventricular conduction delay
Ventricular mechanical changes
Asynchronous ventricular contraction
Interventricular and intraventricular dyssynchrony
Myocardial histopathological change
Myocardial perfusion defect
Regional wall motion abnormality
Reduced LV systolic and diastolic function
Decreased stroke volume
Elevated diastolic filling pressure
Ventricular dilatation
Asymmetric hypertrophy
Others
Functional mitral regurgitation
Left atrial dilatation
Sympathetic nervous system activation

1.4 Alternative Pacing Sites

1.4.1 Alternative Pacing Sites of Dual-chamber Pacing

Given the adverse hemodynamic and clinical effects of RVA pacing, pacing site selection is important but optimal pacing site remains undetermined. It has been showed in animal study that RV septal pacing does not improve LV function compared with RVA pacing (47). Pacing at right ventricular outflow tract (RVOT) did not show any advantages in quality of life after long-term follow up (> 3 months) compared with conventional RVA pacing in patients with heart failure and AF (48). Recently, Liu et al (49) demonstrated that pacing at RVOT acutely affected LV global function and increased intraventricular dyssynchrony in patients with sick sinus syndrome compared with RA appendage pacing only. However, another study found that preserved synchronous ventricular activation with ROVT pacing may mitigate its resultant myocardial perfusion defects and systolic dysfunction in patients with complete atrioventricular block (50). These inconsistent data suggest that the RV septum or RVOT is not the optimal site for permanent dual-chamber pacing.

1.4.2 Upgrading to Biventricular Pacing

Several studies investigated whether the harmful effects induced by RVA pacing could be attenuated by upgrading it to biventricular pacing in patients with or without heart failure or AF (51-54). Tops et al (53) studied LV dyssynchrony in patients with preserved systolic function and treated with His bundle ablation and

pacemaker implantation. After more than 1.2-year follow up, 33 (57%) patients had LV dyssynchrony using time-to-peak radial strain of the anteroseptal and posterolateral segments by speckle-tracking analysis. Furthermore, they reported biventricular pacing may reverse LV dyssynchrony by upgrading RVA pacing to biventricular pacing for 11 patients and after 6 months follow up. Another study, in which heart failure patients with reduced LVEF, it was found that cardiac resynchronization therapy (CRT) upgrade after chronic RVA pacing resulted in a similar improvement in LVEF and LV remodeling compared with those after primary CRT implantation. Investigators also found that CRT led to LV reverse remodeling even after RVA pacing for 10 years. The data suggested upgrading to CRT will benefit patients with systolic heart failure even after long periods of RVA pacing and guidelines now affirmed CRT indication in the treatment of pacemaker-dependent patients with heart failure (54).

1.5. The Role of Echocardiography in RVA Pacing

It is well established that LV function and dyssynchrony assessed by echocardiography is non-invasive, convenient and reproducible and clinically important. LV systolic and diastolic function can be assessed using M-Mode, two-dimensional echocardiography, RT3DE, Doppler echocardiography and color TDI. A novel speckle tracking imaging permits accurate quantification of rotation or twist of the heart. Speckle tracking can also be used to assess LV dyssynchrony and response to CRT (53,55). Given the harmful effects of RVA pacing, it is very

important to detect the therapeutic efficacy of device therapy by these methods for patients with dual-chamber pacing.

1.5.1 Assessment of LV Global and Regional Systolic Function

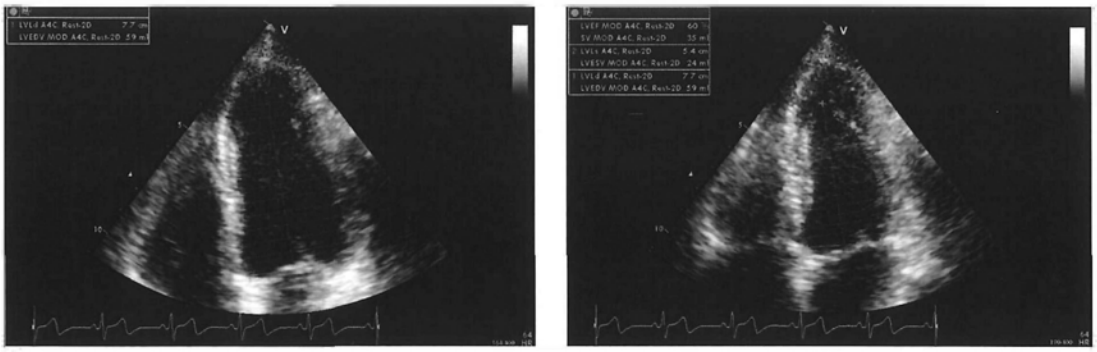
According to the joint European Association of Echocardiography / American Society of Echocardiography guidelines on recommendation for chamber quantification, the most common and relative accurate method is to use transthoracic two-dimensional echocardiography for measurement of ventricular volume and ejection fraction as well as ventricular mass by biplane Simpson's method (56). RT3DE evaluation of LV global systolic function and regional wall motion is highly accurate, however, it is limited by suboptimal echo window and arrhythmias. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), LVEF measured by either two-dimensional echocardiography (Figure 1.3) or RT3DE (Figure 1.4) are recommended for the evaluation of LV remodeling and contractile function. LVEF was calculated by the equation:

$$LVEF = (LVEDV - LVESV) / LVEDV \times 100$$

The normal reference value was $\geq$55% in both men and women (56). The American Society of Echocardiography recommended a 16-segment (57) and the American Heart Association recommended a 17-segment model (58) for LV segmentation. The 16-segment model consists of 6-basal, 6-midventricular and 4-apical segments. The 17-segment model is different from the previous 16-segment model by addition of an apical cap.

Yu et al (24) compared effect of RVA pacing and biventricular pacing on LV remodeling in 177 patients with normal LVEF who suffered from bradycardia due to either sinus node dysfunction or atrioventricular block. They found that eight patients in RVA pacing group had a reduced LVEF less than 45% and only one patient in biventricular pacing group in one year using RT3DE. They concluded that RVA pacing induced adverse LV remodeling with increased LVESV and reduced LVEF, which could be attenuated by biventricular pacing.

(A) (B)



(C) (D)

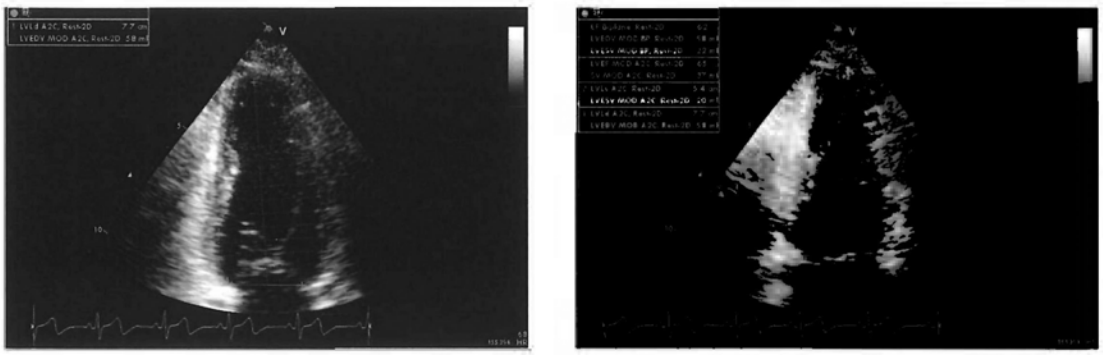
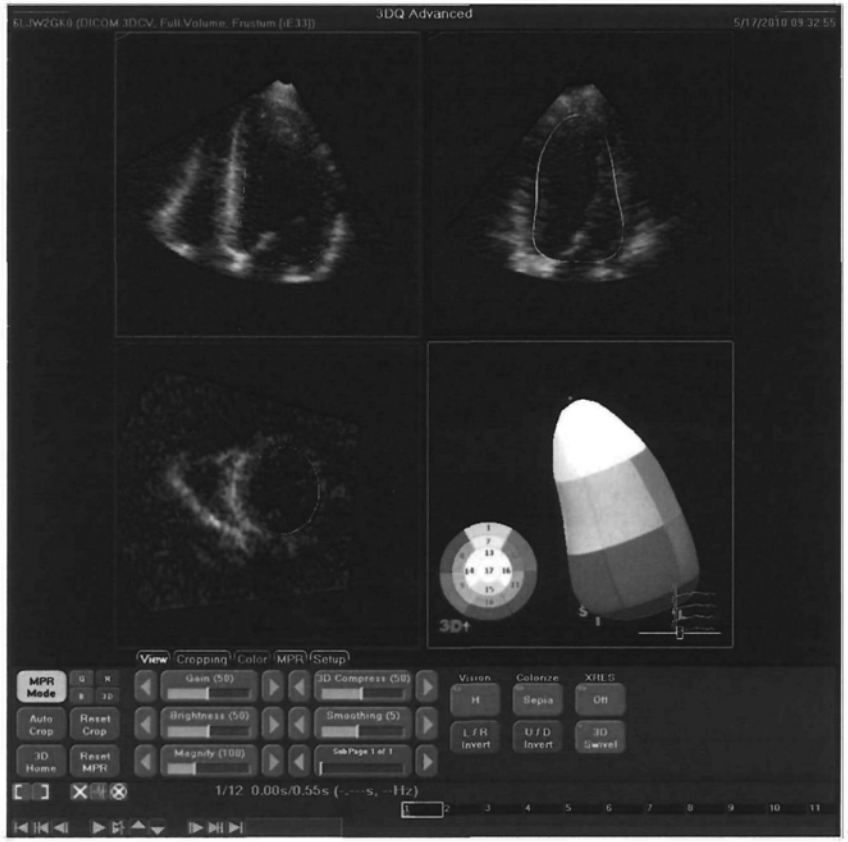


Figure 1.3 Assessment of LV volumes and ejection fraction by biplane Simpson's method on apical four- and two-chamber views of two-dimensional echocardiographic images. The measurement of LVEDV (A and C) in end-diastole and LVESV (B and D) in end-systole is showing. LVEF is calculated by the following formula: LVEF = (LVEDV – LVESV) / LVEDV × 100%.

(a)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View
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3D Home
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3D Compress (50)
Brightness (50)
Smoothing (5)
Magnify (100)
Vision
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Sepia
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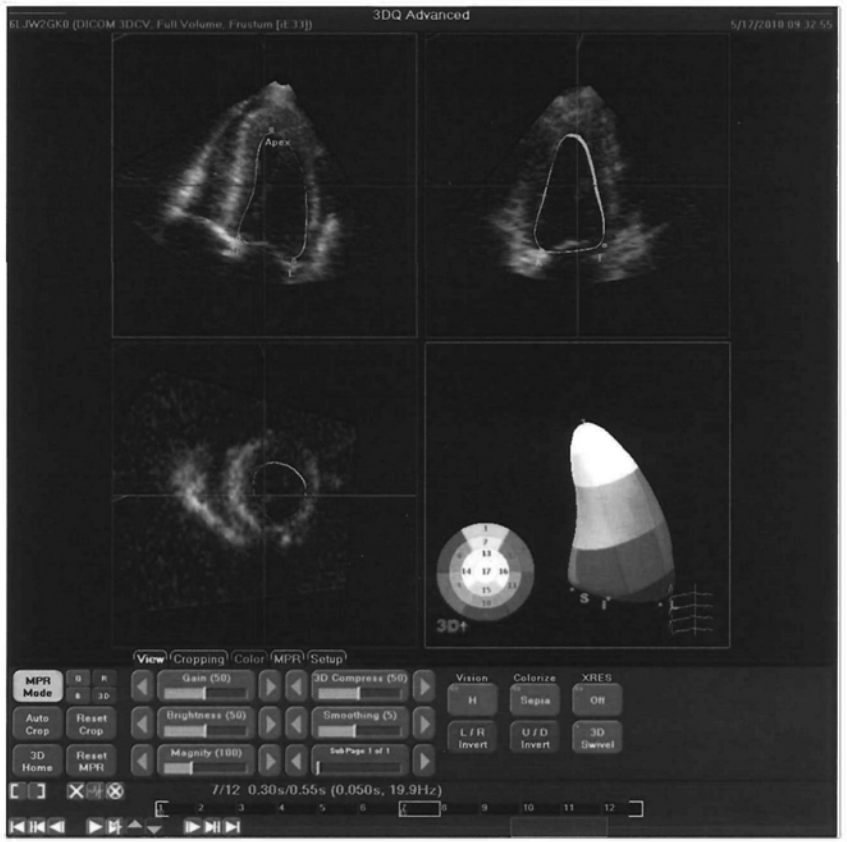
L/R Invert
U/D Invert
3D Swivel
1/12 0.00s/0.55s

(b)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Reset MPR
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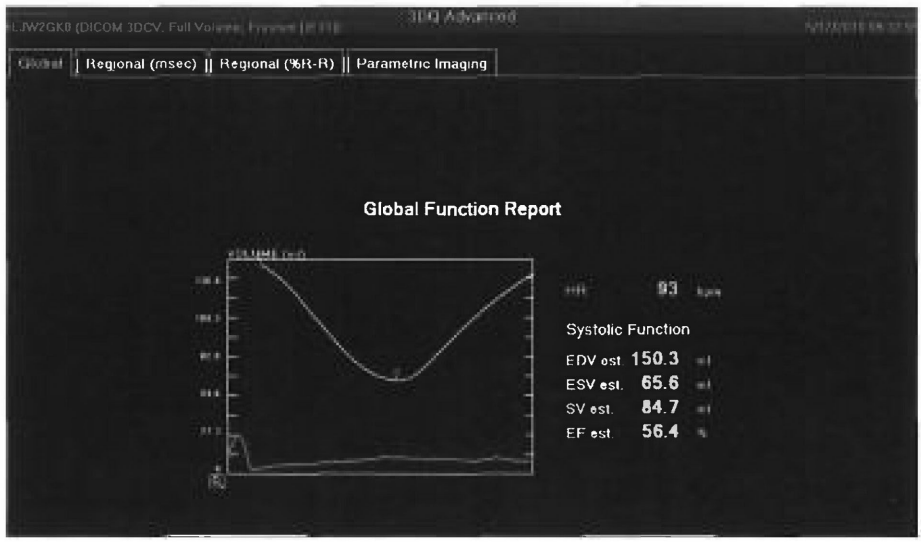
3D Compress (50)
Brightness (50)
Smoothing (5)
Magnify (100)
Vision
Colorize
XRES
H
Sepia
Off
L/R Invert
U/D Invert
3D Swivel
7/12 0.30s/0.55s (0.050s, 19.9Hz)

(c)



(d)

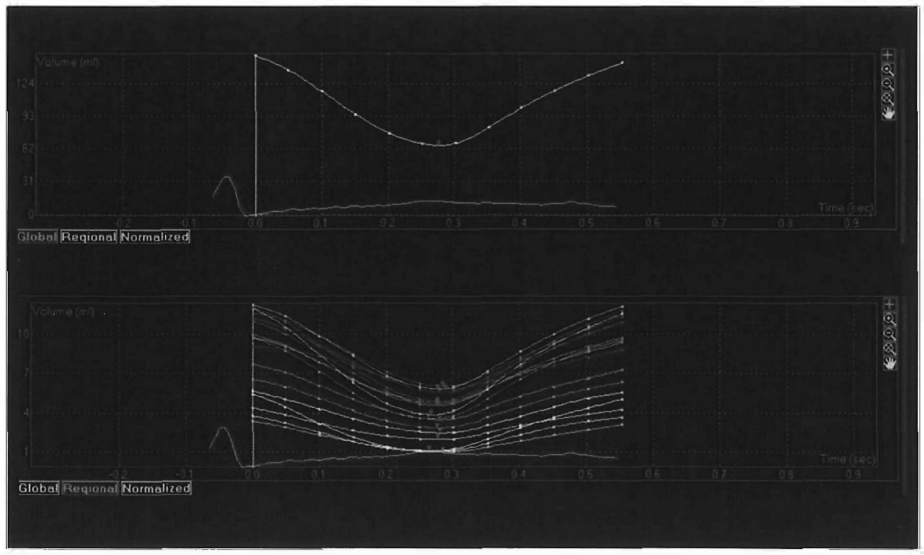


Figure 1.4 Assessment of LV volumes and ejection fraction by real time three-dimensional echocardiographic images. Endocardial and epicardial boundaries are traced manually and used to calculate LV end-diastolic volume (a) and end-systolic volume (b). The report of global systolic function is shown in the upper panel (c). LV volume-time curves (d) described LV global and regional performance beyond ejection fraction.

1.5.2 Assessment of LV Diastolic Function

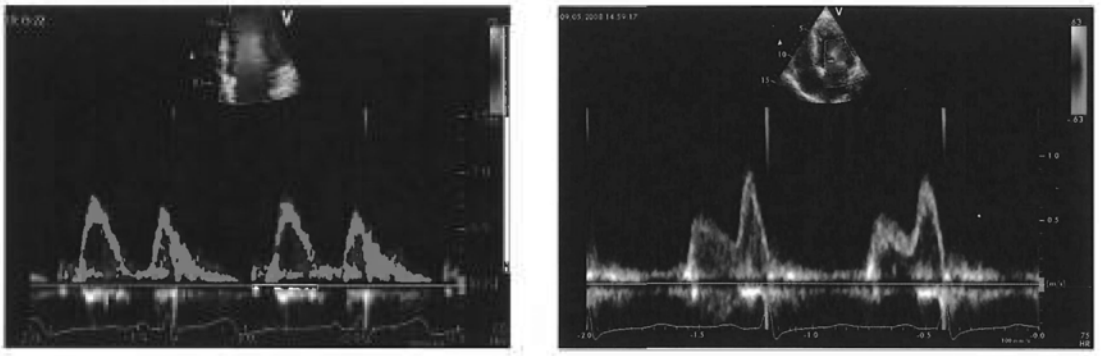
Echocardiography is a very important tool to assess LV diastolic function in cardiac pacing as mentioned previously (26,35,36). Conventional Doppler echocardiographic parameters include E, transmitral atrial filling velocity (A), E/A ratio, diastolic filling time, isovolumic relaxation time (IVRT) and deceleration time (DT) and pattern of pulmonary venous blood flow (interpreted in the next chapter). For the assessment of LV diastolic function by TDI, the potentially useful parameters include: mitral annular early diastolic velocity, myocardial segmental velocity during diastole, E/e' (ratio of transmitral early diastolic filling velocity to mitral annular early diastolic velocity) and diastolic dyssynchrony (59).

Doppler flow velocity curve represents overall diastolic filling characteristics of the heart. E represents the rapid decrease of LV pressure during LV relaxation. A velocity occurs after atrial contraction after ventricular relaxation. The DT depends on the rate of increase in LV pressure in early diastole. There are four filling patterns for the description of diastolic filling: normal, abnormal diastolic relaxation, pseudonormal and restrictive filling pattern according to suggestions from the Mayo Clinic (Figure 1.5). Normal diastolic filling pattern characteristics as $E/A > 1$, DT = 200 ± 40ms (60). In patients with abnormal relaxation, increased A and decreased LV compliance with $E/A < 1$. Further deterioration of diastolic function results in E increased, DT shortened and "normalized" transmitral inflow curve, which is the "pseudonormal" filling pattern. $E/A > 2$, DT < 160ms indicate a restrictive filling

pattern.

The working Group for European Society of Cardiology recommended a set of diagnostic criteria for diastolic heart failure or heart failure with preserved EF including signs or symptoms of heart failure, normal or mildly abnormal LV systolic function, evidence of abnormal LV relaxation, diastolic filling, distensibility and stiffness (61). In patients with preserved ejection fraction (LVEF $>$ 45%), the estimation of LV diastolic function is more complex and challenging. E/e' should be calculated for the assessment of diastolic filling in this group of patients. E/e' $<$ 8 is usually associated with normal diastolic filling pressure, whereas E/e' $>$ 15 suggests increased filling pressure (Figure 1.6). When the ratio is between 9 and 14, maximal LA volume, duration of retrograde pulmonary venous velocity at atrial contraction, a change in E/A ratio with the Valsalva maneuver, IVRT and pulmonary artery systolic pressure are essential (62).

(A) (B)



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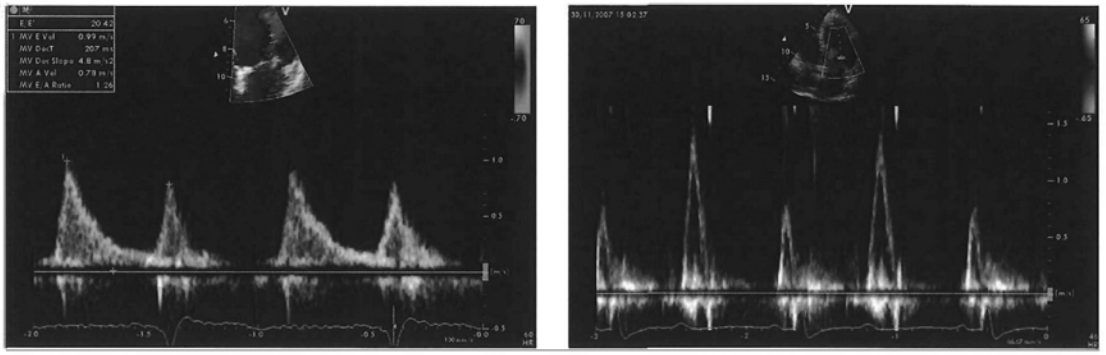
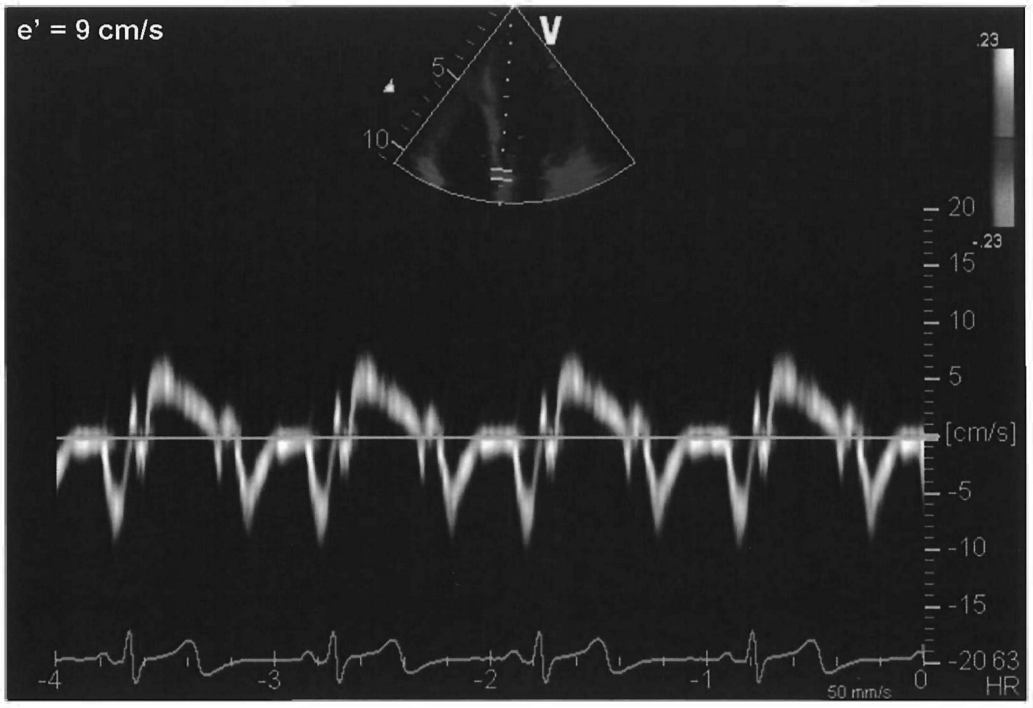


Figure 1.5 Diagram of types of diastolic dysfunction. There are four filling patterns: normal diastolic filling pattern (A), abnormal relaxation pattern (B), pseudonormal diastolic filling pattern (C) and restrictive filling pattern (D).

(A)



(B)

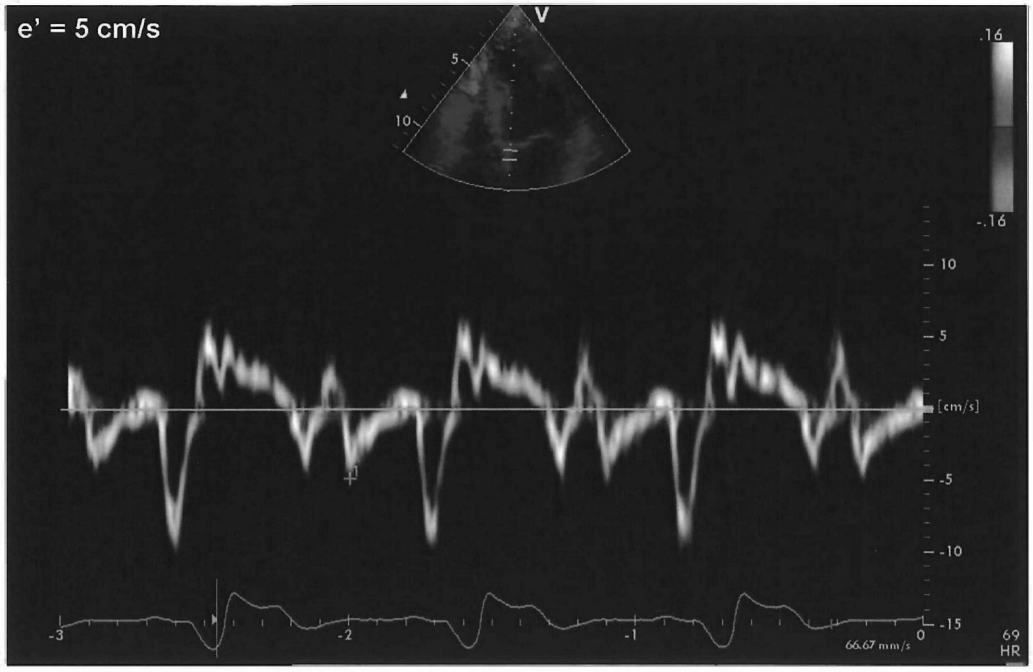


Figure 1.6 Left ventricular diastolic relaxation. Mitral annular early diastolic velocity (e') > 8 represents normal diastolic relaxation (A). A decreased e' (e' = 5) represents abnormal diastolic relaxation (B). E / e' < 8 is associated with normal diastolic filling pressure. E /e' > 15 represents elevated diastolic filling pressure.

1.5.3 Assessment of Inter- and Intraventricular Dyssynchrony

Several echocardiographic techniques are available for the assessment of interventricular (between RV and LV) and intraventricular (within LV) dyssynchrony. Septal-to-posterior wall delay of 130ms by M-mode echocardiography (63), septal-to-lateral wall delay of 65ms (64) and Ts-SD (standard deviation of time to peak systolic velocity during ejection phase of the 12 LV segments) of 33ms (65) by TDI, septal-to-posterior wall delay of radial strain of 130ms by speckle tracking (55) are currently cut-off values of mechanical dyssynchrony (66).

Our previous study demonstrated that LV systolic dyssynchrony was developed in almost half of patients with RVA pacing and preserved LVEF using RT3DE. The cut-off value of systolic dyssynchrony (> 16ms) was derived from twice standard deviation plus the mean value of the 93 normal controls (40). Two-dimensional speckle tracking from routine black-and-white images can be used to quantify dyssynchrony and predict response to CRT (53,55). LV strain is obtained by tracking temporal movement of natural acoustic speckles from two-dimensional echocardiographic images frame by frame. Radial dyssynchrony (time interval $\geq$ 130 ms for the absolute difference in peak septal wall to posterior wall strain) predicted a significant increase in LVEF with 89% sensitivity and 83% specificity after CRT after more than 3-month follow up (55).

CHAPTER 2 LEFT ATRIAL SIZE AND FUNCTION

2.1 LA Mechanical Function and Phasic Volumes

2.1.1 LA Mechanical Function

There are four hollow chambers in a normal heart: two atria and two ventricles. Left atrium (LA) and RA are separated by the IAS. LA receives blood from pulmonary veins and supplies blood to LV. LA function is complex and LA mechanical function includes three components: reservoir, conduit and a contractile component (67). The LA firstly serves as a reservoir that stores blood from pulmonary venous return during LV contraction and isovolumic relaxation. During early diastole, the "conduit" function of LA is to transfer pulmonary venous blood flow to the LV. And thirdly, the LA serves as a contractile (booster pump) chamber for augmentation of LV filling.

LA phasic function has been studied with aging (68,69) and disease states (70). LA reservoir function is difficult to assess non-invasively. A study demonstrated that 66% of atrial emptying occurs during the passive phase and 34% occurs during atrial contraction phase (68). However, the active contractile function is very important in patients with ventricular dysfunction as a "booster pump" to augment ventricular filling.

2.1.2 LA Phasic Volumes

LA size varies during phases of cardiac cycle. There are several of volumes to

describe phasic atrial function (71,72). However, atrial function is usually ignored and only maximal LA volume or size is measured routinely in clinic. They are: (1) Maximal LA volume (LAVmax) is measured at the end-systole on electrocardiogram (ECG) (immediately before mitral valve opening); (2) Pre-atrial contraction volume of LA (LAVpre) is measured at the onset of P wave on ECG; (3) Minimal LA volume (LAVmin) is measured at the end-diastole (mitral valve closure) on ECG; (4) Total LA emptying volume: total LA emptying volume = LAVmax – LAVmin; (5) LA passive emptying volume: LA passive emptying volume = LAVmax – LAVpre; (6) LA active emptying (contractile) volume: LA active emptying volume = LAVpre – LAVmin; (7) LA conduit volume: LA conduit volume = LV stroke volume – total LA emptying volume (LA stroke volume).

2.1.3 LA Emptying Fraction

The parameters reflecting LA function are derived regarding to the various LA volumes. LA emptying fractions were calculated as follows: (a) LA passive emptying fraction, defined as (LAVmax - LAVpre) / LAVmax × 100%; (b) LA active emptying fraction, defined as (LAVpre - LAVmin) / LAVpre × 100%; (c) LA total emptying fraction by volume, defined as (LAVmax - LAVmin) / LAVmax × 100%.

2.2 What is the Importance of Atrial Function?

2.2.1 LA Contribution to Ventricular Filling

In normal subject, the ratios of LA passive emptying and active emptying to LV

stroke volume are approximately 19% and 29% respectively. In patients with myocardial infarction, the ratios were significantly higher than in normal subjects (71). However, the contribution of the pump function to stroke volume is reported relatively lower in an earlier study (73). The contribution of LA phasic volumes to LV filling was also observed in the year 1998 (74). Prioli et al (74) depicted that the reservoir, conduit and contractile function of the LA contributed to ventricular filling were 38%, 36% and 26% as a mean percentage of ventricular filling volume respectively. With abnormal LV diastolic relaxation, reservoir and contractile function of LA augmented, however, conduit function takes precedence with advancing diastolic dysfunction. The trends are: (1) reservoir function and contractile function: impaired relaxation pattern > normal pattern > restrictive filling pattern; (2) conduit function: restrictive filling pattern > normal pattern > impaired relaxation pattern.

In order to maintain adequate LV diastolic filling, LA pressure will increase and atrial myocardium will be stretched. LA contribution to ventricular filling increases representing a compensatory response to abnormal diastolic filling. It is observed in hypertension patients with preserved LVEF. The contribution of LA increases from 34% to 46% during exercise. However, there is no significant change in normal subjects (75). With further progression of diastolic dysfunction, the LA contribution to ventricular filling gradually decreased (76).

2.2.2 LA Compliance, LA Pressure and LV Diastolic Filling

LA is a thin-walled thickness structure and its size may increase with an increased LA pressure. During the LV diastolic phase, LA pressure approximates LV filling pressure through the open mitral valve. During the LV systolic phase, LA receives blood from pulmonary veins and induces LA distension. The ability of myocardial distention means LA compliance. Therefore, the high LA pressure causes the high atrial wall tension and dilatation, however, LA compliance is low. In a resent study, Hsiao et al (77) calculated LA distensibility by the equation: LA distensibility = (LAVmax – LAVmin) / LAVmin. It was shown that LA distensibility correlated with LV filling pressure logarithmically, which was superior to E/e' for identifying acute severe MR. However, both LA distensibility and mitral E/e' had comparable power for estimating a LV filling pressure > 15mmHg. An appropriate LA compliance can increase cardiac output 35-80% (78). In addition, LAVmin > 40 cm^3 is used for identifying a mean pulmonary wedge pressure (approximately LA pressure) > 12 mmHg with a sensitivity 82% and a specificity of 98% (79).

2.2.3 Prognostic Value of LA Size and Function

LA size reflects the duration and severity of LV diastolic dysfunction and high LV filling pressure (79-81). LA dilatation is an important prognostic indictor for a substantial number of cardiac conditions. It has been suggested that LA enlargement is an independent predictor of mortality and cardiovascular morbidity in patients with heart failure, acute myocardial infarction (82), mitral stenosis (83) or

regurgitation (77,84), cardiomyopathy (85), hypertension (86), stroke (87) and AF (88,89). LA remodeling begins early stage of post myocardial infarction (82). LAVpre representing pre-atrial contraction volume of LA is suggested to be the best reflector to early LA remodeling due to hypertensive diastolic dysfunction (90). Large clinical trials demonstrated LAVmax > 32 ml/m^2 was an independent predictor of morbidity and mortality in patients with acute myocardial infarction or ischemic stroke (91,92). An indexed LAVmax > 32 ml/m^2 provided independent predictive information regarding new development of heart failure (93).

2.3 Assessment of Atrial Dimension and Volume

Different noninvasive cardiac imaging modalities are available to assess the size and function of LA. Echocardiography including M-Mode, two-dimensional echocardiography, RT3DE, pulse or tissue Doppler imaging and speckle tracking as well as other techniques is briefly reviewed.

2.3.1 M-Mode Echocardiography

The assessment of LA size by M-Mode echocardiography is obtained by measuring anteroposterior dimension from the leading edge of posterior aortic wall to the leading edge of posterior LA wall. The linear dimension of LA can be measured either by M-Mode echocardiography or two-dimensional echocardiography from parasternal long-axis view (Figure 2.1). Although the linear dimension has been already shown an excellent correlation with cineangiocardiographic measurements

(94), it is considered as an inaccurate evaluation of the true LA size (95), especially in those with a dilated LA. The enlargement of LA is often nonuniform (asymmetric) (96), which may be limited by the thoracic cavity between the sternum and the spine (56). Given this reason, the linear dimension of LA is not a fit method to estimate the LA size.

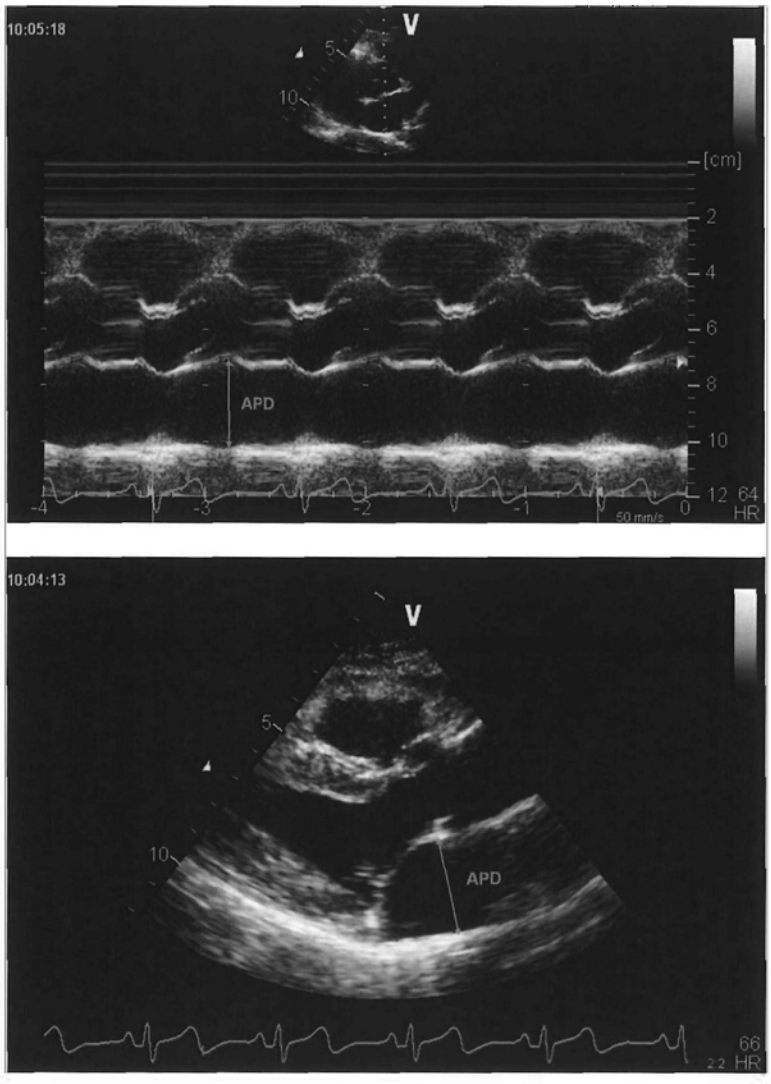


Figure 2.1 Measurement of LA anteroposterior dimension. The linear dimension of LA can be measured either by M-Mode echocardiography (Top) or two-dimensional echocardiography from parasternal long-axis view (bottom). APD, anteroposterior dimension.

2.3.2 Two-dimensional Echocardiography

LA size determined by two-dimensional echocardiography is superior to M-Mode echocardiography (97,98). Although LA area measured from the apical 4- and 2-chamber views represents as alternative method to estimate LA size, LA volume determinations are recommended in clinical practice and research. Tsang et al (99) demonstrate that LA volume is superior to LA area and diameter for prediction of adverse cardiovascular events. Different methods are available for assessment of LA volume with two-dimensional echocardiography including cube formula, ellipsoid method, area-length method and Simpson's rule (100).

Cube method is the simplest one for estimating LA volume, which makes an assumption of LA volume to be a sphere = $4/3\pi\ (APD/2)^3$, where the diameter of the sphere is equal to LA anteroposterior dimension obtained from parasternal long-axis view. However, the method is less accurate than other two-dimensional echocardiographic methods. Ujino et al (101) compared other three two-dimensional echocardiographic methods and demonstrated that biplane area-length method and Simpson's method to evaluate LA volume were well correlated while ellipsoid method (LA volume = $4/3\pi\ (APD/2)\ (D_1/2)\ (L/2)$, APD, anteroposterior diamension, D1, LA transversal diameter in apical 4-chamber view, L, LA length in apical 4-chamber view) underestimated LA volume. Biplane area-length method (Figure 2.2) is suggested by the American Society of Echocardiography to use in routine clinical practice rather than single-plane area-length (102). LA volume estimated by

Simpson's method is similar to its use in LV volume measurements, which assumes LA volume as the sum of small volumes of similar shape (Figure 2.3).

Previous studies demonstrated that body size, age, gender and heart rate are of differences in LA size (103,104). Increasing LA volume is also correlated with LV mass and diastolic and systolic function (105). Therefore, several indexing methods are used to correct LA volume. The most common and recommended is used body surface area (BSA) by the American Society of Echocardiography. The normal indexed LA volume is 22 ± 6 ml/m^2 (56).

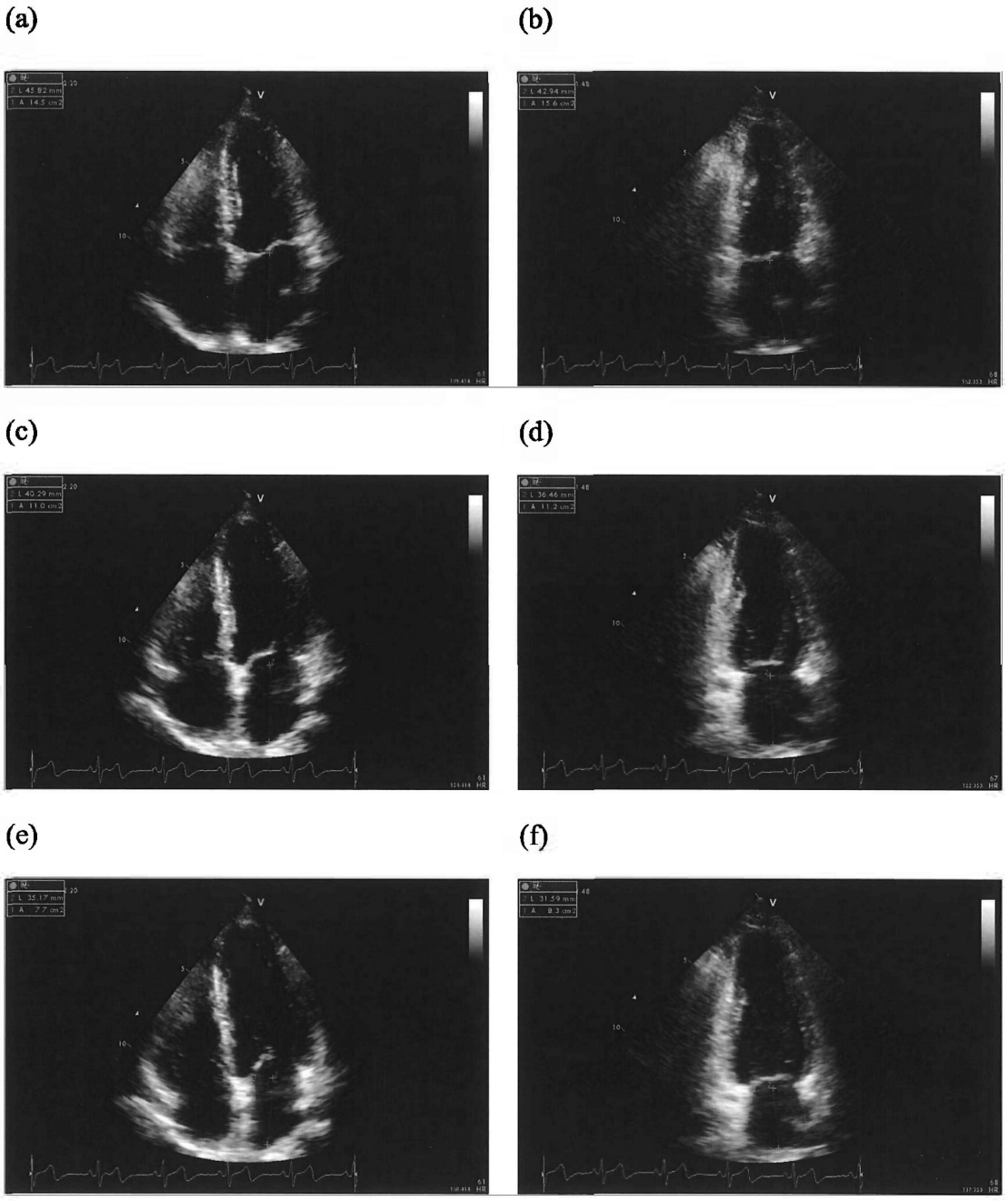
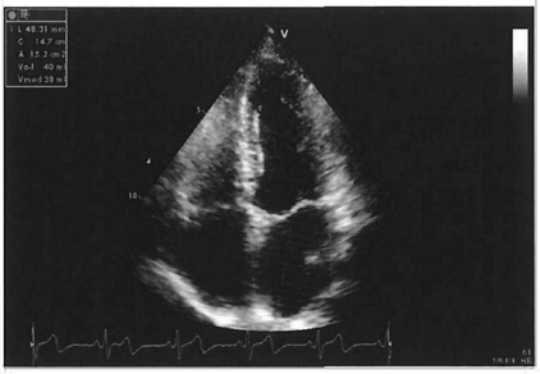


Figure 2.2 Example of measurement LA volume using biplane area-length method. The areas are obtained from apical 4-chamber (A4c) and apical 2-chamber (A2c) and the length (L) is measured from back wall to line across hinge points of mitral valve from either four- or two-chamber view. The formula is LA volume = $8/3\pi$ [(A4c) (A2c)/L]. The maximal LA volume (a, b), pre-atrial contraction volume (c, d) and minimal volume (e, f) are calculated separately using apical four- and two-chamber views by area-length method.

(A)



(B)

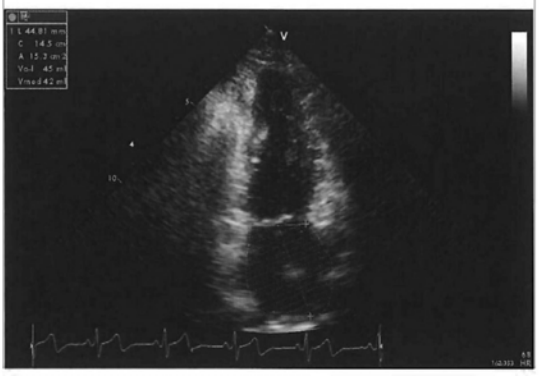


Figure 2.3 Example of measurement LA volume using Simpson's method. The maximal LA volume is measured at end-systole using apical four- (A) and two-chamber (B) views.

2.3.3Three-dimensional Echocardiography

It has been suggested that both unidimensional and volumetric measurement of LA size by two-dimensional echocardiography will be underestimated in comparison of RT3DE method, though LA volume assessed by two-dimensional echocardiography correlated well with RT3DE (106). Anwar et al (107) suggested that LA volume assessed by RT3DE is more sensitive to LA volume changes compared with two-dimensional echocardiography. RT3DE assessment of LA volume is also applied to follow up LA remodeling and function in patients with radiofrequency catheter ablation (108).

2.3.4 Other Cardiac Imaging Modalities

Transthoracic echocardiographic assessments of LA volume have been compared with other cardiac imaging modalities e.g. computed tomography (CT) (109-111)

and MRI (112,113). However, these studies have been shown a tendency for LA volume underestimated by two-dimensional echocardiography or RT3DE compared with either CT or MRI. Therefore, it is suggested that different normal cut-off values should be developed for each modality. However, both CT and MRI are not preferred for routine assessment of LA size (100).

2.4 Assessment of LA Function

2.4.1 Atrial Ejection Force

The atrial ejection force has been proposed as a noninvasive measurement of atrial systolic function and potentially an index of atrial contribution to diastolic performance. This parameter is defined as the product of the density of blood (ρ = 1.06 g/cm^3), mitral valve area and the square of transmitral A velocity. The Manning's formula is as follow: atrial ejection force = 0.5 × ρ × mitral orifice area × (transmitral A velocity)^2. Atrial ejection force represents an estimation of the force exerted by the LA contractility to accelerate blood cross the mitral valve into LV. However, atrial contraction leads to forward flow through the mitral valves as well as reverse flow into the pulmonary veins. Thus, atrial ejection force is underestimated by Manning's method.

Atrial ejection force has been used as an index of restoring sinus rhythm after cardioversion (114). The force increases in the elderly with an increase ejection of blood LV during LA systole, which represents a compensatory mechanism in the

impairment of LV diastolic relaxation (115). It has been proposed that LA ejection force increases in either diastolic heart failure or systolic heart failure in patients younger than 70 years, however, their mechanisms may be different (116). Chinali et al (117) demonstrated that enhanced LA systolic force (> 14.33 kdynes) associated with LV hypertrophy, increased cardiac output and transmitral flow as well as prolonged LV relaxation. They also demonstrated that LA systolic force was independent predictor of ventricular and atrial geometric changes as well as cardiovascular events in patients with hypertension and diabetes and without other cardiovascular disease (118).

2.4.2 Transmitral Inflow and Pulmonary Venous Blood Flow

Transmitral inflow pattern in conjunction with pulmonary venous blood flow velocity by pulse wave Doppler can be used to assess LA mechanical function (72). Transmitral A velocity is relatively independent of ventricular preload and afterload than transmitral E velocity (114). The normal pulmonary venous blood flow pattern reflects the blood from pulmonary veins to LA during different phases of cardiac cycle, which consists of retrograde velocity at atrial contraction (PVar), early systolic forward flow (PVs1), late systolic forward flow (PVs2) and diastolic forward flow (PVd).

The peak velocity and velocity-time integral of the PVs waves are indices of LA reservoir function and are determined by LV systolic function and LA relaxation

(PVs1), LA compliance (PVs1 and PVs2), and RV stroke volume (PVs2). The magnitude and velocity-time integral of PVd reflect LA conduit function and depend on factors that influence LA afterload: LV relaxation and early filling and mechanical obstruction from the mitral valve apparatus. During atrial systole, with the contraction of LA, blood is ejected from the LA into the LV and the reverses into pulmonary veins (Figure 2.4). Thus, assessment of transmitral (transmitral A velocity, velocity-time integral, and atrial filling fraction) as well as pulmonary venous blood flow (PVar) provides additive information for the evaluation of LA booster pump function (72).

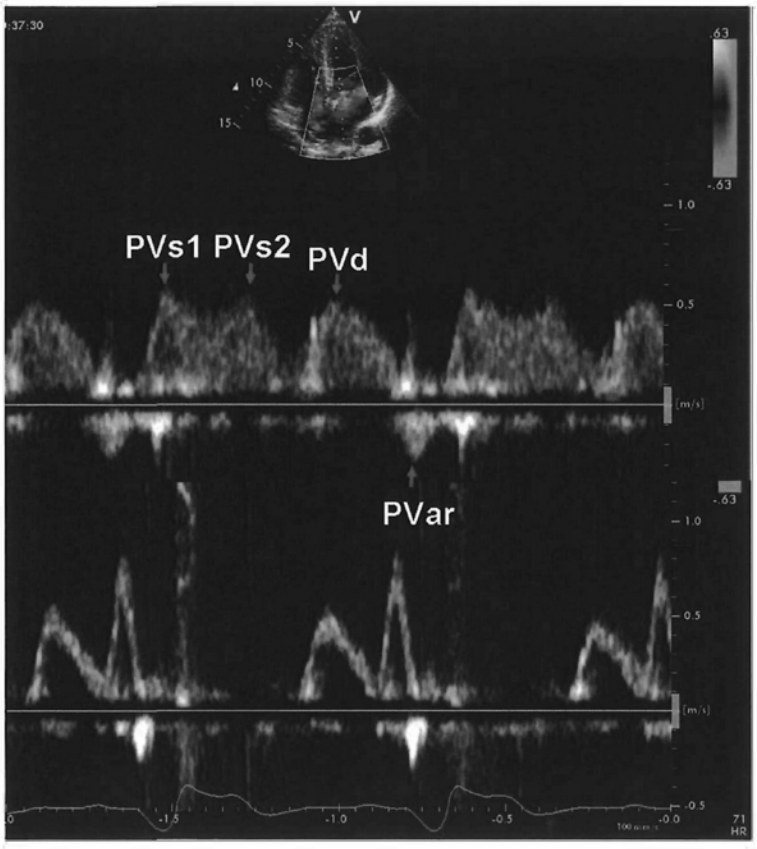


Figure 2.4 Diagram of pulmonary venous blood flow pattern in relation to transmitral inflow pattern.

2.4.3 Tissue Doppler Imaging

2.4.3.1 Tissue Doppler Imaging Velocity

Atrial tissue velocity obtained by placing a sample volume in atrial segments provides insights into regional LA mechanical function. A normal curve consists of three components: peak systolic velocity (Sm-la), early diastolic velocity (Em-la) and late diastolic velocity (Am-la) of LA. In normal individuals, Am-la is higher at LA lateral wall than at IAS in apical 4-chamber view (Figure 2.5), which assessed by TDI (104).

The evaluation of LA regional function by TDI is similar to LV regional function measurement. Wang et al showed that the hazard ratio (HR) of cardiac death was significantly increased in late diastolic tissue velocity at mitral annulus (A') $\leq$4 cm/s (HR 11.53, 95% confidence interval [CI] 4.10 to 11.87) compared with A' > 7 cm/s (119). A study by Wang et al and colleagues, which included 110 patients with coronary artery disease compared with 100 normal controls, measured the atrial contraction velocity at the LA, RA free wall and IAS. It was found to be significant lower in both LA and RA in disease group compared with normal controls. The atrial contraction velocity was even worse in presence of LV systolic dysfunction, or restrictive filling pressure of diastolic dysfunction, which were independent predictors of LA contractile dysfunction. The measurement of atrial contraction velocity provides supplementary information on atrial mechanical function in addition to conventional methods (120).

2.4.3.2 Tissue Doppler Strain and Strain Rate

Tissue Doppler strain and strain rate are derivatives of tissue Doppler velocities. They measure the myocardial deformation and tissue velocity gradient between two samples of pre-defined distance within the myocardium during a cardiac cycle (121). Strain rate derived from tissue Doppler velocity can be used to evaluate longitudinal atrial phasic function in a variety of clinical conditions including AF (122), acute myocardial infarction (123), diabetes mellitus (124) and hypertension(125) (126). Eshoo et al (126) demonstrated early diastolic strain reflecting LA conduit function may be an early marker of atrial dysfunction before presence of overt LA enlargement.

However, angle dependency is an important consideration for all Doppler-derived techniques as well as translational and tethering effects from neighboring myocardium. All measurements should be performed with an angle of interrogation of less than 30° (123,126).

2.4.4 Two-dimensional Strain and Strain Rate

Two-dimensional speckle strain is a novel non-Doppler based method, less time consuming and more reproducible in comparison with TDI strain in evaluation of atrial strain. It also can be measured in all three atrial phases (reservoir, conduit and contractile strain). Paraskevaidis et al showed that two-dimensional contractile strain

(longitudinal strain) with a cut-off value of -10.82% discriminated hypertrophic cardiomyopathy (HCM) from non-HCM left ventricular hypertrophy with a sensitivity of 82% and a specificity of 81% (127). Thus, two-dimensional speckle tracking provides a new technique to measure strain and strain rate (128). Two-dimension strain does not rely on angle dependency, however, large clinical trials on clinical utility of atrial strain are few and there is no consensus on standardisation of the methods.

(A) (B)

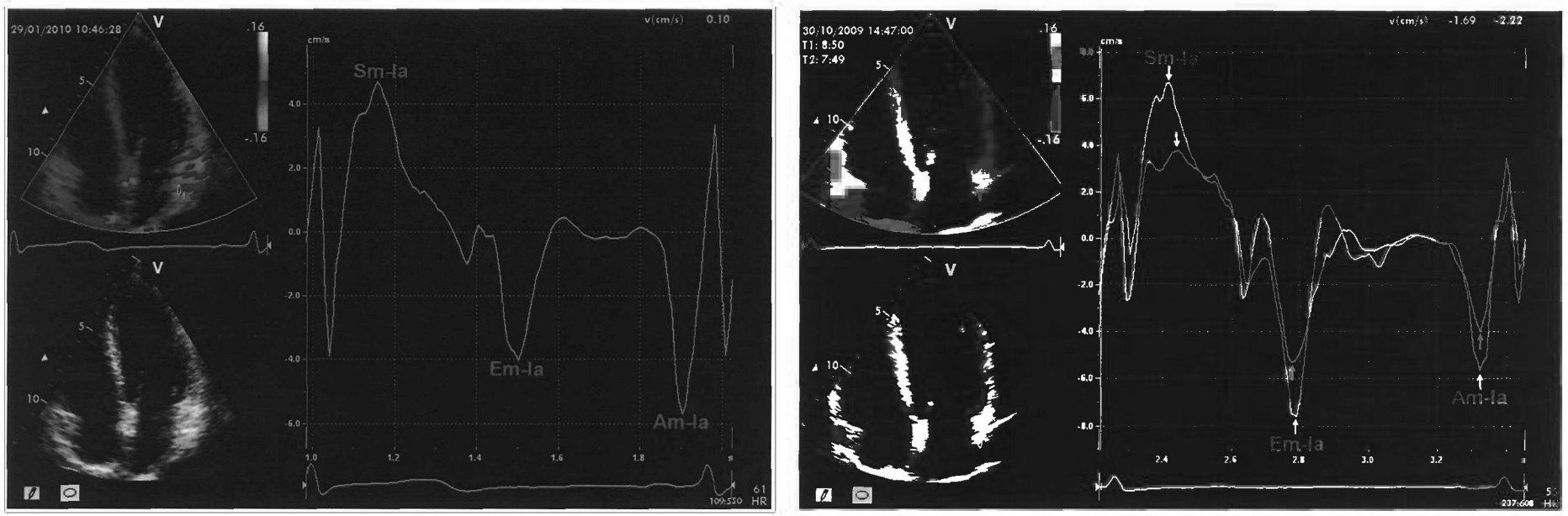


Figure 2.5 Longitudinal atrial velocities (Sm-la, Em-la and Am-la) from apical 4-chamber view using tissue Doppler imaging. A sample volume of 6 × 2 mm placed in mid-lateral of left atrium (LA). Sm-la is positive. Em-la and Am-la are negative velocities (A). In normal subjects, the values of atrial velocities are higher at lateral wall of LA than interatrial septum (B).

CHAPTER 3 RVA PACING AND ATRIAL FUNCTION

3.1 Detrimental Effects of RVA Pacing on Atrium

RVA pacing resulting in LV diastolic and systolic dysfunction has been reviewed in Chapter 1. This part will focus on atrial mechanical and electric changes after RVA pacing.

3.1.1 RVA Pacing on Atrial Remodeling in Non-AF Patients

LA remodeling and dysfunction may also develop after short-term or long-term RVA pacing. However, there is limited large, prospective trial to address this question. It is possible that RVA pacing might increase atrial pressure and impair atrial function. Only a small study (n = 38) examined the acute change of atrial function using two-dimensional echocardiography (129). However, there was no change in LA mechanical functions compared with baseline and after 4 hours > 90% ventricular pacing at 70 beats per minute with optimal AV interval in the study. From above, it is likely RVA pacing can induce atrial remodeling and impair atrial pump function.

3.1.2 Evidence of Atrial Fibrillation after RVA Pacing

AF is frequent by observed after RVA pacing integrated with ventricular dysfunction (22,130) (Figure 3.1). The beneficial effect of atrial pacing over ventricular pacing for sinus node dysfunction is attributed to maintaining atrioventricular synchrony with regard to AF and mortality (131). Nielsen et al (130) compared AAIR and DDDR pacing in 177 patients with sinus node dysfunction with short and long

atrioventricular delay. They demonstrated that patients in both DDDR groups have larger LA size and higher incidence of AF after long-term follow up comparing those with AAIR. This led to subsequent study designed to investigate whether minimizing frequent and unnecessary ventricular pacing can prevent ventricular dyssynchrony and reduce the risk of persistent AF (132). The study enrolled 535 patients with conventional DDDR pacing and 530 patients with dual-chamber minimal ventricular pacing. The time to persistent AF was the primary end point. The results showed a 40% decrease in relative risk of persistent AF at any time interval among patients with minimal ventricular pacing as compared with conventional DDDR pacing. Despite the potential advantages of atrial pacing (22,133), it is not widely used because of concerns regarding the subsequent development of atrioventricular block.

RVA pacing may induce atrial dilatation and increase atrial pressure in sinus node dysfunction patients which induces atrial electrical and mechanical remodeling associated with risks of AF (130,132,134-136). It has been demonstrated that biventricular pacing can prevent progressively LA dilatation in patient with persistent AF after atrioventricular node ablation. However, patients with RVA pacing have opposite findings (137). Most of studies showed favourable response to CRT to prevent new-onset AF in patients with systolic heart failure (138-140) but the mechanism is not clearly known.

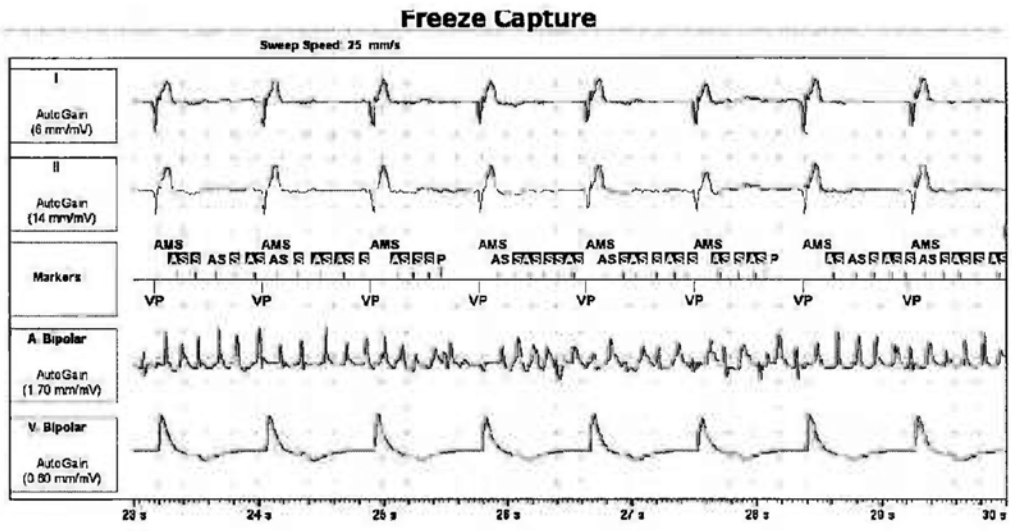


Figure 3.1 AF in stored electrogram (EGM) of a dual-chamber pacemaker. AMS, automatic mode switch; AS, atrial sensing; VP, ventricular pacing.

3.1.3 Atrial High Rate Episodes

Current pacemakers can monitor the patient's cardiac rhythm continuously and can detect and store the information of cardiac arrhythmias by manufacturer-specific algorithms. Event counter is one of the specific algorithms, which provides the percentage of sensing and pacing in each cardiac chamber, the number of premature atrial or ventricular contractions, and automatic mode switching. Therefore, pacemaker follow up can provide the date, time, duration, and frequency of atrial arrhythmia episodes according to programmable detection criteria, which is important for those require medical intervention.

Atrial high rate episodes (AHREs) are frequently detected in patients with dual-chamber pacemakers and are considered as a surrogate of AF (Figure 3.2) (141). The development of AHREs was associated with a history of AF in patients after RVA pacing. Previous study showed that AF was detected in 24% of patients without history of AF within 1 year pacemaker implantation. Early study has been reported that AHREs with more than 5 minutes in duration had a high correlation with AF and atrial flutter (142). Later, the Mode Selection Trial reported that at least one AHRE lasting more than 5 minutes was observed in a half of study patients over median follow up of 27 months (143). Thus, 5minute was considered as the cut-off value of significant atrial high rate episode (142,144,145).

However, most of AHREs are entirely asymptomatic. Nearly 10% of AHREs

observed during follow up are associated with symptoms in patients with dual-chamber multiprogrammable pacemakers. However, only 5% of AHREs reported a symptomatic event in patients without previously diagnosed atrial tachyarrhythmias (145,146). Therefore, early identification of patients with asymptomatic atrial tachyarrhythmias is of noteworthy clinical importance. Clinical trials need to clarify the significance of AHREs, especially its effects on antiarrhythmic and anticoagulant therapy.

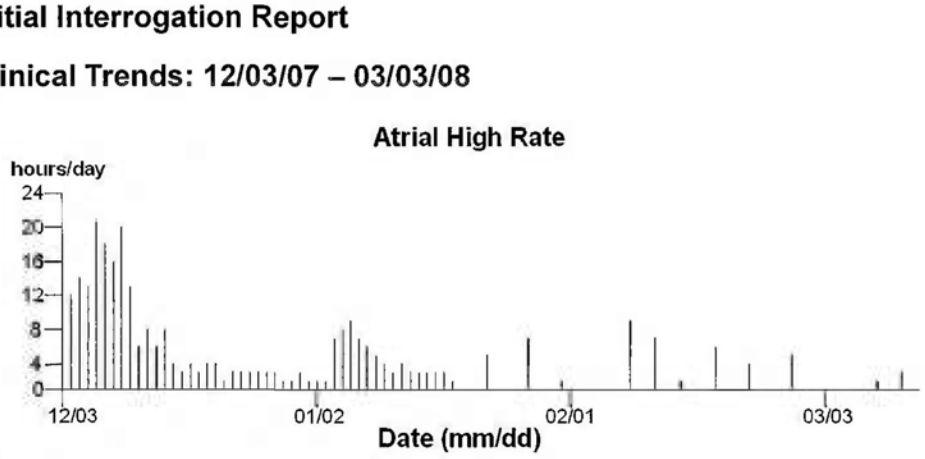


Figure 3.2 Atrial high rate episodes present as a histogram.

3.2 Intra- and Interatrial Dyssynchrony

3.2.1 Intra- and Interatrial Conduction

There are three intra-atrial bundles (anterior, median and posterior) organized in the right atrial septum. The pathways of normal atrial conduction were first described by James (147). These bundles do not connect to any specific tissue of conduction system. They are not histologically different from the other septal atrial tissue but their architectural organization into continuous bundles of parallel fibers enabling them with quicker and preferential conduction properties. In 1962 Bachmann (148) described a bundle which connected the sinoatrial node with LA. The Bachmann's bundle is the preferential conduction pathway from RA to LA. However, the electrical impulse activation in the LA is less well known. There might have functional block lines linked to the preferential orientation of the LA subendocardial fibers, which are important to AF ablation.

3.2.2 Assessment of Intra- and Interatrial Conduction Delay

The importance of intra- and interatrial conduction delay was first noted when optimising atrioventricular delay in patients with dual-chamber pacemakers more than 20 years ago (149). The atrial conduction time (ACT) has been evaluated using Doppler echocardiography, color TDI and ECG markers, P wave duration and P wave dispersion (150,151). P wave duration is usually measured manually on 12-lead surface ECG, which represents as the longest atrial conduction time. P wave dispersion reflects heterogeneous atrial conduction by the detection of abnormal

atrial conduction with surface ECG. It is typically measured the difference between the longest and shortest P wave durations or estimates variations of P wave duration in all ECG leads (152).

In a retrospective study, P wave duration but not its dispersion was significant independent predictor of frequent AF paroxysm (153). However, P wave dispersion was useful to predict transition form paroxysmal AF to permanent AF (154). Despite these, it may be sometimes difficult to measure P wave duration and dispersion on a 12-lead surface ECG because atrial depolarization may generate low voltages and small amplitude of P wave (155). The gold standard for determination of the P-wave duration is by the signal-averaged ECG, but it requires special hardware and time-consuming, which limits its clinical use (155,156). In a validation study, 30 patients were enrolled and P wave duration on surface ECG and signal-average ECG were assessed. They also measured the atrial activation time which was the interval from P wave on ECG to the onset of A wave over mitral valve on Doppler tissue imaging. An example is shown in Figure 3.3. They found that high correlation of these parameters between two methods but not conventional echocardiographic parameters. Using transthoracic TDI to estimate atrial contraction time was easy, fast and highly correlated with the gold standard (151).

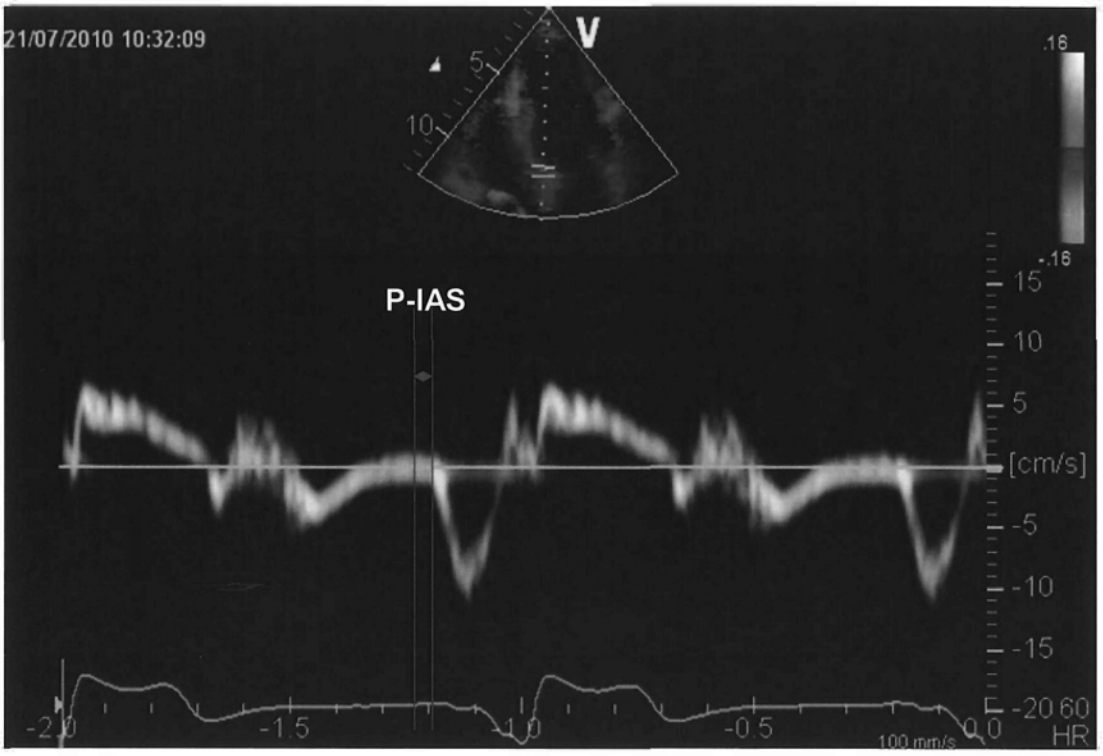


Figure 3.3 Example measurement of the P-IAS interval. Atrial conduction time on interatrial septum (P-IAS) was measured from P wave on ECG (recorded by the echo machine) to the onset of A wave over mitral valve on Doppler tissue imaging. The sweep speed was set at 100 mm/s to improve the measurement accuracy.

3.2.3 Implications of Intra- and Interatrial Conduction Delay

The prolonged P wave duration and P wave dispersion were thought to have interatrial conduction delay and atrial systolic dyssynchrony (157). The prolongation was also recognized as markers of an increased risk of AF (158,159). The prolongation of atrial conduction was also an important predictor of new-onset of AF in acute myocardial infarction (160). In 613 patients with acute myocardial infarction, ACT duration on the lateral wall of the LA can provide incremental value for the prediction of new-onset AF to clinical and other echocardiographic risk factors, including LA size.

3.2.4 The Prolongation of Atrial Conduction and Atrial Size

P wave duration consists of left and right atrial depolarizations. It is common known that atria dilatation cause broad P wave in standard ECG. However, Ishimoto et al expressed P wave duration was influenced by left and total atrial volume (sum of LA and RA volume) but not by RA volume. They postulated that RA depolarization comprises the early phase of P wave and hardly affects the length of P wave, which might explain their findings (161). Thus, intra- and interatrial dyssynchrony may play an important role of P wave prolongation. P wave abnormalities have been demonstrated to be associated with LA enlargement. The atrial conduction delay could be due to a dilated LA because of a longer pathway that electrical impulses have to travel, such as found in patients with mitral annulus calcification and mitral stenosis (150,152).

3.2.5 The Influence of RA Appendage Pacing on Atrial Conduction

RA appendage site is the conventional atrial pacing site, but stimulation at RA appendage can lead to intra- and interatrial conduction delay (162-164). It has been known the close relationship between atrial conduction and the incidence of AF. Bennett (163) performed a small study comparing the acute pacing effects on RA appendage, RA septal, coronary sinus ostium and dual site pacing (simultaneously coronary sinus ostium and RA appendage) on the duration of atrial activation. He found that the duration of atrial activation with RA appendage pacing was notably longer than with atrial septal, coronary sinus ostium and dual site pacing, but the latter three showed no difference between them. Large long-term randomized clinical trials are required to further investigate the superiority of other atrial pacing sites than the RA appendage site.

3.2.6 RA Appendage Pacing and Atrial Fibrillation

Atrial pacing may prevent AF in two ways by: (1) inhibiting triggers associated with bradycardia or by suppressing atrial premature beats, (2) modifying the properties of the substrate (155,165,166). Andersen and colleagues (131) suggested that the treatment of single-chamber atrial pacing in patients with sick-sinus syndrome was associated with less AF and thromboembolism when comparing with single-chamber ventricular pacing in a long-term randomized trial. However, a randomized study demonstrated that DDDR pacing did not prevent recurrence of paroxysmal AF nor

did it delay the development of permanent AF compared with VDD pacing in patients with frequent paroxysmal AF after atrioventricular junction ablation (167).

3.2.7 Alternative Atrial Pacing Sites

The atrial pacing sites might play an important role in atrial arrhythmogenesis. Previous experimental and clinical studies found atrial septal pacing was safe, feasible and might be of more benefit than pacing at the RA appendage (168-172). Apart from high RA pacing site, other single alternative sites (the anterior portion of the IAS at Bachmann's bundle level, the lower septal region near the coronary sinus ostium, and the LA through the coronary sinus), biatrial pacing and multisite atrial pacing have been investigated (173-175). A study enrolled patients with sinus node dysfunction and compared different atrial pacing modes. Patients with RA appendage pacing group had electromechanical delay and interatrial dyssynchrony. Single-site at Bachmann's bundle and multisite atrial pacing restored atrial synchrony (176,177).

3.2.8 Summary

In summary, atrial conduction delay and atrial dyssynchrony during the conventional RA appendage pacing may result in intra- and interatrial conduction disorders. It might be the important genesis of atrial arrhythmia. However, long-term, prospective clinical trials are needed to provide more supporting evidence.

SECTION II
OBJECTIVES AND METHODOLOGY

CHAPTER 4 OBJECTIVES

4.1 Acute Effects of RVA Pacing on Atrial Remodeling and Function

During RVA pacing, the direct electric stimulation of the RV apex leads to abnormal activation and asynchronous ventricular contraction. Animals and human studies had been demonstrated the deleterious effects of short term or long term RVA pacing on LV function. However, whether acute RVA pacing results in LA remodeling and dysfunction was not well studied. Therefore, in the cross-sectional study, we aimed to: (1) observe whether LA remodeling and dysfunction developed after acute RVA pacing; (2) observe whether LA function deterioration was different in patients with or without preexisting diastolic dysfunction.

4.2 Chronic Effects of RVA Pacing on Atrial Remodeling and Function

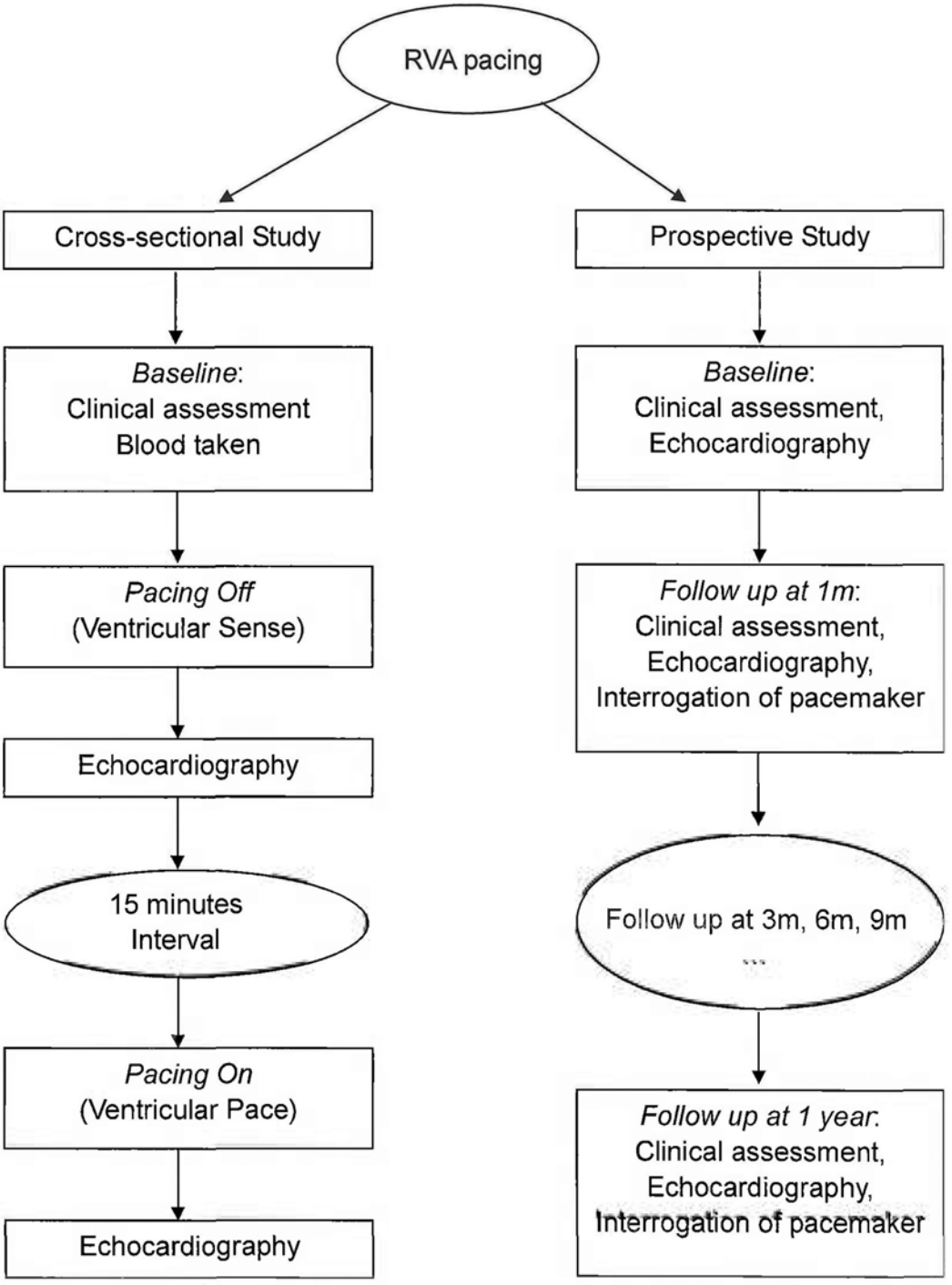
Chronic RVA pacing may induce LA dilatation (130) and indicate elevated LV filling pressure. However, there was no study illustrating LA size and function comprehensively in patients with preserved ejection fraction, especially long-term follow up. The prospective study will address the following questions by the use of advanced echocardiographic techniques: (1) chronic RVA pacing will induce LA dilatation and reduce atrial velocities after one year follow up in patients with preserved systolic function; (2) is there any predictor of atrial dysfunction after long-term RVA pacing?

4.3 Intra- and Interatrial Dyssynchrony

TDI is an established tool to assess LV systolic and diastolic mechanical dyssynchrony and function in heart failure and acute myocardial infarction. It is also widely used in quantitative assessment of ventricular dyssynchrony before and after CRT. It is possible to use TDI to estimate intra-atrial and interatrial dyssynchrony in patients received RVA pacing. The purposes of this study were: (1) to examine if RA appendage pacing can reduce atrial function and induce intra- and interatrial dyssynchrony separately; (2) to investigate if atrial dysfunction and dyssynchrony can predict AHREs burden after the first year of RVA pacing.

CHAPTER 5 METHODOLOGY

5.1 Study Protocol



5.2 Cross-sectional Study

5.2.1 Study Population

The Cross-sectional study enrolled 98 patients who had been implanted dual chamber pacemakers due to sick sinus syndrome. Patients were excluded in the study if they had

(1) Complete heart block or other cardiac conditions such that they are not safe to program the pacemaker to ventricular pacing-off mode temporarily

(2) History of heart failure or in acute clinical heart failure due to systolic dysfunction

(3) Systolic dysfunction with LV ejection fraction < 45%

(4) Biventricular pacemaker implantation

(5) Permanent atrial fibrillation

(6) Received single chamber pacemaker that pace either RA or RV

(7) A ventricular lead placed in a site other than RV apex, e.g. RVOT

(8) Patients with hypertrophic obstructive cardiomyopathy

(9) Refused to participate the study

5.2.2 Pacemaker Implantation

Patients in the cross-sectional study had the implantation of RV apical-based dual chamber pacemakers to achieve physiological pacing.

5.2.3 Clinical Assessment

All patients enrolled in this study had their clinical and demographic information record and will do comprehensive echocardiography.

5.2.4 Echocardiography

5.2.4.1 Echocardiographic Protocol

Echocardiography was performed during intrinsic ventricular conduction (i.e. ventricular sensing that allows intrinsic ventricular beats) and during RV pacing mode (i.e. ventricular pacing) in a random order.

Firstly, pacemaker was interrogated to ascertain the pacing configuration of ventricular sensing. Patients were performed comprehensive echocardiography if they were currently not ventricular pacing dependent, i.e. at atrial sensing and ventricular sensing. If the pacing was having a ventricular pacing configuration, the atrioventricular interval will be prolonged progressively in every 10ms steps to allow ventricular sensing to occur. If patient was found atrial pacing dependent (i.e. atrial pacing and ventricular sensing) due to a high backup pacing rate, the pacing rate should be reduced to allow atrial sensing and ventricular sensing to occur. If the patient was atrial pacing dependent, then echo could be performed at atrial pacing and ventricular sensing configuration. The lowest backup pacing rate allowed was 50/min during the examination.

Echocardiography was repeated during RV pacing when patients had a rest for at

least 15 minutes. To ensure RV pacing to occur, pacemaker was programmed to an atrioventricular interval of 20 ms shorter than otherwise ventricular fusion or ventricular intrinsic beats would occur. Alternatively, if patients were under active ventricular pacing at the time of first pacemaker interrogation, they were adjusted to an atrioventricular interval so that ventricular pacing would be continued but an atrioventricular interval value just 20 ms shorter than otherwise ventricular fusion or ventricular intrinsic beats would occur (i.e. an atrioventricular interval still be short enough to maintain ventricular pacing, which could be different from the initial atrioventricular interval when the pacemaker is first interrogated).

Patients had 15 minutes to rest when switching the pacing programme to perform echocardiography. Upon completion of the echo examination, patient was then programmed back to the original pacemaker setting or other settings as clinically indicated.

5.2.4.2 Echocardiographic System and Transducer

(i) IE33 (Philips, Andover, MA, USA);

(ii) Transducer: S5-1 and X3-1 (1.9/3.8 MHz).

5.2.4.3 Software in Offline Analysis

(i) Workstation: Xcelera

(ii) Qlab 6.0 (Philips, Andover, MA, USA)

5.3 Prospective Study

5.3.1 Study Population

Patients undergoing implantation of dual chamber pacemaker due to symptomatic required atrioventricular block and sinus node diseases were recruited. The RV lead was placed at the RV apex and the RA lead was at RA appendage. The exclusion criteria included:

(1) Patients who have had know history of heart failure or in acute clinical heart failure due to systolic dysfunction

(2) Patients with systolic dysfunction with LVEF < 45%

(3) Patients who are in permanent AF

(4) Patients who had biventricular pacing or received single chamber pacing that pace either RA or RV

(5) Patients who had a ventricular lead placed in a site other than RV apex, e.g. RVOT or high septum

(6) Patient with hypertrophic obstructive cardiomyopathy

(7) Patients who refuse to participate the study

5.3.2 Pacemaker Implantation

Patients enrolled in prospective study were implanted with a standard dual-chamber pacemaker (pacemaker model: Medtronic InSync III 8042) with leads inserted to RA appendage and RV apex.

5.3.3 Clinical Assessment

In the study, investigators performed these following assessments for all patients at baseline and follow up:

(1) ECG or Holter

(2) Echocardiography

(3) 6-minute hall walk test

(4) Quality of life by Short Form-36 (SF-36)

(5) Blood test

5.3.4 Echocardiography

5.3.4.1 Echocardiographic Protocol

Patients at baseline and during 1-, 3-, 6-, 9- and 12-month follow up, echocardiography, ECG, 6-minute hall wall test and questionnaires were performed and assessed following the standard protocol.

5.3.4.2 Echocardiographic System and Transducer

(i) IE33 (Philips, Andover, MA, USA);

Transducer: X3-1 (1.9/3.8 MHz).

(ii) Vivid 7 or E9 (General Electric Vingmed Ultrasound AS, Horten, Norway);

Transducer: S5

5.3.4.3 Software in Offline Analysis

(i) Philips medical system: Qlab 6.0 (Philips, Andover, MA, USA)

(ii) General Electric medical system: EchoPac PC (version 108.1.5, General Electric)

5.4 Echocardiographic Images Acquisition

5.4.1 Standard Views

Series comprehensive echocardiographic images were acquired with five consecutive cycles by experienced echocardiographers.

5.4.1.1 Parasternal Long Axis View

(1) Two-dimensional loop

(2) Zoom on left ventricular outflow tract (LVOT)

(3) M-mode of aorta with LA

(4) M-mode of mid-portion of LV

(5) Color Doppler over mitral valve

(6) Color Doppler over aortic valve

5.4.1.2 Parasternal Short Axis View

(1) Two-dimensional loop at the level of mitral valve

(2) Two-dimensional loop at the level of papillary muscle

(3) Two-dimensional loop at the level of LV apex

(4) Two-dimensional loop at the level of aortic valve

(5) Color Doppler over aortic valve

(6) Zoom on RVOT

(7) Color Doppler over pulmonary valve

(8) Pulsed wave (PW) Doppler in RVOT

(9) Continuous wave (CW) Doppler in RVOT

(10) PW Doppler of tricuspid inflow

(11) CW Doppler of TR

5.4.1.3 Apical 4-chamber View

(1) Two-dimensional loop

(2) Color Doppler over mitral valve

(3) PW Doppler of mitral inflow

(4) CW Doppler of MR

(5) Zoom color Doppler of mitral inflow (if more than mild MR)

(6) Color Doppler over aortic valve

(7) PW Doppler in LVOT

(8) CW Doppler in LVOT

(9) PW Doppler in pulmonary vein

(10) Color Doppler over tricuspid valve

(11) PW Doppler of tricuspid inflow

(12) CW Doppler of TR

(13) Color TDI loop

(14) Pulsed TDI on LV septum

(15) Pulsed TDI on LV lateral wall

(16) Pulsed TDI on RV free wall

(17) Two-dimensional loop of zoom LV

(18) Color TDI loop of zoom LV

5.4.1.4 Apical 2-chamber View

(1) Two-dimensional loop

(2) Color Doppler over mitral valve

(3) CW Doppler of MR (if needed)

(4) Color TDI loop

(5) Two-dimensional loop of zoom LV

(6) Color TDI loop of zoom LV

5.4.1.5 Apical 3-chamber View

(1) Two-dimensional loop

(2) Color Doppler over mitral valve

(3) CW Doppler of MR (if needed)

(4) Color TDI loop

(5) Two-dimensional loop of zoom LV

(6) Color TDI loop of zoom LV

5.4.1.6 Subcostal View

(1) Two-dimensional loop of inferior vena cava (IVC)

(2) M-mode of IVC

(3) PW Doppler of hepatic vein (if needed)

5.4.2 Recommendations on Images Recording and Measurement

ECG was connected during the examination of Echocardiography with clear P wave and R wave. Echocardiographic images were stored in hard disk with optimal gain, filters and frequency. For two-dimensional echocardiographic images, frame rate was > 50 fps. However, for color TDI images, frame rate was > 100 fps.

The velocities measured by Doppler relied on maintaining a parallel orientation between the sound waves and blood flow. The Doppler sound beam should be oriented to the flow as parallel as possible. However, angle correction is not recommended (178).

5.4.3 Echocardiographic Parameters

(i) LV volumetric and geometric parameters

1) End-diastolic and end-systolic volume
2) LV end-diastolic and end-systolic dimensions
3) LV end-diastolic and end-systolic sphericity indices

(ii) LV systolic function

1) Ejection fraction

2) Cardiac output

3) Myocardial performance index

4) Isovolumic contraction time

5) Peak regional systolic velocity by TDI (Sm)

6) Mean of systolic velocity of 12 LV segments (for global LV function)

(iii) LV diastolic function

1) Transmitral early diastolic filling velocity

2) Transmitral atrial filling velocity

3) Early to late filling velocity ratio

4) Deceleration time of early diastolic filling

5) Isovolumic relaxation time

6) LV filling time

7) Peak regional early diastolic velocity by TDI (Em)

8) Peak regional atrial diastolic velocity by TDI (Am)

9) Mean of diastolic velocity of 12 LV segments (for global LV function)

10) Transmitral early diastolic filling velocity to mitral annular early diastolic velocity ratio

(iv) LA volumetric and geometric parameters

1) Maximal LA volume / area and indexes

2) Pre-atrial contraction volume / area and indexes

3) Minimal LA volume / area and indexes

4) LA anteroposterior dimension

5) LA long axis and orthogonal dimensions

(v) LA function by TDI

1) Peak systolic velocity of LA

2) Peak early diastolic velocity of LA

3) Peak late diastolic velocity of LA

(vi) LV dyssynchrony and intra- and interatrial dyssynchrony

1) LV dyssynchrony (standard deviation of time to peak systolic velocity in ejection phase of the 12 LV segments by TDI)

2) Atrial conduction time of IAS

3) Atrial conduction time of lateral wall of LA

4) Atrial conduction time of anterior wall of LA

5) Atrial conduction time of inferior wall of LA

6) LA dyssynchrony (standard deviation of atrial conduction time of IAS, lateral, anterior and inferior walls of LA)

7) RA dyssynchrony (difference of atrial conduction time of RV free wall and IAS)

8) Interatrial dyssynchrony (difference of atrial conduction time of RV free wall

and LA lateral wall)

5.5 Statistics

Data were expressed as mean ± SD or numbers and percentages. Continuous variables between baseline and one year follow up were analyzed by a two-sided paired Student's t-test. Comparison between two independent groups was performed with independent-samples t-test or Chi-square test. One-Way ANOVA followed by SLD method were used in multiple comparisons for testing the significance. Univariate analysis was used to test the association of factors and dependent covariate. Backward stepwise (Likelihood Ratio) regression was run to test the predictors of dependent covariate. Receiver-operating characteristic (ROC) curve was developed to describe the cut-off value. A p value < 0.05 was statistically significant. Statistical analysis was performed using SPSS (SPSS 13.0 or 17.0, SPSS Inc, Chicago, Illinois, USA).

SECTION III
RESULTS AND DISCUSSION

CHAPTER 6 ACUTE EFFECTS OF RIGHT VENTRICULAR APICAL PACING ON LEFT ATRIAL REMODELING AND FUNCTION

6.1 Background

Human studies have demonstrated that RVA pacing may induce LV dysfunction, increase diastolic filling pressure and MR (38,179). Theoretically, the direct pacing at RV apex induces an asynchronous electrical activation pattern and therefore asynchronous ventricular contraction and relaxation (15,53). Acute RVA pacing can adversely affect LV longitudinal shortening and decrease LV rotation and twist (37,38). However, its adverse effects on LA structure and function remain largely unknown.

Echocardiography allows non-invasive assessment of atrial size and function by commercially available software. Conventional two-dimensional echocardiography can assess the change of LA area, volume and ejection fraction. TDI can evaluate regional function of by measuring tissue velocity. It has been demonstrated prognostic value of these echocardiographic methods in ischemia heart disease, heart failure and CRT patients (180). The purpose of this study was to elucidate the pathphysiology of the effect of RVA pacing on LA remodeling and function by echocardiographic techniques in patients with preserved ejection fraction.

6.2 Methods

6.2.1 Patients

Patients who had been implanted RVA-based dual-chamber pacemakers were invited to participate in this cross-sectional study. Patients who had history of heart failure or acute heart failure due to systolic dysfunction, LVEF < 45% or permanent AF were excluded. Patients were not enrolled if they had single chamber or biventricular pacemaker but not dual-chamber pacemaker. The condition in which patients are not safe to program the pacemaker to ventricular pacing-off temporarily was taken into consideration to exclude. All patients joined the study will be performed electrocardiogram, echocardiography and clinical assessment. The study was approved by Institutional Review Board and written informed consent was provided by all patients.

6.2.2 Echocardiography

6.2.2.1 Imaging Acquisition Protocol

Transthoracic echocardiography was performed by experienced echocardiographers using a commercially available system (iE33, Philips, Andover, MA, USA). Comprehensive echocardiographic images were recorded during intrinsic ventricular conduction (V-sense) and RVA pacing (V-pace) modes with 15 minutes between switching modes following standard scanning protocol.

Conventional echocardiography including two-dimensional echocardiography, color Doppler and pulsed Doppler echocardiography was performed using an S5-1

transducer. RT3DE with full volume was performed with X3-1 matrix array transducer (1.9 / 3.8 MHz), which will be used to assess LV volumes and LVEF. Images were optimized with proper gain, compression and depth and avoided foreshortening. To minimize translation artifacts, patients were instructed to hold their breath during full volume set acquisition which was triggered by R wave on electrocardiogram and required a relative stable R-R interval. Configurations and settings of echocardiographic system were adjusted to acquire the highest frame rate (> 100 fps) to optimize TDI images. Digital images with consecutive five cycles were stored for offline analysis.

6.2.2.2 Conventional Parameters of LV Function

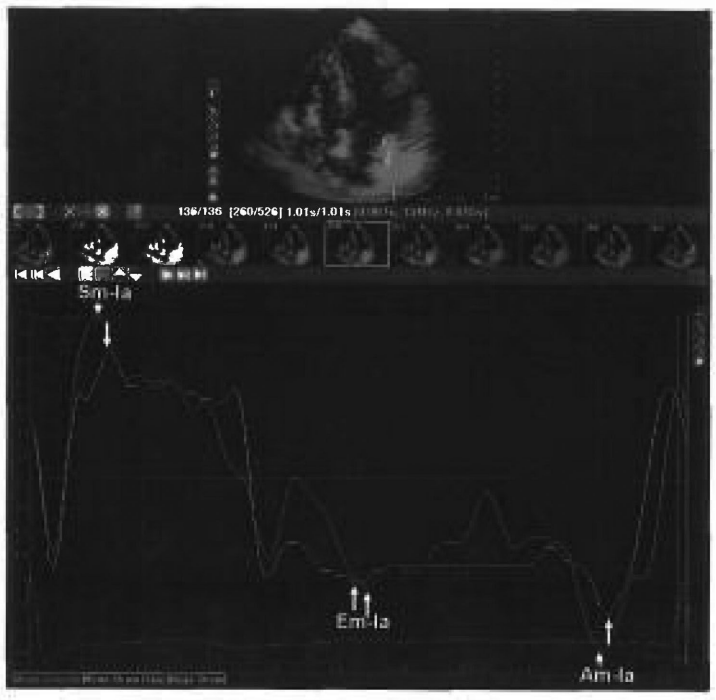
Parameters were measured offline using Xcelera workstation or Qlab software (version 6.0, Philips, Andover, MA, USA). LVEDV, LVESV and LVEF were measured with RT3DE images using Qlab. The endocardial border was traced manually at end-diastolic and end-systolic frames. Then the LV systolic function was reported automatically. LVEF < 45% was ruled out according the inclusion criteria. Two-dimensional biplane Simpson's method was used to assess LVEF for all patients as well. LV dyssynchrony index was defined by the standard deviation of time to peak systolic velocity during ejection phase of the 12 LV nonapical segments by TDI (Ts-SD). Ts-SD > 33ms was considered LV asynchrony as previous study defined (181).

LV diastolic filling patterns were graded into four types: normal, abnormal relaxation pattern, pseudonormal diastolic filling pattern, restrictive diastolic filling pattern as recommended for evaluation of LV diastolic function by echocardiography (182). Transmitral E, A, E/A ratio, DT, and E/e' were taken into account. E/e' > 15 reflects elevated LV filling pressure (183).

6.2.2.3 LA Volume and Tissue Doppler Measurement

The LAVmax, LAVpre and LAVmin were assessed by area-length method as recommended by American Society Association using two-dimensional echocardiographic images (56). The following formulas were used to assess LA emptying fractions: (1) LA passive emptying fraction, defined as (LAVmax - LAVpre) / LAVmax × 100%; (2) LA active emptying fraction, defined as (LAVpre - LAVmin) / LAVpre × 100%; (3) LA total emptying fraction by volume, defined as (LAVmax - LAVmin) / LAVmax × 100%. Peak systolic (Sm-la), peak early diastolic (Em-la) and late diastolic (Am-la) velocities were measured by color-coded TDI in four mid LA walls at apical 4- and 2-chamber views. The Figure 6.1 shows the method of measuring LA myocardial velocities. The mean values of Sm-la, Em-la, and Am-la were calculated manually.

A.



B.

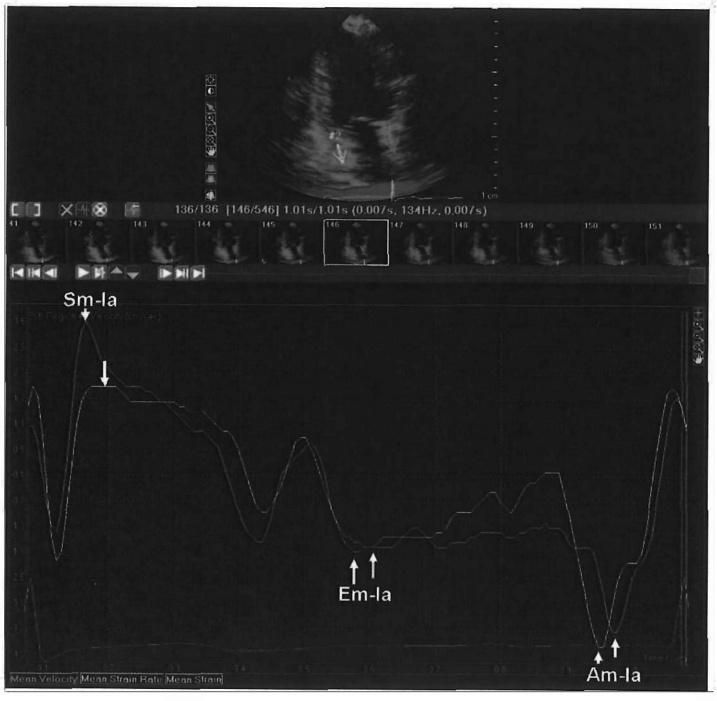


Figure 6.1 Example measurements of atrial velocities (Sm-la, Em-la and Am-la) in apical 4- (A) and 2-chamber (B) view during V-sense.

6.2.3 Statistical Analysis

Continuous variables are reported as mean ± SD. Paired-samples T-test was done to compare the difference of ventricular and atrial function between V-sense and V-pace. Ranked data was analyzed using nonparametric test (Wilcoxon method). To compare the difference between groups of V-sense and V-pace, independent t-test was used. A p value < 0.05 was considered statistically significant. All data was analyzed using SPSS (SPSS 17.0, SPSS Inc, Chicago, Illinois, USA).

6.3 Results

6.3.1 Characteristics of Study Population

Ninety-eight patients with sinus node dysfunction who had the implantation of dual chamber pacemakers were consecutively enrolled in this study. Four patients with pacing dependent were excluded. Finally there were 94 patients analyzed. There were 26 male and 68 female with mean age 68.1 ± 11.1 years (range 34-92 years). The pacemaker implantation period was 55.5 ± 46.4 months. One-fourth of patients had history of coronary heart disease. Hypertension and diabetes mellitus were present in 60.2% and 19.3% of patients respectively. The characteristics of study population are shown in Table 6.1.

Table 6.1 Characteristics of study population (n = 94)

Variable	
Age, years	68.1 ± 11.1
Male / female	26 / 68
Body surface area, m^2	1.6 ± 0.1
Heart rate, beats/min	61.5 ± 10.0
Medical history	
Coronary artery disease, %	25.0
Hypertension, %	60.2
Diabetes mellitus, %	19.3
Medication	
Beta-blockers, %	42.0
ACEI or ARB, %	15.9
Statin, %	26.1
Calcium channel antagonist, %	29.5

ACEI, angiotensin-converting enzyme inhibitor;

ARB, angiotensin receptor blocker.

6.3.2 LV Function and Dyssynchrony

All patients were in sinus rhythm during image acquisition. The comparison of heart rate, QRS duration and LV function is shown in Table 6.2. There was no change in heart rate when switching mode to V-pace (61 ± 10 vs. 62 ± 7 beats/min, p = 0.785). However, the prolongation of QRS was present during V-pace. LVEF measured by two-dimensional biplane Simpson's method was used in seven patients because of suboptimal three-dimensional echocardiographic images. LVESV increased significantly by 9.0% (23.3 ± 6.9 vs. 25.2 ± 7.9 ml, p < 0.001) with the reduction of LVEF by 4.3% (61.3 ± 6.3 vs. 58.8 ± 8.2%, p <0.001) in comparison with V-sense. There were seven patients (7.4%) presented EF < 45% with acute RV pacing. However, there was no significant change in LVEDV. The prevalence of LV dyssynchrony of V-pace was more than V-sense significantly (21.5% vs. 59.1%, χ^2 = 7.051, p = 0.008).

Conventional parameters of diastolic function were not found any difference when switched to V-pace (Table 6.2). But diastolic filling pressure as reflected by E/e' increased significantly. Elevated filling pressure as reflected by E/e' > 15 was present in 24.5% patients during V-sense and 28.7% patients during V-pace (χ^2 = 24.810, p < 0.001). Similarly, diastolic filling patterns deteriorated in some ways (Figure 6.2). There were twenty-three (24.5) patients with normal diastolic filling pattern and function during V-sense. However, nine (39.1%) patients presented abnormal filling pattern or pseudonormal even restrictive filling pattern during V-pace but normal in

V-sense. In addition to this, of patients with diastolic dysfunction, there were ten (14.1%) patients deteriorated to worse filling patterns after short term RV pacing.

Table 6.2 Comparison of LV function and dyssynchrony between V-sense and V-pace

Variable	V-sense	V-pace	p value
Heart rate, bpm	61 ± 10	62 ± 7	0.785
QRS duration, ms	96 ± 18	163 ± 33	< 0.001
LVEDV, ml	60.3 ± 15.3	61.2 ± 14.4	0.216
LVESV, ml	23.3 ± 6.9	25.2 ± 7.9	< 0.001
SV, ml	37.1 ± 10.6	35.6 ± 10.2	0.014
LVEF, %	61.3 ± 6.3	58.8 ± 8.2	< 0.001
Ts-SD, ms	24.7 ± 11.6	39.7 ± 16.8	< 0.001
E, cm/s	0.71 ± 0.19	0.71 ± 0.20	0.974
A, cm/s	0.80 ± 0.24	0.79 ± 0.21	0.578
E/A ratio	0.95 ± 0.35	0.97 ± 0.42	0.268
DT, ms	217.8 ± 52.7	232.7 ± 56.3	0.013
IVRT, ms	105.7 ± 27.6	107.5 ± 33.0	0.571
e', cm/s	6.0 ± 2.2	5.5 ± 2.2	0.016
E/e'	12.9 ± 5.0	14.4 ± 5.9	0.001

DT, deceleration time of transmitral early diastolic filling velocity; E/A ratio, early to late filling velocity ratio; E/e', ratio of transmitral velocity to mitral annular early diastolic velocity; IVRT, isovolumic relaxation time; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; E, transmitral early diastolic filling velocity; A: transmitral late diastolic filling velocity; SV, stroke volume; Ts-SD, the standard deviation of time to peak systolic velocity in ejection phase of the 12 left ventricular nonapical segments by tissue Doppler imaging.

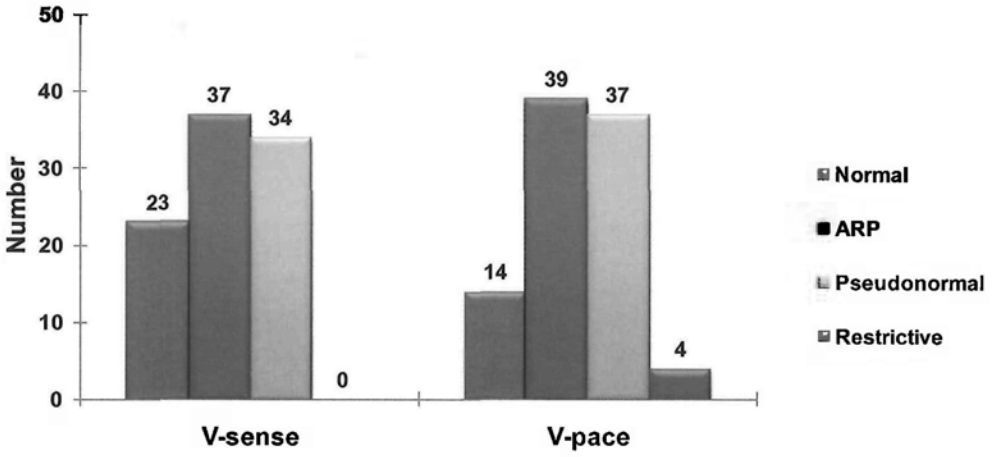


Figure 6.2 Distribution of diastolic filling patterns during V-sense and V-pace. The deterioration of diastolic filling pattern is showing at V-pace mode (Z = -3.399, p = 0.001). Restrictive filling pattern was emerging after acute RVA pacing. The values are numbers. ARP, abnormal relaxation pattern.

6.3.3 LA Phasic Volumes, Emptying Fraction and Tissue Velocities

In the study cohort, during V-pace, LA phasic volumes (LAVmax: 52.0 ± 18.8 vs. 55.2 ± 21.1 ml, p = 0.005; LAVpre: 39.8 ± 16.4 vs. 41.3 ± 16.6 ml, p = 0.014; LAVmin: 27.4 ± 14.0 vs. 29.1 ± 15.1 ml, p = 0.001) and indexed of volume increased slightly but significantly. 55% of patients with V-pace had indexed LAVmax > 32 ml/m^2 in comparison with 45% of patients with V-sense had LAVmax > 32 ml/m^2 (χ^2 = 40.284, p < 0.001). However, there were no significant changes in either passive or active emptying fraction as well as total emptying fraction (all p > 0.05). TDI parameters showed significant reduction in peak systolic velocity (Sm-la: 3.0 ± 1.1 vs. 2.7 ± 0.9 cm/s, p < 0.01), peak early diastolic velocity (Em-la: 2.7 ± 1.1 vs. 2.4 ± 1.0 cm/s, p = 0.001). The mean reduction of Sm-la (9.5%) was more than Em-la and Am-la. However, there was no change in peak late diastolic velocity of LA (Am-la: 3.8 ± 1.2 vs. 3.7 ± 1.3 cm/s, p = 0.106) (Table 6.3). 40 (42.6%) patients presented increased late diastolic velocity of LA at acute RVA pacing.

6.3.4 LA Remodeling and Velocity during V-sense and V-pace in Patients with or without Diastolic Dysfunction Assessed in V-sense

Comparing LA size and atrial velocity in patients present or absent diastolic dysfunction during V-sense, we found that Sm-la and Em-la significantly decreased during V-pace in patients presenting diastolic dysfunction but no significant change in those without. However, Am-la had no change during V-pace in patients with

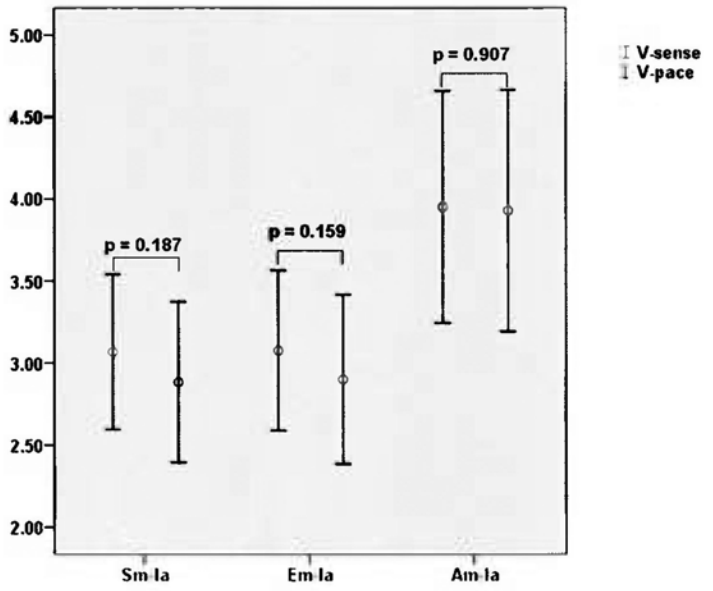
either normal or abnormal diastolic function (Figure 6.3). In both groups of normal and abnormal diastolic function in V-sense, the indexed of LAVmax and indexed LAVmin raised with RVA pacing (Table 6.4).

Table 6.3 Comparison of LA phasic volumes, emptying fraction and tissue velocity between V-sense and V-pace

Variable	**V-sense**	**V-pace**	**p value**
LAVmax, ml	52.0 ± 18.8	55.2 ± 21.1	0.005
LAVmax index, ml/m^2	32.4 ± 10.9	34.3 ± 12.7	0.007
LAVpre, ml	39.8±16.4	41.3 ± 16.6	0.014
LAVpre index, ml/m^2	24.5 ± 9.5	25.5 ± 9.6	0.024
LAVmin, ml	27.4 ± 14.0	29.1 ± 15.1	0.001
LAVmin index, ml/m^2	16.8 ± 8.0	17.9 ± 8.7	0.001
Passive emptying fraction by volume, %	23.3 ± 14.9	24.3 ± 14.9	0.563
Active emptying fraction by volume, %	32.4 ± 14.7	31.5 ± 14.7	0.340
Total emptying fraction by volume, %	48.5 ± 13.5	47.9 ± 15.4	0.608
Sm-la, cm/s	3.0±1.1	2.7±0.9	< 0.001
Em-la, cm/s	2.7±1.1	2.4±1.0	0.001
Am-la, cm/s	3.8±1.2	3.7±1.3	0.106

Am-la, peak late diastolic velocity of left atrium; Em-la, peak early diastolic velocity of left atrium; LAVmax, maximal left atrial volume; LAVmin, minimal left atrial volume; LAVpre, pre-atrial contraction volume of left atrium; Sm-la, peak systolic velocity of left atrium.

(A) Normal diastolic function



(B) Diastolic dysfunction

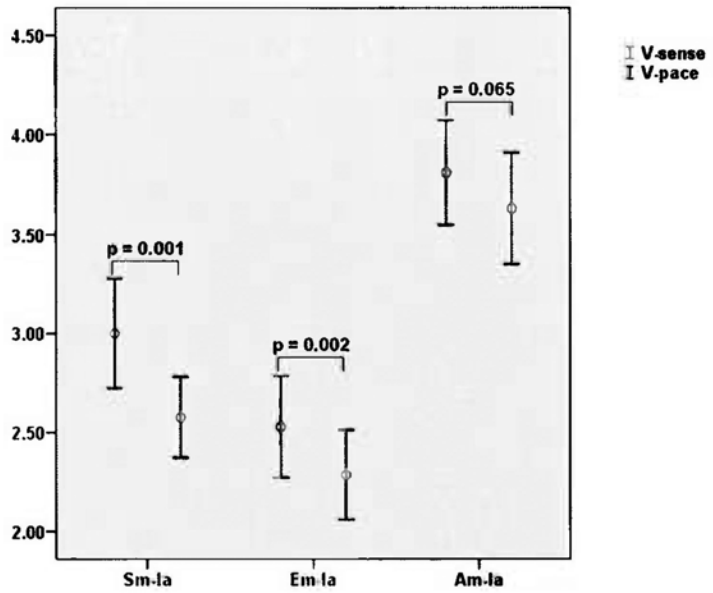


Figure 6.3 Comparison of atrial velocities (Sm-la, Em-la, Am-la) during V-sense (left) and V-pace (right) in patients with normal diastolic function (A) and diastolic dysfunction (B). They showed that Sm-la and Em-la significantly decreased during V-pace in patients presenting diastolic dysfunction (B) but no change in those without. However, Am-la had no change during V-pace either in normal or abnormal diastolic function. The values are mean with 95% CI.

Table 6.4 Comparison of LA phasic volume, index and velocity in patients with or without preexisting diastolic dysfunction during V-sense and V-pace

	Normal diastolic function (n = 23)			Diastolic dysfunction (n = 71)		
	V-sense	V-pace	p value	V-sense	V-pace	p value
LAVmax, ml	49.0 ± 19.2	53.7 ± 19.4	0.011	53.0 ± 18.8	55.7 ± 21.7	0.050
LAVmax index, ml/m^2	30.4 ± 11.1	32.7 ± 11.3	0.040	33.0 ± 10.9	34.8 ± 13.2	0.039
LAVpre, ml	35.5 ± 13.9	38.6 ± 14.2	0.050	41.2 ± 17.0	42.2 ± 17.3	0.117
LAVpre index, ml/m^2	21.5 ± 8.1	23.5 ± 8.5	0.053	25.5 ± 9.8	26.1 ± 9.9	0.170
LAVmin, ml	23.4 ± 10.3	26.6 ± 13.8	0.013	28.7 ± 14.8	30.0 ± 15.6	0.017
LAVmin index, ml/m^2	14.5 ± 6.2	16.5 ± 8.5	0.021	17.5 ± 8.4	18.3 ± 8.8	0.021
Sm-la, cm/s	3.1 ± 1.1	2.9 ± 1.1	0.187	3.0 ± 1.2	2.6 ± 0.9	0.001
Em-la, cm/s	3.1 ± 1.1	2.9 ±1.2	0.159	2.5 ± 1.0 *	2.3 ± 0.9 #	0.002
Am-la, cm/s	4.0 ± 1.6	3.9 ± 1.7	0.907	3.8 ± 1.1	3.6 ± 1.2	0.065

*p = 0.039 vs. the group with normal diastolic function during V-sense, #p = 0.013 vs. the group with normal diastolic function during V-pace

6.4 Discussion

The main findings of this study were: (1) with acute RV pacing, LV systolic function was reduced, diastolic filling pressure elevated and LV systolic dyssynchrony was more prevalent compared with ventricular sensing. (2) LA phasic volumes were significantly increased during ventricular pacing than sensing. (3) Peak systolic velocity and peak early diastolic velocity of LA were significantly reduced without any change of peak late diastolic velocity of LA during RV pacing in the whole group. However, acute changes were only present with abnormal diastolic function in the ventricular sensing group.

6.4.1 LV Dysfunction and Dyssynchrony after Acute RVA Pacing

RVA-based dual-chamber pacing maintains AV synchrony but does not reproduce physiologic activation of LV. Theoretically, LV asynchronous contraction and relaxation induced by acute RVA pacing can be possiblely explained by abnormal electrical activation. This study enrolled patients with preserved LVEF and found that more than half of patients developed LV systolic dyssynchrony, which was consistent with our previous results (40). In patients with sick sinus syndrome, RT3DE is sensitive to detect the deterioration of LV function and mechanical dyssynchrony (184). LV dyssynchrony and dysfunction with heart failure were present after acute RVA pacing. However, it is still controversial as to whether RVA pacing results in LV dyssynchrony leading to LV dysfunction or vice versa (38).

6.4.2 LA Volumetric Changes, Velocity and the Interaction with LV

Previous study demonstrated that there was no significant change in mechanical LA function shortly after acute RVA pacing (129). However, It was not enough to explain the acute deleterious effects of RVA pacing because several items should be concerned in that study. In our study, we found that LA dilated significantly with the changes of ventricular function instantly. TDI provided atrial tissue velocity was further illustrated that atrial passive function impaired but not active (pump) function. This may be explained that the rapid increasing diastolic filling pressure might result in atrial enlargement. However, the remodeling of LA might be reversible if myocardial contractility was not involved in long-term observation.

In our study, we analyzed atrial velocities in patients with or without diastolic dysfunction during normal electrical activation (V-sense). Interestingly, these patients with normal diastolic function showed no significant change in Sm-la, Em-la and Am-la whereas those with abnormal diastolic function, Sm-la and Em-la decreased. Previous study also demonstrated that e' was lower in V-pace than V-sense. The mitral annular late diastolic velocity increased as a result of increased LV filling pressure and atrial compensatory contraction (35). Our study also found increased Am-la developed in 42.6% of patient.

6.5 Limitations

This cross-sectional study enrolled patients that had received RVA pacing for more

than 4 years. The pacing period might be the confounding factor of LA dilatation and dysfunction in patients with or without preexisting diastolic dysfunction. However, the passive function of LA decreased significantly during ventricular pacing in patients with abnormal LV diastolic function. Our study indicated that diastolic function should be assessed before RVA pacing. In theory, the assessment of LA volume by using RT3DE is more accurate than by two-dimensional echocardiography. However, it is difficult to perform in atrium with thin walls. The area-length method for assessing LA volume has its limitations in particular in large LA.

6.6 Conclusions

RVA pacing acutely induced LA dilatation and impaired passive atrial function but did not directly affect active atrial contractility. Patients with preexisting diastolic dysfunction are more vulnerable to develop LA dysfunction.

CHAPTER 7 LEFT ATRIAL REMODELING AND REDUCED ATRIAL PUMP FUNCTION AFTER CHRONIC RIGHT VENTRICULAR APICAL PACING IN PATIENTS WITH PRESERVED EJECTION FRACTION

7.1 Background

RVA pacing has been an effective treatment for patients with symptomatic bradycardia caused by sinus node dysfunction or atrioventricular block (11). However, large clinical trials and studies suggest that chronic RVA pacing is associated with a deleterious effect on LV systolic function and the development of LV dyssynchrony in patients with heart failure (22,46,133). In the Mode Selection Trial (MOST), a modest amount of ventricular pacing has been shown to increase the risk of heart failure hospitalization and prevalence of AF (22). Furthermore, a recent prospective, randomized, multicenter clinical trial demonstrated that RVA pacing resulted in adverse LV remodeling and impaired ejection fraction in patients with normal ejection fraction in comparison with biventricular pacing (24). This is probably a consequence of the disturbed electrical activation sequence with RVA pacing that leads to ventricular dyssynchrony, comparable to left bundle branch block.

Despite the observation that RVA affects LV systolic function adversely, it is not known whether this may also have an impact on LA function. Impairment of LV systolic function might increase LV filling and hence LA pressures (185).

Furthermore, a decline of LA function and atrial remodeling may be an important factor in the increased incidence of atrial arrhythmias in patients who have received RVA pacing (186). Therefore, the objective of the present study was to examine if RVA pacing might have deleterious effects on atrial function. To accurately assess atrial function, segmental atrial velocities were assessed by TDI in addition to the measurement of atrial volumes.

7.2 Methods

7.2.1 Patients

Patients with advanced atrioventricular block or sinus node disease who were candidates for dual-chamber pacemakers implantation were prospectively enrolled into this study. During device implantation, the RA lead was positioned into the RA appendage and the RV lead was positioned into the RV apex. The exclusion criteria included history of persistent AF and LVEF < 45%. Patients were also excluded from the study if they had were planning to receive single chamber pacemaker that paced only the right atrium or right ventricle, or they had a ventricular lead placed at locations rather than the RV apex, e.g., in the RV outflow tract. Patients were followed up on a regular basis and echocardiography was performed at baseline and one year follow up. The study was approved by the Ethical Committee of the institution and written informed consents were obtained from all patients.

7.2.2 Echocardiography

Patients enrolled into the study had echocardiography, ECG, 6-minute walk test, questionnaires and blood tests at baseline and one year follow up. Conventional echocardiography and color TDI were performed with a commercially available ultrasound machine (Vivid7, General Electric) by experienced echocardiographers. To assess LV volumes and LVEF, RT3DE was performed (iE33, Philips, Andover, MA, USA). Echocardiographic parameters were measured offline with the use of dedicated software (EchoPac PC, version 108.1.5, General Electric) apart from LV volumes and LVEF (Qlab, version 7.0, Philips, Andover, MA, USA). LV diastolic filling pressure index was measured by E/e', with a value of > 15 signifies elevated LV filling pressure (183,187). LV remodeling was defined by an increase of LVESV $\geq$ 15% (188). A reduction of LVEF $\geq$ 5% was considered clinically significant in this study.

LA volumes were measured with two-dimensional echocardiographic images by area-length method from apical four- and two-chamber views as recommended by American Society of Echocardiography (56). The maximal length of LA was measured in end-systole in an apical four-chamber view. LAVmax was measured at the end-systole and LAVmin was measured at the end-diastole on ECG. LAVpre was measured at the onset of P wave on ECG. Indexes of LA volumes for body surface area were calculated as well. LA emptying fractions were calculated as follows: (a) LA passive emptying fraction, defined as (LAVmax - LAVpre) / LAVmax × 100%; (b) LA active emptying fraction, defined as (LAVpre - LAVmin) / LAVpre × 100%;

(c) LA total emptying fraction by volume, defined as (LAVmax - LAVmin) / LAVmax × 100%. Mean Sm-la, peak Em-la and Am-la velocities of four mid-portions of LA walls were measured by color TDI at apical four- and two-chamber views with a sample area of 6 × 2 mm (Figure 7.1). At one year follow up, echocardiography was performed following the same standard protocol as baseline. All parameters were analyzed by the same reader.

7.2.3 Statistics

Values were expressed as mean ± SD. Continuous variables between baseline and one year follow up were analyzed by a two-sided paired Student's t-test. Differences in the prevalence between subgroups were compared via Chi-square test. Univariate analysis was used to test the association of clinical factors and reduction of active atrial pump function after chronic RVA pacing. Backward stepwise (Likelihood Ratio) regression was run to test the predictors of impairment of active atrial pump function. A p value < 0.05 was considered significant. Statistical analysis was performed using SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA).

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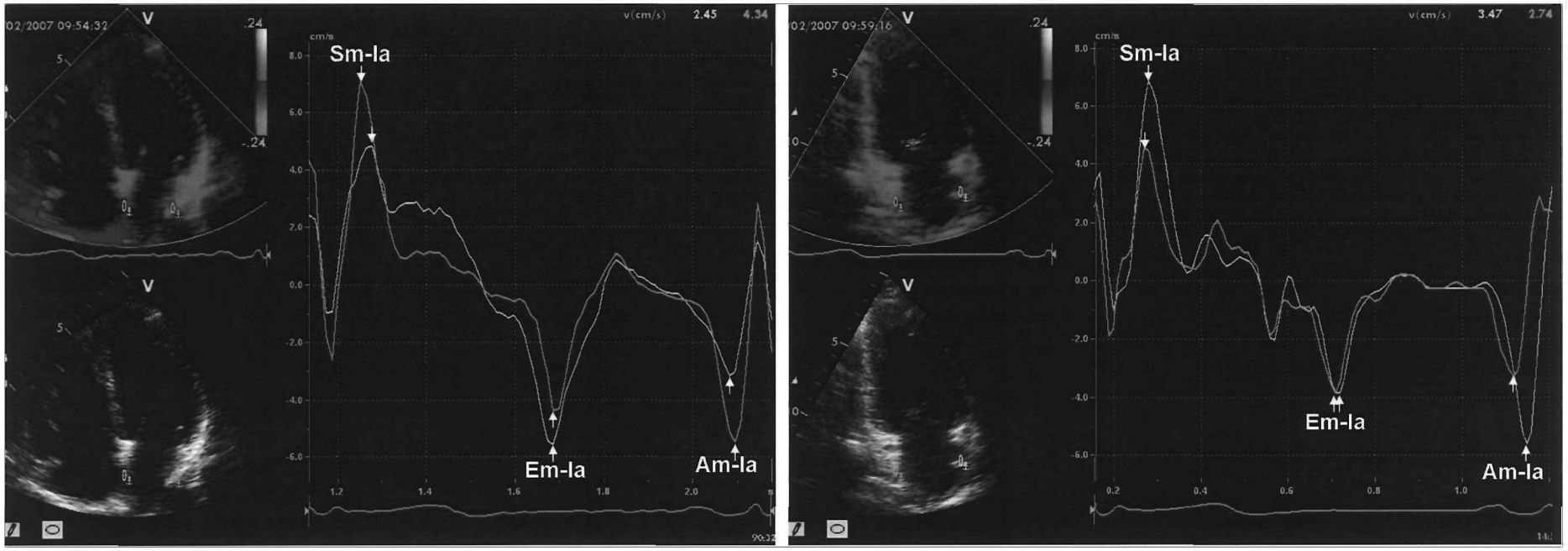

Figure 7.1 Measurement of tissue velocities of left atrium (LA) in apical 4-chamber (A) and apical 2-chamber (B) views. A sample area of 6 × 2 mm was placed in the mid-level of left atrial walls. The peak systolic (Sm-la), early diastolic (Em-la) and late diastolic (Am-la) velocities were measured.

7.3 Results

One patient died before one year visit and was excluded from the study. A total of 103 patients (mean age 70 ± 11 years; 53 men) met the criteria for entry into the study and completed one year follow up. The mean cumulative percentage of RV pacing was 79%. The baseline clinical characteristics are summarized in Table 7.1.

Table 7.1 Baseline clinical characteristics of the study population (n = 103)

Variable	
Age, years	70 ± 11
Male, n (%)	53 (51.5)
Systolic blood pressure, mmHg	142.1 ± 22.4
Diastolic blood pressure, mmHg	69.9 ± 12.7
Heart rate, bpm	61.1 ± 18.3
Body mass index, kg / m^2	23.8 ± 3.8
Medical history	
Hypertension, n (%)	68 (66.0)
Hyperlipidaemia, n (%)	27 (26.2)
Diabetes mellitus, n (%)	32 (31.1)
Heart failure, n (%)	15 (14.6)
Stroke/Transient ischemic attack, n (%)	4 (3.9)
Paroxysmal atrial fibrillation, n (%)	16 (15.5)
Coronary artery disease, n (%)	26 (25.2)
Chronic renal failure, n (%)	4 (3.9)

7.3.1 LV Systolic Function and Filling Pressure

Patients had higher heart rate at one year when compared with baseline (61.1 ± 18.3 vs. 72.3 ± 11.2 bpm, $p < 0.001$). Two-dimensional Simpson's biplane method was used in 11 patients to assess LV volumes and LVEF because the RT3DE images were inadequate. LVEDV and LVESV increased significantly while LVEF decreased at one year ($p < 0.001$) (Table 7.2). LV remodeling with increase in LVESV $\geq$ 15% was observed in 53% of patients while reduction of LVEF $\geq$ 5% was observed in 51% of patients. Twelve patients (11.7%) had an ejection fraction decreased to < 45% at one year after RVA pacing. LV filling pressure index, E/e', increased significantly at one year when compared with baseline ($p = 0.005$) (Table 7.2). Elevation of E/e' > 15 was observed in 35% of patients at one year.

7.3.2 LA Phasic Volumes and Emptying Fraction

As shown in Table 7.2, LAVpre and LAVmin as well as their indexes were significantly increased (all $p < 0.05$) with reduction in passive emptying fraction and total emptying fraction (both $p = 0.01$). LAVmax slightly increased but this was not significant (61.0 ± 21.8 vs. 63.2 ± 23.0 ml, $p = 0.202$). There was no significant difference in active emptying fraction between baseline and one year. There were 64 (62%) patients with LA dilatation at baseline by using indexed LA volume of 32 ml/m^2 as the cut-off value (92,93).

Table 7.2 Comparison of LV and LA functional parameters between baseline and one year in the whole group (n = 103)

Variable	Baseline	One year	p value
LV systolic function			
LVEDV, ml	71.1 ± 19.9	74.9 ± 24.9	0.015
LVESV, ml	27.8 ± 11.0	34.0 ± 18.4	< 0.001
LVEF, %	61.7 ± 7.1	56.4 ± 9.4	< 0.001
LV E/e'	12.3 ± 5.1	14.3 ± 7.2	0.005
LV diastolic function (normal), n (%)	35 (34.0)	10 (9.7)	< 0.001
Left atrial function			
LAVmax, ml	61.0 ± 21.8	63.2 ± 23.0	0.202
LAVmax index, ml/m^2	38.4 ± 13.7	39.3 ± 14.2	0.438
LAVpre, ml	46.1 ± 18.7	50.1 ± 21.1	0.005
LAVpre index, ml/m^2	28.9 ± 11.4	31.1 ± 12.7	0.019
LAVmin, ml	35.4 ± 17.0	39.3 ± 20.1	0.013
LAVmin index, ml/m^2	22.2 ± 10.4	24.4 ± 12.5	0.031
LA passive emptying fraction by volume, %	25.4 ± 12.9	21.7 ± 11.5	0.010
LA active emptying fraction by volume, %	24.2 ± 12.2	23.3 ± 14.8	0.659
LA total emptying fraction by volume, %	43.7 ± 12.2	40.0 ± 14.0	0.014
Mean LA velocities by TDI			
Sm-la, cm/s	5.8 ± 1.3	4.1 ± 1.2	< 0.001
Em-la, cm/s	5.1 ± 2.5	3.3 ± 1.3	< 0.001
Am-la, cm/s	6.5 ± 1.9	5.5 ± 1.9	< 0.001

Am-la, peak late diastolic velocity of left atrium; E/e', ratio of transmitral early diastolic filling velocity to the mitral septal annulus velocity by tissue Doppler imaging; Em-la, peak early diastolic velocity of left atrium; LA, left atrial; LAVmax, maximal left atrial volume; LAVmin, minimal left atrial volume; LAVpre, pre-atrial contraction volume of left atrium; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; Sm-la, peak systolic velocity of left atrium; TDI, tissue Doppler imaging.

7.3.3 LA Velocities Measured by TDI

TDI analysis showed significant reduction in Sm-la, Em-la and Am-la (all $p < 0.001$) when compared with baseline (Figure 7.2). The mean values of velocities were decreased by 28.2% for Sm-la, 25.7% for Em-la and 12.7% for Am-la after chronic RVA pacing. In this study, a reduction of Am-la > 30% was used to define significant decline in active atrial pump function. This occurred in 24% of patients. When the same cut-off value, reduction of active atrial pump function was found in 34.0% of patients who had a reduction of LVEF $\geq$ 5% when compared to only 14.3% in those without such a reduction ($\chi^2 = 5.140$, $p = 0.023$) (Figure 7.3). Furthermore, reduction of active atrial pump function was observed in 32.7% of patients who had an increase in LVESV $\geq$ 15% when compared with 14.9% in those without ($\chi^2 = 4.153$, $p = 0.042$). The reduction of Am-la > 30% was observed in 44.1% of patients who had E/e' > 15 at one year when compared with only 11.7% who had E/e' $\leq$ 15 ($\chi^2 = 12.75$, $p < 0.001$) (Figure 7.3).

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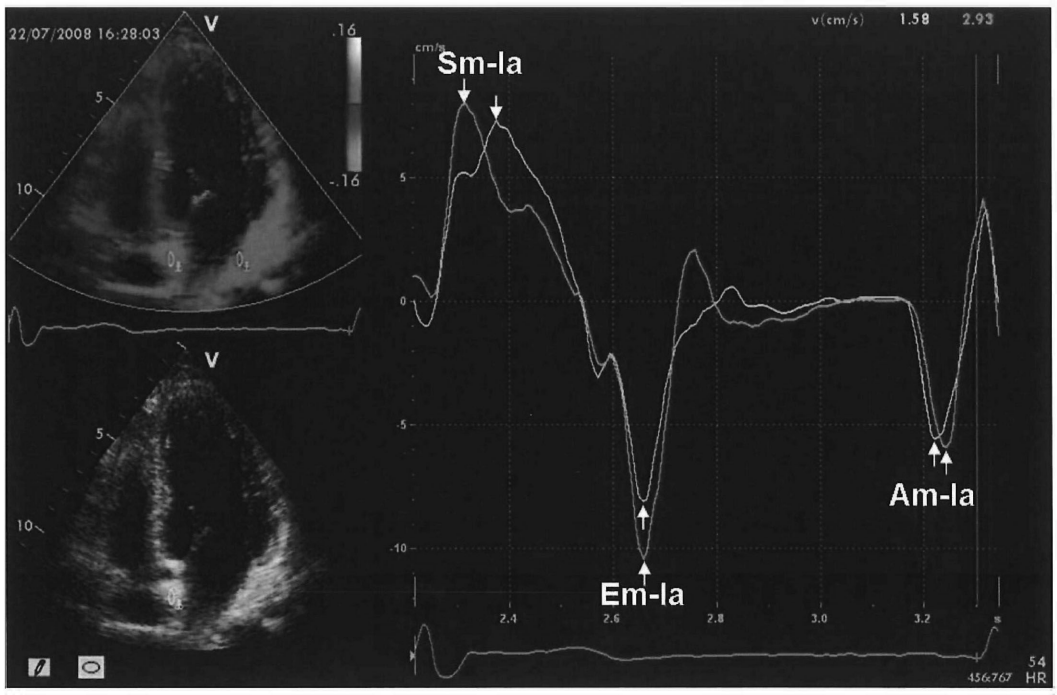

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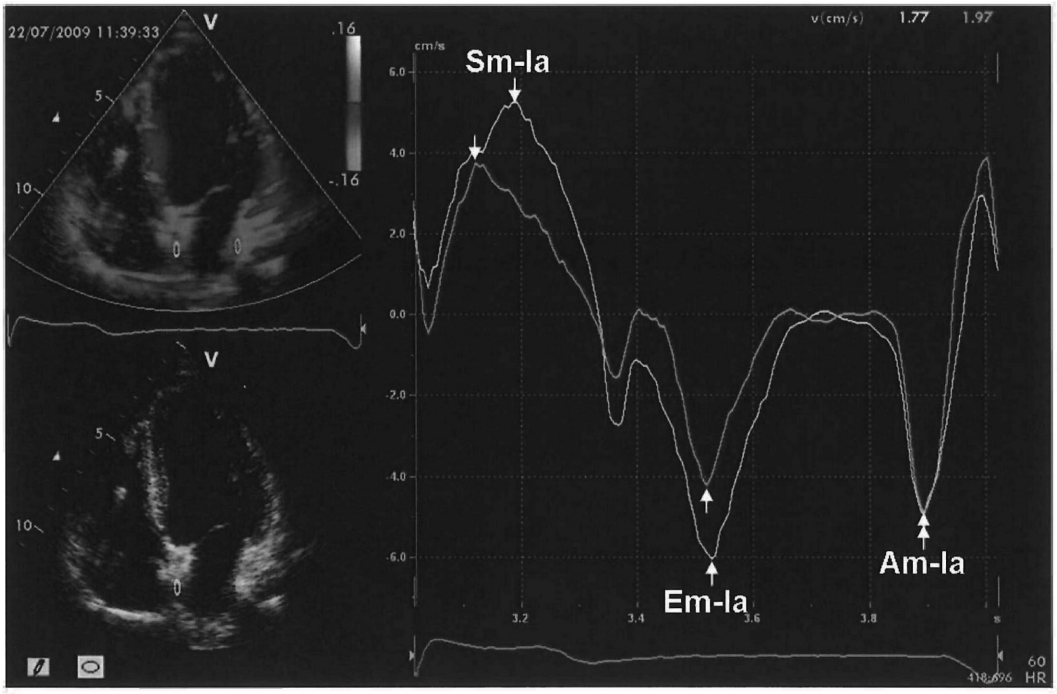


Figure 7.2 A patient with reduction of atrial velocities after received right ventricular apical pacing for one year. The apical 4-chamber view shows comparing baseline (A) and one year (B).

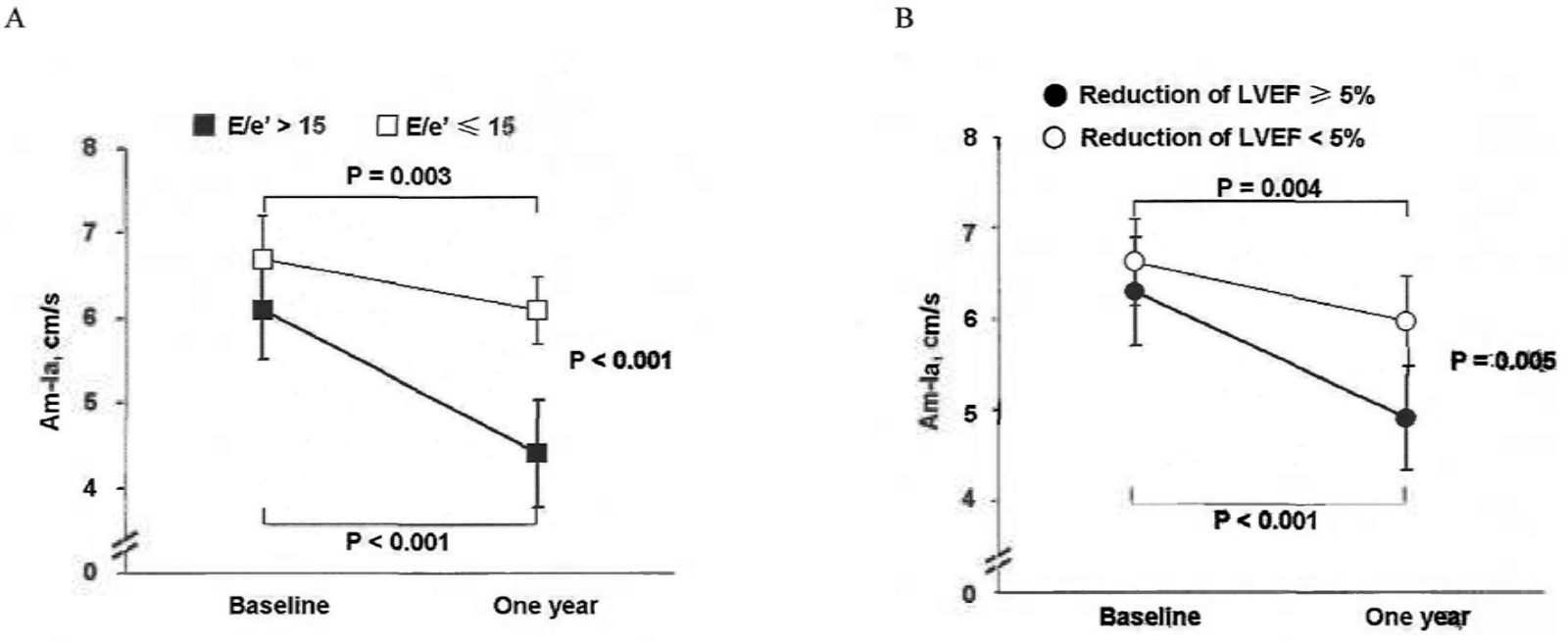


Figure 7.3 Comparison of mean peak late diastolic velocity of left atrium (Am-la) between baseline and one year for patients with and without elevation of left ventricular filling pressure as reflected by the ratio of transmitral early diastolic filling velocity to the mitral septal annulus velocity by pulse tissue Doppler imaging (E/e') > 15 (A), and patients with and without reduction of left ventricular ejection fraction (LVEF) ≥ 5% (B). The values are means and 95% CI bars.

7.3.4 Univariate and Multivariate Logistic Analysis of Reduction of Active Atrial Pump Function Using Am-la > 30%

To examine for predictors of reduction of Am-la > 30%, factors including age, gender, heart rate, medical illnesses, presence of LA enlargement, E/e' > 15 at one year, increase of LVESV $\geq$ 15% and reduction of LVEF $\geq$ 5% were entered into an univariate model. As shown in Table 7.3, E/e' > 15 at one year, reduction of LVEF $\geq$ 5% and increase of LVESV $\geq$ 15% were associated with reduction of Am-la > 30% (all $p < 0.05$). The values of Am-la were significantly lower in patients who possessed these factors (Table 7.4). By multivariate regression analysis, it was found that E/e' > 15 at one year and reduction of LVEF $\geq$ 5% were independent predictors for the deterioration of active atrial pump function (Table 7.3). Patients with E/e' > 15 at one year had a five-fold risk while those with reduction of LVEF $\geq$ 5% had a three-fold risk of significant reduction of LA active pump function.

Table 7.3 Univariate and multivariate analysis for prediction of atrial pump dysfunction defined as a reduction of Am-la > 30%

	Univariate		Multivariate	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Age	1.035 (0.988 - 1.084)	0.148	-	-
Gender	1.121 (0.439 - 2.865)	0.811	-	-
Heart rate	1.014 (0.989 - 1.040)	0.272	-	-
Hypertension	2.966 (0.911 - 9.657)	0.071	2.368 (0.640 - 8.764)	0.197
Diabetes Mellitus	0.720 (0.251 - 2.069)	0.542	-	-
Heart failure	1.516 (0.415 - 5.541)	0.529	-	-
Paroxysmal AF	0.583 (0.112 - 3.049)	0.523	-	-
Coronary artery disease	0.515 (0.156 - 1.699)	0.276	-	-
LAVmax index $\geq$ 32 ml/m^2	1.867 (0.659 - 5.294)	0.240	-	-
E/e' > 15 at one year	5.977 (2.115 - 16.895)	0.001	5.213 (1.778 - 15.281)	0.003
ΔLVESV $\geq$ 15%	2.771 (1.019 - 7.536)	0.046	1.547 (0.434 - 5.519)	0.501
ΔLVEF $\geq$ 5%	3.097 (1.137 - 8.436)	0.027	3.181 (1.045 - 9.686)	0.042

AF, atrial fibrillation; Am-la, peak late diastolic velocity of left atrium; CI, confidence interval; E/e', ratio of transmitral early diastolic filling velocity to the mitral septal annulus velocity by pulse tissue Doppler imaging; ΔESV, change of left ventricular end-systolic volume. LAVmax, maximal left atrial volume; LV, left ventricular/ left ventricle; ΔLVEF, change of left ventricular ejection fraction; OR, odds ratio.

Table 7.4 Comparison of mean Am-la for the presence of specific conditions

Variable	No	Yes	p value
Hypertension	6.0 ± 1.5	5.2 ± 2.1	0.081
E/e' > 15	6.2 ± 1.6	4.4 ± 1.9	< 0.001
ΔLVESV ≥ 15%	5.9 ± 1.8	5.1 ± 2.0	0.026
ΔLVEF ≥ 5%	6.0 ± 1.8	4.9 ± 2.0	0.005

Am-la, peak late diastolic velocity of left atrium; E/e', ratio of transmitral early diastolic filling velocity to the mitral septal annulus velocity by pulse tissue Doppler imaging; ΔESV, change of left ventricular end-systolic volume. ΔLVEF, change of left ventricular ejection fraction.

7.4 Discussion

This study of a large prospective cohort has shown that in patients who have received RVA pacing after one year there was evidence of LA remodeling with increased LA volumes measured just before and after completion of active atrial contraction. Furthermore, active atrial pump function per se was impaired, as evidenced by the atrial velocity derived from TDI. Factors that predict the significant deterioration of atrial pump function after RVA pacing included patients who had elevated E/e' > 15 at one year and a reduction of LVEF $\geq$ 5%.

7.4.1 LA Adverse Remodeling after RVA Pacing

LA function is complex and its mechanical function includes three components during the cardiac cycle: reservoir, conduit and a contractile function (67). LA enlargement is an established prognostic factor for the development of AF following myocardial infarction and heart failure (71,186,189). In addition, active atrial pump function contributes significantly towards overall cardiac output and atrial systolic failure is an important and early feature of heart failure even in those with normal ejection fraction, in particular on exercise (190). Deteriorating active atrial pump function may be an important contributor to symptoms of breathlessness in heart failure (190). It has been shown that two-dimensional echocardiography derived LA volumes give a more accurate measurement of LA size than M-mode which measures antero-posterior linear atrial dimension (95). A large retrospective study found that a LA volume index $\geq$ 32 ml/m^2 has incremental value to age and clinical

risk factors for the prediction of first ischemic stroke in patients with no prior AF (92).

In our study, we used area-length method by two-dimensional echocardiography to assess LA phasic volumes in apical four-chamber and two-chamber views. We observed that the pre-atrial contraction volume and the minimal volume after atrial contraction were significantly increased. A previous acute study showed that LA size and function did not change with short-term RVA pacing for 4 h (129). This might be related to the small sample size of that study (n = 38), and the fact that the sustained deleterious effect on atrial dysfunction may take time to develop. This underscores the importance of performing prospective studies of longer follow up duration.

We observed that the maximal volume of LA as well as active emptying fraction did not change significantly. This might be related to the relatively short period of follow up in which impairment of atrial pump function will be manifested earlier before any chronic pressure or volume overload might have exerted its effect on atrial remodeling. Another possible explanation is that the LA volumes may be underestimated by two-dimensional echocardiography because the atrium expands asymmetrically (96). Of note, we have observed that preexisting LA enlargement does not determine the occurrence of atrial dysfunction and remodeling after RVA pacing.

7.4.2 Reduction of Atrial Pump Function after RVA Pacing

Although a number of studies have used TDI to assess atrial function, there is no consensus about the cut-off value for reduced active atrial pump function. In this study we used a reduction of Am-la > 30% to be a marker of significant atrial dysfunction but this is of necessity rather than arbitrary. We have observed that patients who had a reduction of LVEF ≥ 5% had a three-fold risk of developing LA pump dysfunction. This might be related to the common mechanism of RVA pacing induced systolic dysfunction such as systolic dyssynchrony (40,191). However, the impairment of LV function cannot be totally accounted for by the abnormal activation sequence as myocardial perfusion defects were observed by thallium-201 exercise myocardial scintigraphy and N-labeled ammonia positron emission tomography imaging in long-term RVA pacing (29,31). Previous studies have shown that RVA pacing had deleterious effects on LV function in short- or long-term follow up, which was even worse in those with patients with preexisting LV systolic dysfunction (22,24,40,46,133). Our result is in accordance with the improvement of atrial function and reverse remodeling after CRT for heart failure in those who have a LV reverse remodeling volumetric response (189,192).

Our study also observed that patients who had elevated filling pressure after long-term RVA pacing as reflected by E/e' > 15 had a five-fold risk of developing atrial active pump dysfunction. This is probably explained by the deleterious effect of raised LV filling pressure resulting in atrial pressure and volume overload as well

as reduction of atrial wall compliance as a result of stretching-induced atrial fibrotic changes (193,194). A reduction of Sm-la and Em-la velocities will also reflect compliance changes probably due to fibrotic changes (195) and this may be part of the deleterious process following RVA pacing. A previous study has also reported that in patients with coronary heart disease and LV diastolic dysfunction, TDI showed reduction of Am-la even in those with abnormal relaxation pattern with apparently augmented transmitral atrial velocity (120).

7.4.3 Study Limitations

In this study, atrial volume was assessed by biplane method from two-dimensional echocardiographic images. RT3DE has been recently reported to be useful for such purpose, though technical challenges remain in the thin-walled LA structure (107,196). Another evolving echocardiographic method for assessment of atrial function is two-dimensional speckle tracking, though the same limitation applies (197).

7.5 Conclusions

This prospective study has demonstrated that chronic RVA pacing results in LA remodeling and reduces atrial pump function. The risk is particularly high in those with $E/e' > 15$ and reduction of LVEF $\geq 5\%$. Further studies on whether other modalities of pacing, such as RV septal pacing or biventricular pacing, will reduce the adverse impact on LA function are warranted.

7.6 Acknowledgements

This study was supported by a research grant from Research Grants Council of Hong Kong (CERG 4485/05M).

CHAPTER 8 ATRIAL DYSFUNCTION AND INTERATRIAL DYSSYNCHRONY PREDICT ATRIAL HIGH RATE EPISODES BURDEN: INSIGHT INTO THE SEPARATE EFFECTS OF RIGHT ATRIAL APPENDAGE PACING

8.1 Background

RVA pacing can lead to both ventricular dysfunction and an increased risk of AF. A long-term, prospective study, the MOde Selection Trial demonstrated a 2.6-fold increased risk of heart failure hospitalization when Cum%VP was > 40%. The risk of AF increased by 1% for each 1% increase in Cum%VP up to 85% in DDDR similar to VVIR pacing in patients with sinus node dysfunction (22). However, the incidence of heart failure and AF after RVA pacing might not be totally explained by high Cum%VP alone. A retrospective study found that RA appendage pacing was also significantly associated with AF incidence after CRT (198). However, the separate effects of RA appendage pacing on atrial electrical and mechanical properties are not well known. This might play an additional role in atrial arrhythmogenesis.

It is now established that AHREs correlate highly with AF or atrial flutter, especially when AHREs > 5minutes in duration (137,142-144,199). Thus, AHREs are considered to be a reliable indicator and precursor of AF. Therefore, the current prospective study was conducted to investigate if RA appendage pacing has separate effects on atrial pump function, intra- and interatrial dyssynchrony, and to investigate if atrial dysfunction and dyssynchrony can predict AHREs burden in the first year.

8.2 Methods

8.2.1 Patients

This study prospectively enrolled patients who received a dual chamber pacemaker because of symptomatic bradycardia due to atrioventricular block or sinus node disease. The RV lead was placed in the RV apex and RA lead was placed in the RA appendage. All pacemakers were programmed to RVA-based DDDR mode. An atrial sensitivity of 0.5 mV of a bipolar atrial lead was programmed and automatic mode switch to DDIR pacing was activated when atrial rate exceeded 150 bpm. The tip-to-ring distance of the implanted atrial lead was between 10-12 mm depending on the vendors. Patients who had heart failure with LV ejection fraction < 45% at baseline or had history of permanent AF, had valvular heart disease underwent valvuloplasty or replacement, had biventricular pacing or single-chamber pacing before implantation were excluded. The local Institutional Ethics approved the study and informed written consent was obtained from all patients.

8.2.2 Initial Interrogation and Assessment of AHREs Burden

Interrogation of pacemakers (pacemaker model: Medtronic InSync III 8042) in the study was conducted in the standard manner during follow up. The function of event counters provided information on the cumulative percent atrial pacing and ventricular pacing and the frequency of premature atrial or ventricular contractions. The reports were collected at 1, 3, 6, 9, and 12 months follow up. AHREs burden

was defined as any atrial high rate episode lasting more than 5 minutes with atrial rate $\geq$ 220 bpm during the previous one year (143). The recurrence of AHREs which occurred in some patients during follow up was not double counted. All patients had a 12-lead ECG and Holter monitoring at baseline and follow up.

8.2.3 Echocardiography

Echocardiography including TDI was performed at baseline before implantation and at one year follow up after pacing with commercially available equipments (Vivid 7 or E9, General Electric Vingmed Ultrasound AS, Horten, Norway). Images of consecutive five cardiac cycles were stored by experienced echocardiographers. Gain setting was adjusted to optimize color saturation and avoid too much noise in cardiac images. The cine loop of images was recorded at high frame rate in both two-dimensional (> 50 fps) and tissue Doppler (> 100 fps) echocardiography. Dedicated software (EchoPac PC, version 108.1.5, General Electric Vingmed Ultrasound AS) was used for offline analysis. LVEDV, LVESV and ejection fraction were measured with two-dimensional echocardiography by Biplane Simpson's method before pacemaker implantation. LA volume was measured at end-systole using area-length method as recommended by American Society of Echocardiography in apical four- and two-chamber views (56). Indexed LA was calculated.

LA myocardial velocity and ACT were measured from color tissue Doppler image at

one year follow up. Mean values of peak velocities in four mid-portions of LA: Sm-la, Em-la and Am-la were obtained in apical four- and two-chamber views. ACT was measured from onset of P wave on ECG to onset of Am-la in IAS, LA lateral, LA anterior, LA inferior walls. They were P-IAS, P-LA, P-ALA, and PILA respectively. RA velocities in three phases (Sm-ra, Em-ra, and Am-ra) and ACT were also measured in mid segment of RA free wall (P-RA) in apical four chamber view from the velocity–time curve. RA dyssynchrony was defined as the difference between P-RA and P-IAS. Interatrial dyssynchrony was defined as the difference between P-RA and P-LA (200). LA dyssynchrony was calculated by the standard deviation of P-IAS, PLA, PALA and PILA of LA walls. An example of the measurements is shown in Figure 8.1.

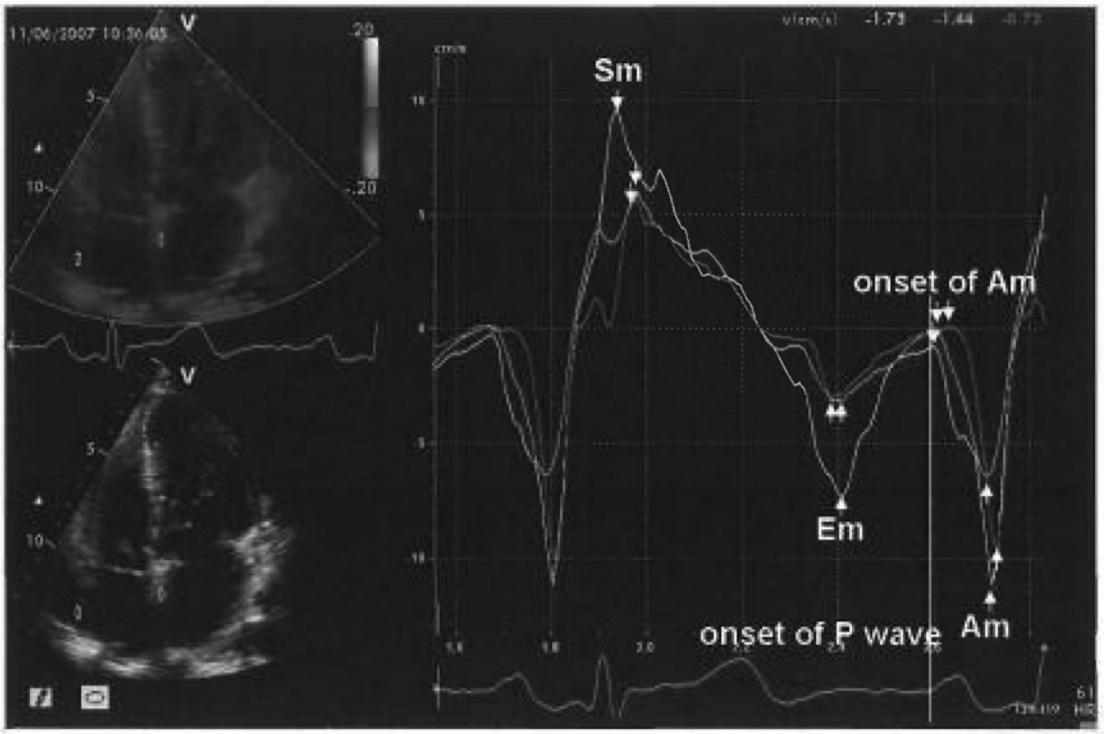


Figure 8.1 An example of the measurements. In apical four-chamber view, peak systolic velocity (Sm), early diastolic velocity (Em) and late diastolic velocity (Am) were measured in right atrial free wall, interatrial septum and left atrial lateral wall. Atrial conduction time was measured from onset of P wave on ECG to onset of Am.

8.2.4 Statistics

All variables were expressed as mean ± SD or numbers and percentages. Comparison between two groups was performed with independent-samples t-test or Chi-square test. One-Way ANOVA was used in multiple comparisons. Univariate and multivariate analysis were used to test the association between atrial velocities, atrial dyssynchrony and AHREs burden. ROC curves were derived to give the cut-off values for prediction of AHREs burden. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, Illinois, USA).

8.3 Results

A total of 110 patients (age 70.5 ± 11.1 years; 53 males) completed regular follow up during the first year of RVA pacing. The mean Cum%VP and cumulative percentage of RA pacing (Cum%AP) were 79% and 42% respectively.

8.3.1 AHREs Burden during the First Year of Pacemaker Implantation

During 1 year follow up, there was no AF episodes documented by 12-lead ECG or Holter monitoring. Seventy-nine (71.8%) patients had pacing beats on ECG. There were 32 (29%) patients who had one or more AHREs lasting more than 5 minutes with atrial rate $\geq$ 220 bpm. The occurrence of AHREs in 1, 3, 6, 9 and 12 months were 19%, 19%, 20%, 17% and 16%, respectively. Seventeen (15%) patients had AHREs more than four time points during one-year follow up. The longest AHRE

lasted 96 hours with atrial rate exceeding 400 bpm. The baseline characteristics of patients with or without AHREs burden are summarized in Table 8.1.

There was no significant difference in Cum%VP in patients with or without AHREs (68.2 ± 40.9% vs.83.8 ± 32.9%, $p = 0.060$) at one year follow up. The majority of patients (75%) developing AHREs had sinus node disease and without had atrioventricular block (63%). Patients with history of AF and heart failure (LV ejection fraction > 45%) were more vulnerable to developing AHREs ($p < 0.001$ and $p = 0.001$, respectively). LVEDV, LVESV and ejection fraction were similar in both groups at baseline (Table 8.1). However, indexed LA volume in patients developing AHREs was slightly larger at baseline, but there were no significant difference in changes at one year follow up in both groups (AHREs: 44.4 ± 16.9 vs. 46.1 ± 16.3 ml/m^2, $p = 0.333$; no AHREs: 37.2 ± 11.8 vs.36.3 ± 10.8 ml/m^2, $p = 0.501$). A similar trend was seen with the whole group (39.1 ± 13.4 vs. 39.1 ± 13.3 ml/m^2, $p = 0.995$).

The prolongation of ACT mostly developed in the LA walls (all $p < 0.05$) (Table 8.2). The LA dyssynchrony and interatrial dyssynchrony were greater in patients with AHREs burden than those without (LA dyssynchrony, 21.5 ± 15.4 vs. 12.0 ± 7.9 ms, $p = 0.002$; interatrial dyssynchrony, 43.8 ± 30.5 vs. 28.6 ± 21.5 ms, $p = 0.013$) but not RA dyssynchrony. LA reservoir function as reflected by Sm-la and atrial pump function as reflected by Am-la appeared lower.

8.3.2 RA Appendage Pacing on Atrial Velocities and Intra- and Interatrial Dyssynchrony

To determine if RA appendage pacing has separate effects on atrial function and dyssynchrony, high Cum%AP more than 75% (Cum%AP > 75) (n=27) over one year were compared to those with low Cum%AP less than 25% (Cum%AP < 25%) (n=43) according to the interquartile range of distribution.

The baseline characteristics of patients with Cum%AP > 75% and Cum%AP < 25% are also summarized in Table 8.1. There was no significant difference in either Cum%VP or history. Indexed LA volume was larger in patients with Cum%AP > 75% than Cum%AP < 25% (46.6 ± 17.7 vs. 36.4 ± 12.1 ml/m^2, $p < 0.001$) before pacemakers implantation. However, there was no significant difference in indexed LA volume between baseline and one-year follow up (both $p > 0.05$).

Atrial velocities of Sm-la, Em-la and Am-la in patients with Cum%AP > 75% were significantly lower than Cum%AP < 25% (all $p < 0.05$). It also showed that ACT was delayed significantly and RA dyssynchrony, LA dyssynchrony and interatrial dyssynchrony were greater in the group of Cum%AP > 75% in each atrial wall in comparison with Cum%AP < 25% (Table 8.2). With increasing the quartiles of Cum%AP, Am-la decreased and interatrial dyssynchrony increased in a stepwise fashion ($p = 0.009$ and $p < 0.001$ between groups) (Figure 8.2). The prevalence of AHREs was greater in patients with Cum%AP > 75% compared with those without

(44.4% vs. 24.1%, $p = 0.043$). However, there was no significant difference between Cum%AP > 75% and Cum%AP < 25% (44.4% vs. 25.6%, $p = 0.102$).

Table 8.1 Baseline characteristics for patients with and without AHREs burden and patients with Cum%AP > 75% and Cum%AP < 25%

	AHREs			Cum%AP		
	yes (n = 32)	**no (n = 78)**	**p value**	**> 75% (n = 27)**	**< 25% (n = 43)**	**p value**
Age, years	71.4 ± 10.2	70.1 ± 11.6	0.569	72.9 ± 8.5	67.9 ± 13.7	0.061
Male, n (%)	15 (46.9)	38 (48.7)	0.861	9 (33.3)	26 (60.5)	0.027
Body surface area, m^2	1.6 ± 0.3	1.6 ± 0.2	0.844	23.6 ± 3.6	23.5 ± 4.1	0.949
Systolic blood pressure, mmHg	141.2 ± 23.8	142.5 ± 22.2	0.788	140.2 ± 24.0	143.0 ± 22.0	0.621
Diastolic blood pressure, mmHg	71.3 ± 13.5	68.4 ± 13.4	0.347	72.2 ± 14.0	67.0 ± 12.4	0.108
Heart rate, bpm	68.8 ± 21.5	57.7 ± 16.7	0.005	68.2 ± 24.0	57.9 ± 18.3	0.047
Cumulative ventricular pacing, %	68.2 ± 40.9	83.8 ± 32.9	0.060	75.8 ± 38.0	91.1 ± 24.0	0.069
Cumulative atrial pacing > 75%, n (%)	12 (37.5)	15 (19.2)	0.043	27 (100)	0	NA
Advanced AV block/ Sinus node dysfunction, n	8 / 24	49 / 29	< 0.001	3 / 24	36 / 7	< 0.001
Medical history						
Prior paroxysmal atrial fibrillation, n (%)	12 (37.5)	4 (5.1)	< 0.001	6 (22.2)	6 (14.0)	0.372
Prior heart failure, n (%)	10 (31.3)	6 (7.7)	0.001	6 (22.2)	6 (14.0)	0.372
Prior hypertension, n (%)	22 (68.8)	52 (66.7)	0.832	21 (77.8)	27 (62.8)	0.189
Prior coronary artery disease, n (%)	7 (21.9)	19 (24.4)	0.781	7 (25.9)	9 (20.9)	0.628
Prior diabetes mellitus, n (%)	9 (28.1)	23 (29.5)	0.886	7 (25.9)	13 (30.2)	0.698

Medication						
Diuretics, n (%)	6 (18.8)	11 (14.1)	0.540	6 (22.2)	4 (9.3)	0.133
Angiotensin-converting enzyme inhibitors, n (%)	11 (34.4)	13 (16.7)	0.041	9 (33.3)	8 (18.6)	0.162
Angiotensin receptor blockers, n (%)	2 (6.3)	4 (5.1)	0.814	2 (7.4)	2 (4.7)	0.629
Beta-blockers, n (%)	18 (56.3)	13 (16.7)	< 0.001	16 (59.3)	5 (11.6)	< 0.001
Alpha-blockers, n (%)	3 (9.4)	7 (9.0)	0.947	3 (11.1)	4 (9.3)	0.806
Anti-platelets, n (%)	15 (46.9)	29 (37.2)	0.346	15 (55.6)	16 (37.2)	0.133
Warfarin, n (%)	6 (18.8)	0	< 0.001	4 (14.8)	1 (2.3)	0.048
Anti-arrhythmic drugs, n (%)	15 (46.9)	12 (15.4)	< 0.001	14 (51.9)	5 (11.6)	< 0.001
Echocardiography						
LV end-diastolic volume, ml	68.8 ± 16.6	75.3 ± 19.6	0.105	69.6 ± 17.4	78.2 ± 22.3	0.093
LV end-systolic volume, ml	25.9 ± 8.6	27.0 ± 9.9	0.574	24.9 ± 9.2	29.4 ± 10.7	0.082
LV ejection fraction, %	62.7 ± 7.1	64.5 ± 7.2	0.245	64.1 ± 7.1	62.8 ± 7.6	0.477
Indexed LA volume, ml/m^2	44.4 ± 16.9	37.2 ± 11.8	0.013	46.6 ± 17.7	36.4 ± 12.1	0.006

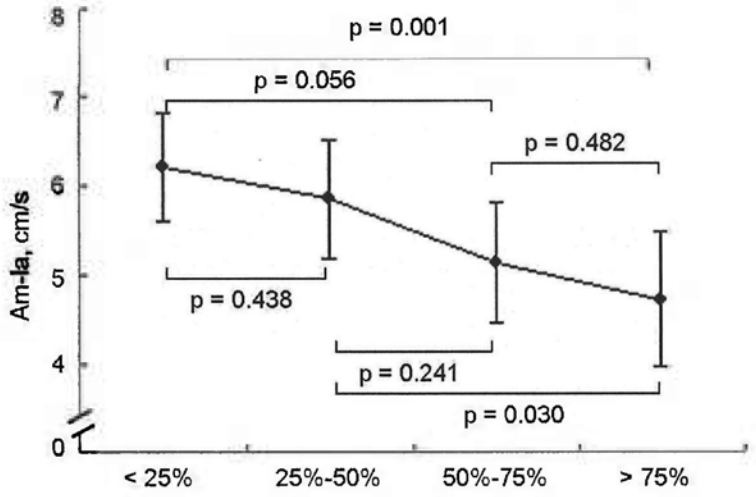
AHREs, atrial high rate episodes ; AV, atrioventricular ; Cum%AP, cumulative percentage of right atrial appendage pacing; LA, left atrial; LV, left ventricular.

Table 8.2 Atrial velocities, atrial conduction time, intra- and interatrial dyssynchrony in whole group and between subgroups

		AHREs			Cum%AP		
	Total (n = 110)	yes (n = 32)	no (n = 78)	p value	> 75% (n = 27)	< 25% (n = 43)	p value
Sm-la, cm/s	4.2 ± 1.2	3.7 ± 1.0	4.4 ± 1.3	0.004	3.8 ± 1.1	4.7 ± 1.4	0.007
Em-la, cm/s	3.3 ± 1.2	3.4 ± 1.2	3.2 ± 1.2	0.633	3.0 ± 0.7	3.6 ± 1.3	0.012
Am-la, cm/s	5.6 ± 1.9	4.1 ± 1.8	6.2 ± 1.6	< 0.001	4.7 ± 2.0	6.2 ± 2.0	0.003
P-RA, ms	49.0 ± 27.3	57.0 ± 36.2	45.7 ± 22.2	0.108	62.9 ± 36.8	44.6 ± 24.6	0.015
P-IAS, ms	53.4 ± 25.0	56.0 ± 30.0	52.3 ± 22.8	0.537	65.2 ± 27.9	49.4 ± 23.4	0.013
P-LA, ms	78.0 ± 32.2	91.0 ± 39.5	72.6 ± 27.2	0.020	104.4 ± 32.6	61.6 ± 25.1	< 0.001
P-ALA, ms	71.2 ± 31.1	81.8 ± 36.4	66.9 ± 27.9	0.023	95.6 ± 31.7	58.4 ± 24.1	< 0.001
P-ILA, ms	68.9 ± 29.2	78.2 ± 33.8	65.2 ± 26.5	0.036	84.6 ± 31.7	57.7 ± 22.3	< 0.001
RA dyssynchrony, ms	14.7 ± 15.1	19.2 ± 18.4	12.9 ± 13.3	0.050	23.4 ± 21.5	10.6 ± 10.3	0.007
LA dyssynchrony, ms	14.8 ± 11.4	21.5 ± 15.4	12.0 ± 7.9	0.002	22.3 ± 12.2	9.5 ± 6.2	< 0.001
Interatrial dyssynchrony, ms	33.0 ± 25.3	43.8 ± 30.5	28.6 ± 21.5	0.013	53.9 ± 29.7	19.7 ± 17.3	< 0.001

Am-la, peak late diastolic velocity of left atrium; AHREs, atrial high rate episodes; Cum%AP, cumulative percentage of right atrial appendage pacing; Em-la, peak early diastolic velocity of left atrium; LA, left atrial; P-ALA, atrial conduction time in left atrial anterior wall; P-IAS, atrial conduction time in interatrial septum; P-ILA, atrial conduction time in left atrial inferior wall; P-LA, atrial conduction time in left atrial lateral wall; P-RA, atrial conduction time in right atrial free wall; RA, right atrial; Sm-la, peak systolic velocity of left atrium.

A



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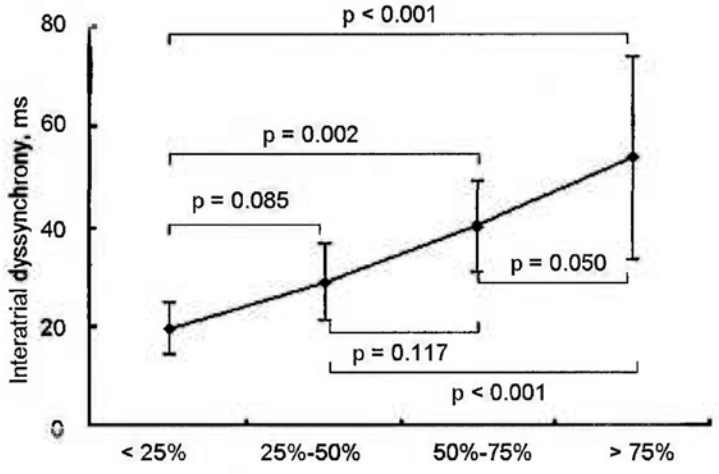

Figure 8.2 Quartiles of right atrial appendage pacing, atrial function and interatrial dyssynchrony. With increasing the quartiles of percent of right atrial appendage pacing, Am-la decreased (A) and interatrial dyssynchrony increased (B) stepwisely ($p = 0.009$ and $p < 0.001$ between groups). The comparison between each two groups is also shown.

8.3.3 The Predictive Value of Atrial Velocities and Dyssynchrony for AHREs Burden

In this study, we found that RA dyssynchrony was not associated with AHREs but LA dyssynchrony and interatrial dyssynchrony, and Sm-la, Am-la, indexed LA volume, Cum%VP as well as Cum%AP > 75% were associated with AHREs burden. In multivariate analysis, Am-la (OR 0.514, 95% CI 0.373-0.707, $p < 0.001$) and interatrial dyssynchrony (OR 1.022, 95% CI 1.000-1.043, $p = 0.048$) independently predicted AHREs burden (Table 8.3). ROC curve was generated to test the cut-off value of Am-la predicting the first year AHREs burden. When the cut-off value was 5.3 cm/s, AUC was 0.822 (95% CI 0.737-0.906), with a sensitivity of 71%, and specificity of 75%, $p < 0.001$ (Figure 8.3). AHREs burden was observed in 53.7% of patients with Am-la < 5.3cm/s but only 13.4% of those without ($\chi^2 = 20.111$, $P < 0.001$).

8.3.4 Correlations between Am-la, Dyssynchrony and RA Appendage Pacing

In the whole cohort, Am-la correlated with LA dyssynchrony ($r = -0.450$, $p < 0.001$) and interatrial dyssynchrony ($r = -0.227$, $p = 0.018$) negatively. A cut-off value of LA dyssynchrony >13.5ms predicted LA dysfunction (Am-la < 5.3 cm/s) (area under curve [AUC] 0.728, sensitivity 71%, specificity 72%, $p < 0.001$) (Figure 8.4). Interatrial dyssynchrony was correlated with Cum%AP ($r = 0.617$, $p < 0.001$) but not with Cum%VP ($r = -0.058$, $p = 0.548$).

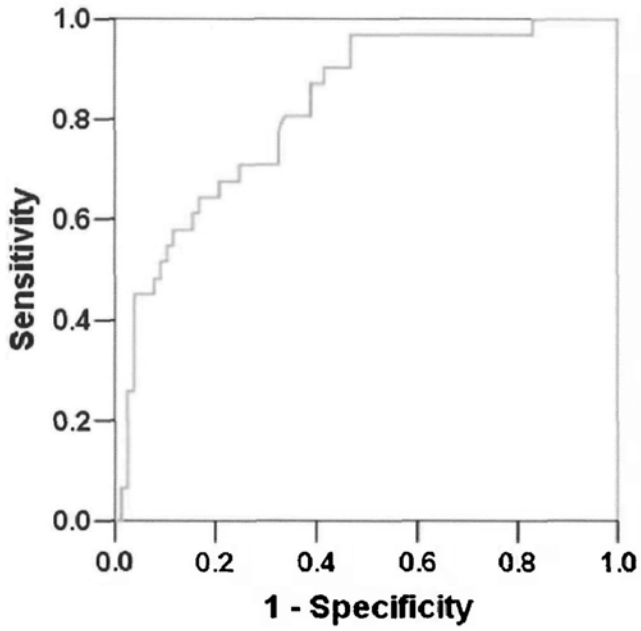

Figure 8.3 ROC curve of late diastolic velocity of left atrium (Am-la) to predict the incidence of AHREs burden. Am-la < 5.3 cm/s predicted the first year AHREs burden with sensitivity 71% and specificity 75%. ROC, receiver operating characteristic; AHREs, atrial high rate episodes.

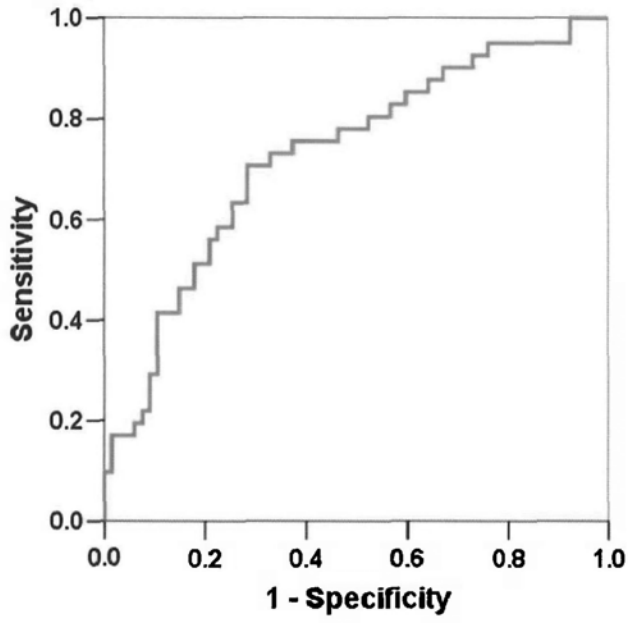

Figure 8.4 ROC curve of LA dyssynchrony to predict LA dysfunction. A cut-off value of LA dyssynchrony > 13.5 ms predicted LA dysfunction (Am-la < 5.3 cm/s) with sensitivity of 71% and specificity of 72%. ROC, receiver operating characteristic; LA, left atrial.

Table 8.3 Univariate and multivariate analysis of atrial velocities and dyssynchrony and association with AHREs burden

	Univariate		Multivariate	
	Odds Ratio (95% CI)	**p value**	**Odds Ratio (95% CI)**	**p value**
Sm-la, cm/s	0.554 (0.363-0.848)	0.006	1.234 (0.677-2.250)	0.493
Em-la, cm/s	1.090 (0.769-1.545)	0.629	-	NA
Am-la, cm/s	0.489 (0.356-0.672)	< 0.001	0.514 (0.373-0.707)	< 0.001
RA dyssynchrony, ms	1.026 (0.999-1.053)	0.059	0.999 (0.961-1.038)	0.956
LA dyssynchrony, ms	1.069 (1.019-1.121)	0.006	1.009 (0.949-1.074)	0765
Interatrial dyssynchrony, ms	1.024 (1.007-1.041)	0.006	1.022 (1.000-1.043)	0.048
Indexed LA volume, ml/m^2	1.060 (1.021-1.100)	0.002	1.026 (0.983-1.070)	0.236
Cum%AP >75%	2.520 (1.014-6.265)	0.047	0.729 (0.204-2.604)	0.626
Cum%VP, %	0.989 (0.978-1.000)	0.041	0.996 (0.983-1.010)	0.580

Am-la, peak late diastolic velocity of left atrium; AHREs, atrial high rate episodes; CI, confidence interval; Cum%AP, cumulative percentage of right atrial appendage pacing; Cum%VP, cumulative percentage of right ventricular pacing; Em-la, peak early diastolic velocity of left atrium; LA, left atrial; RA, right atrial; Sm-la, peak systolic velocity of left atrium.

8.4 Discussion

This study demonstrated that RA appendage pacing prolonged ACT and resulted in intra- and interatrial dyssynchrony separately. Atrial pump function as reflected by Am-la highly correlated with LA dyssynchrony and interatrial dyssynchrony. Both Am-la and interatrial dyssynchrony were independent predictors of the first year AHREs burden on multivariate analysis. The cut-off value of Am-la < 5.3 cm/s to predict AHREs burden had high sensitivity and specificity.

8.4.1 The Separate Effects of RA Appendage Pacing on Atrial Dysfunction and Dyssynchrony

A previous acute study showed VDD mode (RA sensed) was superior to DDD (RA paced) mode in CRT when comparing LV filling time and myocardial performance (201). Other studies have demonstrated the prolongation of ACT in patients with severe LV systolic dysfunction after CRT (202) and patients with recurring AF (203). In our study we compared two groups with comparable ventricular pacing but high and low atrial pacing and found atrial conduction delay and dyssynchrony resulting from RA appendage pacing after one year follow up. Even though there was a difference in Cum%VP in comparing groups, the patients with AHREs had lower cumulative percentage than those without AHREs. It can present that the effects of RVA pacing in this study groups were not different, which emphasize the effects of pacing at RA appendage on atrial function and atrial dyssynchrony. Atrial pump function as reflected by Am-la was correlated with LA dyssynchrony and interatrial

dyssynchrony which provides additional evidence of that atrial function can be adversely affected by RVA pacing and a high percent RA appendage pacing.

The frequent use of RA appendage pacing may enhance intra- and interatrial dyssynchrony and induce failure of atrial contractility. From our study, high atrial pacing was more prevalence in patients with sinus node diseases and associated with a subsequent high AHREs burden. It has been suggested that RVA pacing may increase the risk of AF in large clinical trials and a high percent of RA appendage pacing with atrioventricular asynchrony could not reduce the incidence of post-implantation atrial tachycardia or arrhythmias (22,132). This does not detract from the use of physiological dual chamber pacing in patients with sinus node disease comparing VVI pacing because of other hemodynamic advantages of DDD pacing in this group of patients (10). However, the percentage of RA pacing might not the direct cause of AHREs burden in the first year based on our result.

8.4.2 Atrial Dilatation, Atrial Dysfunction and Dyssynchrony

Dilatation of the LA can also lead to atrial conduction delay because of a longer pathway which electrical impulses have to travel, as was found in patients with mitral annulus calcification and mitral stenosis (150,152). However, our study showed that Am-la was significantly lower even without any significant changes of the maximal LA volume after pacing compared patients with AHREs. The loss of atrial contractility is also probably a major primary cause of atrial arrhythmia (204).

Clearly there is a relationship between atrial dilatation, atrial dysfunction and atrial dyssynchrony. Apart from the direct effect of enlarged size on atrial conduction, atrial dilatation is associated with increased fibrotic changes in the tissue which are integral to the remodeling process but which also will impede electrical conduction (205,206).

8.4.3 Atrial Velocity and Atrial Dyssynchrony Predicted AHREs Burden

Early detection of AHREs burden has important clinical implications as it may be a marker for the development of permanent AF. A prospective study demonstrated that patients with non-valvular paroxysmal AF had high risk of developing chronic AF with interatrial dyssynchrony and atrial systolic dysfunction measured by pulsed TDI (207). Even in those without a history of AF, those with prolonged ACT had an increased risk of developing AF in the following two years (208). Thus it does seem that both atrial dysfunction and dyssynchrony played an important role in atrial arrhythmogenesis. Our finding that interatrial dyssynchrony and atrial dysfunction were independent predictors of AHREs burden provides additional evidence to support this concept.

Interestingly, a previous study found that that the electrical abnormalities in RA hardly affected the P wave duration compared with the LA for the prediction of paroxysmal atrial fibrillation (161). Our result of no association between RA dyssynchrony and AHREs burden coincided with previous findings. This may relate

to the fact that the origin of AF lies within the LA.

8.4.4 Limitations

In addition, beta-blockers were used as the standard of care in the prevention of atrial arrhythmias before and after cardiac surgery and for heart rate control (209) (210). In our study, a potential confounder of these results is the use of beta-blockers which was higher in those without AHREs and higher in those with Cum%AP >75%. Most f patients had sinus node diseases and needed rhythm or heart rate control in these two groups. However, despite this we were still able to demonstrate that atrial function and dyssynchrony predicted AHREs. If anything the use of beta-blockers would be expected to waken this link. The fact that the relationship survived in the model indicates that the use of beta-blockers does not negate it.

8.5 Conclusions

This study demonstrated atrial conduction is significantly delayed in patients with high RA appendage pacing and that both atrial dysfunction and dyssynchrony can be used to predict AHREs burden. The findings are relevant to the prevention of AF after permanent pacing.

CHAPTER 9 LIMITATIONS AND FUTURE PERSPECTIVE

9.1 Study Limitations

To our limited knowledge, this study was the first investigation of atrial function in patients implanted with RVA-based pacemakers and preserved systolic function.

The present study was designed to elucidate the global and regional deterioration of LA function by advanced echocardiographic techniques in patients with acute and chronic RVA pacing. Our findings revealed that RVA pacing can induce ventricular dyssynchrony, intra- and interatrial dyssynchrony, chambers dilatation and reduction of ejection fractions. However, LA function and volume were only assessed at baseline and one year follow up. Serial follow-up studies will provide more information about the mechanism of LA dysfunction after RVA pacing.

In our study, we used RT3DE to measure LV volume and ejection fraction. However, LA volume and emptying fraction were assessed by two-dimensional echocardiographic area-length method. Although this method is indicated in current guidelines, it still has some limitations in particular in patients with dilated LA. RT3DE is an alternative way to measure LA volume. However, it remains challenging to do the measurement in the thin-walled atrium. TDI is an established and reproducible tool to assess atrial tissue velocities quantitatively. In cross-sectional and prospective studies, we used TDI to assess LA regional myocardial velocities for pacing heart. TDI can illustrate the change of LA regional function after acute or chronic RVA pacing in patients with preserved systolic

function. Two-dimensional speckle strain is another evolving echocardiographic method for assessment of regional function of myocardium. However, it has the same limitations of application.

There is no consensus statement of the definition of atrial dysfunction now. We defined a significant decrease of active atrial pump function more than 30% by atrial tissue velocity as the criteria in our prospective study. Our previous data showed that TDI is more sensitive to detect the deleterious change of LA regional function after RVA pacing compared with two-dimensional echocardiography. Therefore, the reduction of atrial pump function and the absence of change in active emptying fraction in this study were evaluated by TDI and two-dimensional echocardiography, respectively.

9.2 Future Perspective

It is clinically important to explore the early change of LA structure and function. Further analysis to compare the results of 1-, 3-, 6- and 9-month follow-up might be helpful to reveal the variation of LA structure and function as well as the mechanism of the development of atrial tachyarrhythmias after RVA pacing in patients with preserved systolic function.

The following issues need to be addressed in future studies. Firstly, the serial analysis of atrial function might describe the progression of deterioration

comprehensively. Secondly, the relationship between LA dysfunction and ventricular dyssynchrony is to be discussed. Thirdly, the present of MR might relate to LA enlargement and reduced global and regional atrial function. Fourthly, is there any predictor of documented AF in a longer follow up period? Fifthly, upgrading RVA pacing to biventricular pacing might benefit patients in atrial remodeling and atrial function.

SECTION IV
CONCLUSION

CHAPTER 10 CONCLUSION

Cardiac pacing has been the mainstay of treatment in patients with symptomatic sinus node dysfunction or atrioventricular block for decades. RV apex remains the most frequently used pacing site because of its easy accessibility and is associated with good sensing and pacing threshold. However, RVA pacing is antiphysiological and disturbs the normal electrical activation sequence. The electrical wave front propagates slowly through the ventricular myocardium instead of the His-Purkinje system with RVA pacing. Recent human studies have addressed the detrimental effects of RVA pacing on ventricular function as result of asynchronous ventricular contraction. Our studies further studied deleterious effects of RVA pacing on LA structure and function and evaluated the relationship between atrial dysfunction and ventricular function in patients with preserved systolic function after RVA pacing.

LA modulates LV filling through three components: reservoir, conduit and contractile chamber during LV systolic and diastolic phases. Therefore, LA volume varies during cardiac cycles. During acute ventricular pacing, 55% of patients with V-pace had indexed LAVmax > 32 ml/m^2 as compared to 45% of patients with V-sense with LAVmax > 32 ml/m^2 ($\chi^2 = 40.284$, $p < 0.001$). Furthermore, the active atrial pump function remained unchanged but the passive atrial function (Am-la measured by TDI) deteriorated.

However, our prospective study found chronic RVA pacing resulted in a decrease in

atrial active pump function as well, which was associated with increased LV filling pressure and reduced LV systolic function. The study proposed a reduction of Am-la > 30% indicating a significant decrease of LA active pump function. Using such cut-off value, both an E/e' ratio > 15 at one year and a reduction of LVEF ≥ 5% were independent predictors of deterioration of LA active pump function. The study also demonstrated that RA appendage pacing resulted in atrial conduction delay and induced intra- and interatrial dyssynchrony beyond of RVA pacing. An Am-la < 5.3 cm/s and the presence of interatrial dyssynchrony were independent predictors of AHREs burden at one year follow-up.

Based on our present findings, RVA pacing resulted in adverse LA remodeling, impairment of atrial function and attenuation of interatrial dyssynchrony. The extent of detrimental effects of RVA pacing on both atrium and ventricles are clearly defined in our study. However, further large-scaled prospective studies warranted to further explore the patho-physiological mechanism leading to these adverse atrial and ventricular adaptations.

APPENDIX I INDICATION FOR PERMANENT PACING

Indication for Permanent Pacing in Sinus Node Dysfunction and Acquired Atrioventricular Block

The most recent guideline for device-based therapy of cardiac rhythm abnormalities is documented in the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) 2008 (11). Recommendations for permanent cardiac pacing in sinus node dysfunction:

Class I

Permanent pacemaker implantation is indicated for sinus node dysfunction with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms.

(1) Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence.

(2) Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions.

Class IIa

(1) Permanent pacemaker implantation is reasonable for sinus node dysfunction with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented.

(2) Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies.

Class IIb

(1) Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake.

Class III

(1) Permanent pacemaker implantation is not indicated for sinus node dysfunction in asymptomatic patients.

(2) Permanent pacemaker implantation is not indicated for sinus node dysfunction in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia.

(3) Permanent pacemaker implantation is not indicated for sinus node dysfunction with symptomatic bradycardia due to nonessential drug therapy.

Recommendations for permanent cardiac pacing in acquired atrioventricular block in adults:

Class I

(1) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level associated with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to atrioventricular block.

(2) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia.

(3) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole greater than or equal to 3.0 seconds or any escape rate less than 40 bpm, or with an escape rhythm that is below the atrioventricular node.

(4) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level in awake, symptom-free patients with AF and bradycardia with 1 or more pauses of at least 5 seconds or longer.

(5) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level after catheter ablation of the AV junction.

(6) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level associated with postoperative atrioventricular block that is not expected to resolve after cardiac surgery.

(7) Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular block at any anatomic level

associated with neuromuscular diseases with atrioventricular block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms.

(8) Permanent pacemaker implantation is indicated for second-degree atrioventricular block with associated symptomatic bradycardia regardless of type or site of block.

(9) Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree atrioventricular block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the atrioventricular node.

(10) Permanent pacemaker implantation is indicated for second- or third-degree atrioventricular block during exercise in the absence of myocardial ischemia.

Class IIa

(1) Permanent pacemaker implantation is reasonable for persistent third-degree atrioventricular block with an escape rate greater than 40 bpm in asymptomatic adult patients without cardiomegaly.

(2) Permanent pacemaker implantation is reasonable for asymptomatic second-degree atrioventricular block at intra- or infra-His levels found at electrophysiological study.

(3) Permanent pacemaker implantation is reasonable for first- or second-degree atrioventricular block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise.

(4) Permanent pacemaker implantation is reasonable for asymptomatic type II second-degree atrioventricular block with a narrow QRS. When type II second-degree atrioventricular block occurs with a wide QRS, including isolated right bundle-branch block, pacing becomes a Class I recommendation.

Class IIb

(1) Permanent pacemaker implantation may be considered for neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of atrioventricular block (including first-degree atrioventricular block), with or without symptoms, because there may be unpredictable progression of atrioventricular conduction disease.

(2) Permanent pacemaker implantation may be considered for atrioventricular block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn.

Class III

(1) Permanent pacemaker implantation is not indicated for asymptomatic first-degree atrioventricular block.

(2) Permanent pacemaker implantation is not indicated for asymptomatic type I second-degree atrioventricular block at the supra-His (atrioventricular node) level or that which is not known to be intra- or infra-Hisian.

(3) Permanent pacemaker implantation is not indicated for atrioventricular block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms).

APPENDIX II FORMULAS

I. Assessment of Left Ventricular Ejection Fraction

LVEF = (EDV – ESV) / EDV × 100%

II. Assessment of Left Atrial Size and Function

LA volume = $8/3\pi$ [(A4c) (A2c) / LA length]

LA passive emptying volume = LAVmax – LAVpre

LA active emptying volume = LAVpre – LAVmin;

LA conduit volume = LV stroke volume – total LA emptying volume

LA total emptying volume = LAVmax – LAVmin

LA active emptying fraction = (LAVpre - LAVmin) / LAVpre × 100%

LA passive emptying fraction = (LAVmax - LAVpre) / LAVmax × 100%

LA total emptying fraction = (LAVmax - LAVmin) / LAVmax × 100%.

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