ULTRASOUND IMAGING IN CLINICAL CARDIAC ELECTROPHYSIOLOGY

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ULTRASOUND IMAGING IN CLINICAL CARDIAC ELECTROPHYSIOLOGY

Echocardiografie in klinische elektrofysiologie

Thesis

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Chapter 1

INTRODUCTION: WHY TO INTEGRATE ULTRASOUND IMAGING IN CLINICAL CARDIAC ELECTROPHYSIOLOGY

Introduction
Why to integrate ultrasound imaging in clinical cardiac electrophysiology?

The evolution of cardiology has closely followed the development and improvement of imaging techniques. This association can be appreciated from the recent diagnostic and therapeutic management of patients with structural heart diseases. Ultrasound is the most important imaging modality and has had the largest impact on the cardiology practice. Interestingly, the relationship between imaging and clinical cardiac electrophysiology has not until recently been implemented and has resulted in a development of arrhythmia management, which is divergent from other interventional subdisciplines. Imaging has not been part of the training of electrophysiologist. While echocardiography is part of the general cardiology training, only very basic knowledge in electrophysiology is required, which can partly be explained by its complexity. Until recently novel echocardiography methods have not been implemented in electrophysiology. It appears that with the increasing complexicity of electrophysiologic procedures, there is an increasing interest in imaging and particularly echocardiography for guiding procedures(1,2). This resulted in a certain level of convergence between the development of interventional cardiac electrophysiology and echocardiography.

What makes cardiac interventional electrophysiology different from other subspecialties of cardiology? It seems that until recently the electrogram, (either surface or intracardiac) had an exclusive role both in the diagnosis of arrhythmias and guiding the interventions. In the mid 80's our understanding of most arrhythmia mechanisms was almost exclusively based on electrogram analysis(3-7). Positioning of both recording and therapeutic catheters in the heart was guided by specific intracardiac electrograms(6). Fluoroscopy was the principle imaging modality for interventional electrophysiology(8). However, it was already realized in these early days, that certain anatomical structures have a critically important role in arrhythmia genesis, electrogram analysis based positioning of diagnostic and ablation catheters were highly efficient for the diagnostic and therapeutical procedures(8). Although, this was an indirect approach, it was still feasible for guiding the development of transcatheter ablation techniques. Transcatheter ablation is a true curative treatment of the tachycardias involving accessory pathways, dual AV nodal reentry and atrial flutters. Since these techniques were proved to be highly successful there was no obvious need for improved imaging. This indeed significantly influenced the attitude of electrophysiologists towards imaging modalities. An appropriate knowledge of fluoroscopy anatomy was sufficient for guiding electrophysiology procedures.

However, in the 90' s direct imaging of specific target sites became more important in electrophysiology. There are several reasons for this noticeable change. Most importantly there were significant new developments in echocardiography. One important direction is the miniaturization which resulted in intracardiac echocardiography catheters and made it more practical and attractive to the electrophysiologist(9). Before intracardiac ultrasound became available echocardiography has played a substantial role in the peri-procedural evaluation of arrhythmia patients, including functional evaluation, thromboembolic risk stratification and detection of procedural complications. Intracardiac catheter-based ultrasound is easy to use during interventions and these catheters can be manipulated by the electrophysiologist during the procedure without substantial extra training. The other direction of the imaging developments is the capability of providing three-dimensional image displays(10,11). Obviously, at this point strong convergence can be observed between the latest developments in electrophysiology and echocardiography with the introduction of three-dimensional electrical activation mapping and navigation systems(12). However, none of these methods provides anatomic images, which is a major pitfall of these systems. Thus, the three-dimensional navigation and electrical propagation is displayed on a virtual anatomy using these systems, which may significantly reduce the accuracy. For better understanding and development of new ablation tools to treat complex arrhythmias the electrical impulse propagation as well as the navigation of intracardiac catheters requires the real anatomy, preferably available real-time.

Fluoroscopy is very limited in this respect as it only provides two-dimensional "shadow"" images. The novel challenge of electrophysiology is the curative treatment of atrial fibrillation and life threatening arrhythmias. From the therapeutic point of view there is a very basic difference between classical electrophysiologically guided procedures and new approaches targeting atrial fibrillation patients. During these procedures the so-called hard electrophysiological endpoint is not available. Therefore, the approaches are based more on targeting specific anatomical structures such as the crista terminalis, pulmonary veins etc(13). This clearly explains the need for direct imaging techniques. Furthermore, mechanistic linear ablations can not be electrophysiologically guided at all(14,15). This means that the apposition of electrode catheters requires direct visualization(14,16,17). The most important potential in this regard is the possible combination of three-dimensional ultrasound imaging with the novel three-dimensional mapping techniques in real-time. In addition, the safety of procedures can be improved as well. Indeed, with real-time echocardiography theoretically the fluoroscopy time during an EP procedure can be significantly reduced and in some patients even avoided. Direct visualization allows to safely approach dangerous sites.

Pacing procedures are also turned into a basically new direction. The classical right ventricular and right atrial pacing sites were developed based on electrode stability issues. Clearly, in a large proportion of the patients these sites are satisfactory, but many patients could benefit from alternative pacing sites(18,19). Some of which cannot be approached by classical electrophysiology mapping techniques. The classical example is the Bachmann's bundle, but this is also the case for right ventricular outflow and left ventricular sites, which are indirectly selected at this moment(20). Direct visualization of the targeted sites could also significantly improve both the procedural and clinical outcome.

Finally, a significant subgroup of cardiac patients should be considered when imaging and electrophysiology is discussed. Congenital heart disease is frequently associated with an increased risk for development of life threatening ventricular and supraventricular arrhythmias. Diagnosis and treatment of these arrhythmias is more difficult and remains suboptimal. This is partly caused by the difficult anatomy especially after surgical repair. Direct imaging can play a role in guidance of electrophysiology procedures for these patients, and may also improve outcome.

In conclusion, our project is aimed to further incorporate echocardiography imaging in clinical cardiac electrophysiology. The studies presented in this thesis demonstrate the possible role of ultrasound imaging and its potential to improve electrophysiology procedures. All phases of the patient management, including pre-procedural evaluation, procedure guiding and post-procedural evaluation are influenced by novel echocardiography findings. I hope that the results of our studies can lead to better understanding of the association of anatomy and cardiac arrhythmias and might lead to further improvement of patient care. Furthermore, I strongly believe that the convergent development of three dimensional mapping systems and three-dimensional echocardiography can finally result in a complex three-dimensional mapping-navigation system which allows real-time guiding of mapping and therapy based on the actual anatomy.

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Chapter 2

OUTLINE OF THE THESIS

Outline of the thesis:

The first two chapters provide a broad background to the thesis. The need for deeper integration of ultrasound imaging in clinical cardiac electrophysiology is described. The main fields where ultrasound may have significant role in clinical cardiac electrophysiology are outlined in the review (chapter 3).

The thesis consists of three parts:

Part I.

This part describes novel possibilities of intravascular ultrasound and three-dimensional reconstruction during pacing procedures. Pacing indications are currently under review, and new indications are considered, since pacing can possibly decreasing the burden of atrial fibrillation in a selected patient population. Although promising clinical results have been reported important questions are raised regarding methodology. Our proposed method of three-dimensional echocardiography guided atrial septal pacing is described in details (chapter 4). In this chapter important physiological observations are also presented regarding the effects of different pacing sites on P-wave duration. The advantage of these techniques can be seen after analyzing of P-wave characteristics and measurements (chapter 5). The case presented in chapter 6 demonstrates the capablities of dynamic three-dimensional echocardiography in identifying intracardiac structures and electrodes.

Part II.

This part discusses the use of intracardiac ultrasound during ablation procedures. Left-sided procedures including an approach to the pulmonary vein require a transseptal puncture with high accuracy and safety. We developed our own technique for transseptal puncture, which is described in details in chapter 7. Although ablation procedures have a reasonably high success rate, some procedures fail. Unfortunately, the reason for unsuccessful ablation is not always obvious. One of the possible reasons is inappropriate lesion formation. In chapter 8 we tested intracardiac echocardiography for visualization of ablation lesions. Since with standard intracardiac echocardiography ablation lesions were not visible, we developed a novel technique for visualization, using contrast echocardiography. We have very promising results and the technique is described in chapter 9. The important role of intracardiac echocardiography in securing catheter-tip and wall contact is demonstrated in chapter 10.

Part III.

Post-procedural follow-up of patients with arrhythmias is a critically important issue, and its importance is underestimated in most cases. In this part of the thesis we describe the importance of functional evaluation of patients undergoing AV node ablation. We show (chapter 11) our pilot results demonstrating slight deterioration of left ventricular function after AV nodal ablation and right ventricular apical pacing. In chapter 12 a results of a multicenter investigation is presented which included similar patients. There was no improvement seen in cardiac function. In chapter 13, we explore the possible reason for the findings described earlier, and we also conclude that the lack of contractile reserve can not predict deterioration of cardiac function in this patient population. One of the possible solutions can be a selection of an alternative pacing site. In chapter 14 we describe a novel imaging modality which might be effectively used as a guiding and evaluation tool for alternative pacing sites for preservation of left ventricular function. Finally in chapter 15, we summarize the most important structures which became important for electrophysiology and therefore for imaging in the last decades.

Chapter 3

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ULTRASOUND IMAGING IN CARDIAC ELECTROPHYSIOLOGY: CURRENT CONCEPTS AND PERSPECTIVES

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Ultrasound imaging in cardiac electrophysiology: current concepts and perspectives

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Introduction

During the last two decades revolutionary diagnostic and therapeutic changes were implemented in the management of patients with arrhythmias. The development of transcatheter ablation provided a curative treatment of most supraventricular tachyarrhythmias including atrioventricular (AV) and AV nodal re-entry tachycardias, and more recently atrial flutters. Life threatening ventricular arrhythmias are effectively palliated by implantable antitachycardia devices and conduction disorders treated by pacemakers, with instantaneous improvement. New challenges are the effective treatment of patients with atrial fibrillation, which is the most frequent and often disabling arrhythmia, and the curative treatment of patients with life threatening arrhythmias. The development of novel ablative procedures is currently being investigated, but the success rate still remains suboptimal. Since the arrhythmia substrate is frequently associated with certain anatomical structures or morphological variants, improved imaging has an increasing role in the improvement of these treatments. Furthermore, novel catheter ablation approaches require catheter placement to sites, which may be associated with increased complication risk. Therefore, imaging has a crucial role, both in guiding and improving safety of electrophysiology (EP) procedures. Also, thromboembolic risk stratification, fine-tuning of the implanted sophisticated devices requires advanced and effective imaging techniques, as does their follow-up. The aim of the present review is to summarise the current and future clinical uses of echocardiography in cardiac electrophysiology.

Ultrasound systems: technical background and approaches

In general, all commercially available transthoracic and transesophageal ultrasound systems can be used for the preprocedural evaluation of arrhythmia patients. Thromboembolic risk stratification and cardiac function assessment is not different from other patients with heart disease. On the other hand, clinical electrophysiology requires invasive procedures since the definitive diagnosis is nearly always made in the EP laboratories, immediately followed by curative treatment. This approach requires an imaging technique, which can be comfortably used long-term, without extra cost and personal. It should increase diagnostic accuracy and decrease the risk for complications. Intracardiac echocardiography (ICE) fulfils most of these criteria.

Two-dimensional intracardiac echocardiography

Recently, two ICE systems became available for interventional EP labs: mechanical and phased-array transducers. The mechanical intravascular ultrasound imaging and ICE system (ClearView, CardioVascular Imaging Systems Inc., Fremont, CA, USA) is an 8F sheath-based catheter that incorporates a 9 MHz bevelled single-element transducer rotating at 1800 rpm (model 9900, EP Technologies, Boston Scientific Corp., San Jose, CA, USA).[1] The catheter is equipped with a sonolucent distal sheath of 1 cm, with a lumen housing the imaging transducer (*Figure 1*). The sheath prevents direct contact of the rotating transducer with the cardiac wall. The ICE catheter is filled with 3-5 cc sterile water, and then connected to the ultrasound console (model I5007, Boston Scientific Corp., San Jose, CA, USA). This catheter obtains cross-sectional images perpendicular to its long axis. The catheter is relatively simple in its design and the data acquisition allows three-dimensional (3D) reconstruction.
The other available system is a 10F catheter-based phased-array transducer operating at 5.5-10 MHz frequency and also has Doppler capabilities (Acuson Corporation, Mountain View, CA, USA).[2] The 64-element phased-array allows scanning a longitudinal 90-degree sector image with a radial depth penetration of 4 cm (*Figure 2*). This catheter does not permit 3D reconstruction in its present form. On the other hand, it is a steerable catheter with excellent depth penetration (12 cm) allowing visualisation of left-sided structures from the right side of the heart, which is a major advantage in clinical electrophysiology.

Three-dimensional echocardiography

Advances in microprocessor technology have made 3D echocardiography a practical imaging modality providing cardiac structure imaging in their realistic forms, which helps

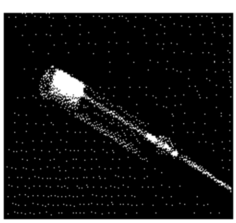

Figure 1. 9 MHz rotating transducer with a sonolucent protective sheath.

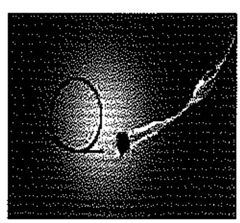

Figure 2. Steerable intracardiac phased-array echocardiography transducer.

to understand complex pathology and to reduce interpretation variability. Two different approaches are followed in 3D echocardiography: 3D reconstruction using a sequence of appropriately timed two-dimensional (2D) images and real-time volumetric imaging. Currently, automated contour analysis allows to measure and monitor global ventricular as well as regional function.

Three-dimensional reconstruction

For 3D reconstructions from intracardiac images, a custom-designed pullback device for the mechanical ICE transducer is used.[3] This device is controlled by the 3D workstation and uses a stepping motor to move the catheter stepwise and linearly in a cephalic-caudal direction through the right atrium. The workstation receives video input from the ICE system and both an ECG- and respiration signal (impedance measurement) from the patient (*Figure 3*). Prior to the acquisition run the range of RR- and breathing intervals are measured to calculate their mean value from the upper- and lower-limits. Cardiac cycles are recorded, those within the preset limit (±10%) around the mean interval are further processed. The workstation starts acquisition of 2D images after detecting the peak of the R wave and in the same phase of respiration, at a speed of 25 images/sec (image interval 40 ms). It stops after 1000 ms, or after detecting the peak of the R wave of the next cardiac cycle. After acquiring one cardiac cycle in the preset ranges, the workstation stores the images in the computer main memory. The catheter is then pulled back by a 0.5-mm axial increment. If the acquired beat falls outside the preset ranges, the ICE transducer is left at the same position, and a new cardiac cycle is acquired. This process is repeated until the level of the inferior vena cava (IVC) is reached. Clearly, the acquisition time will be shortened greatly, when all cardiac cycles are of the same length. Therefore, in practice the right ventricular apex is paced at 100 bpm. In accordance to their timing in the cardiac cycle, all the individual images of each cardiac cycle are formatted in volumetric data sets (256*256*256 pixels/each 8 bits) with 40 ms intervals allowing the display of dynamic 3D imaging. During postprocessing, several algorithms are applied to reduce noise, enhance edges, and reduce spatial artifacts (ROSA filter).[4]

Real-time volumetric echocardiography

During ICE-guided EP procedures, the EP catheters are continuously manipulated in three-dimensions, and the acquisition

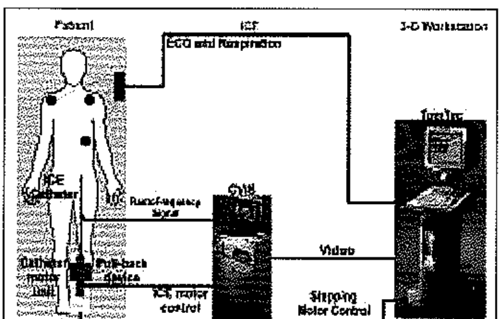

Figure 3. Catheterisation laboratory set-up for three-dimensional reconstruction using an ECG and respiration-gated pullback device.

of the images for 3D reconstruction takes time. Real-time 3D echocardiography, therefore, offers advantages. The volumetrics[2] ultrasound system generates real-time 3D pyramidal scanning, using a matrix array of 512 crystals. The scanner uses 16 parallel receive channels to generate B mode images up to 60 volumes per second. Each image plane can be inclined at any desired angle. The LIVE 3D system uses matrix array with 3000 individual transducers and the system displays real-time images.[5] These systems are only for transthoracic use, and prototype systems were introduces for intracardiac applications. The intracardiac real-time 3D transducer is incorporated in a 12F catheter, operates at 5 MHz frequency or at 7 MHz in a 9F catheter.[6] These catheters were found to be feasible for guiding electrode catheter placement in an open chest sheep model.[7]

Preprocedural evaluation patients with chronic atrial tachyarrhythmias

Atrial fibrillation is the most common supraventricular arrhythmia and leads to cardiac dilatation and dysfunction. Theoretically, restoration of sinus rhythm should result in improvement of the patient's symptoms as well as in cardiac function, although this advantage was not found in mortality and morbidity data in two recent multicentre studies. In these randomised trials presented at the 22nd annual meeting of the American College of Cardiology in Atlanta, 2002, no difference between rate control or rhythm control in patients with atrial fibrillation was found. The AFFIRM trial randomised patients to medical therapy either to restore atrial rhythm, or to control ventricular rate. Whereas, the RACE trial compared rate control (achieved by drugs) with rhythm control by electrical cardioversion. Both studies did not demonstrate any benefit from rhythm control. Electrical cardioversion remains the most frequently used method for restoration of sinus rhythm, but the procedure is associated with an increased stroke risk.[8-10] Transesophageal echocardiography (TEE) has given new insight into the pathogenesis of the thromboembolic sequelae of AF, and expanded the available therapeutic options.[11-13] Studies to date indicate that TEE-guided cardioversion is a safe and reasonable approach when the clinical situation warrants prompt restoration of sinus rhythm, and in stratifying patients into different risk groups in terms of thromboembolic events.[12-15] Information gathered from TEE has helped to elucidate the mechanisms responsible for postcardioversion embolism and has emphasised the importance of anticoagulation during and after the restoration of sinus rhythm. TEE also has the potential to further risk stratify patients with AF. Clinical studies, including multicentre randomised studies (ACUTE) showed that the use of TEE-guided cardioversion is a clinically effective alternative strategy to conventional therapy for patients in whom elective cardioversion is planned.[15] This has been further confirmed by recent large scale studies.[14]

Echocardiography for guiding electrophysiology procedures

Transthoracic echocardiography has several limitations during interventions. It requires additional-trained personal, and violation of sterility is a major problem. TEE is potentially useful, and provides superior images for intracardiac structure identification. The major problem with this technique is the need for general anaesthesia, since EP procedures are often complex and lengthy, which may result in a significant patient discomfort. Recently, ICE became available, providing excellent accuracy in direct visualisation of anatomical landmarks.

Transseptal puncture

Percutaneous puncture of the interatrial septum was in 1960 introduced for catheterisation of the left heart.[16] Recently, there has been renewed interest in transseptal left heart catheterisation due to the development of left-sided catheter ablations.[17-20] However, a significant number of acute and potentially lethal complications with transseptal puncture may occur, including tamponade, systemic emboli, and even death secondary to aortic perforation.[17,20] The conventional technique relies on fluoroscopic landmarks to define anatomic boundaries and detection of the movement of the tip of the device from the thicker muscular septum to the thin wall of the fossa ovalis. Since fluoroscopy does not allow direct visualisation of the fossa ovalis, transseptal catheterisation remains a difficult procedure, particularly in the cases where the atrial anatomy is atypical. Therefore imaging techniques such as TEE and 2D transthoracic echocardiography were used for the assessment of the interatrial septum during transseptal puncture.[21-26] Both techniques have limitations. Transthoracic ultrasound may not be able to accurately locate the thin wall of the fossa ovalis. Furthermore, transthoracic echocardiography is fairly uncomfortable to perform without a risk of violation of sterility during the intervention. TEE is an alternative method but causes lengthening of the procedure because the introduction of the oesophageal probe requires intravenous sedation for a longer period, limits the communication with the patient during the procedure, and needs an experienced operator. Intracardiac ultrasound allows visualisation of the fossa ovalis in all patients with excellent image quality (*Figures 4 and 5*).[27-30] This is a direct method and a possibility to avoid complications. In recent

Figure 5. Transseptal puncture guided by intracardiac echocardiography (left panel: phased-array transducer, right panel: rotating transducer). In both situations the tenting of the membranous fossa ovalis is clearly visible.

studies, in which patients underwent transseptal puncture under ICE guidance, the success rate was always higher than with fluoroscopy and there were no complications.[31,32] In our institute we always confirm the success of the puncture by a contrast injection through the Brockenbrough needle and its appearance in the left atrium detected by ICE.[32,33]

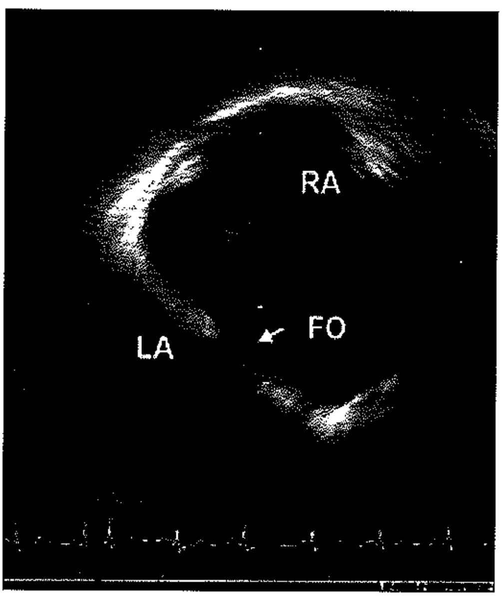

Figure 4. Horizontal cross-sectional intracardiac echocardiography image with a typical appearance of the fossa ovalis.

Inappropriate sinus tachycardia

The technique for describing ablative modification of sinus node function guided by intracardiac echocardiography has been extensively described in animals and in humans.[34-36] At present there are no clear guidelines to describe which patients should undergo such a procedure, as the recurrence rate remains fairly high. Moreover, it seems that patients undergoing multiple sinus node modification procedures are at higher risk for superior vena cava syndrome.[36,37] CARTO mapping has potential to guide this procedure, but the method is indirect and the advantage of continuos monitoring of the diameter of vena cava superior is lost.[35]

Atrial tachycardia

Atrial tachycardias originate from specific identifiable anatomical structures that are not seen on fluoroscopy. Crista terminalis in the right atrium and the pulmonary veins in the left atrium are most frequently involved. Kalman and colleagues have demonstrated that approximately two-third of focal right atrial tachycardias in patients without structural heart disease, arise along the crista terminalis. Direct visualisation of these structures undoubtedly facilitate mapping and ablation of these tachycardias.[39]

Atrial flutter

Atrial flutter (AFL) is a frequent arrhythmia due to re-entry around the large vascular structures in the right atrium.[40,41] ICE is an excellent imaging tool to understand the anatomy of cavo-tricuspid isthmus and its variations, which is a slow conducting zone of the macro-re-entry circuit.[42-44] Because the manoeuvrability of the mechanical transducer is limited, it is difficult to optimally visualise the isthmus and the adjacent intracardiac structures.[28] In these cases introduction of the ICE catheter through the subclavian vein was helpful.[28] Using phased-array and steerable probes this problem seems to be overcome.[45] In flutter ablation ICE has also a role to identify anatomical obstacles such as the Eustachian ridge, Thebesian vein and the tricuspid annulus, and the catheter wall contact can be monitored appropriately. Although the diagnosis is not difficult in most cases, transcatheter ablation of scar macro-re-entry tachycardias remains a challenge. Direct visualisation of the scar tissue by contrast echocardiography and/or tissue characterisation would be a great asset for these complicated procedures.

Linear ablations for the treatment of atrial fibrillation

Recently, attempts have been made to treat atrial fibrillation by creating multiple linear atrial lesions with RF energy. ICE offers imaging of endocardial anatomy and the ablation electrode tissue interface, which is not available with standard fluoroscopy. Compared with fluoroscopy, ICE guidance has been shown to improve targeting, energy delivery, lesion formation, and prevent energy delivery to potentially dangerous sites in a canine model.[46] ICE also demonstrates significant sliding of the catheter despite apparent catheter stability assessed by electrograms.[47] We have a similar experience, which demonstrated inappropriate wall contact with acceptable impedance measurements.[48] Theoretically, with high-resolution ultrasound systems and/or tissue characterisation, gaps in the line can be visualised in the future.

Pulmonary vein ablation for atrial fibrillation

Triggers originating from various sites of the atria can initiate atrial fibrillation. However, the origin of the triggers lies in the atrial tissue extending in the pulmonary veins. Correct identification of the anatomy is important since significant variations exist, including a common vestibule of the left pulmonary veins and additional small branches. ICE has a critically important role in ablation in this region. ICE can guide the transseptal puncture. Pulmonary venous anatomy can be assessed using the phased-array transducer without entering the left side of the heart. During ablation the wall contact of the catheters can be monitored. Knowing that pulmonary vein stenosis is the most frequent and potentially life threatening complication of the procedure[49], one of the major advantage of ICE appears to be that after ablation pulmonary vein stenosis can be reliably assessed using vessel diameter measurement and Doppler flow measurements. Recent reports suggest that pulmonary venous anatomy can be extensively studied by 3D intracardiac echocardiography, including visualisation of ablation catheters in the vein.[50,51]

Ventricular tachycardia

In general, association of structural abnormalities and arrhythmogenesis can be confirmed with ICE. The site of origin of idiopathic ventricular tachycardia (VT) arising from the left ventricular outflow tract (LVOT) may be closely-related to the aortic valve leaflets, and RF delivery can potentially damage them. Idiopathic VT of the LVOT can be treated successfully with RF ablation. ICE can identify accurately the ablation electrode and the anatomic landmarks, while the contact with the endocardium is easily assessed.[52] Scar-related ventricular tachycardias can also be mapped with the assistance of ICE by identifying scar tissue and adjacent isthmuses of viable tissue.

Ablation in the region of Koch's triangle

AV nodal re-entry tachycardias and AV nodes are successfully ablated in more than 97% of the patients, suggesting that imaging is not particularly necessary for these ablations. On the other hand, testing novel ablation approaches such as cryothermy can be performed under echocardiographic monitoring. During cryoablation of the AV node the cryocatheter-endocardial contact and iceball growth could be effectively monitored with ICE.[56]

Figure 6. Ablation lesion visualised as low contrast area in human Koch's triangle using myocardial contrast echocardiography.

Assessment of ablation lesions

ICE could theoretically detect tissue changes. Crater formation and increased echodensity were reported immediately after RF ablation.[34] However, we could not see RF lesions 20 min after ablation.[28] Therefore, local wall thickness was studied as an indirect sign and had some relation with the lesion size, although this is insufficient to make intraprocedural decisons.[34] There is a need for direct visualisation of the ablation such lesions. Myocardial contrast echocardiography together with intracardiac echocardiography is currently being studied to directly visualise radio frequency lesions after focal and linear ablation (*Figure 6*). This method can be combined with 3D reconstruction technique.[55]

Assessment of procedural complications

EP procedures are relatively safe, and have a low complication rate.[56] One of the most frequent complications is related to cardiac wall perforation with consequent pericardial effusion and tamponade. ICE, especially the one with phased-array transducer (deeper penetration), allows continuous monitoring of the pericardial space during EP procedures. This permits prompt detection of a pericardial effusion and an immediate guidance of a therapeutic puncture. Phased-array transducers are equipped with Doppler capabilities, allowing assessment of the pulmonary venous flow pattern after pulmonary vein ablation on top of diameter measurements to exclude pulmonary vein stenosis. This is the most important complication of this procedure.[45] ICE also allows detection of intracardiac thrombi during the procedures, especially during left-sided ablations.

Guiding pacing procedures

Pacemaker implantation without the use of fluoroscopy

Echocardiography has been used to guide temporary electrode catheter insertion in the emergency room and intensive care setting, when fluoroscopy is not promptly available.[57] Pacemaker implantations were guided by TEE during the first trimester of pregnancy in patients with second-degree heart block and syncope. TEE was found to be very appropriate to confirm satisfactory electrode position in the right atrial appendage.[58,59]

Specific site pacing techniques

Recently, novel ways of pacing have been proposed for the treatment of patients with various types of arrhythmias.[57,60,61] There is growing evidence suggesting that pacing on the atrial level in the region of Bachmann's bundle, the interatrial septum (IAS) or even multiple atrial sites may have advantages in patients with atrial fibrillation.[60-62] On the ventricular level, novel pacing techniques may play a role in preserving or even improving ventricular performance in patients with or without heart failure.[63] However, these specific site pacing techniques require an extremely accurate lead positioning, compared with the conventional bradycardia indications. This may explain that adequate results are not obtained with these new pacing therapies in a considerable number of patients. One of the explanations is possibly related to the anatomical variations, resulting in a variable and less efficient lead positioning. Transesophageal echocardiography and new electro-anatomical mapping systems have been used to improve procedural success.[64,65] We developed and tested a novel technique based on 3D ICE for specific site pacing (*Figures 7, 8 and 9*).[66] The initial clinical results of this guided pacing modality are very promising. We achieved a remarkable 43 ms mean reduction of the P wave duration, with Bachmann's bundle pacing without complications. This is more than is ever reported in any previous study.

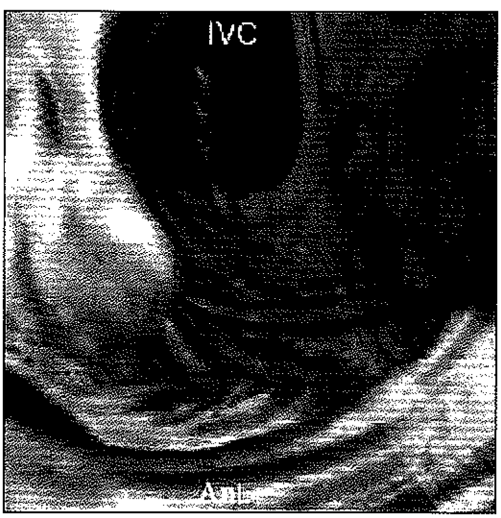

Figure 7. 'En face' view of the interatrial septum after three-dimesional reconstruction.

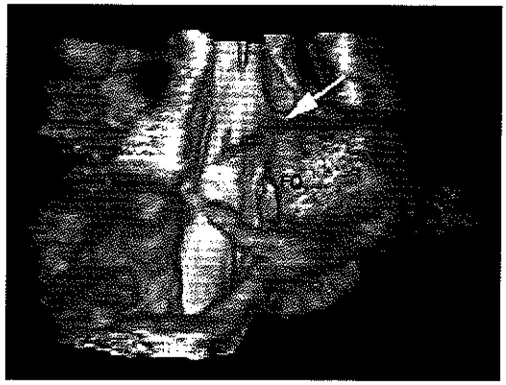

Figure 8. Three-dimensional visualisation of a pacemaker electrode in the right atrium.

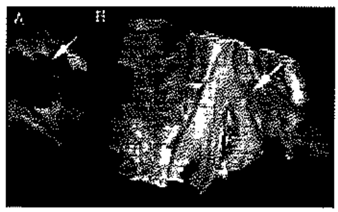

Figure 9. Bachmann's bundle pacing could be achieved with three-dimensional echocardiography guiding.

Transvenous lead extraction

Transvenous lead extraction procedures have a high success rate, but significant complications including death may occur. Currently, fluoroscopy is almost exclusively used as a guiding imaging tool. TEE has a significant role in visualisation of vegetations in a preprocedural period, but it may underestimate the real occurrence of vegetations.[67] ICE has a potential role to visualise the vegetations in the superior and inferior caval vein during lead extractions, and more vegetations were reported than with TEE.[68] Furthermore, complications associated with the procedures can be detected earlier.

Postprocedural evaluation: the role of echocardiography in the follow-up of arrhythmia patients

Recurrence of atrial fibrillation: predictive value of echocardiographic measurements

There are several proposed echocardiographic predictors for arrhythmia recurrence in patients with successful cardioversion of atrial fibrillation. Smaller left atrial size, preserved left ventricular function, and the lack of mitral valve disease are all associated with longer maintenance of sinus rhythm.[69,70] TEE not only allows the assessment of thromboembolic risk, but also accurate measurement of left atrial appendage (LAA) flow velocity.[71] Results, obtained form TEE studies after cardioversions, suggest that higher LAA flow velocity identifies patients with greater likelihood to remain in sinus rhythm.[71]

Optimisation of pacing therapy using echocardiography
Echocardiography plays a major role in assessment of ventricular function in patients undergoing pacemaker implantation for various reasons. RV apical stimulation is not physiological because normal ventricular activation along the natural conduction system is bypassed and the ventricles are activated in an abnormal sequence. Chronic apical ventricular pacing is associated with myocardial cellular changes and may lead to dysfunction of the left ventricle in a considerable number of patients.[73] These findings initiated studies where alternative right ventricular and/or multiple ventricular pacing sites were searched for.[63,74] The completed trials of biventricular pacing in congestive cardiac failure are impressively encouraging as a novel therapy for the symptoms of this devastating disease. It is clear that not all patients with heart failure respond favourably. It seems that biventricular pacing provides the best haemodynamic benefit when the most delayed wall of the left ventricle is paced.[75] This was elegantly confirmed by means of tissue myocardial Doppler imaging.[76] Therefore, echocardiography has a significant role in preselection, guiding, and follow-up of these patients.[76-78] Furthermore, optimisation of the pacing parameters can effectively be performed by echocardiography including optimisation of the AV delay.[78]

Conclusions
Two basic directions of development of ultrasound imaging were seen in the past decades: miniaturisation and 3D imaging. Clinical electrophysiology had significant benefit from both directions, allowing the use of intracardiac transducers and 3D imaging for better intracardiac structure identification. The clinical application of these current devices in clinical electrophysiology is the focus of ongoing research. When real time 3D echocardiography will be routinely available, EP and pacing procedures could be guided with improved safety and accuracy without any use of fluoroscopy. This will be a major asset for imaging and interventional cardiac electrophysiology.

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PART I.
GUIDANCE OF PACING PROCEDURES

Chapter 4

T Szili-Torok, GP Kimman, MF Scholten, J Ligthart, N Bruining, DAMJ Theuns, APJ Klootwijk, JRTC Roelandt, LJ Jordaens: **INTERATRIAL SEPTUM PACING GUIDED BY THREE-DIMENSIONAL INTRACARDIAC ECHOCARDIOGRAPHY**

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Cardiac Pacing and Electrophysiology

Interatrial Septum Pacing Guided by Three-Dimensional Intracardiac Echocardiography

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OBJECTIVES Currently, the interatrial septum (IAS) pacing site is indirectly selected by fluoroscopy and P-wave analysis. The aim of the present study was to develop a novel approach for IAS pacing using intracardiac echocardiography (ICE).

BACKGROUND Interatrial septum pacing may be beneficial for the prevention of paroxysmal atrial fibrillation.

METHODS Cross-sectional images are acquired during a pull-back of the ICE transducer from the superior vena cava into the inferior vena cava by an electrocardiogram- and respiration-gated technique. Both atria are then reconstructed using three-dimensional (3D) imaging. Using an "en face" view of the IAS, the desired pacing site is selected. Following lead placement and electrical testing, another 3D reconstruction is performed to verify the final lead position.

RESULTS Twelve patients were included in this study. The IAS pacing was achieved in all patients including six suprafossal (SF) and six infrafossal (IF) lead locations all confirmed by 3D imaging. The mean duration times of atrial lead implantation and fluoroscopy were 70 ± 48.9 min and 23.7 ± 20.6 min, respectively. The IAS pacing resulted in a significant reduction of the P-wave duration as compared to sinus rhythm (98.9 ± 19.3 ms vs. 141.3 ± 8.6 ms; $p < 0.002$). The SF pacing showed a greater reduction of the P-wave duration than IF pacing (59.4 ± 6.6 ms vs. 30.2 ± 13.6 ms; $p < 0.004$).

CONCLUSIONS Three-dimensional ICE is a feasible tool for guiding IAS pacing. (J Am Coll Cardiol 2002; 40:2139–43) © 2002 by the American College of Cardiology Foundation

Recently, nonconventional pacing approaches have been proposed for the treatment of patients with paroxysmal atrial fibrillation (AF) (1–5). Pacing the interatrial septum (IAS) has been reported to be effective to attenuate the progression of AF (6–8), but the optimal atrial pacing site remains controversial (9,10). Fluoroscopy does not allow the visualization of anatomically important structures including the fossa ovalis (FO), aortic arch, aortic valve, crista terminalis, and tricuspid valve. Thus, selection of the septal pacing site using X-rays may be inadequate for both optimal pacing and for avoiding problems related to lead fixation (acute and long-term). The aim of the present study was to develop a novel approach for IAS pacing based on three-dimensional (3D) intracardiac echocardiography (ICE) and to test its feasibility.

METHODS

Study patients. Twelve consecutive patients (six women) who underwent dual chamber (n = 11) or atrial pacemaker (n = 1) implantation were included in this study (Table 1). Their mean age was 65.5 ± 13.4 years (range, 32 to 77 years).

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ICE. The ClearView system (CardioVascular Imaging Systems, Fremont, California) was used with an 8F sheath-based ICE imaging catheter that incorporated a 9-MHz beveled single-element transducer rotating at 1800 rpm (model 9900, EP Technologies, Boston Scientific, San Jose, California). A custom-designed electrocardiogram (ECG)- and respiratory-gated pullback device and a 3D-ultrasound workstation (EchoScan, TomTec GmbH, Munich, Germany) were used to acquire and process the ICE images (11).

ECG- and respiration-gated image acquisition. The pullback device is controlled by the 3D workstation and uses a stepping motor to move the catheter stepwise and linearly through the right atrium. The workstation receives video input from the ICE system and an ECG- and respiration-signal (impedance measurement) from the patient. Before the acquisition run, the range of RR and breathing intervals are measured to define both upper and lower limits. The workstation starts acquisition of two-dimensional images after detecting the peak of the R-wave and in the same phase of respiration, at a speed of 25 images/s (image interval 40 ms). After acquiring one cardiac cycle, the workstation stores the images, and the catheter is then pulled back by 0.5-mm axial increment. This process is repeated until the inferior vena cava (IVC) is reached. The acquisition time is much shortened when all cardiac cycles are of the same length. Therefore, the right ventricular apex is paced at 100 beats/min.

Abbreviations and Acronyms

ECG = electrocardiogram
FO = fossa ovalis
IAS = interatrial septum
ICE = intracardiac echocardiography
IF = infrafossal
IVC = inferior vena cava
SF = suprafossal
SVC = superior vena cava
3D = three-dimensional

The 3-D image processing. In accordance to their timing in the cardiac cycle, all images are formatted in volumetric data sets (256·256·256 pixels/each 8 bits). During postprocessing, several algorithms are applied to reduce noise, enhance edges, and reduce spatial artifacts (ROSA filter).

Insertion of ICE transducer and pacemaker implantation. Initially, a 12-lead ECG is recorded with a high-resolution electrophysiology system (Prucka Engineering, Houston, Texas) using 1-kHz sampling frequency with 30- to 500-Hz filtering. The ICE catheter is advanced into the superior vena cava (SVC) through the right femoral vein. After an ICE catheter pullback, the right atrium is 3D reconstructed. Using a reconstructed "en face" view of the IAS the position of the FO is determined, serving as a landmark for the selection of the septal pacing site (Fig. 1). The chosen pacing sites are defined according to their relation to the FO (suprafossal [SF] and infrafossal [IF] pacing sites). At the level of the selected pacing site a horizontal cross-sectional template is reconstructed from the data set for real-time guiding of the implantation procedure. The active fixation lead is introduced into the right atrium by standard technique. The ICE operator moves the ICE catheter to the level of the tip of the atrial pacing lead. In the SF pacing sites an anterior spot is targeted. After the atrial pacing lead is fixed into the muscular IAS, standard pacing tests are performed to assess sensing, pacing threshold, and pacing impedance. If the values are acceptable the ICE transducer is repositioned in the SVC and a second catheter pullback is performed during dual chamber pacing at 100 beats/min. This second 3D reconstruction allows verifying the final lead position (Fig. 2).

Table 1. Demographic Data of the Patients

	Total Group	Suprafossal	Infrafossal
No. of patients	12	6	6
Age (yrs)	62.7 ± 16	65 ± 18.8	61.1 ± 15.1
Gender (M/F)	6/6	4/2	2/4
Indication for PM implantation			
SND (n)	6	4	2
AV block (n)	6	2	4
Medication at implant			
Ca channel-blocker (n)	1	1	0
Beta-blocker (n)	2	1	1
Amiodarone (n)	2	1	1
Diuretics (n)	3	2	1
ACE inhibitor (n)	3	1	2

ACE = angiotensin-converting enzyme; AV = atrioventricular; n = number of patients; PM = pacemaker; SND = sinus node disease.

The ECG measurements. Simultaneous 12-lead ECG was displayed on the screen, doubled in amplitude at a speed of 100 mm/s. The P-wave duration was defined as the difference between the first atrial activity and the last atrial activity including all surface leads in sinus rhythm. During atrial pacing the onset of atrial activation was measured from the stimulus artifact.

Echocardiographic measurements. Distances between the FO and IVC, the FO and SVC, and the FO and right atrial lateral wall (at the level of the SF region) were measured from 3D reconstruction of the right atrium.

Statistical analysis. Continuous variables are expressed as mean ± SD. Nonparametric data are compared using the Wilcoxon rank-sum test. Comparisons were made between sinus rhythm and paced rhythm for the total, the SF, and for the IF groups using paired Student *t* test. The level of significance was set at a p value of 0.05.

RESULTS

Implantation results. The SF pacing site was achieved in six patients and IF site in the other patients. All procedures were successful. Pacing data are summarized in Table 2. There were no complications related to ICE catheterization and/or pacemaker implantation. The atrial threshold was higher in the SF group. No differences were seen in other pacing parameters between the SF and IF groups. The atrial lead implantation time was significantly longer in the SF group than in the IF group (75.2 ± 37.6 min vs. 27.1 ± 10.2 min; $p = 0.01$). The fluoroscopy time was similar in SF and IF groups (26.9 ± 13.4 min vs. 16.9 ± 6.4 min; p = NS). There was no lead dislodgment or significant change in pacing parameters after a three-month follow-up period.

Results of 3D ICE. After 3D reconstruction the SVC, IVC, FO, crista terminalis, aortic arch, and left atrium were visualized in all 12 patients (100%). The location of the tip of the atrial lead could be identified in all cases after lead implantation. The desired spot and the final pacing spot were virtually identical in all patients. The distance between the FO and the lateral wall of the right atrium was 28.1 ± 8.9 mm (range, 20 to 42 mm). The distance between the FO and the IVC was 46.1 ± 15.4 mm (range, 16 to 56 mm), and between the FO and the SVC was 25.1 ± 9 mm (range, 15 to 31 mm). Tissue thickness between the septal part of the high RA and the ascending aorta was small (range, 2 to 8 mm).

The P-wave duration after septal pacing. The findings related to changes in P-wave duration are shown in Table 3. The duration of the P-wave showed significant reduction after septal pacing in the total group (sinus rhythm: 141.3 ± 8.6; septal pacing: 98.9 ± 19.3; $p = 0.002$). Reduction of the P-wave duration was greater in SF patients than in IF patients (59.4 ± 6.6 ms vs. 30.2 ± 13.6 ms; $p < 0.004$).

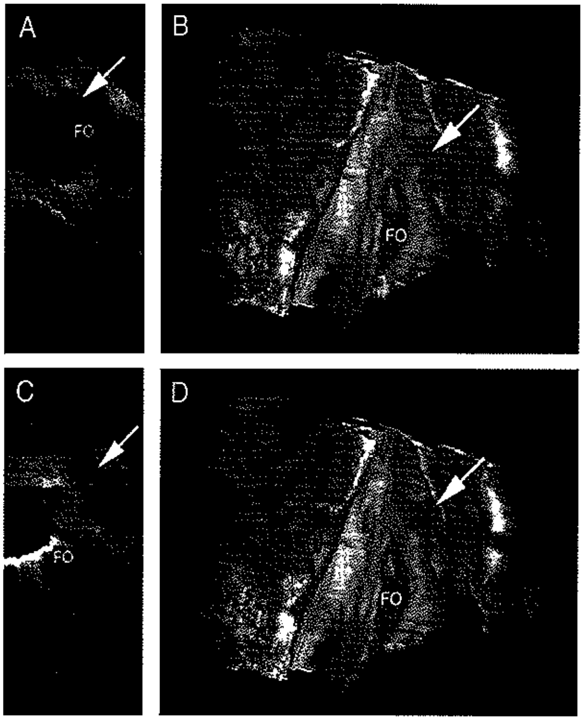

Figure 1. An "en face" view of the interatrial septum (IAS) before (A, B) and after (C, D) pacemaker lead implantation. The fossa ovalis (FO) is clearly visible in both situations. Arrows (A, B) show the selected spot for pacing of the IAS. A virtually perfect positioning of the atrial lead was achieved in this case, as the arrow on panels C and D indicate the cross-section of the atrial lead in front of the anterior-superior edge of the muscular interatrial septum and the membrane of FO. The achieved spot is identical to the desired spot shown by two-dimensional and three-dimensional images.

DISCUSSION

This is the first study demonstrating a practical application of 3D ICE in clinical cardiac electrophysiology. It appears from this study that 3D ICE is a safe and feasible tool to guide placement of IAS pacing electrodes. Our findings further indicate that an anatomically based localization of the atrial pacing lead results in a substantial reduction of the P-wave duration.

The importance of guided septal pacing. Although promising results are reported with septal pacing for the prevention of paroxysmal AF, the optimal pacing site still

Figure 2. A longitudinal cross-sectional (A) and a real three-dimensional image (B) reconstructed from a volumetric data set with a schematic representation (C) shows the right atria (RA) and left atria (LA) in a patient after suprafossal pacing. In this case the fossa ovalis (FO) is placed fairly downward. Ao = aorta; CT = crista terminalis; IVC = inferior vena cava; SVC = superior vena cava.

Table 2. Implantation Data

	Total Group	Suprafossal	Infrafossal	p Value Suprafossal vs. Infrafossal
Procedure time (min)	157.7 ± 48.4	156.2 ± 52.3	158.4 ± 49.9	NS
Fluoroscopy time (min)	35.3 ± 20.3	38.1 ± 23.4	33.2 ± 19.2	NS
Atrial lead implantation time (min)	70 ± 48.9	90 ± 75.2	27.1 ± 10.2	0.01
Atrial lead fluoroscopy time (min)	23.7 ± 20.6	26.9 ± 13.4	16.9 ± 6.4	NS
Atrial lead sensing (mV)	2.0 ± 1.0	2.3 ± 1.5	1.8 ± 0.7	NS
Atrial lead threshold (V)	0.8 ± 0.9	1.3 ± 1.4	0.6 ± 0.3	0.02
Atrial lead impedance (Ω)	601.2 ± 139.8	584.6 ± 108.1	611.2 ± 167.5	NS

NS = nonsignificant.

remains unknown. Stimulation at the conventional site (right atrial appendage) delays both intra-atrial and interatrial conduction (9,10,12). Therefore, alternative pacing sites within the right atrium have been investigated. The antifibrillatory effect of Bachmann's bundle pacing was demonstrated in both an acute and chronic setting (3,6). Alternative pacing sites were also tested, such as the posteroseptal region just above the ostium of the coronary sinus (7). The optimal lead positioning technique is still being searched for. Spencer et al. (1) showed the feasibility of transesophageal echocardiography and 12-lead ECG-guided septal pacing. The transesophageal echocardiography is uncomfortable for patients during long-lasting procedures, has its own complications, and the visualization of intracardiac structures is less accurate. The ICE allows visualization of important anatomical landmarks with an excellent accuracy and can effectively guide interventions in clinical electrophysiology (13–15). With 3D reconstruction, ICE provides an outstanding opportunity for online evaluation of the anatomy. Our experience indicates that by using 3D echocardiography the most relevant right atrial structures are readily recognized. In addition, after implantation the atrial lead can be accurately visualized. The results of our intracardiac measurements demonstrate that significant variations exist in right atrial anatomy and distances between structures. The location of the FO is quite unpredictable. Therefore, visualization of this landmark has advantages during the implantation procedure.

In former reports on septal pacing, the reduction of the P-wave duration ranged widely from 9 ms to 36 ms (6,7,12). Interestingly, the technically difficult pacing of the BB decreased the P-wave duration to a less extent than the early study pacing near the ostium of the coronary sinus (6,7). Using our technique we achieved a remarkable 43 ms mean reduction of the P-wave duration, which is more than reported by previous studies.

Table 3. The Effect of Septal Pacing on P-Wave Duration

	Total Group	Suprafossal	Infrafossal	p Value*
Sinus P-wave (ms)	141.3 ± 8.6	142.4 ± 6.1	140.5 ± 10.5	NS
Paced P-wave (ms)	98.9 ± 19.3	83 ± 9	110.2 ± 16.3	0.005
p Value†	0.002	0.04	0.01	

*p = suprafossal vs. infrafossal; †p = sinus vs. paced.
NS = nonsignificant.

Study limitations. Intracardiac echocardiography with 3D-reconstruction software is currently available in a limited number of centers; it requires additional training, experience, and the extra cost of the technique is considerable. Our data suggest that, whereas SF pacing yields the shortest P-waves, it is associated with a higher pacing threshold and longer procedure time. It is to be expected that the latter can be reduced in the near future by using improved reconstruction software. This also implies the need for development of dedicated tools such as steerable stylets and vascular sheaths with specially designed curves for pacing in this region. Furthermore, the correlation between the magnitude of P-wave reduction and the value for prevention of paroxysmal AF necessitates further investigation.

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Chapter 5

T Szili-Torok, N Bruining, M Scholten, GP Kimman,
JRTC Roelandt, L Jordaens:

EFFECTS OF GUIDED SEPTAL PACING ON P-WAVE CHARACTERISTICS

Pacing Clin Electrophysiol 2003; 26:253-256

Effects of Septal Pacing on P Wave Characteristics: The Value of Three-Dimensional Echocardiography

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From the Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands

SZILI-TOROK, T., ET AL.: Effects of Septal Pacing on P Wave Characteristics: The Value of Three-Dimensional Echocardiography. *Interatrial septum (IAS) pacing has been proposed for the prevention of paroxysmal atrial fibrillation. IAS pacing is usually guided by fluoroscopy and P wave analysis. The authors have developed a new approach for IAS pacing using intracardiac echocardiography (ICE), and examined its effects on P wave characteristics. Cross-sectional images are acquired during pullback of the ICE transducer from the superior vena cava into the inferior vena cava by an electrocardiogram- and respiration-gated technique. The right atrium and IAS are then three-dimensionally reconstructed, and the desired pacing site is selected. After lead placement and electrical testing, another three-dimensional reconstruction is performed to verify the final lead position. The study included 14 patients. IAS pacing was achieved at seven suprafossal (SF) and seven infrafossal (IF) lead locations, all confirmed by three-dimensional imaging. IAS pacing resulted in a significant reduction of P wave duration as compared to sinus rhythm (99.7 ± 18.7 vs 140.4 ± 8.8 ms; $P < 0.01$). SF pacing was associated with a greater reduction of P wave duration than IF pacing (56.1 ± 9.9 vs 30.2 ± 13.6 ms; $P < 0.01$). P wave dispersion remained unchanged during septal pacing as compared to sinus rhythm (21.4 ± 16.1 vs 13.5 ± 13.9 ms; NS). Three-dimensional intracardiac echocardiography can be used to guide IAS pacing. SF pacing was associated with a greater decrease in P wave duration, suggesting that it is a preferable location to decrease interatrial conduction delay. (PACE 2003; 26[Pt. II]:1–4)*

atrial fibrillation, septal pacing, atrial mapping, echocardiography

Introduction

Alternative pacing approaches have recently been introduced for the management of patients with paroxysmal atrial fibrillation (PAF).[1–3] Pacing the interatrial septum (IAS) has been reported to be effective in slowing the progression of atrial fibrillation (AF).[4–6] Fluoroscopy does not allow the visualization of the fossa ovalis, aortic arch, aortic valve, crista terminalis, and tricuspid valve. Thus, the accuracy of lead positioning when selecting septal pacing sites with fluoroscopy is limited. The aim of the present study was to develop a new approach for IAS pacing based on three-dimensional intracardiac echocardiography (ICE) and to test its feasibility. Using this technique, the effects of septal pacing on P wave characteristics were examined.

Patients and Methods

Patient Population

Fourteen consecutive patients (7 women; mean age 63.1 ± 15.4, range 32–77 years) who underwent dual chamber (DDD, $n = 13$) or atrial (AAI, $n = 1$) pacemaker implantation were included in this study, which was reviewed by the Medical Ethical Committee of the Thoraxcentrum.

Three-Dimensional ICE

The ClearView system (CardioVascular Imaging Systems Inc., Fremont, CA, USA) was used with an 8 Fr sheath-based ICE imaging catheter that incorporated a 9-MHZ beveled single element transducer rotating at 1,800 rpm (model 9900, EP Technologies, Boston Scientific Corp., San Jose, CA, USA). A custom-made electrocardiogram (ECG) and respiratory-gated pullback device and a three-dimensional ultrasound workstation (EchoScan, TomTec GmbH, Munich, Germany) were used to acquire and process the ICE images.[7,8] The custom-made pullback device is controlled by the three-dimensional workstation and uses a stepping motor to move the catheter stepwise and linearly through the right atrium. The workstation receives video input from the ICE system and an ECG and respiration signal (impedance measurement) from the patient. In accordance to their timing in the cardiac cycle, all images are formatted in volumetric data sets (256*256*256 pixels/each 8 bits).

Insertion of ICE Transducer and Pacemaker Implantation

A 12-lead ECG was initially recorded with a high resolution electrophysiology system (Prucka

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Engineering, Houston, TX, USA) using a 1-kHz sampling frequency with 30–500-Hz filtering. The right femoral vein was punctured and a 9 Fr straight, 80-cm long vascular sheath (Arrow, International, Reading, PA, USA) was advanced into the superior vena cava (SVC). The ICE catheter was introduced into this sheath and advanced to the SVC. After an ECG and respiration-gated ICE catheter pullback the right atrium was three-dimensionally reconstructed. Using a reconstructed frontal view of the IAS, the position of the fossa ovalis was determined, serving as a landmark for the selection of the septal pacing site. The chosen pacing sites were defined according to whether they were suprafossal (SF) or infrafossal (IF) pacing sites. The active-fixation lead was introduced into the right atrium by standard techniques through the cephalic or the subclavian vein. Two-dimensional real-time ICE was used by the operator to rotate the lead towards the IAS. After the selected site was reached and real-time ICE confirmed an optimal wall contact, the atrial pacing lead was fixed into the muscular IAS. When satisfactory sensing, capture threshold, and pacing impedance values were obtained, regular atrial pacing was performed during continuous 12-lead ECG recording. The ICE transducer was then repositioned in the SVC and a second catheter pullback was performed. This second three-dimensional reconstruction allowed the verification of the final lead position (Figs. 1 and 2).

P Wave Measurements

P wave measurements were made at high resolution. The 12-lead ECG was displayed on the screen, doubled in amplitude, at a speed of 100 mm/s. Total P wave duration was defined as the difference between onset and offset of atrial activity, including all surface leads during sinus rhythm. During atrial pacing the onset of atrial activation was measured from the stimulus artifact. Pmax was defined as the longest and Pmin as the shortest P wave in any of the available leads. P wave dispersion was defined as the difference between Pmax and Pmin.

Figure 1. *Three-dimensional image of atrial lead in suprafossal position (arrow).*

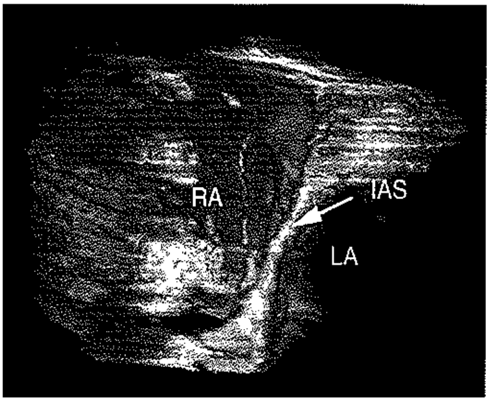

Figure 2. *Three-dimensional image of atrial lead in infrafossal position (arrow).*

Statistical Analysis

Continuous variables are expressed as mean ± SD. Nonparametric data were compared by Wilcoxon and Mann-Whitney tests. Comparisons were made between sinus rhythm and paced rhythm for all patients, and separately for the SF and for the IF groups. The level of significance was set at a P value of 0.05.

Results

Implantation Results

All lead implantation procedures were successful. There were no complications related to ICE catheterization and/or pacemaker implantation. The atrial capture threshold was higher in the SF group. There were no other differences in sensing, ventricular capture threshold, or pacing impedance measurements between the SF and IF groups. The atrial lead implantation time was significantly longer in SF group than in IF group (100 ± 68.9 vs 27.1 ± 10.2 minutes, P = 0.01). The duration of fluoroscopic exposure was similar in both groups (37.0 ± 26.6 vs 16.9 ± 6.4 minutes, NS). There was no lead dislodgment or significant change in pacing parameters at the 3-month follow-up.

Table I.

Comparison of P Wave Characteristics Before and After Septal Pacing

	Sinus Rhythm	Paced (Total Group)	P Value
Ptotal (ms)	140.4 ± 8.8	99.7 ± 18.7	0.01
Pmax (ms)	132 ± 12.3	101.6 ± 17.7	0.001
Pmin (ms)	110 ± 12.4	88 ± 12.6	0.005
P dispersion (ms)	21.4 ± 16.1	13.5 ± 13.9	NS

P value = sinus rhythm vs paced rhythm; NS = nonsignificant.

Results of Three-Dimensional ICE

After three-dimensional reconstruction the SVC, inferior vena cava, crista terminalis, aortic arch, and left atrium were visualized in all patients. The location of the tip of the atrial lead could be identified in all cases after lead implantation. The desired pacing site was nearly the same as the final pacing site in all patients.

P Wave Characteristics During Septal Pacing

The changes in P wave characteristics are shown in Tables I and II. There was no significant difference in P wave duration between the SF and the IF groups during sinus rhythm (140.3 ± 7.4 vs 140.5 ± 10.5 ms, NS). The duration of the P wave was significantly shortened during septal pacing in the overall population (sinus rhythm 140.4 ± 8.8 ms, septal pacing 99.7 ± 18.7 ms, $P < 0.01$). Shortening of the P wave was greater in SF than in IF patients (56.1 ± 9.9 vs 30.2 ± 13.6 ms, $P < 0.01$). In the overall population there was a significant reduction in Total P, Pmax, and Pmin values during septal pacing (Table II). P dispersion during sinus rhythm and during septal pacing was similar (Table II).

Discussion

This study suggests that intracardiac three-dimensional echocardiography is safe and effective to guide the placement of permanent IAS pacing electrodes. The current results indicate that the accurate placement of the atrial pacing lead is associated with a greater shortening of P wave duration than suggested in earlier reports. With regard to the decrease in interatrial conduction delay, SF pacing seemed to be the preferred site of IAS pacing, since P wave duration was significantly more shortened than by IF pacing.

The right atrial appendage is the usual atrial pacing site, though pacing at this site delays both intraatrial and interatrial conduction.[9–11] Furthermore, recent multicenter trials have failed to show a benefit from atrial appendage pacing in patients with PAF.[12] Therefore, alternative pacing sites within the right atrium have been investigated like the posteroseptal region immediately above the ostium of the coronary sinus, dual site right atrial pacing, and biatrial stimulation.[2,5,13] The short- and long-term antifibrillatory effect of Bachmann's bundle pacing has been reported, including in a randomized multicenter study.[4,14] However, using conventional fluoroscopic imaging, P wave duration shortening has varied between 9 and 36 ms in earlier reports of IAS pacing.[4,5,11] It is noteworthy that, in a study by Bailin et al.,[4] pacing of the Bachmann's bundle region was associated with less shortening of the P wave than in the early study of Padeletti et al.,[5] where the septum was paced near to the ostium of the coronary sinus. A possible explanation for this difference with our remarkable 41 ms mean shortening in P wave duration, is the lower accuracy of the pacemaker lead positioning in these other studies. Pacing in the IF region was associated with nearly the same P wave shortening as observed by Padeletti et al.,[5] probably because low septal pacing could be guided by the location of the coronary sinus ostium. In contrast, pacing of Bachmann's bundle is technically difficult, and cannot be guided by anatomic structures. These data suggest the importance of guided IAS pacing. Although septal pacing for prevention of PAF seems beneficial, optimal guiding techniques are still needed. Spencer et al.[1] showed the

Table II.

The Effect of Septal Pacing on P Wave Duration

	Total Group	Suprafossal	Infrafossal	P Value
Ptotal (ms)	99.7 ± 18.7	87.5 ± 13.6	110.2 ± 16.3	0.01
Pmax (ms)	101.6 ± 17.7	86.5 ± 5.2	110.2 ± 16.3	0.001
Pmin (ms)	88 ± 12.6	76.7 ± 10.5	94.5 ± 8.6	0.01
P dispersion (ms)	13.5 ± 13.9	9.7 ± 8.3	15.7 ± 16.5	NS

P value = suprafossal vs infrafossal; NS = nonsignificant.

feasibility of transesophageal echocardiography and 12-lead ECG-guided septal pacing. Though transesophageal echocardiography was feasible, it is limited by patient discomfort during long procedures, inherent complications, and less accurate visualization of intracardiac structures. ICE allows an accurate visualization of important anatomic landmarks and appears highly effective to guide interventions in clinical electrophysiology.[15–17]

The results from this study suggest that, while SF pacing resulted in the greatest shortening of the P wave, it was also associated with a higher atrial capture threshold and longer procedures. Dedicated tools such as stylets and introducer sheaths should be developed to target this region. The correlation between the magnitude of P wave reduction and the prevention of PAF remains to be established.

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Chapter 6

T Szili-Torok, LJ Jordaens, N Bruining, J Ligthart, JRTC Roelandt:

DYNAMIC THREE-DIMENSIONAL ECHOCARDIOGRAPHY OFFERS ADVANTAGES FOR SPECIFIC SITE PACING

Circulation 2003; 107:e30

Dynamic Three-Dimensional Echocardiography Offers Advantages for Specific Site Pacing

T. Szili-Torok, MD; L.J. Jordaens, MD, PhD; N. Bruining, PhD;
J. Ligthart; J.R.T.C. Roelandt, MD, PhD, DSc

We have developed a novel technique for specific site pacing. Our approach is based on three-dimensional (3D) intracardiac echocardiography (ICE) and allows excellent visualization of the interatrial septum (IAS) and specific intracardiac structures (Movie I). Using a standard catheterization technique, the ICE catheter (model 9900, EP Technologies, Boston Scientific Corp) is introduced into the superior vena cava and connected to an ultrasound console (model I5007, Boston Scientific Corp). An ECG and respiration gated and triggered catheter pullback is performed, and the right atrium is reconstructed on-line (Surgical View, TomTec). After 3D reconstruction, the details of the right atrial anatomy are readily recognized and a specific pacing site can be selected. After lead placement and electrical testing, another reconstruction is performed to verify the final position (Movies I through III).

This technique was first tested in pacing of the IAS, which has a fairly characteristic appearance on echocardiography. The clinical results in 15 patients are very promising with this guided pacing modality. We achieved a remarkable 43 ms mean reduction of the P-wave duration. This is more than reported in any previous study. Furthermore, in several patients, we observed that the roof of the right atrium is close to the aorta, and that the tissue between these structures is fairly narrow. Therefore, our approach may have advantages regarding safety issues as well.

The major limitation of this sophisticated lead positioning technique is that ICE with 3D reconstruction capabilities is currently available in a limited number of centers and requires additional training and experience. However, if real time 3D echocardiography is available, the desired pacing site could be achieved with 100% accuracy without use of fluoroscopy. This will be a major asset for imaging and interventional cardiac electrophysiology.

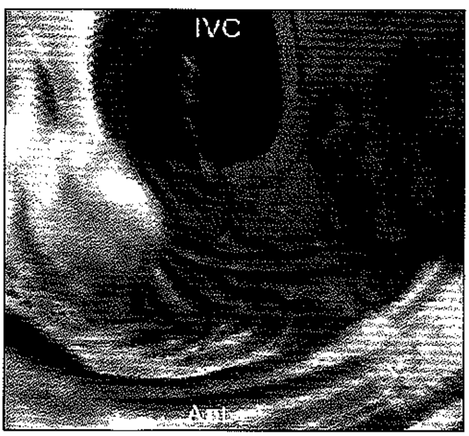

Figure 7. 'En face' view of the interatrial septum after three-dimesional reconstruction.

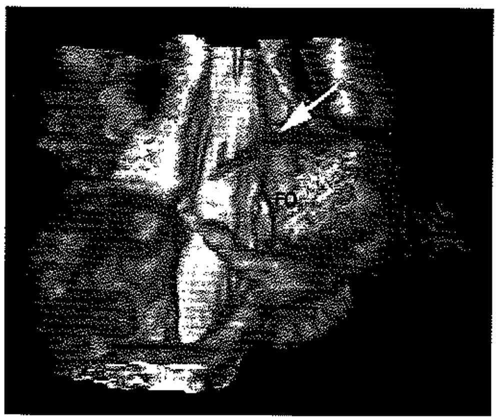

Figure 8. Three-dimensional visualisation of a pacemaker electrode in the right atrium.

From the Thoraxcentre, Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands.
Movies I, II, and II are available as an online-only Data Supplement at http://www.circulationaha.org.
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PART II.

GUIDANCE OF ELECTROPHYSIOLOGY PROCEDURES

Chapter 7

**T Szili-torok, GP Kimman, D Theuns, J Res, JRTC Roelandt ,
LJ Jordaens:**

TRANSSEPTAL LEFT HEART CATHETERIZATION GUIDED BY INTRACARDIAC ECHOCARDIOGRAPHY

Heart 2001; 86:e11

Transseptal left heart catheterisation guided by intracardiac echocardiography

T Szili-Torok, GP Kimman, D Theuns, J Res, J R T C Roelandt, L J Jordaens

Abstract

Objective—To develop a novel approach of transseptal puncture guided by intracardiac echocardiography and to assess its efficacy.

Methods—Transcatheter intracardiac echocardiography with a 9 MHz rotating transducer was performed to guide transseptal puncture in 12 patients (mean age 43.1 years, range 31–68) who underwent radiofrequency catheter ablation of left sided accessory pathways. Initially, the echocardiography and transseptal catheters were placed adjacent to each other in the superior vena cava and were withdrawn to the level of the fossa ovalis.

Results—The successful puncture site was associated with visualisation of the fossa ovalis (12 patients, 100%) and the aorta (12 patients, 100%), tenting of the fossa (six patients, 50%), penetration of the needle visualised by the ultrasound catheter (12 patients, 100 %), and echocardiographic contrast material applied in the left atrium (12 patients, 100%). The characteristic jump of the needle onto the fossa ovalis was observed simultaneously with fluoroscopy and intracardiac ultrasound (12 patients, 100%). All procedures were successful. There were no complications associated with the transseptal procedure.

Conclusions—Intracardiac echocardiography is feasible to guide transseptal puncture. The optimal puncture site can be assessed by simultaneous detection of the characteristic downward jump of the transseptal needle onto the fossa ovalis by intracardiac ultrasound and fluoroscopy.
(*Heart* 2001;86:e11)

Keywords: intracardiac echocardiography; transseptal catheterisation

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Echocardiography provides potentially useful information for electrophysiological studies and pacemaker implantation by visualisation of important anatomical landmarks and structures.[1 2] Transoesophageal echocardiography (TOE) improves visualisation for specific indications.[3] More recently, intracardiac echocardiography was used to guide radiofrequency catheter ablation for atrial flutter and other supraventricular arrhythmias.[4-6] Recently there has been renewed interest in transseptal left heart catheterisation caused by the development of left sided radiofrequency catheter ablation.[7-10] Although conventional left sided accessory pathway ablation is effectively performed with a retrograde approach, severe complications have been reported including damage of the aortic valve, peripheral arterial thromboembolic events, transient ischaemic attacks, dissection of the aorta, and endocarditis.[11-13] Some investigators prefer a transseptal approach towards the mitral ring, which gives improved catheter stability and has a comparable success rate.[8 14] However, a significant number of acute and potentially lethal complications with transseptal puncture may occur.[7 10] The aim of the present study was to establish a novel technique that can minimise the potential risks for acute complications in patients undergoing transseptal puncture.

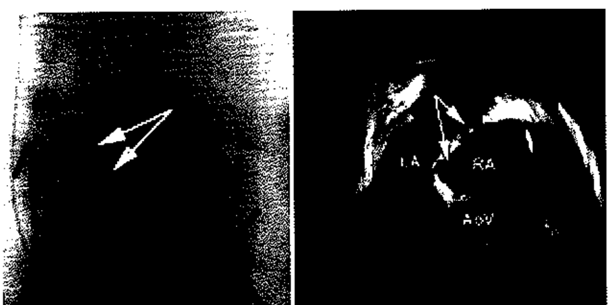

Figure 1 (A, left) Anteroposterior fluoroscopy view of the dilator sheath (double arrows) and the intracardiac ultrasound catheter at the time of the picture in panel B. (B, right) View of interatrial septum and fossa ovalis with intracardiac echocardiography. The double arrow is pointing to the dilator sheath and the intracardiac echocardiography probe. The dilator sheath is moving in the direction of the fossa ovalis from the contralateral side of the aortic valve. AoV, aortic valve; LA, left atrium; RA, right atrium.

Methods

PATIENT POPULATION

Twelve consecutive patients were recruited in this study who underwent left heart catheterisation for ablation of left sided accessory pathways. The mean age of the patients was 43.1 years (range 31–68); eight patients were women. None of the patients had structural heart disease.

ELECTROPHYSIOLOGICAL PROCEDURE

Standard electrophysiological study was undertaken under intravenous sedation with 5–10 mg diazepam. After a subclavian venipuncture, a 5 French decapolar diagnostic catheter (Supreme CS, DAIG Corp, St Jude Medical Inc, Minneapolis, Minnesota, USA) was inserted into the coronary sinus. Three 6 French quadripolar diagnostic catheters (Viking, Bard Electrophysiology, Lowell, Massachusetts, USA) were placed high in the right atrium, across the tricuspid valve to record the His potential and in the right ventricular apex. Bipolar intracardiac electrograms, filtered at a bandpass of 30–500 Hz, were

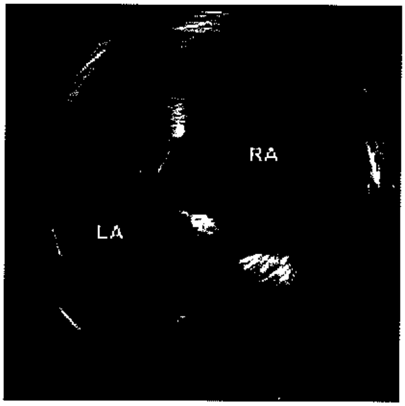

Figure 2 Tenting of the fossa can become very characteristic, as it in this case.

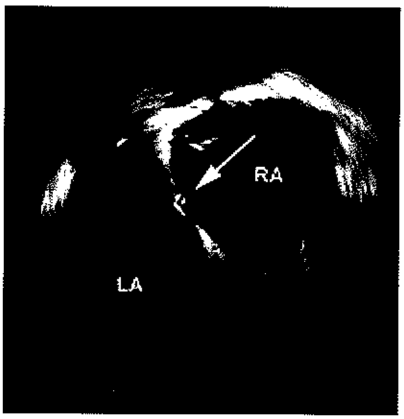

Figure 3 Image of the fossa ovalis after transseptal puncture. The transseptal sheath is penetrating the membrane of the interatrial septum.

recorded simultaneously with a 12 lead ECG (Prucka Engineering, Houston, Texas, USA). Electrophysiological testing was used to confirm the existence of left sided accessory pathways using antegrade and retrograde mapping with atrial and ventricular pacing.

TRANSSEPTAL PUNCTURE

After electrophysiological testing confirmed the existence of a left sided accessory pathway, the left femoral vein was punctured and an 8.5 French multipurpose introducer sheath with a long curve type (model 5662, EP Technologies, Boston Scientific Corp, San Jose, California, USA) was introduced into the superior vena cava (SVC). A 9 MHz rotating, intracardiac ultrasound transducer catheter (model 9900, EP Technologies, Boston Scientific Corp) was filled with 3–5 cm^3 sterile water and then connected to an ultrasound console (model I5007, Boston Scientific Corp). The images were displayed on a monitor and recorded on videotape. The ventricular pacing catheter was removed and replaced by a transseptal sheath (SL1, SL2, DAIG Corp), which was introduced to the SVC adjacent to the echocardiography catheter (fig 1A). The transseptal sheath was loaded with a Brockenbrough needle (DAIG Corp), which was advanced to within 1 cm of the dilator tip. The position was checked in three fluoroscopy views (anteroposterior, left anterior oblique, and right anterior oblique). The intracardiac echocardiography catheter was manually pulled back from the SVC in the direction of inferior vena cava. The pull back was stopped when the fossa ovalis appeared on the screen (fig 1B). The entire transseptal sheath was then withdrawn from the SVC to the right atrium. The movement of the transseptal dilator sheath from the SVC to the level of the fossa ovalis was simultaneously detected by fluoroscopy and intracardiac echocardiography. After a characteristic downward "jump" of the sheath, which is described as an indirect radiological sign of the position in the fossa, the sheath appeared directly in the view of the intracardiac echocardiography catheter. The transseptal sheath was always moving in the direction of the fossa ovalis from the contralateral site of the aortic valve (fig 1B). After the dilator sheath jumped onto the fossa ovalis, confirmed by the intracardiac ultrasound, the septum was approached with the needle (figs 2 and 3). Fluoroscopy and intracardiac echocardiography followed all of the attempts for transseptal puncture simultaneously. Echocardiographic contrast material was injected in to the left atrium and detected by echocardiography to confirm successful puncture. The dilator and the needle were withdrawn and 7000 IU of heparin was administered intravenously. The total procedure time was registered until successful puncture was achieved and confirmed.

Table 1 Results of intracardiac measurements and findings

Patient number	*FO size (mm)*	*FO-AW distance (mm)*	*Tenting*	*TFO-AW distance (mm)*	*AoV-FO*	*AoV-FO distance (mm)*	*Jump*	*Needle*	*Contrast detection in LA*
1	4.8	15.9	+	14.1	+	17.9	+	+	+
2	9.2	24.2	+	15.7	+	8.2	+	+	+
3	12.0	40.1	+	15.6	–	NA	+	+	+
4	9.0	40.0	–	NA	+	22.1	+	+	+
5	5.6	16.0	–	NA	+	9.3	+	+	+
6	11.2	33.4	–	NA	–	NA	+	+	+
7	6.2	42.7	–	NA	+	11.6	+	+	+
8	14.4	15.6	+	10.3	+	17.6	+	+	+
9	11.5	38.2	–	NA	–	NA	+	+	+
10	8.4	26.1	+	18.2	+	20.2	+	+	+
11	7.2	15.0	+	8.0	–	NA	+	+	+
12	5.4	23.3	–	NA	+	32.6	+	+	+

AoV, aortic valve; AW, atrial wall; FO, fossa ovalis; LA, left atrium; NA, not available; TFO, tented fossa ovalis.

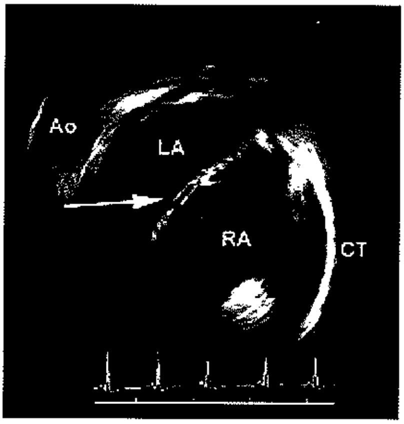

Figure 4 A rare case: a double membrane is clearly visible in the fossa ovalis. Next to the left atrium the aortic arch is visualised. Ao, aorta; CT, crista terminalis.

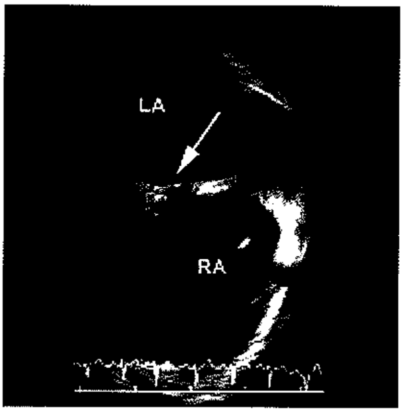

Figure 5 Small fossa ovalis detected by intracardiac echocardiography. In this patient the size of the fossa ovalis was 4.8 mm.

INTRACARDIAC MEASUREMENTS

Intracardiac measurements were taken off line. The size of the fossa ovalis, the distance between the fossa ovalis and left atrial wall, and the distance between the tented fossa and left atrial wall were measured.

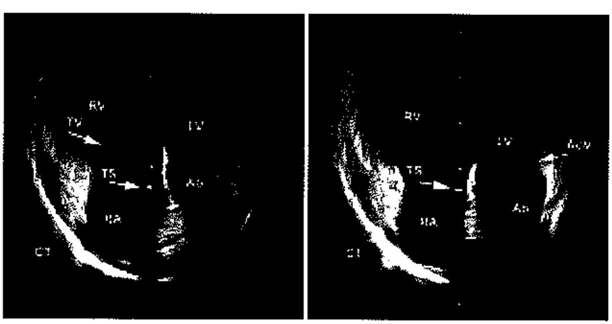

Figure 6 (A, left) The heart at the time of closure of the tricuspid valve. The morphology of the valve in the left side of the heart may be mistaken for the mitral valve; however, the location of the chambers and the asynchronous closure of the valves clearly indicates that this is the aortic valve. (B, right) The same chambers 400 ms later at the time of closure of the aortic valve. LV, left ventricle; MV, mitral valve; RV, right ventricle; TS, transseptal sheath (the dilator sheath that is pointing towards the membranous right atrial wall adjacent to the aorta at the level of aortic valve).

ABLATION PROCEDURE

After successful transseptal puncture, a standard ablation procedure was undertaken. A 7 French quadripolar mapping/ablation catheter (Model Celsius, type B, D, Biosense Webster Inc, Diamond Bar, California, USA) was used to map the mitral annulus and to deliver radiofrequency energy. Radiofrequency energy was applied to the atrial side of the mitral annulus with continuous atrial and ventricular signals during atrial pacing or during sinus rhythm. The successful pulses resulted in an abrupt loss of accessory pathway conduction. After ablation, ventricular pacing and the administration of intravenous adenosine (12 mg) were used to assess the loss of accessory pathway conduction.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean (SD). Non-parametric data were compared using Wilcoxon t test. Correlation analysis was performed using the Pearson test. The level of significance was set at $p = 0.05$.

Results

The mean duration of transseptal puncture was 17.4 (7.9) minutes (range 7.5–38 minutes). Intracardiac echocardiography visualised the following anatomical structures in all cases (12 patients, 100%, table 1): SVC, crista terminalis, and aortic valve. The pulmonary veins were visualised in only one case (8%). The view of the fossa ovalis was optimal in all patients. The fossa ovalis, the tip of the needle, the aortic valve, and the left atrial wall were visualised in a single ultrasound image in eight patients (66%) (fig 1B). In one patient a double membrane was detected in the fossa ovalis (fig 4). The image of the membrane of the fossa ovalis was stable throughout the procedure in 10 cases. In two cases minor adjustments of the ultrasound catheter were necessary to optimise the image during the procedure. The size of the visualised fossa ovalis was 8.7 (2.9) mm (range 4.8–14.4 mm). There was no correlation of the size of the fossa ovalis and the time to successful puncture (NS, $r = 0.11$). The distance between the fossa ovalis and the left atrial wall was 27.5 (10.8) mm (range 15–42.7 mm).

Movement of the transseptal sheath was visible in every case in real time. The characteristic downward jump of the catheter on to the membrane of the fossa ovalis was detected in every patient (12 patients, 100%). After the jump, the needle was visible in the fossa in every case (12 patients, 100%) (fig 5). Ultrasound showed the characteristic tenting of the fossa in six cases (50%) (fig 4). In the cases where the needle tented the fossa ovalis, the mean distance between the peak point of the fossa ovalis and the left atrial wall decreased from 27.5 (10.8) mm (range 15–42.7 mm) to 13.6 (3.7) mm (range 8.1–18.2 mm) ($p < 0.05$). The tented fossa did not abut on the left atrial wall in any of our cases. The distance between the needle before approaching the membrane and the aortic valve was 19.8 (6.2) mm (range 11–26.9 mm). The first attempt of transseptal puncture guided by intracardiac ultrasound was successful in 10 patients (83%). In one patient, the dilator sheath became dislocated after the septum was approached by the needle. The second attempt was successful. In one case only the third attempt was successful as the dilator sheath jumped twice onto the small thin wall between the right atrium and the aorta after the pull back (fig 6). Echocardiographic contrast injection was detected in the left atrium after every successful puncture (12 patients, 100%). There were no complications associated with the procedure.

Discussion

TRANSSEPTAL LEFT HEART CATHETERISATION

Percutaneous puncture of the interatrial septum was introduced for catheterisation of the left heart in 1960.[15] The technique relied on fluoroscopic landmarks to define anatomical boundaries.[15] In addition, the movement of the tip of the device from the thicker muscular septum to the thin wall of the fossa ovalis is an important sign that can be detected by experts without the need to puncture the femoral artery. Some investigators introduce additional anatomical landmarks such as a pigtail catheter in the aorta (which requires arterial puncture) or use the His bundle or coronary sinus catheters as a reference. However, transseptal catheterisation remains a difficult procedure, particularly in cases where the atrial anatomy is atypical or the fossa ovalis is small. Recently this technique became a frequently used method for left sided radiofrequency ablation.[11] Further, some sites in the left side cannot be reached with the retrograde technique. The major advantages of this technique are the stability of the catheter and the lack of peripheral arterial puncture. However, a complication rate between 3% and 5% has been reported. Most of the complications occur in the periprocedural period. A review of 1279 transseptal punctures in a single centre retrospective study found a 90% overall success rate, with 1.2% life threatening complications, including pericardial tamponade, systemic emboli, and death secondary to aortic perforation.[10] Another centre reported a 91% success rate with a slightly higher complication rate. Aortic puncture (0.7%), pericardial tamponade (3.2%), and systemic embolisation (1.1%) were the major complications.[7]

IMAGING TECHNIQUES GUIDING TRANSSEPTAL PUNCTURE

Imaging techniques such as TOE and two dimensional transthoracic echocardiography have been used for the assessment of the interatrial septum during transseptal puncture.[2 16-19] Both techniques have significant limitations. Transthoracic ultrasound may not be able to locate accurately the thin wall of the fossa ovalis. Furthermore, transthoracic echocardiography is fairly uncomfortable to perform without a risk of violation of sterility during the intervention. TOE was found to be feasible, but cardiac perforation was reported because of inadequate localisation of the fossa ovalis.[18] Furthermore, it carries the risk of oesophageal bleeding[18] and limits communication with the patient during the procedure. TOE may cause lengthening of the procedure because of the introduction of the oesophageal probe and requires intravenous sedation for a longer period.

INTRACARDIAC ULTRASOUND FOR TRANSSEPTAL PUNCTURE

Intracardiac ultrasound gives a view of the fossa ovalis with 100% accuracy.[5 20-22] This is a direct method and a possibility to avoid complications. In a recent study 53 patient underwent transseptal puncture by the guidance of intracardiac echocardiography.[23] The success rate of the first attempt was 96% and there were no complications associated with the procedure.[23] In previous studies, identification of the dilator tip was difficult.[24] In our study we confirmed a successful puncture by using contrast injection through the Brockenbrough needle. The appearance of contrast in the left atrium is a direct sign of successful puncture.

METHODOLOGICAL DIFFERENCES

In contrast with previous findings, in this study tenting of the membranous interatrial septum was detected in only one half of the patients. This is because of the differences in approaching the septum. After localisation of the transseptal sheath, we approached the septum directly with the needle. In the study of Daoud and colleagues[23] the dilator was used to cause tenting and the needle was forwarded after the sign of tenting was observed. This resulted in abutting of the fossa on the left atrial wall in a considerable proportion of the patients.[23] The dilator should then have been readjusted. In our study abutting on the left atrial wall was not detected. We recommend that after the jump, which can be detected simultaneously with fluoroscopy and intracardiac ultrasound, the interatrial septum be approached directly by the needle. This method requires confirmation of the location of the needle in the left atrium. By injection of echocardiographic contrast material this was achieved in all of our patients.

CLINICAL IMPACT

Compared with other imaging techniques intracardiac echocardiography has some significant advantages. The major advantage is excellent visualisation of the fossa ovalis. Furthermore, it provides the possibility of flexible planning of the procedure. Firstly, it does not require deep sedation. Secondly, it can be used comfortably for a longer time. No additional arterial puncture is required.

In conclusion, on the basis of growing experience with intracardiac echocardiography the method seems to be an additional tool to minimise the risk for dangerous complications during the puncture of interatrial septum.[15] In addition, the most useful indication of the optimal puncture site is the characteristic downward jump of the transseptal needle on to the fossa ovalis detected simultaneously with intracardiac ultrasound and fluoroscopy.

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Chapter 8

T Szili-Torok, GP Kimman, D Theuns, J Res, JRTC Roelandt,
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VISUALIZATION OF INTRACARDIAC STRUCTURES AND RADIOFREQUENCY LESIONS USING INTRACARDIAC ECHOCARDIOGRAPHY

Eur J Echocardiogr 2003; 4:17-22

Visualisation of Intra-cardiac Structures and Radiofrequency Lesions Using Intracardiac Echocardiography

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Aims: Fluoroscopy does not allow identification specific anatomical landmarks during electrophysiological studies. Intra-cardiac echocardiography permits visualization of these structures with excellent accuracy, but the optimal method has not been fully described. The aim of this study was to assess the capability of intra-cardiac echocardiography for the visualization of such structures using two different approaches. We also assessed its capability for the evaluation of radio frequency lesions 20 min after catheter ablation of the cavo-tricuspid isthmus.

Methods: Intra-cardiac echocardiography was performed using a 9 MHz rotating transducer in eight consecutive patients (age range: 37–76 years) after radio frequency ablation of the cavo-tricuspid isthmus. The ultrasound catheter was inserted through the femoral vein into the superior vena cava and was pulled back to the inferior vena cava. The echo catheter was then reinserted through the subclavian vein and advanced into the right ventricular apex and was pulled back from the right ventricular to the superior vena cava. Qualitative evaluation and intra-cardiac measurements were performed off-line.

Results: The fossa ovalis, the tricuspid valve, and the terminal crest were visible in all patients regardless of the method of introduction of the echo catheter. Left-sided structures were less accurately seen by intra-cardiac echocardiography. The horizontal diameter of the fossa ovalis was $8{\cdot}9 \pm 1{\cdot}8$ mm. The cavo-tricuspid isthmus was visible using the femoral approach in three patients. The isthmus could be visualized in all patients, and in three patients together with the ostium of the coronary sinus, using the subclavian approach. radio frequency lesions were not visible 20 min after ablation. Additionally, both the left and right ventricles could be seen using the subclavian approach.

Conclusions: The subclavian approach is feasible, safe and superior to visualize the isthmus. Twenty minutes after radio frequency ablation of the cavo-tricuspid isthmus radio frequency lesions are not visible using intra-cardiac echocardiography.
(Eur J Echocardiography 2003; 4: 17–22)

Key Words: intracardiac echocardiography; ablation; isthmus; flutter.

Introduction

Arial flutter is a frequent arrhythmia due to re-entry around the large vascular structures in the right atrium[1,2]. Radio frequency (RF) catheter ablation is an effective method in management of atrial flutter[3]. However, a considerable proportion of the cases is unsuccessful and a substantial number of patients have recurrences[3]. One possible explanation for the unsuccessful procedures and recurrences is related to anatomical variations of the cavo-tricuspid isthmus. Furthermore, radio frequency lesions can be inadequate, allowing slow conduction through the cavo-tricuspid isthmus. Fluoroscopy does not allow identification of important anatomic landmarks during electrophysiological studies. Improved imaging techniques such as

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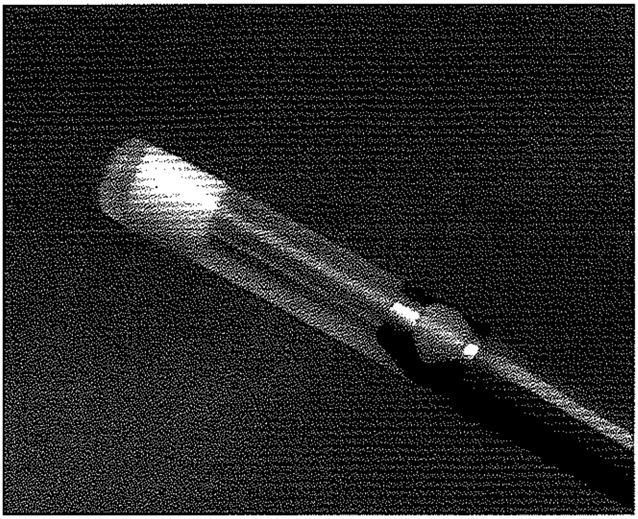

Figure 1. The ultrasound transducer, showing a distal sonolucent sheath, which houses the rotating echotransducer.

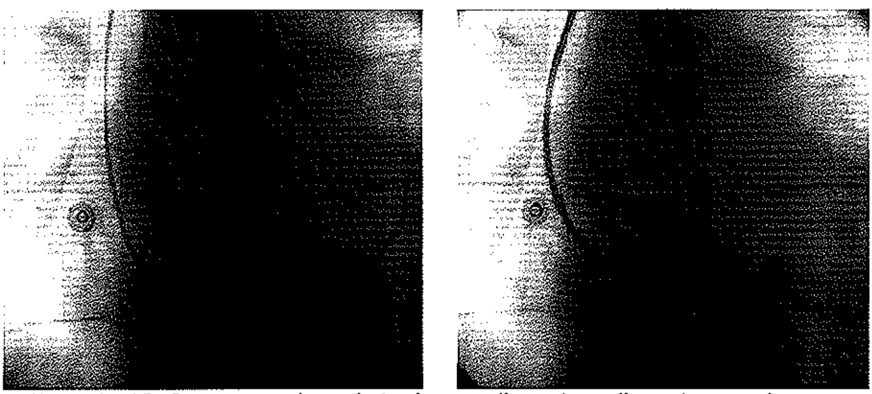

Figure 2. AP fluoroscopy view of the intra-cardiac echocardiography transducer introduced into the heart. Left panel: femoral approach; right panel: subclavian approach.

intra-cardiac echocardiography may have a role to improve success rate of radio frequency ablations by guiding these procedures[4,5]. Although intra-cardiac echocardiography allows guiding of electrophysiological procedures by visualizing important structures, there are controversial data available about its capability to assess the radio frequency lesions after ablation[6–8]. The aim of the present study was to test two different approaches for visualization of anatomical structures and radio frequency lesions. We compared the capability of intra-cardiac echocardiography imaging using two different entry sites such as the femoral vein (inferior approach) and the subclavian vein (superior approach). Furthermore, we assessed radio frequency lesions in the cavo-tricuspid isthmus region 20 min after radio frequency ablation of the cavo-tricuspid isthmus.

Methods

Study Patients

Eight consecutive patients who underwent radio frequency ablation of typical atrial flutter were included in this study. The mean age of the patients was 56 ± 11·1 years (range: 37–76). Three patients were women.

Electrophysiological Procedure

Standard electrophysiological studies were performed under intravenous sedation with 5–10 mg diazepam. After a subclavian venipuncture, a 5 F decapolar diagnostic catheter (Supreme CS, DAIG Corp. St. Jude

Table 1. Demographic and echocardiography data of the patients

No. of patients (*n*)	8
Age (years)	56 ± 11·1
Gender (M/F)	5/3
Other/underlying cardiac disease	
Other SVT (*n*)	1
Hypertension (*n*)	3
Afib (*n*)	4
VHD (*n*)	4
Cardiac dimensions	
LA (mm)	42·5 ± 7·3
LV EDD (mm)	55·6 ± 7·5
LV ESD (mm)	34·5 ± 9·8
IVS (mm)	10·1 ± 3·7

n=number of patients, M=male, F=female.
SVT=supraventricular tachycardia; Afib=atrial fibrillation; VHD=valvular heart disease; LA=left atrium; LV EDD=end-diastolic diameter of left ventricle; LV ESD=end-systolic diameter of left ventricle; IVS=intra-ventricular septum.

Medical Inc, Minnesota, MN, U.S.A.) was inserted into the coronary sinus through a short vascular sheath. In one patient there subclavian venous access could not been achieved. A steerable 20-pole Orbiter catheter (Bard, U.S.A.) was positioned around the tricuspid annulus. 5000 IU of heparin was administered intravenously. A Cosio radio frequency mapping/ablation catheter (Medtronic, U.S.A.) was used for mapping the critical isthmus between the inferior vena cava and the posterior tricuspid annulus. All patients underwent an anatomically guided catheter-based ablation with creation a line of lesions from the posterior part of the tricuspid annulus to the inferior vena cava. Successful ablation was assessed by demonstration a bi-directional block using conventional pacing techniques.

Intra-cardiac Echocardiography Imaging

The mechanical intravascular ultrasound and intracardiac echocardiography system ClearView (CardioVascular Imaging Systems Inc, Fremont, CA) was used with a 8F sheath-based intra-cardiac echocardiography imaging catheter that incorporated a 9 MHz bevelled single-element transducer rotating at 1800 rpm (model 9900, EP Technologies, Boston Scientific Corp., San Jose, CA, U.S.A.). These catheters are equipped with an 1-cm long sonolucent distal sheath, which has a lumen housing the imaging transducer (Fig. 1). This sheath prevents direct contact of the imaging core with the cardiac wall. The intra-cardiac echocardiography catheter is filled with 3–5 cc sterile water and then connected to an ultrasound console (model I5007, Boston Scientific Corp., San Jose, CA, U.S.A.). This catheter obtains cross-sectional images in a plane, which is perpendicular to its long axis. The images are displayed on a monitor and recorded on videotape. The position of the catheter is checked in three fluoroscopy views (AP, LAO, RAO). The ultrasound catheter is initially inserted through the femoral vein into the superior vena cava and is pulled back to the inferior vena cava inferior vena cava. The multipolar electrode catheter was removed from the coronary sinus, and the short vascular sheath was exchanged for an 8F and 60 cm long straight vascular sheath. The echo catheter is then reinserted through this sheath into the right ventricular apex and pulled back from the right ventricle to the superior vena cava during continuous recording of two-dimensional images (Fig. 2). Qualitative analysis and intra-cardiac measurements are performed off-line. Data are reported as mean ± standard deviation.

Results

Clinical characteristics of the patients are shown in Table 1. Radio frequency catheter ablation of the flutter circuit was successful in all cases. The mean number of radio frequency applications was 19 ± 4·2. The procedure and fluoroscopy times were 203 ± 91·6 min and 55 ± 34·4 min, respectively. The results regarding visualization of anatomically important structures and radio frequency lesions are shown in Table 2. The fossa ovalis, the tricuspid valve, the terminal crest were visible in all cases regardless the way of introduction of the echo catheter (Fig. 3). The size of the fossa ovalis was 8·9 ± 1·8 mm. Left-sided structures such as the mitral valve, aortic valve and the aorta were less visible but were not different using the two approaches. The cavotricuspid isthmus was poorly visible (three patients/37%) using the femoral approach (Fig. 4). The isthmus could be visualized in all patients using the subclavian approach (eight patients/100%). In addition, in three patients the ostium of the coronary sinus was visible (three patients/37%) (Fig. 5). Both the left and right ventricles could be seen using the subclavian approach, and were not visualized by the femoral approach (Fig. 6). Radio frequency lesions and more particularly craters were not observed 20 min after ablation. There were no observable differences between the ablated region and other cardiac walls (Figs 4 and 5). The echodensity of the wall was not different from adjacent regions. There were no complications related to radio frequency ablation and/or intra-cardiac echocardiography catheterization.

Discussion

The main findings of our study are that, the isthmus is better visualized using the subclavian approach rather than by the femoral approach using a non-steerable catheter. The radio frequency lesions are not visible using this technique 20 min after the procedure.

The Role of Intra-cardiac Echocardiography in Ablation of Atrial Flutter

Radio frequency catheter ablation is an option in management of atrial flutter[3]. The aim of the procedure to

Table 2 Comparison of visualisation of intracardiac structures

Pt. no.	Ao	AoV	TV	MV	PV	PA	CS	isthmus	FO	Size: FO (mm)
Femoral approach										
1.	–	–	+	–	–	–	–	–	+	7·7
2.	+	–	+	+	–	+	–	+	+	7·2
3.	+	–	+	–	+	–	–	–	+	12·1
4.	+	–	+	+	–	–	–	+	+	10·9
5.	+	–	+	–	–	–	–	+	+	7·2
6.	+	–	+	–	–	–	–	–	+	7·4
7.	+	+	+	–	–	+	–	–	+	10
8.	+	+	+	–	–	+	–	–	+	9·1

Pt. no.	LV, RV	Ao	AoV	TV	MV	PV	PA	CS	isthmus	FO
Subclavian approach										
1.	+	–	+	+	–	–	–	–	+	–
2.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
3.	+	+	+	+	–	–	–	+	+	+
4.	+	+	–	+	+	–	–	+	+	+
5.	+	+	–	+	–	–	–	–	+	+
6.	+	+	–	+	–	–	–	–	+	+
7.	+	+	+	+	+	–	+	+	+	+
8.	+	+	+	+	+	–	+	–	+	+

Ao=Aorta; AoV=Aortic valve; TV=tricuspid valve; Mv=mitral valve; PV=pulmonary veins; PA=pulmonary artery; CS=coronary sinus; FO=oval fossa; LV=left ventricle; RV=right ventricle.

create a lesion over the isthmus, the region between the inferior vena cava and the posterior region of the tricuspid valve interrupting the re-entry circuit. Although the procedure has a success rate over 90%, approximately 10% of the patients have recurrences necessitating a second procedure. Obviously, these procedures add significant radiation exposure and a risk of other complications[3]. Intra-cardiac ultrasound can visualize intra-cardiac structures[9–11]. Occasionally, atrial malformations can be detected in the region of interest. Dimensions of the isthmus can be measured and the alignation and correct apposition to the tissue of the catheters can be judged[12]. According to our results, pulling back the intra-cardiac echocardiography catheter from the right ventricle through the tricuspid valve after left subclavian venipuncture provides a better image than a pullback from the superior vena cava to inferior vena cava on this important region. Therefore visualization of important anatomical structures and observation anatomical variations is more appropriate with a superior approach.

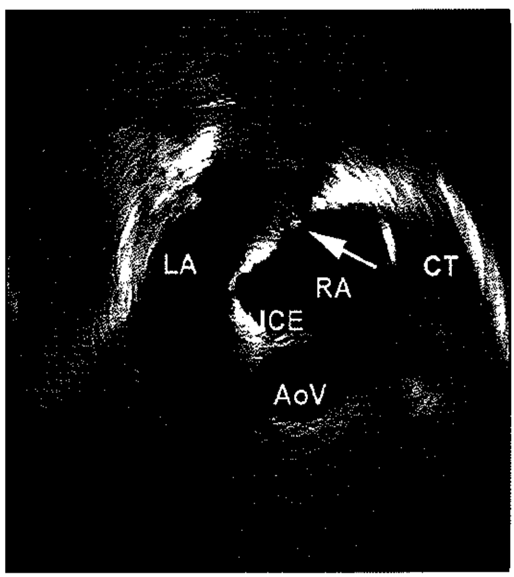

Figure 3. Visualization of electrophysiologically important structures obtained by the femoral approach. The crista terminalis, the aortic valve, and the fossa ovalis are visible together with the left atrium. The arrow shows the cross-section of a diagnostic catheter. LA=left atrium, RA=right atrium, AoV=aortic valve, CT=crista terminalis, ICE=central artefact of the intra-cardiac echo transducer.

Ablation Lesion Assessment

It was hypothesized that tissue changes may be detected using intra-cardiac echocardiography. Crater formation and increased echodensity was reported immediately after radio frequency ablation[7]. Despite these early and

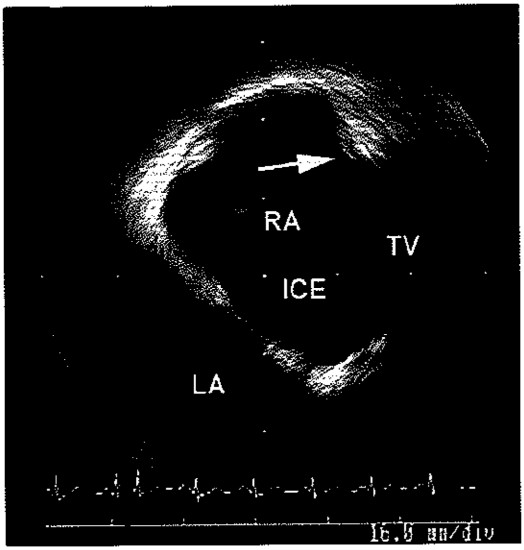

Figure 4. Visualization of the cavo-tricuspid isthmus using the femoral approach. The isthmus can be seen above the tricuspid valve (arrow). RA=right atrium, LA=left atrium, TV=tricuspid valve, ICE=central artefact of the intra-cardiac echo transducer

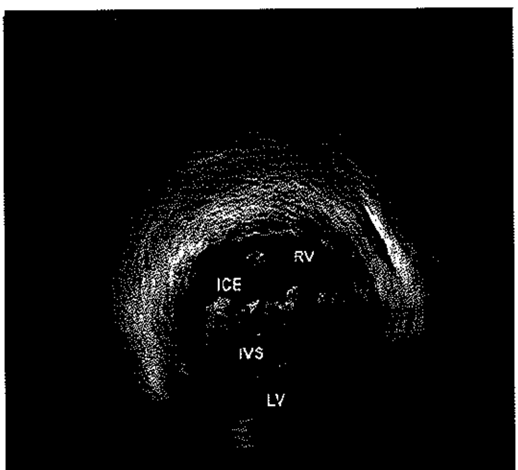

Figure 5. The isthmus is optimally visualized using the subclavian approach (arrow). The ostium of the coronary sinus is also visible. CT=crista terminalis, RA=right atrium, IVC=inferior vena cava, TV=tricuspid valve, os CS=ostium of the coronary sinus, ICE=central artefact of the intra-cardiac echo transducer.

promising reports we could not observe any changes in the ablated region after linear ablation. We did not see craters 20 min after radio frequency ablation. Possible

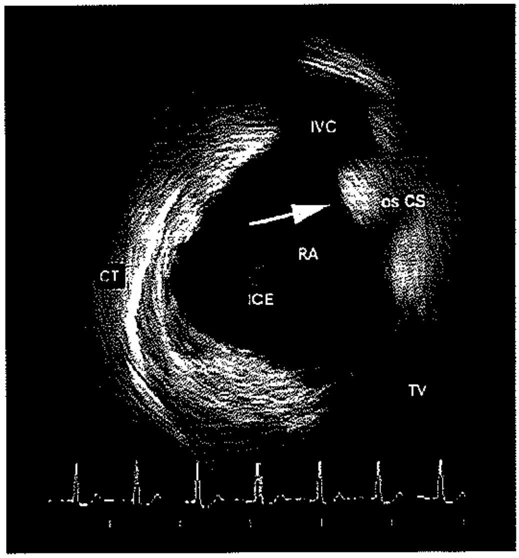

Figure 6. The left and right ventricles are exclusively visualized by the subclavian approach. RV=right ventricle, LV=left ventricle, IVS=intraventricular septum, ICE=central artefact of the intra-cardiac echo transducer.

explanation for this finding is related to the timing of our examinations, as we assessed the lesions 20 min after radio frequency ablation to exclude temporary changes.

Future Clinical Applications

The ostium of the coronary sinus could be optimally visualized in some patients during subclavian insertion of the intra-cardiac echocardiography catheter. Similar images could not be obtained using the femoral approach and this non-steerable ultrasound system. Novel, steerable catheters are also available[13]; however, these catheters substantially increase the cost of the procedure. Regardless this issue, intra-cardiac echocardiography seems to be a feasible guiding tool for cannulation the ostium of the coronary sinus if necessary during electrophysiology and multisite pacing procedures. For visualization of radio frequency lesion further developments such as tissue characterization are necessary.

In conclusion, the subclavian approach is a feasible technique to perform intra-cardiac echocardiography and using a non-steerable echocardiography probe it is more appropriate to visualize the inferior vena cava-tricuspid annulus isthmus than the conventional femoral approach. Radio frequency lesions cannot be identified 20 min after creation using this 9 MHz fixed frequency intracardiac ultrasound probe in the absence of baseline pre-ablation intra-cardiac imaging.

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Chapter 9

T Szili-Torok, GP Kimman, MF Scholten, FJ Ten Cate, LJ Jordaens, JRTC Roelandt:

THREE-DIMENSIONAL MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY: A NOVEL METHOD TO ASSESS ABLATION LESIONS IN KOCH'S TRIANGLE IN HUMANS

(submitted for publication)

Ablation Lesions in Koch's Triangle Assessed by Three-Dimensional Myocardial Contrast Echocardiography

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Submitted for publication

Abstract:

Background: Myocardial contrast echocardiography (MCE) allows visualization of radiofrequency (RF) ablation lesions in the left ventricle in an animal model. Aim: To test whether MCE allows visualization of RF and cryo ablation lesions in the human right atrium using three-dimensional echocardiography. Methods: 12 patients underwent catheter ablation of a supraventricular tachycardia and were included in this prospective single-blind study. Eight patients were ablated inside Koch's triangle and 4, who served as controls, outside this area. Three-dimensional echocardiography of Koch's triangle was performed before and after the ablation procedure in all patients, using respiration and ECG gated pullback of a 9 MHz ICE transducer, with and without continuous intravenous echocontrast infusion (SonoVue, Bracco). Two independent observers analyzed the data off-line. Results: MCE identified ablation lesions as a low contrast area within the normal atrial myocardial tissue. Craters on the endocardial surface were seen in all 8 patients after ablation. Lesions were identified in 7 out of 8 patients (87%). None of the control patients were recognized as having been ablated. The confidence score of the independent echo reviewer tended to be higher when the number of applications increased. Conclusions: 1. MCE allows visualization of ablation lesions in the human atrial myocardium. 2. Both RF and cryo energy lesions can be identified using MCE.

Introduction:

Catheter ablation is a curative treatment for most patients with arrhythmias. In some patients, the results are still suboptimal(1) because of inadequate lesion formation during ablation. Therefore, in these patients direct visualization of ablation lesions may have significant impact on the outcome of the ablation procedures. Direct visualization can also provide additional information for both the development and testing of new dedicated ablation tools. Intracardiac echocardiography (ICE) has been extensively investigated for this purpose(2-5), but the reported results are disappointing(4,6). Recently, myocardial contrast echocardiography (MCE) has been tested for visualization of ablation lesions in animals in the left ventricle during continuous intracoronary echocontrast infusion(7). The aim of the present study was to assess the potential use of MCE to demonstrate ablation lesions in human atrial myocardial tissue with continuous venous echocontrast administration.

Methods:

Patients and study protocol:

Twelve patients were included into this study. The clinical characteristics of the patients are shown in Table 1. All patients underwent EP study and subsequent ablation procedures for supraventricular tachycardia. The ethics committee of Erasmus MC, Rotterdam, The Netherlands approved this study. Written, informed consent was obtained. Regardless of the final diagnosis, Koch's triangle was visualized with ICE in all patients at baseline without echocontrast and immediately thereafter, during continuous echocontrast infusion (SonoVue, Bracco). After the ablation procedure, which was either inside or outside Koch's triangle, the ICE procedure was repeated using echocontrast. All ICE procedures were performed using a respiration and ECG gated and triggered pullback technique allowing three dimensional (3D) reconstruction of Koch's triangle. All 2D recordings were analyzed off-line by two independent echocardiographers and they provided confidence scores using a 1-10 grade scale. 3D reconstruction of the ablation lesions was performed in patients where ablation lesions were seen. This protocol implies that the study was double controlled. In principle, all patients served as their own control (self-controlled study design). On the other hand patients ablated outside Koch's triangle served as a second control group. Since the echo reviewers were independent this was a single blind study.

Electrophysiology testing and ablation:

Standard electrophysiology (EP) and ablation procedures were undertaken. Three 6F quadripolar electrode catheters were inserted into the right femoral vein and positioned in the high right atrium, across the tricuspid valve to record the His bundle electrogram, and in the right ventricle. A decapolar diagnostic electrode catheter was inserted into the coronary sinus (CS) through the subclavian vein. The initial portion of the EP procedure was directed at determining the presence of dual AV nodal physiology or accessory pathways, measuring the conduction properties and refractory periods of the fast and slow AV nodal pathways (if present), and determining the mechanism of the paroxysmal SVT. Programmed stimulation and incremental pacing were used in the right atrium and ventricle. Mapping was performed and after the target site was identified, ablation was applied. Cryothermy and radiofrequency energy were used alternately during the study period.

Myocardial contrast echocardiography:

MCE was performed using SonoVue (Bracco), which is a second generation contrast agent made of microbubbles stabilized by phospholipids and containing sulphur hexafluoride, an innocuous gas. The mean bubble diameter is 2.5 μm and more than 90% of the bubbles are smaller than 8 μm. The blood level curve shows a distribution half-life of about 1 minute and an elimination half-life of about 6 minutes(8). In this study we administered SonoVue by continuous intravenous infusion through the cubital vein at a rate of 100 ml/hour. Gain settings were not changed throughout the study.

Intracardiac echocardiography (ICE):

The ClearView™ system (CardioVascular Imaging Systems Inc, Fremont, CA) was used with an 8F sheath-based ICE imaging catheter that incorporates a 9 MHz beveled single-element transducer rotating at 1800 rpm (model 9900, EP Technologies, Boston Scientific Corp., San Jose, CA, USA).

ECG- and respiration-gated image acquisition and 3-D image processing:

A custom-designed ECG- and respiratory-gated pullback device and a 3D-ultrasound workstation (EchoScan, TomTec GmbH, Munich, Germany) were used to acquire and process the ICE images. The pullback device is controlled by the 3D workstation and uses a stepping motor to move the catheter stepwise and linearly through the right atrium. The workstation receives video input from the ICE system and an ECG- and respiration-signal (impedance measurement) from the patient. Prior to the acquisition run, the range of RR- and breathing-intervals are measured to define the upper- and lower-limits. The workstation starts acquisition of 2D images after detecting the peak of the R-wave and in the same phase of respiration, at a speed of 25 images/ sec (image interval 40 ms). After acquiring one cardiac cycle, the workstation stores the images, and the catheter is then pulled back by a 0.5-mm axial increment. This process is repeated until the inferior vena cava (IVC) is reached. The acquisition time is much shortened when all cardiac cycles are of the same length, therefore, the right ventricular apex is paced at 100 bpm. In accordance with their timing in the cardiac cycle, all images are formatted in volumetric data sets (256*256*256 pixels/each 8 bits). During post-processing, several algorithms are applied to reduce noise, enhance edges, and reduce spatial artifacts (ROSA filter).

Statistical analysis:

Continuous variables are expressed as mean ± standard deviation. Correlation analysis between the confidence scores and number of ablation lesions were performed using Pearson's test. The level of significance was set at a p value of 0.05.

Results:

Ablation results (Table 1):

Of the 12 patients undergoing catheter ablation of supraventricular arrhythmias 8 had AVNRT tachycardia. 4 out of these 8 patients were ablated using cryothermy. All but one patient were successfully ablated (one patient with AVNRT). The number of applications in Koch's triangle was 6±4.9, ranging from 1 to 15 applications. The fluoroscopy and procedure times were 45.7±30.8 min and 196±80.2 min, respectively.

Myocardial contrast echocardiography (Table 2):

MCE identified ablation lesions as a low contrast area within the normal atrial myocardial tissue (Figure 1). Lesions were identified in 7 out of 8 patients (87%) ablated in Koch's triangle. In only one patient with a single radiofrequency application, was the lesion not recognized. None of the control patients were recognized as having been ablated. The average confidence scores of the independent echo reviewers were 8.5±2.4 and 8.1±2.4, respectively. Both reviewer's confidence scores ranged from 3-10. The confidence score of the independent echo reviewer tended to be higher when the number of applications increased ($r=0.87$, $p< 0.05$). Craters on the endocardial surface were seen in all 8 patients after ablation, by both echo reviewers (Figures 1 and 2).

3D reconstruction of the lesion:

Koch's triangle was successfully reconstructed in 3D in all patients in whom the ablation lesion was previously identified. Lesions could be easily found by 3D echocardiography. An "en face" view of the lesion could be reconstructed in all of these patients (Figure 2).

Discussion:

This study demonstrates that MCE allows visualization of ablation lesions in the human right atrial myocardium during continuous venous echocontrast infusion. This potentially opens a new avenue for objective, and easily accessible evaluation of ablation lesions. Since transmural lesion formation is critical for successful ablation, the MCE method may have a significant impact on the outcome of ablation procedures.

The role of echocardiography in assessment of ablation lesions:

Crater formation and tissue changes as increased echo-density have been detected using ICE immediately after RF ablation(9,10). However, the lesions are not always seen after ablation and indirect signs are being searched for such as changes in local wall thickness(2,3,6). The magnitude of the observed changes showed a certain level of correlation with the lesion size. These indirect signs may indicate appropriate lesion formation, but there is an obvious need for direct visualization of the lesions. MCE offers this potential and has allowed visualization of ablation lesions in animals in the left ventricle during continuous intracoronary echocontrast perfusion(7). The investigators demonstrated high accuracy and reliability in visualizing tissue damage. Human use does not seem to be practical in this way and neither was safety assessed. In the present study we used continuous peripheral venous echocontrast infusion and we screened lesions in Koch's triangle in humans. We showed in atrial myocardial tissue that the lesions can be visualized and continuous venous infusion provides sufficient differences in echo contrast intensity to directly visualize ablation lesions after focal ablation. In this study we used cryothermy as well as radiofrequency energy for creating lesions in Koch's triangle. We do not have a sufficient number of patients for volumetric comparison of ablation lesions using this method, but it seems that both types of ablation lesion can be reliably visualized using this technique.

Limitations of the study:

This single blind double controlled study allowed two independent reviewers to examine the 2D ICE recordings. Although in none of the control patients a lesion in the area of interest was recognized, there was one patient with a single ablation lesion who was not identified by the two independent reviewers. This may suggest that the sensitivity of the technique is still suboptimal. One possible reason is that the concentration of the echocontrast infusion was titrated too low. This is also reflected in the results of the confidence scores. These showed a linear correlation with the number of applications.

The role of 3D reconstruction and future clinical implications:

MCE in combination with a 3D-reconstruction technique allows study of the depth and the shape of the ablation lesion more accurately. Theoretically, with 3D reconstruction, the volume of the lesion can be determined. This could potentially be a major asset for clinical electrophysiology since on line 3D echocardiography would allow real-time assessment of ablation lesions. Most importantly, the appropriateness of such lesions could be judged during linear ablations and the continuity of the lines could be checked.

In conclusion, MCE is a safe and promising new method to detect ablation lesion in the human atrial tissue.

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Table 1

Clinical characteristics and procedural outcome of the study patients

	Overall group	RF group	Cryo group
Number of patients (n)	12	6	6
Gender (F/M)	6/6	4/2	2/4
Age (years±SD)	48.8±16.6	46±13	51.6±20.4
AVNRT (n)	8	4	4
AP (n)	4	2	2
Successful ablation (n)	11	6	5
Procedure time (min±SD)	196±80.2	174.5±48.7	204.6±93.4
Fluoroscopy time (min±SD)	45.7±30.8	45.5±31.8	45.8±33.5
RF/cryo applications (n)	6±4.9	7.6±7.0	5±3.8

n= number, F= female, M= male, AVNRT= atrio-ventricular nodal reentry tachycardia, AP= accessory pathway, min= minutes, RF= radiofrequency, cryo= cryothermy, SD= standard deviation

Table 2

Results of myocardial contrast echocardiography in patients ablated in Koch's triangle

		Reviewer 1			Reviewer 2		
Pt. No	Ablation energy	Lesion before ablation	Lesion after ablation	CS	Lesion before ablation	Lesion after ablation	CS
1	RF	-	+	10	-	+	10
2	Cryo	-	+	5	-	+	6
3	RF	-	-	3	-	-	3
4	Cryo	-	+	8	-	+	6
5	RF	-	+	10	-	+	10
6	Cryo	-	+	10	-	+	10
7	RF	-	+	10	-	+	7
8	Cryo	-	+	10	-	+	10

RF= radiofrequency, Cryo= cryothermy, No= number, CS= confidence score, Pt= patient

Figure legends:

Figure 1

Two-dimensional intracardiac echocardiography images showing the postero-septal aspect of the tricuspid valve under three different conditions. Left hand panel: native 2D horizontal cross-sectional echocardiography image before ablation. Middle panel: the same region before ablation with use of echocontrast. Right hand panel: The same region after cryo energy ablation and echocontrast infusion. The ablation lesion (arrow) is visualized as a low contrast area within the atrial myocardial tissue. A crater can be seen on the ventricular side. ICE= central artifact of the intracardiac echocardiography catheter, TV= tricuspid valve, RV= right ventricle, RA= right atrium

Figure 2

Three-dimensional reconstruction of Koch's triangle: "En face" view of a radiofrequency ablation lesion (arrow). The crater on the right atrial endocardial surface is also well visualized directly to the right.

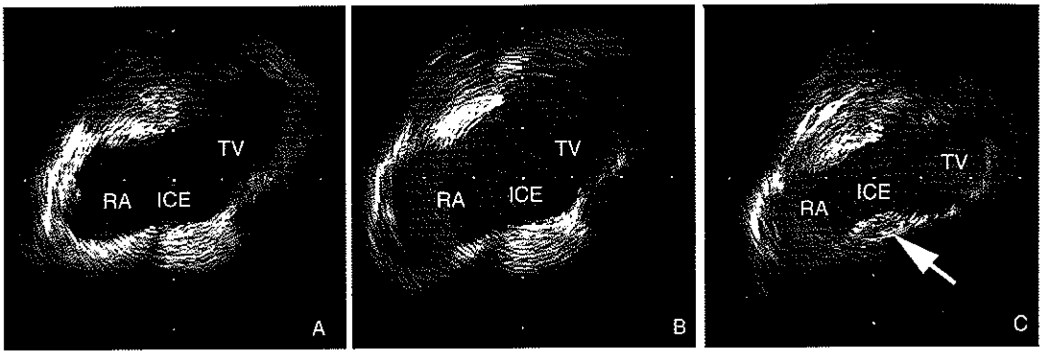

Figure 1

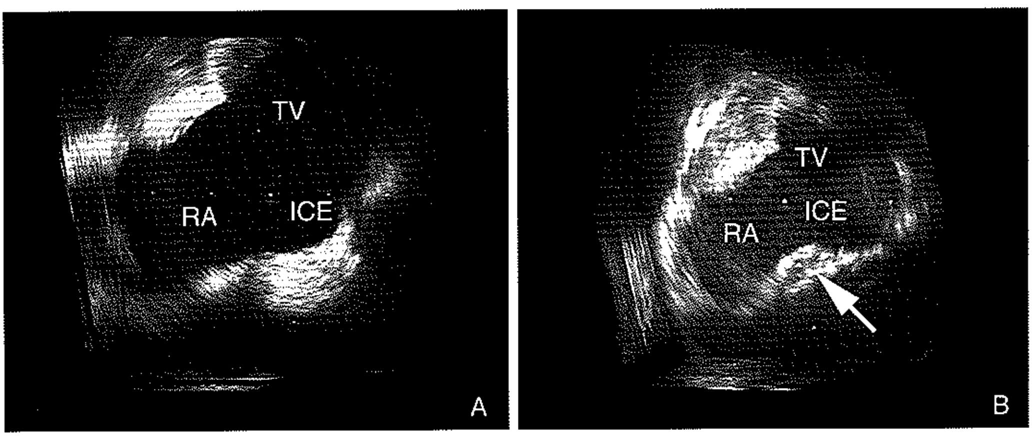

Figure 2

Chapter 10

MF Scholten, T Szili-Torok, GP Kimman, J Res, DAMJ Theuns, LJ Jordaens:

RIGHT ATRIAL LINEAR ABLATION FOR PAROXYSMAL AF GUIDED BY INTRACARDIAC ECHOCARDIOGRAPHY

Thoraxcentre Journal 2002; 14:27-29

CASE REPORT

Right atrial linear ablation for paroxysmal AF guided by intracardiac echocardiography

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Introduction

Atrial fibrillation (AF) is an entity with a significant increase in mortality and morbidity including thrombo-embolic events, worsening of heart failure and is associated with a diminished quality of life. The main therapeutic options are maintenance of sinus rhythm (SR) or control of ventricular rate. Maintenance of SR with class Ia or class III anti-arrhythmic drugs (AADs) is a option, however the shortcoming of this approach is the potential pro-arrhythmic effect and the lack of efficacy. Rate control can be achieved either by drugs or by AV node ablation and permanent pacemaker implantation.

The aim of this case report is to demonstrate the possible role of a novel combined approach of ablation and drug therapy in maintaining sinus rhythm in a patient with highly symptomatic paroxysmal AF. The second aim is to show how intracardiac echocardiography can contribute to the efficacy of radio frequency (RF) catheter ablation.

Case presentation

A 58-year-old man presented with highly symptomatic paroxysmal AF (*Figure 1*) resistant to treatment with anti-arrhythmic drugs (AADs) including amiodarone. Despite treatment with varying AAD's during the past years he experienced long (several hours) attacks of palpitations every three days, accompanied by severe dyspnoea and occasionally angina. The patient had hypercholesterolaemia, hypertension and had coronary artery bypass operation five years earlier. He was referred for AV node ablation and permanent pacemaker implantation. On admission the patient was on amiodarone and metoprolol. Amiodarone was replaced by flecainide 100 mg BID, which didn't alter the frequency of tachycardia attacks.

On physical examination no coarse abnormalities, particularly any signs of heart failure, were found. His blood pressure was 180/80 mmHg. Echocardiography showed a slightly enlarged (50 mm) left atrium and a mildly depressed left ventricular function. Electrocardiography (ECG) showed sinus rhythm with a PR duration of 200 ms and a left bundle branch block (LBBB).

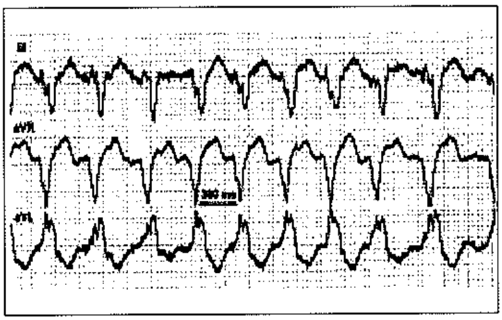

Figure 1. AF, rapid ventricular rate, LBBB

During palpitations, AF was recorded on a Holter-ECG with a high average ventricular rate (180 bpm) (*Figure 1*). A certain degree of "organisation" was detected (*Figure 2*). Because we wanted to avoid pacemaker implantation we proposed a modified radiofrequency catheter ablation (RF ablation) in two sessions.

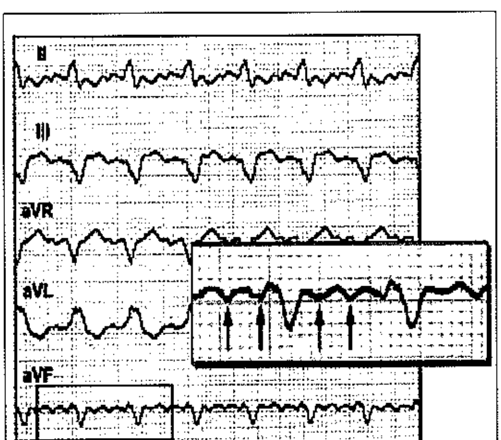

Figure 2. "Organisation" of the AF in to a flutter-like type arrhythmia

All surface ECG and intracardiac signals were recorded on a digital acquisition system (Cardiolab 4.0, Prucka Engineering, Inc., Houston, TX, USA). The RF current for focal and linear ablation was generated by a Stöckert generator (Cordis Webster, Baldwin Park, CA, USA) to achieve a tip-tissue interface temperature of 60 °C for up to 60 seconds.

RF ablation of the isthmus

In the first session, a 5 Fr decapolar electrode catheter (Supreme CS , Daig Corp, St Jude Medical Inc, Minnetonka, MN, USA) was advanced through the left subclavian vein and positioned in the coronary sinus (CS). Via the right femoral vein a 7 Fr steerable multipolar electrode catheter (Orbiter ST, Bard Electrophysiology, Billerica, MA, USA) was positioned in the right atrium along the anterolateral wall with the proximal electrodes at the level of the low atrial septum and the distal electrodes at the low right atrium close to the lateral edge of the cavo-tricuspid isthmus.

RF ablation of the inferior vena cava-tricuspid annulus isthmus was performed during sinus rhythm using an ablation catheter with a deflectable 8 mm tip (Conductor, Medtronic, Minneapolis, MN, USA). The target sites for RF ablation were selected using an anatomical approach. A line of overlapping lesions was created from the tricuspid valve towards the inferior caval vein. Success of ablation was assessed by demonstration of a bi-directional conduction block during pacing from the coronary sinus and low lateral right atrium after the isthmus ablation.

RF ablation of slow AV nodal pathway region

AV node modification was done using an ablation catheter with a 4 mm deflectable tip (Celsius D, Cordis Webster, Baldwin Park, CA, USA) introduced through the right femoral vein. The end point of AV node modification was set as appearance of a fast junctional rhythm during RF ablation.

Right atrial linear ablation

In the second session three multi-electrode catheters were inserted through a right femoral venous access. A quadripolar electrode catheter (Viking Cournand, Bard Electrophysiology, Billerica, MA, USA) catheter was introduced to record a stable His-potential. A bipolar pacing catheter (Bard Electrophysiology, Billerica, MA, USA) was positioned in the right ventricular apex. Three linear lesions in the right atrium were created using a novel RF ablation microcatheter system (3.7 Fr decapolar ablation catheter, Revelation T-x, Cardima Inc, Fremont, CA, USA) introduced through a long rigid vascular sheath (SR0, Daig Corp, Minnetonka, MN, USA). Lines between vena cava superior to vena cava inferior, vena cava superior to fossa ovalis and fossa ovalis to vena cava inferior were drawn. Successful ablation was defined as a clear reduction in the amplitude of the atrial signals.

Endocardial contact was secured continuously using intracardiac echocardiography (*Figure 3*) using an intracardiac echocatheter (ICE 9900, Boston Scientific Inc., San Jose, CA, USA) inserted through the left femoral vein and using a long sheath (Boston 5662, Boston Scientific Inc, San Jose, CA, USA). After RF ablation the patient continued his anti-arrhythmic medication. Four months after the treatment patient is without symptoms. A Holter-ECG showed continuous sinus rhythm with a occasional premature atrial contraction (PAC), but no AF or Afl. The PR time is 180 ms.

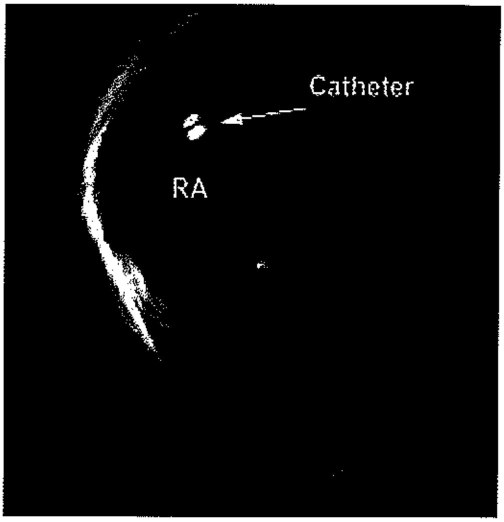

Figure 3a. Echocardiographic view showing the Revelation T-x ablation catheter without proper wall contact

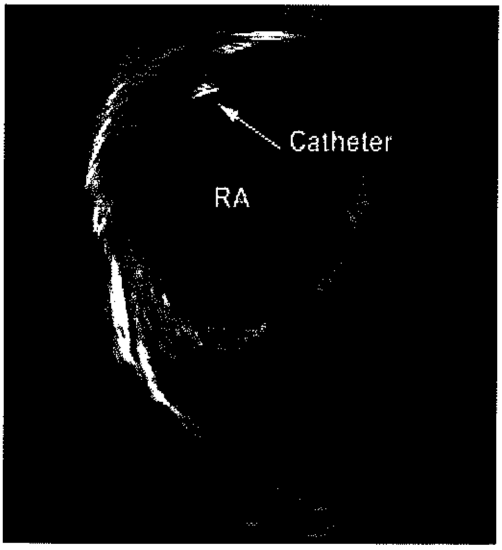

Figure 3b. Intracardiac echocardiographic view of the Revelation T-x ablation catheter in the right atrium showing good wall contact

Discussion

Atrial Fibrillation (AF) remains a challenge for every physician as it is an arrhythmia which affects a large proportion of the patients referred to the cardiologist.

Electrocardiographically AF is characterised by rapid, irregular, fibrillatory waves that vary in size and shape, mostly associated with an irregular ventricular response. The incidence of AF increases with age and is associated with a number of cardiac and non-cardiac diseases. These diseases can result in an atrial abnormality, acting as a substrate necessary for the initiation of AF. Triggers include atrial premature beats, sympathetic and parasympathetic stimulation. For the persistence of AF perpetuating factors are required. Persistence may result from electrical and structural remodelling, characterised by atrial dilatation and shortening of the atrial ERP.[1] Atrial fibrillation and atrial flutter (AFl) are both intra-atrial reentrant tachycardias and frequently associated in an individual patiënt.[2,3] In AF multiple, small reentrant circuits (wavelets) are arising in the atria, colliding, being extinguished, and arising again.[4,5] A single macro re-entrant wave front exists in the case of AFl.

Spontaneous and pharmacological (class Ic and III anti-arrhythmic drugs) transformation of AF into AFl has been reported, suggesting a causative relation between the two in such cases. A certain amount wavelets and therefore a certain amount of contiguous myocardium is necessary to maintain AF. Catheter ablation for atrial fibrillation aims to compartmentalise the atria by the creation of linear lesions, thereby reducing the amount of contiguous myocardium necessary for the propagation of multiple activation wave fronts. This approach was supported by the success of the MAZE procedure.[6] Early attempts at creating right atrial linear lesions with conventional catheter tip technology provided limited success.[7] Although more efficacious, the creation of extensive left atrial lesions has been associated with a high rate of thromboembolic stroke.[8] The advantage of linear ablation as described above is that it is less time consuming then the standard techniques and it is likely that we can create more continuous linear transmural lesions by using such microcatheter system. As there is no direct evidence of successful ablation we used intra-cardiac echocardiography to ensure good wall-contact. Ablation of the inferior vena cava-tricuspid annulus isthmus reduces the frequency of recurrences in these patients.[9-11] Modulation of the AV node allows a long-term control of the ventricular rate and prevents the recurrence of severe clinical symptoms in more than 75% of patients with drug refractory AF.[12]

Other non-pharmacological therapies such as the MAZE procedure[6], catheter ablation of foci in the pulmonary veins[13] and the implantable atrioverter[14] can be considered. All these therapies are successful in specific patient groups but are too invasive (MAZE) or are still experimental with unknown long term (side) effects. Because our patient showed the combination of AF and pharmacological induced atrial flutter (AFl) it was decided to treat him with the above described combined ablation-pharmacological approach. Recent reports about right atrial linear ablation so far showed conflicting results, possibly due to inappropriate catheter design an/or insufficient wall contact of ablation catheters.[15-17] By using intracardiac echocardiography a better wall contact can be guarantied. This could explain the success of our approach. Further investigations are necessary to define the patient group in which this novel combined approach can be successful.

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PART III.

THE ROLE OF ULTRASOUND IMAGING IN FOLLOW-UP OF ARRHYTHMIA PATIENTS: ASSESSMENT OF CARDIAC FUNCTION

Chapter 11

T Szili-Torok, GP Kimman, D Theuns, D Poldermans,
JRTC Roelandt, LJ Jordaens:

DETERIORATION OF LEFT VENTRICULAR FUNCTION FOLLOWING ATRIO-VENTRICULAR NODE ABLATION AND RIGHT VENTRICULAR APICAL PACING IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION

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Deterioration of left ventricular function following atrio-ventricular node ablation and right ventricular apical pacing in patients with permanent atrial fibrillation

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Aims Transcatheter radiofrequency ablation of the atrio-ventricular (AV) node followed by ventricular pacing has been shown to improve symptoms and quality of life of patients with atrial fibrillation (AF). It is assumed that function improves, but this has been less well demonstrated. The aim of this study was to assess the long-term effect of AV node ablation and ventricular pacing on left ventricular ejection fraction (LVEF) in patients with permanent AF.

Methods and Results All 12 patients studied had permanent AF for at least 12 months (mean age 70 years, range 41 to 78). LVEF was determined 6 days and 3 months after AV node ablation by radionuclide ventriculography, at a paced rate of 80 beats . min^{-1}. Cardiac dimensions were measured by means of transthoracic echocardiography. No major changes in pharmacological therapy were made during 3 months follow-up period. LVEF showed a significant deterioration after 3 months follow-up period for the group (47·5 ± 14·4%; 6 days after ablation vs 43·2 ± 13·7%; 3 months after ablation, P<0·05). There were no significant differences in left ventricular cavity dimensions directly after AV node ablation and 3 months later (LVEDD 51·2 ± 10·7 mm vs 52·6 ± 8·6 mm, P=NS; LVESD: 36·1 ± 14·2 mm vs 36·6 ± 9·7 mm, P=NS). Left atrial size did not show reduction 3 months after AV node ablation (50·8 ± 13·6 mm vs 51·0 ± 14·1 mm, P=NS).

Conclusion The restoration of a regular ventricular rhythm following AV node ablation for patients in permanent AF does not result in improvement in left ventricular function.

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Key Words: Atrial fibrillation, ablation, atrioventricular node, cardiac function.

Introduction

Atrial fibrillation (AF) is a common supraventricular arrhythmia, which leads to cardiac dilatation and dysfunction[1]. Theoretically, the management of this arrhythmia including restoration of sinus rhythm or regular ventricular paced rhythm should result in an improvement in the patient's symptoms as well as in cardiac function. Some authors advocate achieving this by ablating the atrio-ventricular (AV) node followed by right ventricular (RV) apical pacing. Although the advantage of a regular ventricular response seems to be important[2], RV apical stimulation is not physiological because normal ventricular activation along the natural conduction system is bypassed and the ventricles are activated in an abnormal sequence[3,4]. Chronic apical ventricular pacing is associated with myocardial cellular changes and leads to dysfunction of the left ventricle[5,6]. However, some studies, including a prospective multi-centre randomized trial, indicated that exercise tolerance and the quality of life improved after AV node ablation and RV apical pacing[7–9]. The reversibility of cardiac dysfunction after such intervention was one of the reasons that the concept of tachycardiomyopathy was introduced. However, it is clear that when atrial function is lost, ventricular performance will suffer in the long term. Since only limited and confusing data are available

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Table 1 Clinical and demographic characteristics of the patients

Pt. no.	Age	Sex	Duration of AF (months)	QRS duration (s)	Cardiac disease	Medication
1	67	F	12	0·12	SSS	3, 4, 7, 8
2	68	M	108	0·08	DCMP	2, 3, 4, 6
3	66	M	38	0·14	Atrial flutter	4, 6, 7
4	78	F	12	0·12	Atrial flutter	2, 3, 4, 6
5	70	F	24	0·08	Hypertension	4, 7, 8
6	74	F	48	0·12	ASD	1, 3, 8
7	66	M	48	0·08	Non obstr. HCMP	1, 2, 3, 6
8	41	M	48	0·08	VHD	2, 4, 7
9	67	F	12	0·12	SSS, Atrial flutter, Hypertension	1, 4, 7, 8
10	55	M	156	0·08	VHD	2, 3, 4
11	63	M	12	0·16	Hypertension	2, 3, 4, 7, 8
12	76	F	16	0·12	—	4, 8

SSS=sick sinus syndrome; AF=atrial fibrillation; F=female; M=male; DCMP=dilatative cardiomyopathy; ASD=atrial septal defect; HCMP=hypertrophic cardiomyopathy; VHD=valvular heart disease; in medication: 1=beta blocker; 2=ACE inhibitor; 3=diuretics; 4=digoxin; 5=vasodilators; 6=amiodarone; 7=Ca channel blocker; 8=other antiarrhythmics.

on the long term effect of AV node ablation and RV apical pacing, we aimed to conduct a study to assess long term effects of AV node ablation and RV apical pacing on the left ventricular performance using a completely different approach from previous investigators. To exclude the possible bias[2,10,11] of comparing pre- and post-ablation states respectively in fast conducted AF and paced rhythm, we determined the left ventricular ejection fraction (LVEF) 6 days after (not before) and 3 months after AV node ablation in 12 patients with permanent AF.

Methods

Patients were eligible if they had permanent AF and if the ventricular rate could not be adequately controlled by drug therapy. From February 1999 to February 2000, 12 patients with permanent AF underwent ablation of the AV node and insertion of a VVIR pacemaker and RV apical pacing. There were six men and six women with an age range from 41 to 78 (mean 70) at the time of ablation.

Study patients

The clinical and demographic characteristics of the patients are shown in Table 1. All patients were in NYHA functional class II or III. The type of AF was permanent in all 12 patients. Only two patients had an increased QRS duration (140–160 ms) before AV node ablation. All had complete heart block after the ablation, with QRS duration less than 120 ms in 8/12 patients. There were no major changes in medication during the 3 month follow up period. VVIR pacing with rate responsive mode was used in all patients. For LVEF measurements VVI 80 bpm pacing mode was temporarily programmed 1 h before measurement.

Ablation procedure

A temporary pacing electrode was inserted via a femoral vein into the RV before the ablation procedure. One patient already had a permanent pacemaker inserted. Third degree AV block was achieved using a conventional right sided approach in every case with radiofrequency energy. Webster D or F curve thermocouple mapping/ablation catheters were used to map the antero- and/or mid-septal region and to deliver radiofrequency (RF) energy. A permanent cardiac pacemaker was inserted 30 min after successful ablation. No major or minor complications related to RF ablation and pacemaker insertion were observed. Patients were subsequently followed-up in the outpatient clinic.

Evaluation of left ventricular ejection fraction (LVEF)

LVEF was measured with radionuclide ventriculography (red blood cells, marked with Technetium^{99} pertechnetate, 25 mCi). Imaging was performed in 45° left anterior oblique (LAO). The R wave was used for gating, and 16–24 frames per cycle were stored until 400 000 counts per image were acquired. Measurement was made 6 days after and 3 months after the ablation procedure, always at the paced rate of 80 bpm.

Echocardiographic measurements

M-mode and cross-sectional echocardiograms were obtained at the time of measurement of LVEF by

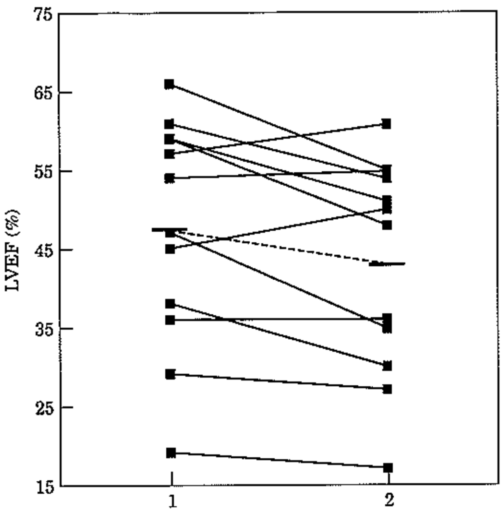

Figure 1 **Individual representation of left ventricular ejection fraction (LVEF) 6 days after (1) and 3 months (2) after AV node ablation.**

radionuclide ventriculography. Left atrial (LA) size, end systolic (LVESD) and end diastolic diameters (LVEDD) were measured according to the recommendations of the American Society of Echocardiography. Fractional shortening was calculated according to the following formulae: FS%=(LVEDD-LVESD)/LVEDD × 100. In all patients the echocardiograms were recorded in the same paced (80 bpm) rhythm. After analysis the pacemaker was reprogrammed to VVIR mode.

Statistical analysis: The measured values are expressed as mean ± SD. Non-parametric data were compared using the Wilcoxon test. Correlation analysis was performed using the Pearson test. The level of significance was set at 0·05.

Results

Effect of AF on left ventricular function

The initial LVEF was lower in patients with longer duration of AF (r= − 0·74, $P<0·05$). A longer duration of AF was associated with larger LVEDD dimension (r= − 0·833, $P<0·01$) and LVESD dimension (r= − 0·795, $P<0·05$).

Effect of pace and ablate therapy on left ventricular function

The mean LVEF decreased from 47·5 ± 14·4% to 43·2 ± 13·7% ($P<0·05$). Only two patients showed obvious (>5%) improvement in LVEF (Fig. 1). Left ventricular dimensions did not show significant change during 3 months follow up (Table 2).

Left atrial dimensions

LA dimensions did not show changes after AV node ablation and RV apical pacing (Table 2).

Fractional shortening (FS)

Fractional shortening did not show significant changes 6 days and 3 months after AV node ablation.

Discussion

The major finding of our study was that LVEF deteriorated 3 months after AV node ablation with chronic RV apical pacing. Secondly, the LV dimensions and the LA size did not show significant changes during the study period. Our data confirm the hypothesis that LV function becomes depressed after long term duration of AF.

Causes of LV dysfunction in patients with atrial fibrillation

It is now generally accepted that supraventricular incessant arrhythmias can lead to myocardial dysfunction and dilation[1]. Factors contributing to HF when atrial arrhythmias are present are the loss of an effective, well timed atrial contraction and the fast and irregular ventricular response. These factors impair diastolic function and finally may lead to tachycardiomyopathy[1]. Inappropriately fast heart rates occur even during minor exercise in patients with atrial fibrillation. This is accompanied by depressed heart rate at peak exercise in cases of left ventricular dysfunction[12–14]. Therefore, the aims of improving function of the patients can be reached by restoration of sinus rhythm, but also (to a less complete extent) by control of the ventricular rate. It is believed that rate control, with drugs or RF catheter ablation alone is sufficient to improve the outlook of these patients. However, evidence has been presented that rhythm control in heart failure has disadvantages[15]. Several investigators have considered it acceptable to randomize patients to rhythm or rate control, as many questions remain unanswered[16].

LV function after AV node ablation

After ablation, pacemaker dependency is the rule, with implantation of a VVIR system when atrial electrical activity is no longer thought to be present. Although the advantage of a regular ventricular response is important[2], RV apical stimulation is not physiological because normal ventricular activation along the natural

Table 2 Echocardiographic findings at the time and 3 months after RF ablation of AV node

	Six days after ablation (mm)	Three months after ablation (mm)	*P* value
LA size (mm)	50·8 ± 13·6	51·0 ± 14·1	NS
LV end diastolic dimension (mm)	51·2 ± 10·7	52·6 ± 8·6	NS
LV end systolic dimension	36·1 ± 14·2	36·6 ± 9·7	NS
Fractional shortening (FS%)	31 ± 0·1	31 ± 0·1	NS

LA=left atrial; LV=left ventricular; NS=non significant.

conduction system is not present or bypassed and the ventricles are activated in an abnormal sequence[3,4]. Some investigators found significant improvement in left ventricular function after AV node ablation and RV apical pacing. Heinz *et al.* reported improvement of LV function after AV node ablation in patients with chronic AF and atrial flutter. This was attributed to decrease in end-systolic dimension[17]. Rodriguez and co-workers showed a beneficial effect of the 'ablate and pace' therapy in patients with lone AF in the subgroup where the baseline LVEF was lower than 50%. They also showed a significant decrease in LV end systolic and end diastolic dimensions after ablation[7]. A long term improvement in systolic and diastolic left ventricular function was reported by Edner *et al.* in patients with left ventricular dysfunction[18]. Ablation of the AV node had no adverse effect on normal left ventricular function. In contrast to these findings, in the present study the LVEF decreased independently from the initial value (Fig. 1). In a recent study by Redfield *et al.* 63 patients underwent AV node ablation and pacing therapy with atrial fibrillation and reduced systolic function. Sixteen patients (25%) had improvement in systolic function after AV node ablation[19]. These results lead to the concept of tachycardia-related cardiomyopathy which diagnosis should be considered in all patients in whom systolic dysfunction occurs subsequent to atrial fibrillation. More convincing are some studies showing that quality of life indices significantly improved after ablation of the atrio-ventricular node[9]. In a prospective multicentre randomized study of Brignole and co-workers a mixed population of patients with AF and HF was recruited. The 'ablate and pace' therapy was superior to drug therapy in controlling symptoms, but the efficacy appeared to be less than was observed in previous uncontrolled studies. Importantly, objective cardiac performance did not show any improvement by the treatment. However, less hospital admissions and less physician visits were necessary after ablation[8].

Methodological problems

The three major differences between the former and present studies are: the timing of the measurements, the composition of the study group and the method used for the measurement of LVEF. Some authors described that less than 40% of their patients had heart failure, measured with some more or less objective parameters[8]. Our study group was composed of patients with long standing AF, who all had signs of moderate to severe heart failure. Concerning the timing, all of the significant former studies compared LV function before and after AV node ablation[7–9,17,18]. Some studies were retrospective and the timing of the measurement of LVEF varied in a wide time range[7,17,18]. In our prospective study the timing was more appropriate. We tried to minimize the effects of possible acute haemodynamic changes caused by a restoration of a regular ventricular response. Therefore we compared the LVEF 6 days and 3 months after AV node ablation and pacemaker implantation exactly under the same conditions. One of the other possible explanations for the difference between the results of previous and the present study could be the significant difference in measurements. In this study, LVEF was measured by means of radionuclide ventriculography (RNV). RNV is highly reproducible and has an error of less than 3%. Probably RNV is less sensitive to the errors caused by the change in ventricular geometry during RV pacing. The formula used for routine calculation of LVEF during transthoracic echocardiography is based on constant ventricular geometry during contraction. The shape of the ventricle during RV apical pacing is changing, therefore a planimetry based measurement is more appropriate for the evaluation of LV function. We emphasize the importance of using RNV in further pacing studies assessing left ventricular function. Furthermore, none of the former investigators evaluated left ventricular performance exactly under the same conditions immediately and 3 months after AV node ablation[7–9,17,18]. Both assessments of LVEF in this study were measured during the same 80 beats . min^{-1} paced cardiac rhythm.

Survival after AV node ablation

Finally, the natural history of patients treated by AV node ablation is still not known. Sudden death has been reported in some subgroups of patients. It was first attributed to the technique of DC shock ablation[20]. However, it was also observed after RF ablation[21,22]. In a meta-analysis of 21 studies with a total of 1181 patients by Wood *et al.* the ablation and pacing therapy showed that the calculated 1-year mortality was comparable with medical therapy[23]. A considerable proportion of these deaths can be related to the acute effects of AV node ablation with QT prolongation and slow pacing rate and/or unreliable escape rhythms[21,24]. Another subgroup of deaths was reported late after AV node ablation, mainly in patients with HF[21,25]. The deterioration of pump function late after AV node ablation may play a role in this mortality. Therefore, careful adjustment of the medical therapy for these patients with LV dysfunction is very important including beta-blocker therapy ACE inhibitors, adjustment of electrolytes and avoidance of antiarrhythmic therapy[26,27]. The follow up of these patients must not be limited to the technical control of pacemaker function.

Limitations of study

This study is of a relatively small number of patients. The change in ejection fraction is statistically significant, but may not have great clinical significance. A factor influencing this may have been the long duration of atrial fibrillation in most of the patients with consequent lack of ability to recover. Quality of life measures were not employed in this work. Future studies should include such measures to achieve more clinical relevance of the left ventricular function data. Follow-up of the patients in this report is only 3 months and the long-term effects on left ventricular function remain to be ascertained.

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Chapter 12

Weerasooriya R, Davis M, Powell A, Szili-Torok T, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M:

THE AUSTRALIAN INTERVENTION RANDOMISED CONTROL OF RATE IN ATRIAL FIBRILLATION TRIAL (AIRCRAFT)

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The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT)

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OBJECTIVES The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial was a multicenter trial of atrioventricular junction ablation and pacing (AVJAP) compared with pharmacologic ventricular rate control (MED) in patients with mild to moderately symptomatic permanent atrial fibrillation (AF).

BACKGROUND There have been very few prospective randomized trials, undertaken in highly symptomatic patients, comparing AVJAP with pharmacologic methods of ventricular rate control for patients with permanent AF.

METHODS There were 99 patients (70 men, mean age 68 ± 8.6 years) at five centers. Forty-nine patients were randomized to AVJAP while 50 patients were randomized to pharmacologic control. The primary end point was cardiac function measured by echocardiography and exercise tolerance. The secondary end points were ventricular rate control, evaluated by 24-h ambulatory electrocardiographic monitoring, and quality of life. Data were collected at randomization and then at one month, six months, and 12 months post-randomization.

RESULTS At 12 months follow-up there was no significant difference in left ventricular ejection fraction (AVJAP: 54 ± 17%; MED: 61 ± 13% [p = ns]) or exercise duration on treadmill testing (AVJAP: 4.1 ± 2 min; MED: 4.6 ± 2 min [p = ns]); however, the peak ventricular rate was lower in the AVJAP group during exercise (112 ± 17 beats/min vs. 153 ± 36 beats/min, $p < 0.05$) and activities of daily life (117 ± 16 beats/min vs. 152 ± 37 beats/min, $p < 0.05$). The CAST quality-of-life questionnaire revealed that patients in the AVJAP group had fewer symptoms at six months ($p = 0.003$) and at 12 months ($p = 0.004$). The observed relative risk reduction in symptoms at 12 months was 18%. Global subjective semiquantitative measurement of quality of life using the "ladder of life" revealed that the AVJAP group reported a 6% better quality of life at six months ($p = 0.011$).

CONCLUSIONS In this trial, AVJAP for patients with mild to moderately symptomatic permanent AF did not worsen cardiac function during long-term follow-up, and quality of life was improved. (J Am Coll Cardiol 2003;41:000–000) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common chronic tachyarrhythmia, affecting 5% of people over the age of 60 (1). Ventricular rate control is a major treatment aim for patients with permanent AF. Although several studies have compared atrioventricular junction ablation and pacing (AVJAP) with pharmacologic ventricular rate control in AF, earlier studies were not randomized (2–4), and the few published randomized prospective studies comparing the two treatment options have included very symptomatic patients with a mean left ventricular ejection fraction (LVEF) <50 (5,6).

The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT) was a multicenter, prospective randomized trial of AVJAP versus pharmacologic treatment for ventricular rate control and was undertaken in patients with permanent AF who had mild to moderate symptoms, preserved LVEF, and a ventricular rate that was controlled pharmacologically. AVJAP has not been compared to pharmacologic therapy in this population, which represents the great majority of patients with permanent AF.

The primary end point was cardiac function measured by echocardiography and exercise tolerance. The secondary end points included ventricular rate control, evaluated by 24-h ambulatory electrocardiographic monitoring, and quality of life (QoL).

METHODS

Study protocol. The study protocol was approved by the ethics committees of all participating hospitals. The study was completely explained to each prospective patient before he or she consented, in writing, to participate in any study-related procedures. Ethics committee approval for the study was obtained in May 1998 and the first patient was enrolled in June 1998. The last patient completed follow-up in July 2001.

The study inclusion criteria were: 1) age >40 years, 2)

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Abbreviations and Acronyms

AF	= atrial fibrillation
AQoL	= Assessment of Quality of Life Questionnaire
AIRCRAFT	= Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial
AVJAP	= atrioventricular junction ablation and pacing
ECG	= electrocardiogram
HR	= heart rate
LVEF	= left ventricular ejection fraction
MED	= medication
QoL	= quality of life
SIP	= Sickness Impact Profile

symptomatic permanent AF (>12 months or with failed cardioversion or medication therapy) with uncontrolled ventricular rate in which a good rate control (defined as rest heart rate [HR] <80 and exercise HR <150) could be achieved by drugs during a three-month screening period, 3) ability to give informed consent, and 4) ability to perform a treadmill test.

The exclusion criteria were: 1) clinical indication for ablation and pacing; 2) the likelihood of surgery or transcatheter valvuloplasty within 12 months of enrollment; 3) untreated resting mean ventricular rate <80 beats/min (averaged over 1 min on three separate occasions) and <150 beats/min during maximum exercise (averaged over 1 min during a treadmill test using the modified Bruce protocol); 4) unstable angina pectoris; 5) Wolff-Parkinson-White syndrome; 6) severe tricuspid valvular regurgitation (by echo criteria) or tricuspid prosthetic valve; 7) New York Heart Association (NYHA) functional class IV despite pharmacologic treatment; 8) unwillingness or inability to cooperate or to give informed consent; 9) any other serious medical condition (such as terminal illness) that, in the opinion of the investigator, would preclude optimal participation in the study; 10) an occupation or hobby that precluded permanent pacing; and 11) inability to travel to the study center for follow-up.

Upon entry into the trial all patients had intensive medical therapy directed by a cardiologist for three months before randomization in an attempt to maximize pharmacologic ventricular rate control. Successful ventricular rate control was arbitrarily defined as a resting mean ventricular rate <80 beats/min (measured during a period of 1 min on three separate occasions) and <150 beats/min during maximum tolerated exercise (during a treadmill test using a modified Bruce protocol). Randomization was conducted independently by the biostatistical consulting service of the University of Western Australia. Patients were stratified according to echocardiographic estimation LVEF >45% or <45% at the end of the initial three-month observation period. The randomization code was computer generated and was balanced within each site as well as for LVEF >45% or <45%. Patients were randomized regardless of the clinical results of the period of intensive medical management, and the randomization code was hidden from the treating cardiologist until the time of allocation.

Pharmacologic treatment. In the pharmacologic treatment group, drugs were prescribed to achieve satisfactory control of the ventricular rate. Drugs used for ventricular rate control included digoxin, metoprolol, atenolol, verapamil, and diltiazem either alone or in combination. The choice of drugs was at the discretion of the treating clinician. Patient compliance was monitored by patient interview at each visit.

Catheter ablation and pacing. In the AVJAP group patients underwent a combined ablation and pacemaker insertion procedure. For atrioventricular junction ablation a deflectable tip ablation catheter was positioned across the tricuspid annulus to record atrial and ventricular electrograms and a His bundle potential. Radiofrequency energy was then delivered with power and duration determined by impedance response or catheter tip temperature monitoring as well as observed response. The end point of the ablation procedure was the development of complete heart block.

The pacemaker implanted was a Pacesetter Trilogy SR model 2250L (Pacesetter Inc., Sylmar, California) programmed VVIR, with rate-response functions optimized for each patient. The minimum pacing rate was 80 to 90 beats/min for one month after ablation, with reprogramming to a lower rate determined by the treating cardiologist thereafter.

Concomitant medication. Patients continued all noncardiovascular medications unchanged. Use of warfarin or antiplatelet agents was not altered by involvement in the trial. Patients randomized to the AVJAP group ceased ventricular rate-controlling drugs following the procedure. Where patients were on beta-blockers, calcium channel blockers, or digoxin for reasons other than ventricular rate control, these drugs were continued.

Patient evaluation at each visit. At baseline (at the end of the three-month lead-in period), patients had an exercise (treadmill) test, 24-h ambulatory electrocardiogram (ECG), and echocardiogram. One month after randomization, patients had an exercise test and 24-h ambulatory ECG. Six and 12 months after randomization patients had an exercise test, 24-h ambulatory ECG, and echocardiogram. A modified Bruce protocol, more aggressive in terms of slope and speed increments than a standard Bruce protocol, was used for exercise testing in order to determine the peak exercise heart rate in an efficient way. Complete two-dimensional color Doppler echocardiography was performed. Left ventricular volumes and ejection fraction were calculated using Teicholz formula. The mean of 10 consecutive cardiac cycles was used for patients in AF and three cardiac cycles for patients in paced rhythm.

Quality-of-life assessment (Appendix). Patients completed health-related QoL questionnaires at baseline, six months, and 12 months. The following questionnaires were

Table 1. Baseline Characteristics of Study Population

	MED n = 50	AVJAP n = 49	p Value	Global population n = 99
Age, yr	67.9 ± 9	68 ± 8.5	0.973	68 ± 8.7
Male gender	72%	69%	0.775	71%
Ischemic heart disease	38%	43%	0.622	40%
Dilated cardiomyopathy	2%	6%	0.362	4%
Valvular heart disease	31%	35%	0.667	33%
Hypertension	38%	51%	0.192	44%
Diabetes	18%	10%	0.266	14%
Duration of AF (months)	78 ± 131	58 ± 66	0.322	68 ± 104
Symptom frequency/month	4 ± 5.3	3.5 ± 0.92	0.352	4 ± 3.8
Warfarin treatment	76%	78%	0.855	77%
Aspirin treatment	28%	35%	0.942	34%

AF = atrial fibrillation; AVJAP = atrioventricular junction ablation and pacing; MED = medication.

administered: the Assessment of Quality of Life Questionnaire (AQoL) (7), the CAST Quality of Life Questionnaire (8), and the Sickness Impact Profile (SIP) (9).

Statistical analysis. Independent statistical analysis was undertaken by the biostatistical consulting service of the University of Western Australia (demographic, cardiac function, and ventricular rate data) and the Centre for Health Program Evaluation (QoL data). Data were analyzed using the SAS software package. The intent-to-treat principle was used for all analyses. Continuous variables were compared using the *t* test and categorical variables were compared using Fisher's exact test. The QoL questionnaires were scored according to rules of the original authors. The QoL data were analyzed using the Mann-Whitney *U* test (2-sided) for nonparametric independent samples; because a large number of statistical tests were performed, only p values <0.01 were considered statistically significant. For all data other than the QoL data, a p value <0.05 was considered statistically significant. A parametric two-sample *t* test was used at each time point to compare the mean values for medication (MED) group versus AVJAP group. The hypothesis we were testing was that there was no difference in the mean values for the two groups at each time point.

RESULTS

Study population (Table 1). After randomization, 49 patients were allocated to the AVJAP group and 50 to the MED group. As outlined in Table 1, the two groups were well matched for age, gender ratio, structural heart disease, ischemic heart disease, hypertension, symptom frequency, and duration of AF.

Patient flow (Fig. 1). The majority of patient withdrawals were among the AVJAP group before the ablation procedure; the most common reason for withdrawal was the patients "felt too well." Two patients in the MED group had AVJAP three and six months following randomization. In both cases, the reason for crossover was "troublesome symptoms in addition to a mean resting heart rate >80 beats/min or >150 beats/min during maximum exercise."

Pharmacologic treatment. In the MED group the proportion of patients on single ventricular rate-control agents and combinations remained constant during the study. In contrast, 21 of 34 (62%) of the AVJAP group were not on any ventricular rate-controlling drugs or combinations following the ablation procedure. Hypertension and ischemic heart disease were the most common reasons for AVJAP patients to continue ventricular rate-controlling drugs.

Catheter ablation and pacemaker insertion. All patients in the AVJAP group had successful ablation of the AV junction at the initial procedure, with a median of two applications of radiofrequency energy at 30 to 50 W using the right heart approach. One patient developed a large groin hematoma immediately following the procedure and two patients developed pacemaker pocket hematomas; none had any long-term adverse sequelae.

Echocardiographic evaluation of LVEF (Table 2). No significant change in echocardiographically measured LVEF was observed in either group during the study.

Treadmill test. The total exercise time did not improve with ablation and pacing (Table 2). At one month post-randomization, the AVJAP group had a higher resting heart rates and lower maximum heart rates than the medical treatment group. At six months post-randomization, the AVJAP group had lower resting and maximum heart rates than the MED group, whereas at 12 months post-randomization, the AVJAP group had similar resting heart rates and lower maximum heart rates than the medical treatment group.

Holter monitor (Table 2). At one month post-randomization, the AVJAP group had a higher minimum and mean heart rates and lower maximum heart rates than the MED group. At six months post-randomization, the AVJAP group had a higher minimum and lower maximum heart rate, whereas at 12 months post-randomization, the AVJAP group had higher lower and mean heart rates and lower maximum heart rates than the MED group.

Quality of life (Table 2). Even though the results of the AQoL and SIP QoL questionnaires were not significantly different for the two treatment groups, analysis of the CAST QoL questionnaire data revealed that the AVJAP

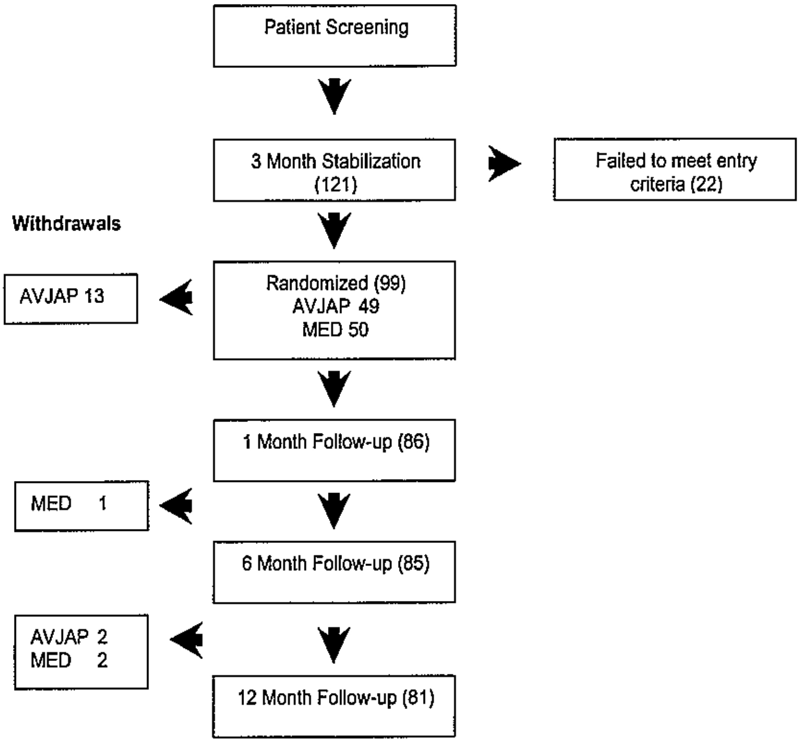

Figure 1. Patient flow.

group had significant improvements in quality of life. The CAST QoL "symptom scale" ranges from 9 to 54, and the AVJAP group had a reduction of 8 units on this scale at six months whereas the medical treatment group had a reduction of 0.4 units (<1% change). The reduction in symptoms in the AVJAP group was maintained at 12 months, when there was a 6.6-point reduction compared to baseline. The observed relative risk reduction in symptoms at 12 months was 18% ($p = 0.004$). Global subjective semiquantitative assessment of QoL using the "ladder of life" revealed that

Table 2. Echocardiographic LVEF, Treadmill Test, and Holter Results

	Baseline		1 Month		6 Months		12 Months	
Number of Patients	MED 50	AVJAP 49	MED 50	AVJAP 36	MED 49	AVJAP 36	MED 47	AVJAP 34
Echocardiogram								
LV ejection fraction (%)	57 ± 14	55 ± 16	—	—	56 ± 19	54 ± 14	61 ± 13	54 ± 17
Treadmill Test								
Exercise time (minutes)	4.3 ± 3	4.2 ± 2.1	4.3 ± 2.3	4.4 ± 1.9	4.3 ± 2	5.2 ± 4	4.6 ± 2	4.1 ± 2
Exercise rest HR (bpm)	79 ± 23	82 ± 25	81 ± 16	87 ± 8*	82 ± 17	74 ± 8*	77 ± 19	75 ± 8
Exercise maximum HR (beats/min)	151 ± 45	158 ± 33	154 ± 31	115 ± 14*	159 ± 32	112 ± 19*	153 ± 36	112 ± 17*
Holter								
Minimum HR (bpm)	41 ± 12	41 ± 17	44 ± 14	80 ± 12*	42 ± 12	70 ± 7*	39 ± 9	70 ± 9*
Mean HR (bpm)	77 ± 13	79 ± 20	76 ± 12	87 ± 9*	76 ± 17	77 ± 6	71 ± 11	76 ± 7*
Maximum HR (beats/min)	154 ± 37	152 ± 41	147 ± 44	117 ± 14*	150 ± 39	116 ± 19*	152 ± 37	117 ± 16*
QoL								
AQoL Utility score	0.64 ± 0.24	0.71 ± 0.22			0.64 ± 0.16	0.71 ± 0.22	0.66 ± 0.18	0.75 ± 0.18
SIP Total score	7.13 ± 5.81	7.43 ± 8.91			7.46 ± 5.12	9.98 ± 5.38	6.76 ± 4.63	8.89 ± 8.32

*p <0.05.
Values are mean ± SD
AQoL = Assessment of Quality of Life Questionnaire; bpm = beats/min; HR = heart rate; LV = left ventricular; SIP = Sickness Impact Profile. Other abbreviations as in Table 1.

Table 3. Adverse Events

	MED	AVJAP	p
Death	1	2	0.617
Acute MI	1	2	0.617
Unstable angina	1	4	0.204
Hematoma	0	3	0.117
Pulmonary embolism	0	1	0.495
Drug reaction	3	0	0.242
Total	6	12	0.125

MI = myocardial infarction. Other abbreviations as in Table 1.

the AVJAP group reported a 6% better QoL at six months and 12 months than the MED group ($p = 0.01$).

Patients with baseline LVEF ≤45%. Nine patients in the MED group and 10 patients in the AVJAP group had an LVEF <45% at baseline. Predefined subgroup analysis revealed no differences in LVEF, exercise tolerance, or heart rates on treadmill testing or Holter monitoring for LVEF <45% patients.

Adverse events. Adverse events seen during the study are outlined in Table 3. Comparing the two treatment groups, there was no significant difference in the occurrence of any adverse event. Two patients in the AVJAP group died during the study. Both deaths were sudden out-of-hospital events and occurred six months postablation in patients with low LVEF. One patient in the MED group had a sudden out-of-hospital event one month post-randomization.

DISCUSSION

Our study addresses the question posed by Wood et al. (10): "what is the role of ablation and pacing therapy in the wider population of patients with less symptomatic AF?" The main findings of AIRCRAFT were that, in this patient population, AVJAP had a neutral effect on cardiac function measured by echocardiography or treadmill testing and QoL was improved.

It is well established that, for patients with highly symptomatic medically refractory permanent AF, AVJAP provides superior symptom relief compared with pharmacologic management (2–6,10). Early nonrandomized studies suggested that AVJAP also improves cardiac function (2–4), and the reasons suggested for this improvement were reversal of tachycardia-related cardiomyopathy (11,12) as well as the favorable hemodynamic effects of a regular ventricular rhythm (13). Two prospective randomized trials (5,6) reported results while the present study was underway. Brignole et al. (5) showed a neutral effect on LVEF following AVJAP in highly symptomatic permanent AF patients with congestive heart failure, whereas Ueng et al. (6) showed a modest improvement in the LVEF of patients with a mean baseline LVEF of 44% and previously well-controlled ventricular rates.

The AIRCRAFT patient population is unique because it includes patients with mild to moderate symptoms. The exclusion and inclusion criteria were chosen to determine if there is a benefit of AVJAP in the wider population of patients with permanent AF because AVJAP has not previously been compared to pharmacologic ventricular rate control in a controlled prospective manner in this population. Subgroup analysis of patients with baseline LVEF <45 was prespecified in the study protocol because earlier studies suggested that patients with impaired LVEF were most likely to have improvement of LVEF following AVJAP (2–4).

Analysis of the prespecified subgroup of patients with LVEF <45% failed to show any benefit of AVJAP on echocardiographically measured LVEF. There were, however, very few patients in this subgroup, so these results must be interpreted with caution. These findings contrast with those of Twidale et al. (2), Edner et al. (3), and the "Ablate and Pace" trial (4). In an uncontrolled study Twidale et al. studied 14 patients with a mean LVEF of 42 ± 3% and found that this improved to 49 ± 4% ($p < 0.02$) following AVJAP during a mean of nine months follow-up (2). The study of Edner et al. lacked a control treatment arm, and only post-hoc analysis of those patients with baseline LVEF <50% showed a significant improvement in LVEF (from 32 ± 11% to 45 ± 11%, $p < 0.001$) a mean of 216 days following AVJAP (3). The larger "Ablate and Pace" trial, which was also nonrandomized, similarly showed an improvement in LVEF by post-hoc analysis of the patients, with a baseline LVEF < 45% (from 30 ± 9% to 45 ± 11%, $p < 0.01$) during one-year follow-up (4). The patient populations in these studies were different in terms of symptoms and ventricular rate control to the present AIRCRAFT study. The prospective randomized study of Ueng et al. (6) was smaller than AIRCRAFT and showed an improvement in acute hemodynamic variables as well as LVEF. A possible reason for the difference in results between our study and that of Ueng et al. (6) is the difference in baseline LVEF of the two patient populations.

There has been recent interest in the importance of synchrony of cardiac contraction in patients with impaired LVEF. Patients who undergo AVJAP (with a right ventricular apical pacing lead position) have iatrogenic cardiac dyssynchrony that may counteract the beneficial effects of rate and rhythm regulation. In patients with impaired LVEF and permanent AF a biventricular pacing system may be superior; this has not been studied in a controlled prospective manner (14,15), however.

The mean ventricular rate measured by ambulatory electrocardiography was higher in the AVJAP group at one month because the minimum ventricular pacing rate was set at 80 to 90 beats/min for one month following ablation. This has been reported to reduce the risk of sudden cardiac death (16). The ventricular rate during times of physical activity was significantly better controlled in the AVJAP group because, following ablation, the peak ventricular rate and rate response function are programmable. Excessive control of ventricular rate during exertion may result in chronotropic incompetence, but this was not seen in the

AIRCRAFT trial, as evidenced by the fact that the exercise duration by treadmill testing at six and 12 months follow-up was not significantly different from the MED group.

The improvement in QoL was only apparent from analysis of the CAST quality-of-life questionnaire data. This questionnaire was chosen for the study because it was designed for patients with arrhythmias. The AQoL and SIP questionnaires are not disease specific and provide a global impression of health-related QoL. It is apparent from our study that the improvement in QoL following AVJAP is due to symptom control, which was sensitively measured by the CAST QoL questionnaire but not by the AQoL or SIP questionnaires. It is unlikely that the improvement in QoL was due to a placebo effect of having an invasive procedure, as the results were durable during 12 months follow-up.

There was no significant difference in the mortality rate in the two groups, although the study was not sufficiently powered to examine this as an end point. There have been concerns about sudden death following AVJAP (16,17), possibly due to bradycardia-dependent QT prolongation leading to ventricular fibrillation (16,17), but recent publications have reported that AVJAP is not associated with increased risk of sudden cardiac death (18,19).

In summary, AVJAP is a safe and effective means of controlling ventricular rate in permanent AF. In the wider population of patients with permanent AF, having mild to moderate symptoms, our study supports the use of this treatment strategy when symptom control and improved QoL are the primary goals. This strategy does not cause deterioration of cardiac function.

Conclusions. In this trial, AVJAP for patients with mild to moderately symptomatic permanent AF did not worsen cardiac function during long-term follow-up and QoL was improved.

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APPENDIX

For a complete list of Quality of life questionnaires used in AIRCRAFT, please see the May 21 issue of *JACC* at www.cardiosource.com

Chapter 13

T Szili-Torok, M Bountioukos, AJQM Muskens, DAMJ Theuns, D Poldermans, JRTC Roelandt, LJ Jordaens:

THE PRESENCE OF CONTRACTILE RESERVE HAS NO PREDICTIVE VALUE FOR THE EVOLUTION OF LEFT VENTRICULAR FUNCTION FOLLOWING ATRIOVENTRICULAR NODE ABLATION IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION

(submitted for publication)

The presence of contractile reserve has no predictive value for the evolution of left ventricular function following atrioventricular node ablation in patients with permanent atrial fibrillation

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Abstract

Aims: Transcatheter ablation of the atrio-ventricular (AV) node followed by ventricular pacing has been shown to improve symptoms and quality of life (QOL) of patients with permanent atrial fibrillation (AF). In a considerable number of patients, cardiac function deteriorates after AV node ablation. We aimed to determine whether the absence of contractile reserve assessed by low dose dobutamine stress echocardiography (LDDSE) could identify those patients whose left ventricular (LV) function deteriorates after AV node ablation. **Methods:** All 25 pts studied had permanent AF for at least 12 months. LVEF was determined 6 days and 3 months after AV node ablation by radionuclide ventriculography (RNV), at a paced rate of 80 beats/min. Deterioration in cardiac function was defined as a decrease in LVEF >5 %. LDSE was performed in all patients before and after ablation. The presence of contractile reserve was defined as an improvement in regional function of $\geq$ 1 grade at low dose dobutamine in at least 4 segments. QOL measurements were taken using Minnesota, NHBP and MPWB questionnaires. **Results:** LVEF showed no improvement in the overall group (52.8±11.1% vs. 51.8±9.8%, p=NS). QOL showed significant improvement in all questionnaires (Minnesota: 4.1±2.1 vs. 2.5±2, p=0.001; NHBP: 54.8±43.3 vs. 34.2±34.3, p=0.002; MPWB: 22.2±4.6 vs. 19.4±6.2, p= 0.03). There was no significant difference in change of LVEF between patients with and without contractile reserve (-0.4±8.7 vs. 1.6±11.3, p=NS). However patients with a preserved LVEF at baseline showed more frequently a reduced LVEF after AV node ablation (62.2±10.4 % vs. 47.5±7.6%, p=0.001). **Conclusions:** 1. The absence of contractile reserve does not predict deterioration of cardiac function after AV node ablation. 2. AV node ablation results in a significant improvement in QOL, which is not necessarily associated with improvement of LVEF. 3. Higher baseline LVEF predicts deterioration of cardiac function. These data suggest that although AV node ablation is an excellent way of controlling symptoms, it should be avoided in patients with normal LV function.

Key words: atrial fibrillation, AV node ablation, cardiac function, contractile reserve

Introduction:

Atrial fibrillation (AF) is a common supraventricular arrhythmia, which leads to cardiac dilatation and dysfunction. Theoretically, ablation of the atrio-ventricular (AV) node followed by right ventricular (RV) apical pacing may result in an improvement of the patient's symptoms as well as in cardiac function because of the advantage of a regular ventricular response and adequate rate control(1-4). Controversial results were reported about the course of patients following AV junction ablation. Quality of life (QOL) and exercise tolerance improved in several studies(3). However, more recent studies indicate that left ventricular (LV) function does not improve or even may deteriorate(5-7). Contractile reserve of the myocardium as determined with echocardiography under pharmacological stress, can be used as a prognostic parameter in patients with LV dysfunction(8). The aim of the present investigation was to determine whether the absence of contractile reserve assessed by low-dose dobutamine stress echocardiography (LDDSE) could identify those patients whose LV function deteriorates after AV node ablation and RV apical pacing.

Methods:

Patients were eligible if they had permanent AF, were highly symptomatic and if the ventricular rate could not be adequately controlled by drug therapy. 25 patients with permanent AF underwent ablation of the AV node and insertion of a VVIR pacemaker and RV apical pacing. There were 16 men and 9 women with an age ranging from 44 to 80 years (63±11.4, mean±SD) at the time of ablation. There were no major changes in medication during three months follow up period.

Study protocol

After being informed all patients gave consent for participation in the study. All patients who met the inclusion criteria had LDDSE, cardiac peptide measurements, QOL measurements and 6-min walk test before the procedure. 4-6 days after AV node ablation and PM implantation left ventricular ejection fraction (LVEF) was determined with radionuclide technique. At three-month follow-up all measurements (LDDSE, QOL, cardiac peptides, 6-min walk test and LVEF) were repeated.

Ablation procedure. A temporary pacing electrode was inserted via a femoral vein into the RV before the ablation procedure. One patient had already a permanent pacemaker inserted. Third degree AV block was achieved using a conventional right sided approach. A permanent cardiac pacemaker was inserted 30 minutes after successful ablation. Neither major nor minor complications related to ablation and pacemaker insertion were observed. Patients were subsequently controlled at the outpatient clinic.

Echocardiographic measurements. M-mode and cross-sectional echocardiograms were obtained at the time of measurement of LVEF by radionuclide ventriculography. Left atrial (LA) size, end left ventricular systolic (LVESD) and end diastolic diameters (LVEDD) were measured according to the recommendations of the American Society of Echocardiography.

Dobutamine stress echocardiography: Two-dimensional images were acquired from three apical views (4 chamber, 2 chamber and long axis) and 1 parasternal view (short axis). After the acquisition of rest images, dobutamine was infused at a starting dose of 5 μg/kg/min for 5 min, followed by 10 μg/kg/min for 5 min (low-dose stage). Dobutamine was then increased by 10 μg/kg/min every 3 minutes to a maximum dose of 40 μg/kg/min. Atropine (up to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. The baseline, low dose, peak stress and recovery images were displayed as a cineloop format. A 16-segment model for left ventricular wall function analysis was used, as recommended by the American Society of Echocardiography, and visually scored by 2 experienced reviewers. Each segment was scored as follows: 1=normal; 2=mildly hypokinetic; 3=severely hypokinetic; 4=akinetic; 5=dyskinetic. For each patient, wall motion score (WMS) was calculated at rest, at low dose dobutamine infusion and at peak heart rate. Reduction of wall thickening and new wall motion abnormalities during the stress test were considered to be hallmarks of ischemia. The transition of akinesia to dyskinesia was considered a mechanically induced phenomenon. The presence of contractile reserve was defined as an improvement in regional function of ≥ 1 grade at low dose dobutamine in at least 4 segments.

Evaluation of other parameters. LVEF was measured with radionuclide ventriculography (red blood cells, marked with Technetium^{99} pertechnetate, 25 mCi). Imaging was performed in 45 degrees left anterior oblique (LAO) view. The R wave was used for gating, and 16-24 frames per cycle were stored until 400 000 counts per image were acquired. Measurement was made 4-6 days after and 3 months after the ablation procedure. For all patients VVI 80 bpm pacing mode was temporarily programmed one hour before LVEF measurements. Deterioration in cardiac function was defined as a decrease in LVEF >5 %.

Cardiac peptide measurements: Before stress echocardiography a blood sample was drawn from a peripheral vein, after the patient had rested for at least 30 minutes in a supine position. Plasma concentrations of ANP, BNP levels were measured with radio-immunoassays using standard commercial kits (Shionoria ANP and BNP kits, Shionogi, Osaka, Japan). The 6 minute walk was done according to established methods(9).

Quality of life (QOL) was measured using the Dutch version of Minnesota living with heart failure, the Dutch version of Nottingham Health Profile, and the MPWB questionnaires (10,11).

Statistical analysis: The measured values are expressed as mean±SD. Data showing Gaussian distribution were compared using paired (data before and after ablation) and student t tests (comparing data in the subgroups). Dichotomous variables were compared using chi-square test. Non-parametric data were compared using Wilcoxon test. The level of significance was set at 0.05.

Results:

Patient data (Table 1)

Complete heart block was achieved in all patients, except in one, who was rescheduled and only included for follow-up after a successful redo procedure. Junctional escape rhythm was achieved in 18 patients (72%). The remaining patients had a ventricular escape rhythm. There were no complications related to the ablation and pacing procedures.

Evolution of objective and subjective parameters during the follow-up period

None of the measured objective parameters showed improvement during the follow-up period. QOL showed highly significant improvement in all questionnaires (Table 2). The distribution of deteriorators and stable/improving patients were statistically not significant in subgroups of patients with or without contractile reserve (Table 3).

Correlation of contractile reserve and changes over time (Table 4)

There was no significant difference in change of LVEF between patients with and without contractile reserve (-0.4±8.7 vs. 1.6±11.3, p=NS). However patients with a preserved LVEF at baseline showed more frequently a reduced LVEF after AV node ablation (62.2±10.4 % vs. 47.5±7.6%, p=0.001). There was no other statistically significant difference in baseline values including cardiac peptide serum levels, 6-min walk distances and WMS and QOL scores.

Evolution of subjective and objective parameters in subgroups of patients (Table 5)

In both subgroups QOL showed improvement. Apart from LVEF (which served as a grouping value in this comparison) no objective parameters showed change during the three-month follow-up. LVEF decreased from 62.2±10.4 to 51.4±13% in the deteriorating group. LVEF showed substantial improvement in the improving group from 47.5±7.6 to 52±8.1%.

Discussion:

Effect of AV node ablation and RV apical pacing on the function of the heart:

Diminished LV function during pacing at the RV apex has been known for decades from numerous animal and human studies(12-14). Ventricular pacing results in an abnormal sequence of activation, associated with decreased fiber shortening, contractile work, and myocardial blood flow and oxygen consumption in regions activated early and increases in these parameters in those regions with delayed activation leading to a depressed left ventricular function(15-17). Experimental animal data have also indicated that RV apical pacing may decrease regional myocardial blood flow within the interventricular septum(18,19). These animal data have been confirmed by human studies, where ventricular pacing decreased resting coronary flow velocity in some patients(20).

Furthermore, long term RV apical pacing results in a high incidence of myocardial perfusion defects associated with apical wall motion abnormalities and impaired global LV function(21). Furthermore, so-called functional mitral regurgitation plays a crucial role in suboptimal hemodynamics. According to these data, abnormal activation of the ventricles by RV apical pacing may result in multiple abnormalities of cardiac function, which may ultimately affect clinical outcome. On the other hand, reports were showing improvement of LV function after AV node ablation and pacing. These are the patients most likely having a tachycardiomyopathy(1,2). Unfortunately, there was no available method, which was able to predict which particular patient will improve function after ablation. This can be recognised examining the course of patients with AV node ablation and RV apical pacing. Clinically it is seen, and also shown by most studies that a relatively large proportion of the patients is deteriorating while others are improving(2,6,7). To the best of our knowledge this is the first study aiming to determine which patient will deteriorate and which will improve after such a therapy. This question becomes even more important after consideration of the QOL data. Because there is a uniform improvement in QOL life it seems to be important to recognise patients with a potential deterioration of cardiac function.

Rationale for measuring contractile reserve in patients undergoing AV node ablation and permanent RV pacing

After AV node ablation the chronotropic response of the sinus node node is lost and hemodynamic adaptation will be more dependent on changes in contractility than by changes in heart rate. The presence of preserved contractility is hence of vital importance for a good outcome after AV node ablation. Patients with tachycardiomyopathy usually suffer from long lasting fast heart rates and their LV function will likely improve after such intervention(1,22,23). It has been shown that in patients with idiopathic dilated cardiomyopathy and long lasting atrial fibrillation (having normal coronary arteries) the LVEF does not improve with low dose dobutamine. However, patients with a tachycardiomyopathy do improve(8). This can be the rationale for using LDDSE as a screening test before patients undergoing AV node ablation and pacing. Our data did not confirm that it would useful for these patients. There was significant difference between the duration of AF between our study patients and the previous study when LDDSE was predictive for improvement. The latter patients had persistent AF, while our patients had permanent long lasting AF regardless their LV ejection function. The fact that almost all patients had symptomatic improvement in our study can be explained by the fact, that circulating cathecolamines can no longer accelerate the heart rate, but will only affect the pump function. This will not necessarily improve the outcome of the patients with contractile reserve, but will definitely not influence the ones without contractile reserve.

Left ventricular function after AV node ablation and RV apical pacing for patients with permanent AF: Discordant evolution of subjective and objective parameters

Our data confirm that the functional course of patients following AV junction ablation is unpredictable. Although noticeable improvement in QOL associated with improved LVEF has been reported in many studies, some other studies reported no improvement or sometimes a decreased LV function(1-3,6,7,22-24). An important aspect of these controversial data is that in most available large studies only data on the overall group was reported, despite the obvious fact that some patients deteriorated. After careful analysis of our data and the data extracted from the above mentioned studies, it seems that during the follow up, objective and subjective parameters show somewhat of a discordant evolution. Correct interpretation of these data may allow us to develop a better understanding of the natural course of these patients and the reasons for this discordance. After AV node ablation numerous factors are influencing LV function. Some of them act in the direction of improvement, but some of them may cause deterioration. Regularisation and ventricular rate control appear to be the most important factors that may have an impact on improvement(4). On the other hand RV apical pacing results in disadvantageous cellular changes and worsened hemodynamics(5,7,13,16,25,26). It seems so far, that the net effect of interplay between the beneficial and the worsening factors is unpredictable. The almost uniform improvement in quality of life supports the idea that subjective parameters are more influenced by the beneficial factors, however function reacts independently. In some patients, concordant with the QOL, function improves, however in others, despite the improvement in QOL, it may deteriorate. Therefore, in symptom control, regularisation and rate control are important factors, but their role in functional changes is not that clear. This variable outcome is of clinical significance as per the important question of Wood, as to whether AV node ablation is applicable to a wider spectrum of patients(2). According to our present data we can conclude that the effect of AV node ablation and RV apical pacing on cardiac function is highly dependent on the baseline LVEF. It seems that patients with preserved LV function will more likely deteriorate their LV function. Therefore, this therapy should be avoided in patients when only symptom control is the goal and when the cardiac function is normal. This is in concordance with the concept of tachycardiomyopathy. It seems, that AV node ablation and RV apical pacing is the best for patients with tachycardiomyopathy. However, this can not be predicted with the presence of contractile reserve in these patients.

In conclusion, in this study subjective and objective parameters as obtained at short and midterm after AV node ablation showed discordant evolution. Our data suggest, that the presence of baseline contractile reserve does not predict improvement after AV node ablation. Furthermore, subjective parameters (measurement by QOL questionnaires) are markedly improving in most patients but parameters associated with LV performance are not improving and in a subset of patients these latter parameters even display deterioration. A good baseline LVEF is the best predictor of deterioration.

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Table 1
Clinical characteristics and ablation data of the study patients

	Overall group
Number of patients (n)	25
Gender (F/M)	9/16
Age (years)	63±11.4
Duration of AF since permanent (months)	49±11.5
LA (mm)	47.8±8.4
LVEDD (mm)	48.7±7.2
LVESD (mm)	34.9±7.8
QRS width after ablation (ms)	95±22.4
Rate of escape rhythm (bpm)	41.5±6.9

Data are presented as mean±SD, n= number, F= female, M= male, AF= atrial fibrillation, LA= left atrial dimension, LVEDD= left ventricular end-diastolic diameter, LVESD= left ventricular end-systolic diameter, bpm= beats per minute

Table 2
Evolution of objective and subjective parameters following AV node ablation in the overall group

	Before ablation	After ablation	p value
Objective parameters			
EF (%)	52.8±11.1	51.8±9.8	NS
ANP (pmol/l)	25±22.7	26.7±23.2	NS
BNP (pmol/l)	38.2±55.7	35.1±39	NS
6-min walk test (m)	353.8±123.4	358.1±160.2	NS
WMS (low dose dobutamine)	22.2±9	21.5±7.6	NS
Subjective parameters			
Minnesota QOL	4.1±2.1	2.5±2	0.001
NHBP	54.8±43.3	34.2±34.3	0.002
MPWB	22.2±4.6	19.4±6.2	0.03

NS= non-significant, EF=left ventricular ejection fraction, ANP= serum level of atrial natriuretic peptide, BNP= serum level of brain natriuretic peptide, m= meter, WMS= regional wall motion score,

Table 3
Frequency of deteriorators and stable/ improving patients in the groups with and without contractile reserve

	With CR (n)	Without CR (n)	p value
Deteriorators (n)	4	2	NS
stable/ improving (n)	9	6	NS
p value	NS	NS	

NS= non-significant, n= number of patients, CR= contractile reserve

Table 4
Comparison of baseline objective and subjective parameters following AV node ablation between stable or improvers and deteriorators

	stable/ improving	deteriorator	p value
Objective parameters			
EF (%)	47.5±7.6	62.2±10.4	0.001
ANP (pmol/l)	21±10.1	29.6±32	NS
BNP (pmol/l)	25.5±11.3	54.9±81.5	NS
6-min walk test (m)	385.3±95	297.7±152.5	NS
WMS (low dose dobutamine)	21.1±8.2	24.6±11.5	NS
Subjective parameters			
Minnesota QOL	4.3±2	4±2.4	NS
NHBP	52.1±33.7	59±56.9	NS
MPWB	23.4±4.6	19.7±3.5	NS

NS= non-significant, EF=left ventricular ejection fraction, ANP= serum level of atrial natriuretic peptide, BNP= serum level of brain natriuretic peptide, m= meter, WMS= regional wall motion score, CR= contractile reserve

Table 5
Evolution of objective and subjective parameters following AV node ablation in subgroups defined as stable or improvers and deteriorators

A, DETERIORATORS			
	Before ablation	After ablation	p value
Objective parameters			
EF (%)	62.2±10.4	51.4±13	0.0001
ANP (pmol/l)	29.6±32	20.6±13.4	NS
BNP (pmol/l)	54.9±81.5	37.8±40.5	NS
6-min walk test (m)	297.7±152.5	320.2±187.9	NS
WMS (LDD)	24.6±11	23.6±10	NS
Subjective parameters			
Minnesota QOL	4±2.4	2.4±1.7	0.009
NHBP	59±56.9	41.4±43.7	0.05
MPWB	19.7±3.5	16.8±8	NS
B, STABLE/ IMPROVING			
Objective parameters			
EF (%)	47.5±7.6	52±8.1	0.02
ANP (pmol/l)	21.2±11.3	31.6±28.6	NS
BNP (pmol/l)	24.5±11.8	32.9±39.76	NS
6-min walk test (m)	385.3±95	379.5±144.5	NS
WMS (LDD)	21.1±8.2	20.5±6.6	NS
Subjective parameters			
Minnesota QOL	4.2±2	2.6±2.2	0.002
NHBP	52.2±34.9	29.8±28.2	0.005
MPWB	23.6±4.7	20.8±4.7	0.008

NS= non-significant, EF= left ventricular ejection fraction, ANP= serum level of atrial natriuretic peptide, BNP= serum level of brain natriuretic peptide, m= meter, WMS= regional wall motion score, CR= contractile reserve, LD= low dose dobutamine

Chapter 14

BJ Krenning, T Szili-Torok, MM Voormolen, DAMJ Theuns, LJ Jordaens, CT Lancée, N de Jong, AFW van der Steen, FJ Ten Cate, JRTC Roelandt:

GUIDING AND OPTIMIZATION OF RESYNCHRONIZATION THERAPY WITH DYNAMIC THREE-DIMENSIONAL ECHOCARDIOGRAPHY AND SEMI-AUTOMATED BORDER DETECTION: A FEASIBILITY STUDY

(submitted for publication)

Guiding and optimization of resynchronization therapy with dynamic three-dimensional echocardiography and semi-automated border detection: a feasibility study

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Abstract:

Objective: To assess a new approach for guiding and hemodynamic optimization of resynchronization therapy, using three-dimensional (3D) transthoracic echocardiography.

Background: Resynchronization therapy for heart failure provides the greatest hemodynamic benefit when applied to the most delayed left ventricular (LV) site. Currently, the ideal LV pacing site is selected according to acute invasive hemodynamic assessment and/or tissue Doppler imaging.

Methods: A total of 11 patients with advanced heart failure and an implanted biventricular pacemaker were included in this study. Transthoracic apical LV images at equidistant intervals were obtained using a prototype, fast rotating second harmonic transducer to reconstruct 3D LV datasets during sinus rhythm (SR), right ventricular (RV) apical and biventricular pacing mode. A semi-automated contour analysis system (4D LV analysis, TomTec, Germany) was used for segmental wall motion analysis and identification of the most delayed contracting segment and calculation of global LV function. Results: Data acquisition duration was 10 sec. and analyzable 3D images were obtained in 8 patients. Of these patients, data during SR were available in 5 and during biventricular pacing in 7. The greatest contraction delay during SR was found in the anterior and antero-septal segments in 3 of 5 patients. Biventricular pacing resulted in reduction of the contraction delay in 3 of 5 patients. The global LV function did not change significantly.

Conclusion: 3D echocardiography with appropriate analytic software allows detection of the most delayed LV contracting segment and can be used to select the optimal pacing site during resynchronization therapy.

Keywords: resynchronization therapy, three-dimensional echocardiography, automated border detection

Abbreviations:

3D	Three-dimensional
EF	Ejection Fraction
RV	Right Ventricle
LV	Left Ventricle
NYHA	New York Heart Association
SR	Sinus Rhythm
TDI	tissue Doppler imaging
TVC	Time Volume Curve
LVESV	Left Ventricular End Systolic Volume
LVEDV	Left Ventricular End Diastolic Volume

Introduction:

Delayed intraventricular depolarization leads to dyssynchrony of ventricular contraction and worsens left ventricle (LV) dysfunction (1-4). Resynchronization by simultaneous electrical stimulation of both ventricles significantly improves hemodynamics, resulting in increased exercise tolerance and hence quality of life (5-12). Reduction in morbidity and mortality awaits confirmation from ongoing large-scale studies (5,13). Recent data indicate that biventricular pacing provides the greatest hemodynamic benefit when applied to the LV segment with the most delayed contraction (14). Tissue Doppler imaging (TDI) is currently used to identify the most delayed contraction site before the implantation of a resynchronization device (14-16). This method cannot be used online and the assessment of the hemodynamic effects requires additional studies. It has been demonstrated in previous studies that time-volume curves (TVCs) provide quantitative information on LV performance (17,18). The aim of the present study was to test the feasibility of 3D echocardiographic TVCs for determining the optimal pacing site. This allows simultaneous hemodynamic evaluation by measuring global LV function.

Methods:

Study patient:

We studied 11 patients with severe heart failure and a permanent biventricular pacemaker. All patients gave informed consent. Patient characteristics are listed in Table 1. Criteria for biventricular pacing were severe heart failure (NYHA II-IV) and dilated cardiomyopathy associated with complete left bundle branch block and a QRS duration of >125 ms. The LV pacing lead was positioned in the coronary sinus and the right atrial and right ventricular (RV) leads in standard locations.

Three acquisitions for 3D reconstruction were performed as follows: The first acquisition was performed in the biventricular pacing mode and the second after the pacemaker was reprogrammed for RV pacing. In patients with intact atrio-ventricular conduction and sinus rhythm (SR), the pacemaker was reprogrammed in order to perform acquisitions during SR. In every patient, the pacemaker was finally reset to the original settings. Acquisitions were performed 5 minutes after the pacing mode was switched. Data analysis was performed off-line for this feasibility study.

Image acquisition:

We used a prototype transthoracic, fast-rotating ultrasound transducer for 3D-echocardiographic image acquisition (19) (figure 1), which is connected to a commercially available ultrasound system (GE Vingmed Vivid FiVe, Horton, Norway). The 64-element transducer array has a center frequency of 3 MHz and second harmonic capabilities (20). It continuously rotates inside the transducer assembly at a maximum speed of 8 revolutions/ sec. The frame rate of the ultrasound system is 100 frames per second. The typical acquisition time is 10 seconds during a single end-expiratory breath hold. Patients were studied in the left lateral decubitus position with the transducer in the apical position and the image plane rotating around the LV long axis. The depth setting was adjusted to visualize the entire LV and part of the left atrium. Gain and power settings were optimised for endocardial border visualization. The ECG signal was simultaneously recorded for 3D reconstruction.

Image processing:

Data are transferred via a network connection to a dedicated workstation for processing and analysis. With self-developed software, using MatLab (The MathWorks, Inc, Natick, MA, USA), the original 2D images are post-processed by placing them in their correct spatial and temporal (ECG reference) position using multi beat data fusion (21). The cardiac cycle is divided in 12 equal intervals, which allows to create 12 3D-datasets. Due to the continuous rotation of the transducer-array, the original 2D images have a curved shape. However, these are not suited for automated contour analysis with currently available software. Therefore, 20 equidistant plane cross-sectional images (9^0 interval) are re-sampled from these 12 datasets and used for further analysis.

Image analysis:

All the 20 cross-sectional images re-sampled from each of the 12 datasets are subsequently imported into the TomTec® 4D LV-analysis software (TomTec® Imaging Systems GmbH, Germany) and displayed (figure 2). Their orientation in 3D space is determined by marking the mitral valve, aortic root and apex as landmarks. An elliptical model is placed over one of the images of each cross-sectional position. After this, the software automatically performs endocardial border detection in all images of each cross-sectional position in the 12 datasets. A spatio-temporal spline model is used to generate smooth contours for both the temporal and spatial domain.

Two experienced investigators verified and corrected the results from the automated border detection where necessary. This was done blinded, without knowledge of the pacing mode for each analysis. The papillary muscles within the LV cavity are not taken into account for the definition of the contour. After completion of the endocardial border tracing, the program performs a dynamic surface rendered endocardial reconstruction of the LV (figure 3A). For each pacing mode, a TVC is plotted from which global LV end-diastolic volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (EF) are calculated applying Gaussian quadrature formulas.

The LV endocardial surface is subdivided in 16 segments, which are colour coded for orientation (figure 3B). A *segmental* volume represents the prismatic volume of a segment to the central LV axis. The volume change of a segment over the cardiac cycle is plotted in a TVC (figure 4), in which time is defined as percentage of the total cardiac cycle. The end-systolic moment, at which a segment has completed maximal myocardial contraction, is represented by the nadir of the segmental volume curve. This moment was extracted from the TVC for every segment in every pacing mode. The difference in time to maximal myocardial contraction between segments was used to assess regional mechanical delay and a measure of segmental dyssynergy. From the TVC that represents segmental volume changes in SR, the first contracting segment and the most delayed segment were identified. The delay in contraction was calculated as the difference in time to maximal contraction between these segments and is expressed as percentage of the total cardiac cycle. Using the RR-interval, this was re-calculated in milliseconds. When a segment is hypo- or akinetic, which we defined as a segmental volume change during any part of the cardiac cycle of less then 20%, the segment is not included. In both biventricular and RV pacing mode, the most delayed segment is determined and the delay between this segment and the first contracting segment calculated.

Statistical Analysis:

Data are presented as mean ± SD. 3D measurements of LV volume were calculated by the analysis software after completion of the endocardial border tracing. To assess accuracy, analysis of TVCs was performed by two observers and analyzed by linear regression and a limits-of-agreement analysis, expressed as the mean difference and 2 SDs of the difference between the measurements of the two observers. To determine whether the difference in the values between the two observers and between pacing-modes was statistically significant, a paired t-test was performed. A probability level of $p < 0.05$ was considered significant.

Results:

Of the eleven patients, three were excluded from analysis because of inadequate echocardiographic image quality for faithful automated analysis. In three of the remaining 8 patients, no spontaneous sinus rhythm was present and therefore only acquisitions in biventricular and RV pacing mode were performed. In one patient, we did not perform an acquisition in biventricular pacing mode because of LV lead displacement.

Global LV function:

The mean ejection fraction of all patients before implantation, by equilibrium radionuclide angiography, was 24.7 ± 6.2%. During sinus rhythm, the mean LVEDV, LVESV and LVEF derived from the TVC were 310 ± 92, 231 ± 109 and 28% ± 4%, respectively. During RV pacing these values were 287 ± 111, 218 ± 89 and 24% ± 6% and during biventricular pacing, 276 ± 115, 227 ± 105 and 19% ± 5%, respectively. No significant difference was present between these values.

Dyssynchrony:

Table 1 shows the most delayed segment for every pacing mode and the delay between the first contracting and most delayed segment. The mean delay was 106 ± 78 during SR, 102 ± 43 during biventricular pacing (p = NS; SR vs biventricular pacing) and 137 ± 65 during RV pacing (p = NS; RV vs biventricular pacing). In three of five patients the anterior or antero-septal segment was most delayed during SR. Biventricular pacing resulted in reduction of the contraction delay in three patients, compared to SR. Also, in three patients the contraction delay was less during biventricular pacing compared to RV pacing.

Interobserver agreement:

Linear regression analysis indicated a good correlation (r = 0.96) between measurements of delay in contraction between the first contracting segment and the most delayed site by two observers (figure 5). The standard error of estimate was 2.27%. The limits-of-agreement analysis demonstrated a small mean difference (-1.05 ± 4.45%) between measurements. A paired t-test indicated no significant mean difference between the two observers.

Discussion:

This study shows that transthoracic dynamic 3D echocardiography performed with a fast rotating transducer and combined with automated contour analysis allows to identify LV segments with dyssynchrony together with hemodynamic evaluation. Our data indicate that this method is feasible for the selection of the optimal pacing site during resynchronization therapy.

Rationale for measuring mechanical delay in patients undergoing resynchronization device implantation:

A delay in intraventricular conduction leads to dyssynchrony of ventricular contraction which can be corrected by biventricular pacing and subsequently improve hemodynamics. and consequently exercise tolerance and quality of life in patients with severe heart failure. Large-scale trials are ongoing to study long-term effects including morbidity and mortality (5,13,22). However, a substantial proportion of the patients does not show improvement. This may be partly related to methodological reasons. Indeed, a prolonged QRS-complex cannot quantify the degree of dyssynchrony. Clearly, biventricular pacing provides the most benefit when applied to the segment of the LV that is most delayed in contraction. Therefore pacing should be applied to this site but it must be noted that this site will not always be approachable during implantation.

The role of improved imaging techniques to guide and evaluate biventricular pacing:

Echocardiography has an important role in the evaluation of patients with mechanical dyssynchrony before biventricular pacing implantation (23,24). Sogaard et al. (25) previously used 3D echocardiography for hemodynamic assessment in patients before and after biventricular pacemaker implantation. Currently, TDI is most often used as a guiding tool for the implantation (15,16) and is useful for identifying LV myocardial contraction dyssynchrony at discrete points in patients after ventricular resynchronization (14). It is suggested that TDI analysis could serve in the future both as a tool for pre-implantation assessment and as a guide to select the most optimal pacing site. However, this approach requires a lengthy echo study and analysis before the implantation, while only the longitudinal function in the basal and mid-segments are studied. 3D echocardiography with appropriate analytic software allows to determine dyssynchrony between all segments. Additionally, the position of the RV lead has a significant impact on the LV conduction pattern. Therefore, the optimal technique should provide the information during the implantation procedure and additional hemodynamic data. This is possible with a fast-rotating ultrasound transducer and appropriate software for analysis.

Limitations of the study:

We used prototype equipment for this proof-of-principle study requiring further refinements. The post-processing time to obtain a 3D dataset must be shortened to make this technique a practical guiding tool during the intervention. The automated border detection algorithms are user friendly, but manual interaction remains often a necessity.

This was not a prospective study and the patients studied had already their resynchronization device in place. Therefore, we could only study the feasibility of the method and whether dyssynchrony in segmental contraction could be measured.

In conclusion, 3D echocardiography is a feasible approach for determination of the most delayed LV site with the additional option to assess hemodynamic information, such as LVEDV, LVESV and EF. This preliminary data suggest that 3D echocardiography can be used for selection of the most optimal pacing site before and during resynchronization device implantation. Further studies with prospective study design are required to validate this data against other techniques, e.g. TDI.

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Figure legends:

Figure 1:

Latest prototype of the continuous fast-rotating transducer.

Figure 2:

From each dynamic 3D data set, up to 20 cross-sectional images can be selected. The orientation of each cross-section is shown.

Figure 3:

Three-dimensional reconstruction of the LV (A) and bulls-eye view according to which the endocardial surface is subdivided in 16 colour-coded segments (B).

Figure 4:

Example of time-volume curves of four different segments. During sinus rhythm, each segment completes myocardial contraction at a different moment (indicated with an arrow for every segment), causing LV dyssynchrony. From the various delays, the largest delay is shown with a dotted line (A). During biventricular pacing, synchrony in segmental contraction is present (B).

Figure 5:

Regression analysis for measurement of delay between the two most delayed segments by two observers.

Table I. Patient characteristics and results for contraction delay measurements

						SR		BiV		RV	
Patients	age	NYHA class	type of CM	pacing site	FCS	MDS	delay (ms)	MDS	delay (ms)	MDS	delay (ms)
1.	76	III	2	ant	16	9	64	1	69	9	61
2.	56	III	2	pcv	7	10	20	*	*	3	50
3.	56	II	1	plcv	16	2	177	8	80	2	167
4.	71	II	2	lcv	11	7	200	4	143	8	137
5.	64	III	1	plcv	8†	*	*	11	130	8	230
6.	68	III	2	plcv	3†	*	*	6	261	6	198
7.	67	II	2	plcv	10†	*	*	3	53	9	45
8.	62	III	1	plcv	6	2	68	6	66	3	205

ant = anterior, CM = cardiomyopathy (1 = dilated cardiomyopathy, 2 = ischemic cardiomyopathy), BiV= biventricular pacing, FCS = first contracting segment, lcv = lateral cardiac vein, MDS= most delayed segment, NYHA = New York Heart Association, pcv = posterior cardiac vein, plcv = postero-lateral cardiac vein, RV= right ventricular pacing, SR= sinus rhythm, * = not applicable, † = during biventricular pacing

figure 1

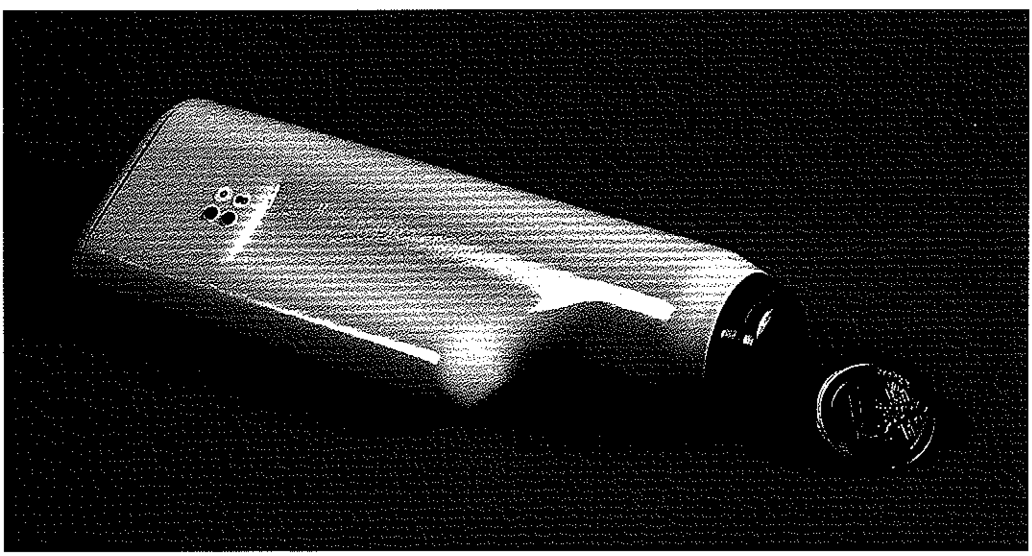


figure 2

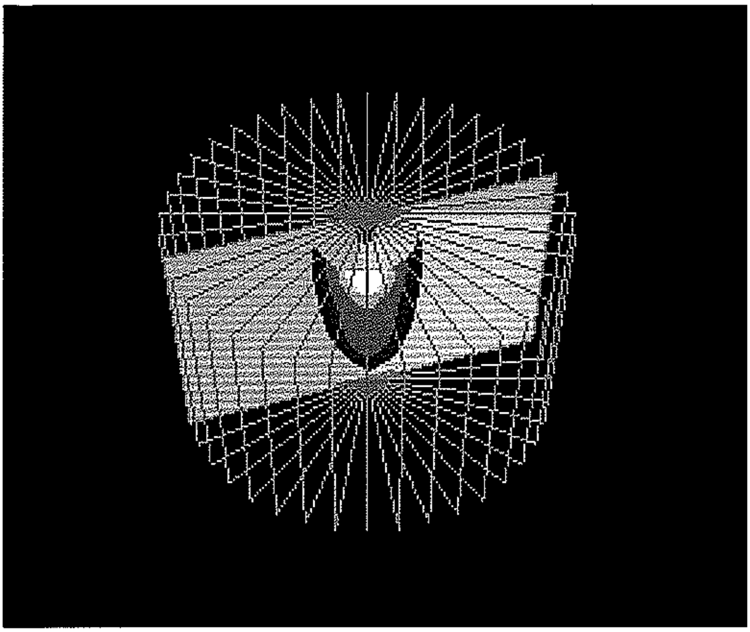


figure 3

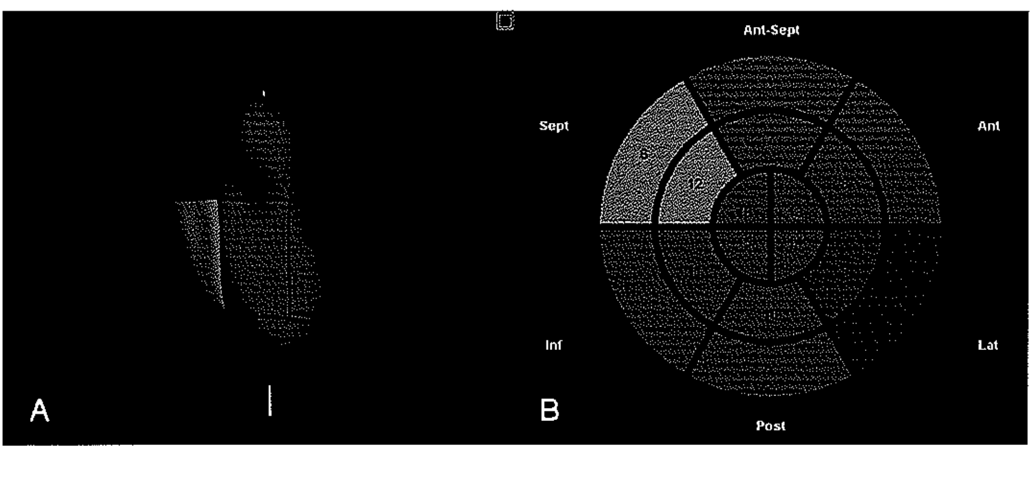


figure 4A

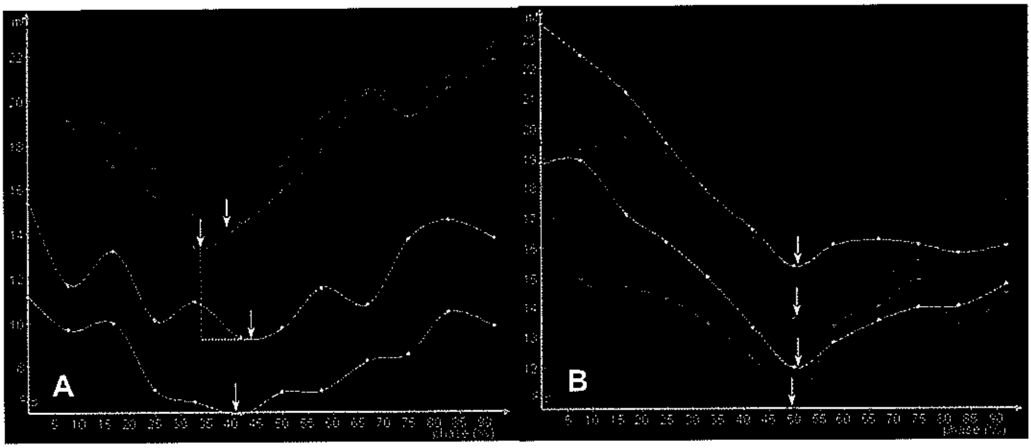
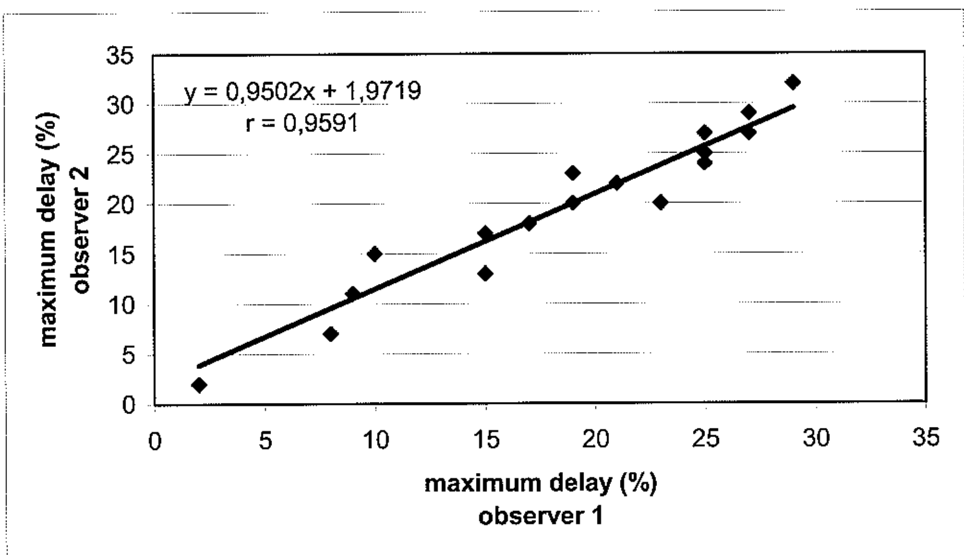


Figure 5:



Chapter 15

T Szili-Torok, JRTC Roelandt:

VISUALIZATION OF ELUSIVE STRUCTURES USING INTRACARDIAC ECHOCARDIOGRAPHY: INSIGHTS FROM ELECTROPHYSIOLOGY

Visualization of elusive structures using intracardiac echocardiography: Insights from electrophysiology

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Background

Electrophysiological mapping and ablation techniques are increasingly used to diagnose and treat many types of supraventricular and ventricular tachycardias. These procedures require an intimate knowledge of intracardiac anatomy and their use has led to a renewed interest in visualization of specific structures(1-3). This has required collaborative efforts from imaging as well as electrophysiology experts. Classical imaging techniques may be unable to visualize structures involved in arrhythmia mechanisms and therapy. Novel methods, such as intracardiac echocardiography and three-dimensional echocardiography, have been refined and these technological improvements have opened new perspectives for more effective and accurate imaging during electrophysiology procedures(4-8). Concurrently, visualization of these structures noticeably improved our ability to identify intracardiac structures. The aim of this review is to provide electrophysiologists with an overview of recent insights into the structure of the heart obtained with intracardiac echocardiography and to indicate to the echo-specialist which structures are potentially important for the electrophysiologist.

The interatrial septum (Figure 1)

Anatomically and echocardiographically the most prominent part of the atria is the interatrial septum with its very characteristic appearance. It is defined as the thin wall separating the two atria, running obliquely from the front, extending posteriorly and to the right. When it is seen from the right atrium, the most prominent feature is the fossa ovalis surrounded by a muscular rim. When seen from the left atrium, the crater-like appearance of the right side is absent. The membrane in the fossa itself is predominantly composed of fibrous tissue with relatively few myocytes. Certainly its definitive form can be explained by its development, however describing the process of development in details is outside the scope of this review. Although the interatrial septum was a focus of interest for congenital disorders, electrophysiologists have discovered additional reasons to explore the interatrial septum. A significant number of accessory pathways are located septally(9). Their close relation to the natural atrioventricular conduction system means that direct visualization of the septum can theoretically improve the safety of ablation procedures. Furthermore left atrio-ventricular accessory pathways can be approached using the transseptal approach, which provides improved stability for the ablation catheter. This requires puncture of the interatrial septum. Although it can be done without direct imaging, data clearly demonstrate improved safety and increased efficacy using intracardiac echocardiography(10-12). Another important electrophysiological aspect of interatrial septum is related to the natural conduction pathways between the two atria. These special fibers are located both anteriorly above the fossa ovalis and posteriorly near the orifice of the coronary sinus. Recent data suggest that interatrial conduction delay may play a significant role in the onset mechanism of atrial fibrillation(13). Therefore stimulation of these regions may play role in preventing atrial fibrillation(14,15). To the best of our current knowledge specific electrograms are not informative for these regions. Thus, electrogram analysis cannot guide positioning of electrodes in this area. This stimulated the development of imaging modalities for guiding such procedures. Three-dimensional echocardiography proved to be effective for guiding suprafossal pacing(16).

Coronary sinus (Figure 2)

The coronary sinus (CS) is a small tubular structure just above the posterior left atrioventricular junction. The coronary sinus (CS) is of special interest to the electrophysiologist and pacemaker-implanting physician. It opens into the right atrium between the inferior vena cava and the tricuspid valve orifice. Its tributaries are the great, small and middle cardiac veins, the posterior vein of the left ventricle and the oblique vein of the left atrium (Marshall's vein), all except the last having valves at their orifices. Left atrial recording for electrophysiology (EP) studies is routinely done indirectly from the coronary sinus. The left atrium or the left ventricle can also be paced via the CS(17,18). The CS can be cannulated from the jugular, subclavian or femoral vein and insertion of pacing/diagnostic electrode catheters is easy in most patients. However in some patients cannulation of the CS or its tributaries can pose significant difficulties and may result in excessive procedural and fluoroscopy time. Theoretically intracardiac echocardiography (ICE) can identify anatomical variants and may facilitate such procedures(7). The presence of supraventricular arrhythmias influences significantly the function of the coronary sinus(19). It is well known that the CS narrows during atrial contraction in persons with sinus rhythm, but does not narrow at all if atrial fibrillation is present(20). Attenuation of CS narrowing occurs in patients with congestive heart failure. Patients with poor left ventricular systolic function show mild CS dilatation(20). Greater CS dilatation is present in patients with persistent left superior vena cava, and huge dilatation when this anomaly is accompanied by absence of a right superior vena cava(20). This has a significant impact on pacemaker implantation for these patients. Apart from its obvious role in providing access to the left atrioventricular junction during electrophysiology testing, the coronary sinus is an important structure for the electrophysiologist. Resynchronization by simultaneous electrical stimulation of both ventricles significantly improves hemodynamics, resulting in increased exercise tolerance and hence quality of life in patients with advanced heart failure and intra-ventricular conduction delay(21). Reduction in morbidity and mortality was recently reported. This simultaneous stimulation is achieved by positioning of the left ventricular electrode through coronary sinus into its left ventricular side branches. Furthermore biatrial stimulation was also reportedly effective in the preventive treatment of patients with paroxysmal atrial fibrillation(13). Recently, using cryothermy, safe ablation procedures are possible within the coronary sinus for accessory pathways running in close proximity to this vascular structure(22).

Valves in the coronary sinus (Figure 3)

In the majority of cases the great cardiac vein possesses a prominent valve where the vein turns around the obtuse margin to become the coronary sinus(23). This valve was first described by the French scientist R. Vieussens in his book "Nouvelles découvertes sur le coeur" (Paris, 1706). Until recently, all of these anatomical variants are known from post-mortem human studies. A certain level of anecdotal relationship is proposed between difficulties during interventions in cardiac electrophysiology and anatomical differences, but there is no systematically conducted study, which provides direct evidence. One of the reasons is that fluoroscopy –which is an almost exclusive tool for guiding EP procedures- does not allow visualization of anatomical landmarks. Recently, ICE became available providing excellent accuracy in direct visualization of anatomical landmarks including valves serving as obstacles during diagnostic and interventional electrophysiology procedures.

Eustachian ridge and valve and the Thebesian valve (Figure 4)

The right and left venous valves of the sino-atrial orifice regulate the flow of blood from the sinus venosus to the atrium in fish, amphibians, and reptiles. In bird, mammals and humans, the venous valve loses its hemodynamic function and only comes to medical attention when congenital anomalies occur that are related to it(2). The right venous valve persists in humans as the crista terminalis, Eustachian and Thebesian valves. An intraluminal muscle band has been described located inside the right atrium, and coursing in the line of the crista terminalis between the septum spurium and inferior vena cava. This abnormality is possibly derived from the right venous valve. Usually it has a triangular shape and is a flap of fibrous fibro-muscular tissue that is inserted on the Eustachian ridge. The Eustachian ridge separates the orifices of the inferior caval vein and coronary sinus. In some cases the valve is particularly large and can be an obstacle to catheters passing from the inferior caval vein. Occasionally the valve is perforated or takes the form of delicate filigreed mesh. The free border of the valve is called as the tendon of Todaro. This tendon runs in the musculature of the sinus septum (Figure 5). This is indeed one of the borders of Koch's triangle. The detailed information and clinical significance of the Eustachian valve have not yet been elucidated. In the cases of atrial fibrillation with severe tricuspid regurgitation, the valve remains at the semi-closed position throughout systole and opened in rapid filling phase. A small crescentic flap, the Thebesian valve usually guards the orifice of the coronary sinus. Frequently it is fenestrated. An imperforate valve completely covering the ostium is very rare, but can be a major obstacle for positioning electrode catheters into the coronary sinus.

The Koch's triangle (Figure 6)

The structures delaying the cardiac impulse and then insuring its rapid propagation to the ventricular myocardium constitute a continuous axis of histologically discrete cells(1,24). The atrial components are located at the base of the atrial septum, located at the apex of a triangular region first illustrated by Koch. The anterior border is marked by the hinge of the septal leaflet of the tricuspid valve. Superiorly, the central fibrous body is the landmark for penetration of the bundle of His. The inferior border of the triangle is the orifice of the coronary sinus and the vestibule immediately anterior to it. This part is the area, which is targeted for ablation of the slow pathway in atrio-ventricular nodal reentrant tachycardia. The so-called fast pathway corresponds to the area of musculature close to the apex of the triangle. Ablation in the Koch's triangle was of special interest in the last two decades. Large number of patients with supraventricular tachycardia have an AVNRT. The occurrence of inadvertent complete AV block is an infrequent but serious complication(25). Imaging of this region using intracardiac echocardiography is not particularly difficult, because of the very characteristic appearance of the borders. Intracardiac ultrasound was reported during AVNRT ablation to improve the outcome of the procedures. During cryo-ablation of the AV node the cryocatheter-endocardial contact and ice-ball growth could be effectively monitored with ICE(26).

The terminal crest (Figure 7)

From the epicardial aspect of the right atrium a fat-filled groove structure can be seen at the lateral wall. This structure corresponding internally to the terminal crest. Close to its origin the terminal crest is joined to by a prominent bundle called septum spurium. The terminal crest sweeps like a twisted "C" originating from the septal wall, passing anterior to the orifice of the superior caval vein, descending posteriorly and laterally and then turning anteriorly to skirt the right side of the of the orifice of the inferior caval vein. The echocardiographic appearance of the terminal crest is very typical; it can be visualized along the lateral wall as a very echo-dense structure. The complexity of atrial geometry is responsible for the fact spread of activation from site of the origin of the electrical impulse is restrained by natural barriers and orifices. It has been suggested by numerous reports that the terminal crest can serve as such a physiological barrier and therefore can play important role in some arrhythmia mechanisms(27-30). From the electrophysiology point of view it is a transverse barrier to conduction during typical atrial flutter. The above-mentioned findings support the idea that direct visualization of the terminal crest may facilitate certain types of transcatheter ablations. Since mapping techniques have proven that atrial tachycardias can originate from the terminal crest, visualization can improve the outcome of these procedures(31). Using intracardiac echocardiography a subgroup of so-called "crista tachycardias" were identified(31). ICE guided ablation of such tachycardias were highly effective. ICE facilitated both positioning of mapping multipolar electrode catheters along the crista and mapping with the ablation catheter. From these studies it was concluded the approximately two third of the atrial tachycardia originating from the right atrium are anatomically associated to the crista terminalis. Most importantly direct imaging of the terminal crest has a substantial role during ablation of inappropriate sinus tachycardia(32-34). Because of the vicinity of the sinus node to the epicardial surface at the junction of the superior vena cava and the right atrial appendage, the sinus node is easily damaged if an epicardial approach is used during surgery. If an endocardial approach is used however more energy is needed to penetrate the greater musculature of the terminal crest and additionally the centrally located nodal artery has a cooling effect reducing the damage. From the anatomical standpoint it is suggested therefore, that positioning the ablation catheter at the site of the terminal crest halfway between the caval veins, where the tail of the sinus node is intra-myocardially located is effective without the risk of causing venous occlusion(34,35).

The cavo-tricuspid isthmus region (Figure 8)

The atrial wall inferior to the orifice of the coronary sinus is usually pouch-like. It forms the posterior part of the so-called "flutter isthmus" between the inferior vena cava and tricuspid valve. Three morphological zones are usually distinguishable in the flutter isthmus. It receives a variable number of muscular branches with varying morphology from the crista terminalis. The isthmus of atrial tissue bordered by the inferior vena cava and the tricuspid annulus forms a critical zone of slow conduction in the reentry circuit of atrial flutter. Animal models and mapping studies of human atrial flutter have proven the importance of barriers in this reentrant arrhythmia(30). The consistency of rate and morphology of typical atrial flutter suggest a common anatomic substrate for this arrhythmia. The unique endocardial architecture of the right atrium provides anatomic barriers around which reentry occurs(30). In typical human atrial flutter, the crista terminalis, Eustachian ridge, and tricuspid annulus have been identified as barriers to conduction.

The pulmonary veins: visualization of muscular bands and sleeves (Figure 9)

The pulmonary venous wall in the human comprises a thin endothelium and media consisting of fibrous tissue and smooth muscle, with or without an irregular middle layer of atrial myocardial tissue, and thick fibro-fatty adventitia on the outside. The presence of myocardial sleeves extending from the left atrium onto the pulmonary veins towards the lung is well documented (36,37). This atrial myocardium, with bundles arranged in varying orientations passes between the adventitia and the media of the venous wall. Theses muscle sleeves are believed to have role in the pathogenesis of atrial fibrillation providing triggers. These left atrial pulmonary vein muscle sleeve connections are targeted during isolation of the pulmonary veins(38-40). Currently the pulmonary veins are visualized by angiography during the procedure, and the procedure is guided by electrogram analysis. Low frequency ultrasound was used to detect post-procedural stenosis after ablation, which is the most severe complication of the procedure. Intracardiac echocardiography is proved to be useful technique during ablation of pulmonary veins in guiding positioning of the ablation catheter and allowing visualization of appropriate tip-tissue contact(41-43). Unfortunately these low frequency echo-transducers provide useful information about the vein, but do not allow detailed study of the structure of the venous wall. Recently, convincing data have been presented with high frequency intravascular ultrasound in visualizing such structures(44). Correct identification of the anatomy is important since significant variations exist including a common vestibule of the left pulmonary veins and additional small branches. ICE has a critically important role in ablation in this region. First, the transseptal puncture can be guided by ICE. Pulmonary venous anatomy can be assessed using the phased-array transducer without entering the left side of the heart. During ablation the wall contact of the catheters can be monitored. Knowing the fact that pulmonary vein stenosis is the most frequent and potentially life threatening complication of the procedure, one of the major advantage of ICE appears to be that after ablation pulmonary vein stenosis can be reliably assessed using vessel diameter measurement and Doppler flow measurements. Recent reports suggest that pulmonary venous anatomy can be extensively studied by 3D intracardiac echocardiography, including visualization of ablation catheters in the vein.

Left ventricular outflow tract (Figure 10)

The left ventricular outflow tract can be visualized by using intracardiac echocardiography, without additional arterial puncture or transseptal puncture(45). The ultrasound catheter should be positioned on the anterior interatrial septum (His bundle region) or at the base of the right ventricular outflow tract. The ostium and the initial part of the left main coronary artery can be also visualized which allows safe ablation in this region. It was demonstrated that in patients with idiopathic left ventricular tachycardia originating from the left ventricular outflow tract intracardiac echocardiography could accurately guide catheter ablation by permitting the identification of anatomical landmarks, endocardial contact and ablation electrode movement(45). Using intracardiac ultrasound the aortic root and the tip of the ablation catheter could be visualized in details. Interestingly enough the ablation site was always safely above the coronary cusp.

In conclusion, clinical electrophysiology had significant benefit form the latest developments in echocardiography. Intracardiac transducers are now available, and this allows better intracardiac structure identification. The clinical application of these devices is a subject of ongoing studies. The results are very promising, and with further improvement in imaging the electrophysiology procedures will require significantly less fluoroscopy time with increased accuracy and efficacy.

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Figure legends:

Figure 1

Typical appearance of the interatrial septum with the fossa ovalis recorded by a mechanical intracardiac echo-transducer providing horizontal cross-sectional images.

Figure 2

Three-dimensional echocardiographic "en face" view of the ostium of coronary sinus.

Figure 3

The Thebesian valve guarding the ostium of the coronary sinus. The image was obtained with a 9MHz rotating mechanical transducer. The Eustachian ridge is very prominent in this patient.

Figure 4

Eustachian valve recorded by a phased array steerable intracardiac ultrasound transducer.

Figure 5

The tendon of Todaro reconstructed form a three-dimensional data-set.

Figure 6

Image showing the bottom of Koch's triangle with an ablation lesion in the area of slow pathway as visualized by echo-contrast infusion.

Figure 7

The crista terminalis

Figure 8

Image of the cavo-tricuspid isthmus in a patient who underwent ablation of typical atrial flutter.

Figure 9

Visualization of the pulmonary veins from the right atrium using a 5MHz phased array intracardiac echocardiography transducer.

Figure 10

LV outflow tract visualized using a 9Mhz rotating transducer place at the level of the tip of Koch's triangle.

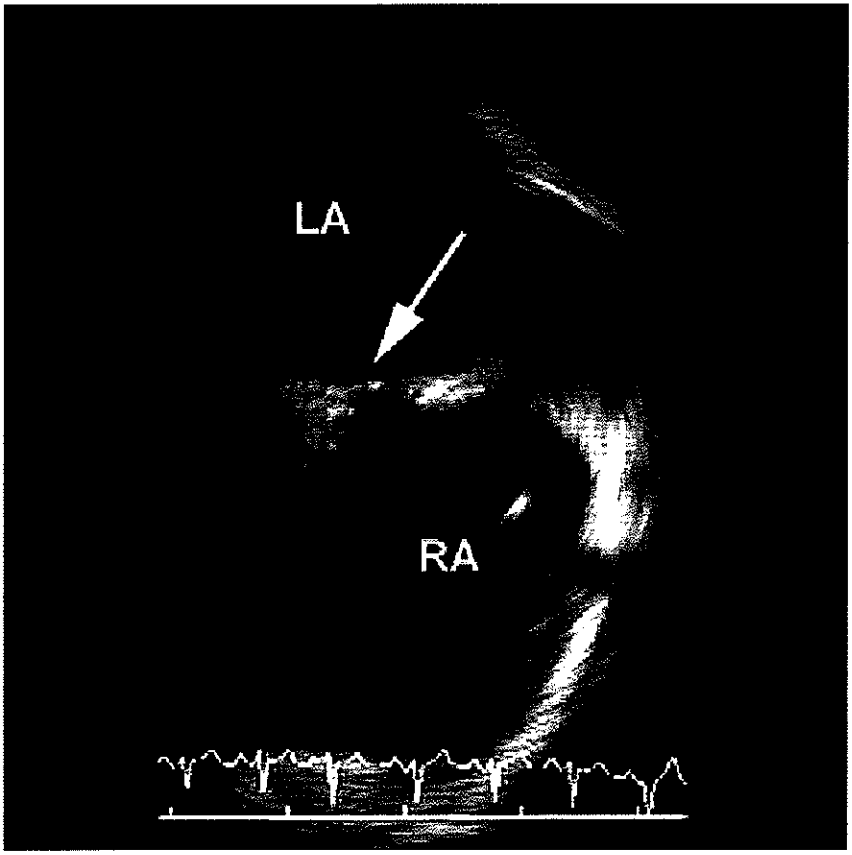


Figure 1

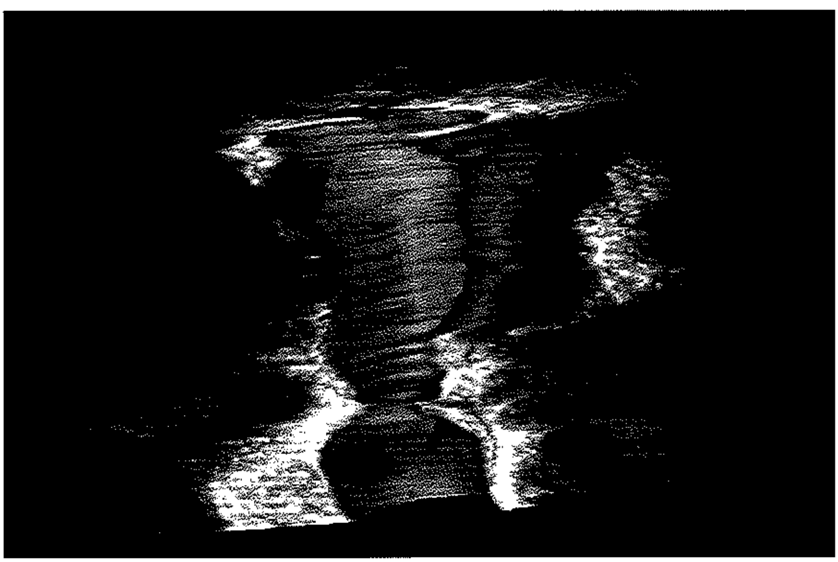
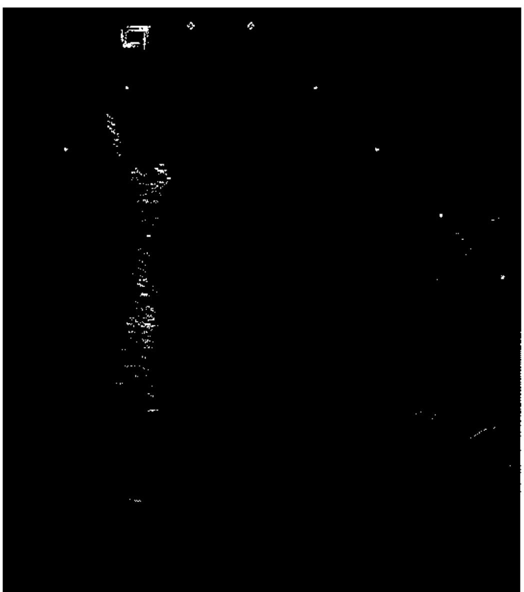


Figure 2

Figure 3



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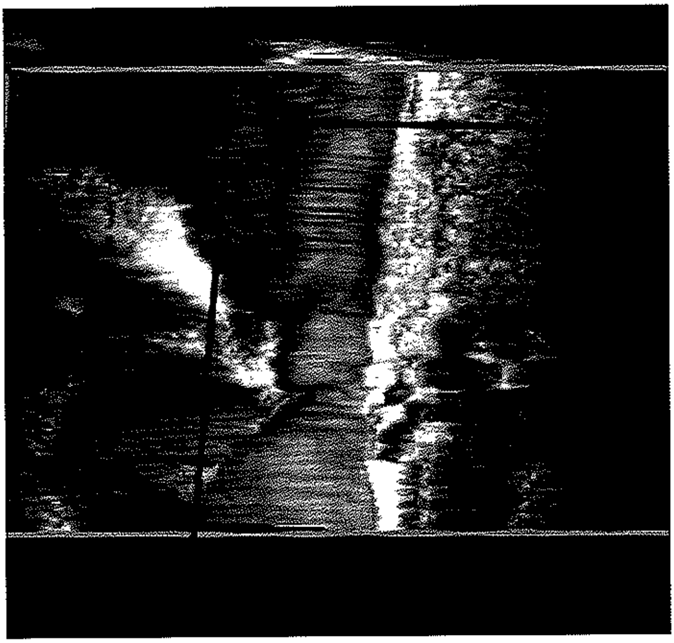

Figure 5

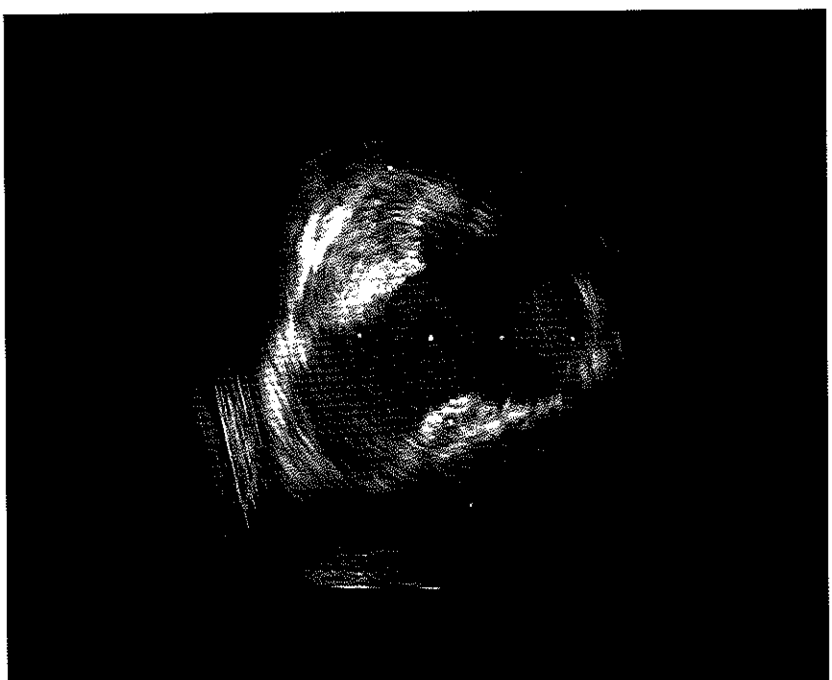

Figure 6

Figure 7

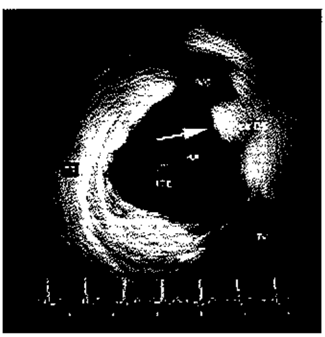

Figure 8

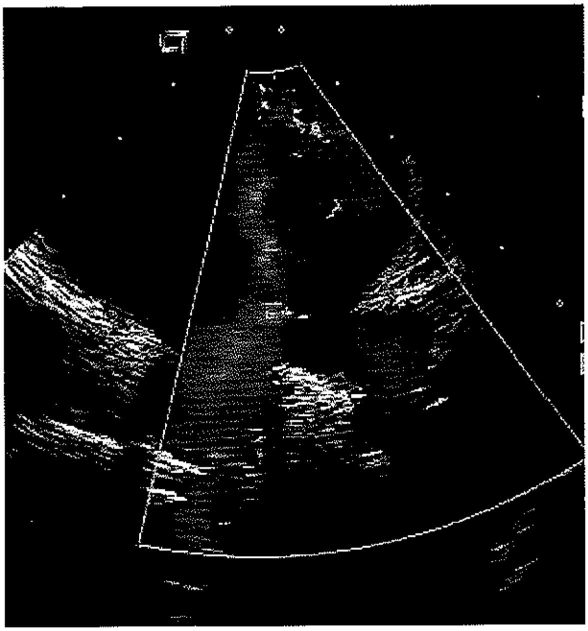

Figure 9

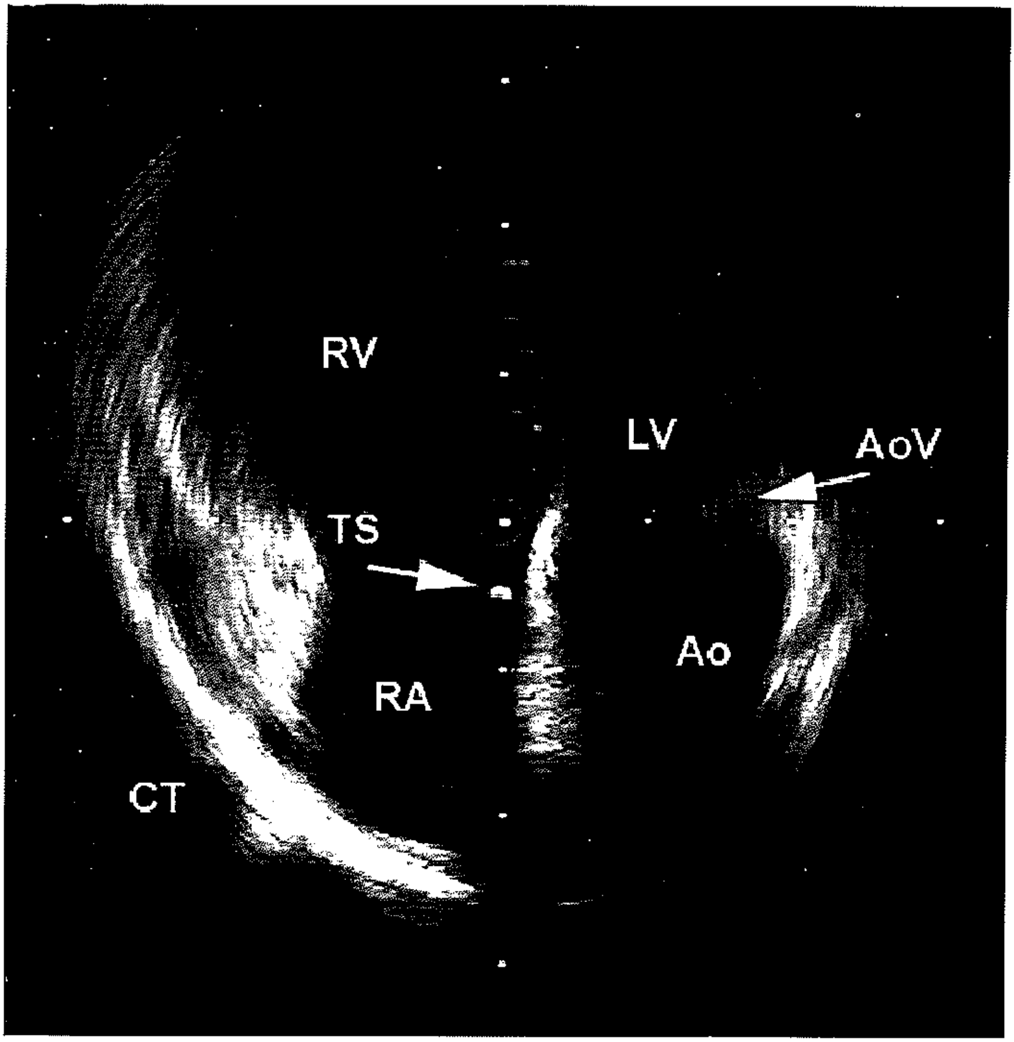

Figure 10

SUMMARY AND CONCLUSIONS

Summary and Conclusions

Two directions in the development of ultrasound imaging were seen in the past decade: miniaturization and 3D imaging. Clinical electrophysiology has a significant benefit from both of these directions allowing the use of intracardiac transducers and 3D imaging for improved intracardiac structure identification. The application of these devices in clinical electrophysiology was in the focus of the research presented in this thesis. It appears that electrophysiology and pacing procedures can be guided by intracardiac echocardiography with improved safety, accuracy and a significant reduction of fluoroscopy. This represents a major step in the integration of imaging with interventional cardiac electrophysiology.

Part I. Guiding pacing procedures

In the first part of this thesis we describe how specific pacing sites can be selected with a use of three-dimensional echocardiography. Recently, novel ways of pacing have been proposed for the treatment of patients with various types of arrhythmias. There is growing evidence suggesting that pacing on the atrial level in the region of Bachmann's bundle, the interatrial septum (IAS) or even multiple atrial sites may have advantages in patients with atrial fibrillation. On the ventricular level, novel pacing techniques may have a role in preserving or even improving ventricular performance in patients with or without heart failure. However, these specific site pacing techniques require an extremely accurate lead positioning as compared to the conventional bradycardia indications. This explains why adequate results are not always obtained with these new pacing therapies in a considerable number of patients. One of the explanations may be related to the anatomical variations which results in a variable and less efficient lead positioning. Our aim was to develop and test a novel technique based on three-dimensional ICE for specific site pacing.

Our studies are the very first demonstrating the capabilities of three-dimensional (3D) echocardiography in clinical cardiac electrophysiology. It appears that intracardiac 3D echocardiography is both feasible and safe to guide the positioning of atrial pacing electrodes for permanent IAS pacing. Our findings indicate that, accurate localization of the atrial pacing lead results in a greater reduction of the P-

wave duration than has been suggested in earlier reports. Regarding reduction of interatrial conduction delay, suprafossal, seems preferable.

Part II. Guiding ablation procedures

In the second part of the thesis the usefulness of intracardiac echocardiography is demonstrated during ablation procedures.

We aimed to develop a safe and effective way of transseptal left heart catheterization based on intracardiac echocardiography. Percutaneous puncture of the interatrial septum was introduced for catheterization of the left heart in 1960. Recently there has been renewed interest in transseptal left heart catheterization for left-sided catheter ablations. However, a significant number of acute and potentially lethal complications with transseptal puncture may occur, including tamponade, systemic emboli, and even death secondary to aortic perforation. Since fluoroscopy does not allow direct visualization of the fossa ovalis, transseptal catheterization remains a difficult procedure, particularly in patients with atypical atrial anatomy. Intracardiac ultrasound allows visualization of the fossa ovalis in all patients with excellent image quality. This is a direct method and a possibility to avoid complications.

Our results suggest that intracardiac echocardiography offers excellent visualization of the fossa ovalis which has significant advantages for transseptal puncture. It also provides the possibility of flexible planning of the procedure not requiring deep sedation and it can be used comfortably for a longer time. The method seems to be an additional tool to minimize the risk for dangerous complications during the puncture of interatrial septum. From a technical point of view, the most useful indication of the optimal puncture site is the characteristic downward jump of the transseptal needle onto the fossa ovalis detected simultaneously with intracardiac ultrasound and fluoroscopy.

Catheter ablation is an effective method in management of atrial flutter. However, a considerable proportion of the cases is unsuccessful or a substantial number of patients have recurrences. One possible explanation for the unsuccessful procedures and recurrences is related to anatomical variations of the cavo-tricuspid isthmus. Furthermore, RF lesions can be inadequate, allowing slow conduction through the cavo-tricuspid isthmus. Although ICE allows guiding of electrophysiological procedures by visualising important structures, there are controversial data available about its capability to assess the radiofrequency lesions after ablation. We assessed radiofrequency (RF) lesions in the cavo-tricuspid isthmus region 20 minutes after radiofrequency ablation.

We concluded that intracardiac echocardiography using subclavian approach is a feasible technique to visualise the cavo-tricuspid isthmus. It should be noted that RF lesions cannot be identified after 20 minutes using this 9 MHz fixed frequency intracardiac ultrasound probe in the absence of baseline pre-ablation intracardiac imaging.

Catheter ablation is a curative treatment for most patients with arrhythmias. In some patients, the results are still suboptimal because of inadequate lesion formation during ablation. Based on this and the results of the previous study we attempted to develop a technique, which allows visualisation of ablation lesions. Direct visualization of ablation lesions may a have significant impact on the outcome of the ablation procedures. The aim of our study was to assess the potential use of myocardial contrast echocardiography (MCE) to demonstrate ablation lesions in human atrial myocardial tissue during continuous venous echocontrast administration.

This study demonstrated that MCE allows visualization of ablation lesions in the human right atrial myocardium during continuous venous echocontrast infusion. This potentially opens a new avenue for objective, and easily accessible evaluation of ablation lesions. Since transmural lesion formation is critical for successful ablation, the MCE method may have a significant impact on the outcome of ablation procedures.

Part III. Assessment of cardiac function in arrhythmia patients

Echocardiography plays a major role in assessment of ventricular function in patients undergoing pacemaker implantation for various reasons. RV apical stimulation is not physiologic because normal ventricular activation along the natural conduction system is bypassed and the ventricles are activated in an abnormal sequence. Chronic apical ventricular pacing is associated with myocardial cellular changes and may lead to dysfunction of the left in a considerable number of patients. These findings stimulated studies to search for alternative right ventricular and/or multiple ventricular pacing sites. Echocardiography has a significant role in preselection, guiding and follow-up of these patients. Furthermore, optimization of the pacing parameters can be effectively performed by echocardiography. In this part of the thesis we present results describing the functional course of patients undergoing AV node ablation and chronic right ventricular apical pacing. We also aimed to predict which patient would develop deterioration or improvement after such a therapy. Furthermore, we developed a novel echocardiograpohic method for assessment of alternative pacing sites from the functional point of view.

The major finding of our pilot study was that LVEF deteriorated three months after AV node ablation with chronic RV apical pacing. Secondly, the LV dimensions and the LA size did not show significant changes during the study period. Our data confirm the hypothesis that LV function may become depressed after long term duration of AF. In the following project we studied subjective and objective parameters as obtained at short and midterm after AV node ablation. These parameters showed a discordant evolution. Our data suggest that the presence of baseline contractile reserve does not predict improvement after AV node ablation. Furthermore, subjective parameters (measurement by QOL questionnaires) are markedly improving in most patients but parameters associated with left ventricular performance are not improving. In a subset of patients these parameters even deteriorated. Baseline ejection fraction is the best predictor of deterioration we could find. Our data regarding 3D echocardiography show, that it is a feasible approach for determination of the most delayed LV site with the additional option to assess hemodynamic information, such as LVEDV, LVESV and EF. Our preliminary data suggest that 3D echocardiography can be used for the selection of the most optimal pacing site before and during resynchronisation device implantation.

In conclusion, anatomical structures have potentially important role in arrhythmia genesis. Visualization of these structures improves our understanding of the arrhythmia mechanism and increases the accuracy and the efficacy of interventional procedures. Until recently, direct visualization of such structures was not implemented in clinical electrophysiology. The principle goal of the present thesis was to integrate ultrasound imaging in the management of patients with arrhythmias. The studies presented in this thesis clearly show how echocardiography can facilitate both the diagnostic work-up and treatment of patients with arrhythmias.

SAMENVATTING

Samenvatting en conclusies:

In de afgelopen decades hebben twee voorname ontwikkelingen in echografische beeldvorming plaatsgevonden: miniaturisering en ontwikkeling van 3D beelden. Klinische electrofysiologie haalde zijn voordeel uit beide richtingen omdat intracardiale transducers en 3 dimensionele beeldvorming beschikbaar kwamen voor betere identificatie van intracardiale structuren. De klinische toepassing hiervan was het onderwerp van ons huidige onderzoek. De manuscripten in dit proefschrift tonen aan dat zowel electrofysiologische als pacing procedures geleid kunnen worden door intracardiale echocardiografie met hogere veiligheid, nauwkeurigheid en verminderd belang van radiologie. Dit is een belangrijke stap bij het integreren van beeldvorming in de interventionele electrofysiologie van het hart.

Deel 1. Het begeleiden van procedures voor hartstimulatie.

In het eerste deel van dit proefschrift laten we zien hoe alternatieve (of specifieke) stimulatieplaatsen benaderd kunnen worden met het gebruik van 3 dimensionele echocardiografie. Recent werden immers nieuwe benaderingen voorgesteld om patiënten met diverse ritmestoornissen te behandelen. Er is meer en meer bewijsvoering dat stimulatie op atriaal niveau in de nabijheid van de bundel van Bachmann, het interatriale septum (IAS) of zelfs meerdere atriale plaatsen voordelen zou kunnen hebben bij patiënten met atriumfibrilleren. Op kamerniveau hebben nieuwe stimulatietechnieken een rol bij het behoud of zelfs het verbeteren van de kamerfunctie bij patiënten met of zonder hartfalen. Deze specifieke technieken vereisen echter zeker in vergelijking met conventionele bradycardie behandeling een zeer accurate positionering van de elektroden. Mede gezien de anatomische variatie kan een variabele en minder efficiente electroden positie worden verklaard. Het uitgangspunt van dit proefschrift was een techniek te ontwikkelen gebaseerd op 3 dimensionele intracardiale echografie om specifieke stimulatie van deze nieuwe pacing plaatsen te ontwikkelen en te testen.
Onze studies zijn de eerste die aantonen dat 3 dimensionele echocardiografie een rol heeft in klinische cardiale electrofysiologie. Het blijkt dat intracardiale 3 dimensionele echocardiografie veilig en ook haalbaar is als instrument voor juiste positionering van atriale stimulatie-electroden voor permanente IAS pacing. De bevindingen tonen bovendien aan dat door accuratere plaatsing van atriale stimulatie-elektroden een

belangrijke reductie van de P-golf duur wordt verkregen, zelfs belangrijker dan in vroegere rapporten. Indien men interatriale conductievertraging wil beperken is suprafossale pacing te verkiezen.

Deel 2. Het begeleiden van ablatie procedures.

In het tweede deel van dit proefschrift wordt het nut van intracardiale echografie tijdens ablaties aangetoond. Het streven was een veilige en effectieve manier van transseptale linker hartcatheterisatie te ontwikkelen gebaseerd op intracardiale echocardiografie. Percutane punctie van het interatriale septum werd reeds geïntroduceerd voor linkszijdige catheterisatie in 1960. Recent was opnieuw belangstelling voor transseptale linkszijdige catheterisatie vanwege de ontwikkeling van linkszijdige catheterablaties. Het nadeel van transseptale punctie is dat een aantal belangrijke acute en potentieël dodelijke complicaties kunnen optreden. Hierbij kan gedacht worden aan tamponade, trombo-embolische processen in de systeemcirculatie en zelfs overlijden ten gevolge van perforatie van de aorta. Transseptale catheterisatie blijft moeilijk omdat men met röntgenstralen de fossa ovalis niet direct kan visualiseren zeker wanneer de atriale anatomie afwijkend is. Met intracardiale echografie is het mogelijk de fossa ovalis bij alle patiënten met een uitstekende kwaliteit aan het licht te brengen. Deze directe methode helpt ook bij het vermijden van complicaties.
Onze resultaten suggereren dat intracardiale echografie belangrijke voordelen biedt bij transseptale punctie waarbij ook een uitstekende visualisatie van de fossa ovalis wordt verkregen. Verder biedt het de mogelijkheid om de procedure op flexibele wijze te organiseren omdat geen narcose nodig is en echografie voor een langere tijd gebruikt kan worden zonder ongemak voor de patiënt. Er is geen additionele arteriële punctie noodzakelijk. Deze methode lijkt een belangrijk bijkomend hulpmiddel om het risico voor gevaarlijke complicaties tijdens punctie van het IAS te vermijden. Vanuit een technisch standpunt gezien is de belangrijkste indicatie voor een goede punctieplaats de karakteristieke verplaatsing naar beneden van de transseptale naald in de fossa ovalis dat simultaan met intracardiale echografie en met radiologie kan worden gedocumenteerd.

Catheterablatie is een effectieve behandelingsmethode voor atriale flutter. Een aanzienlijk aantal van deze gevallen mislukt echter en een belangrijk aantal patiënten heeft een recidief. Een mogelijke uitleg voor de mislukkingen en recidieven is terug te brengen op anatomische variatie van de "cavotricuspidale isthmus". Ablatieletsels met

radiofrequente energie zijn daarenboven niet transmuraal waardoor trage geleiding door deze isthmus mogelijk blijft. Alhoewel intracardiale echografie voor hulp bij visualisatie van belangrijke structuren nuttig is, blijft controverse bestaan over de mogelijkheid om met echografie radiofrequente letsels te zien na catheterablatie.
Er vond een evaluatie plaats van toegebrachte letsels in de “cavotricuspidale isthmus” 20 minuten na radiofrequente catheterablatie.
Hieruit kan geconcludeerd worden dat intracardiale echocardiografie vanuit de vena subclavia een haalbare techniek is om de isthmus ter hoogte van de vena cava inferior en tricuspidalus klep te evalueren. Letsels aangebracht met radiofrequente energie kunnen 20 minuten na het aanbrengen hiervan niet geïdentificeerd worden met een 9 MHz ultra sound probe wanneer geen voorafgaand echografisch onderzoek in het hart werd uitgevoerd.

Catheterablatie is curatief voor de meeste patiënten met ritmestoornissen. Bij sommige zijn de resultaten suboptimaal omdat tijdens catheterablatie de letselvorming niet diep genoeg is. Hierop gebaseerd en ook omwille van de vorige studie werd geprobeerd om een nieuwe techniek te ontwikkelen om een betere visualisatie van toegebrachte letsels mogelijk te maken. Dit kan immers een belangrijk impact hebben op het resultaat van de ablatieprocedures. Het doel van de huidige studie was dan ook om het mogelijke nut van contrast echocardiografie in het hart te onderzoeken door met continue toediening van veneus contrast ablatieletstels in menselijk atriaal weefsel aan te tonen.
De resultaten van deze studie toonde aan dat myocardiale contrastechografie het mogelijk maakt om ablatieletsels in het menselijke rechter atriale myocard te zien d.m.v. continue toediening van intraveneus echocontrast. Dit opent mogelijk een nieuwe richting om ablatieletsels op objectieve en gemakkelijke manier te evalueren. Transmurale letselvorming kan van kritisch belang zijn voor succesvolle ablatie. Daarom is myocardiale contrastechografie belangrijk voor de toekomst van catheterablatie.

Deel 3. Beoordeling van myocardfunctie bij patiënten met ritmestoornissen.

Echocardiografie speelt een belangrijke rol in het bepalen van de kamerfunctie bij patiënten na pacemakerimplantatie om verschillende redenen. Stimulatie van de rechter ventrikel apex is niet fysiologisch omdat normale kameractivatie volgens de

normale geleidingsweefsel kortgesloten wordt en de kamers op abnormale manier geactiveerd worden. Permanente pacing in de rechter ventrikel apex is geassocieerd met veranderingen op cellulair vlak en leidt tot dysfunctie van de linker kamer in een belangrijk aantal patiënten. Deze bevindingen vormen ook de achtergrond voor recent onderzoek naar een alternatieve plaats in de rechter kamer of multisite pacing in de rechter kamer. Echografie speelt een belangrijke rol bij het selecteren en vervolgen van deze patiënten. Verder is het mogelijk om de stimulatie parameters te optimaliseren middels echocardiografie. In dit deel van het proefschrift wordt het functionele beloop beschreven van patiënten die ablatie ondergingen van de AV knoop gevolgd door permanente stimulatie in de rechter ventrikel apex. De opzet was ook te kunnen voorspellen wie zou verbeteren en wie zou verslechten met een dergelijke aanpak. Verder werd een nieuwe echocardiografische methode ontwikkeld om de functionele impact te zien van hartstimulatie op alternatieve plaatsen.
De belangrijkste bevinding van dit pilotonderzoek was dat de linker kamerfunctie 3 maanden na AV ablatie verslechterde. Daarnaast vond geen verandering plaats in de linker kamerdimensie en de linker atriale diameter tijdens de studieperiode. Deze gegevens bevestigen dat de linker kamerfunctie na langdurige atriumfibrilleren verslechterd. In het daaropvolgende project werden zowel subjectieve als objectieve parameters bestudeerd die verzameld werden kort en iets later na de ablatieprocedure. Deze parameters waren niet in overeenstemming: onze gegevens suggereren dat de aanwezigheid van een basale contractiele reserve geen verbetering na AV ablatie voorspelt. Verder blijkt dat subjectieve parameters (zoals levenskwaliteit, gemeten met een vragenlijst) aanzienlijk verbeterden bij de meeste patiënten. Dit in tegenstelling tot de parameters die verband houden met de linker kamerfunctie die niet verbeterden en in een bepaalde patiëntengroep zelfs een verslechting laten zien. Een goede ejectiefractie bij het begin van het onderzoek had de beste voorspellende waarde voor een daaropvolgende verslechting. Onze gegevens met 3 dimensionele echocardiografie tonen aan dat het mogelijk is de meest vertraagde linker kamerpositie op te zoeken met de bijkomende mogelijkheid om hemodynamische informatie te evalueren (volumina en ejectiefractie). Deze preliminaire resultaten suggereren dat 3 dimensionele echografie gebruikt kan worden om de beste stimulatieplaats te vinden voor en tijdens implantatie van een resynchronisatie pacemaker of ICD.

Samenvattend spelen anatomische structuren een belangrijke rol bij het ontstaan van ritmestoornissen. Het direct in beeld brengen van deze structuren verbetert ons inzicht in het mechanisme van de ritmestoornis en verbetert de nauwkeurigheid en het resultaat van interventies. Tot recent was het direct in beeld brengen van dergelijke structuren niet toegepast in de klinische electrofysiologie. Het voornaamste doel van het huidige proefschrift was om echografische beeldvorming verder te integreren in de algemene aanpak van patiënten met ritmestoornissen. De studies die in dit werk gepresenteerd worden tonen duidelijk aan hoe echografie zowel de voorbereiding van dergelijke patiënten als de uiteindelijke behandeling gemakkelijker maakt.

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Tamas Szili-Torok

ULTRASOUND IMAGING IN CLINICAL CARDIAC ELECTROPHYSIOLOGY

PROPOSITIONS

- Propositions are those 'lines' that bear truth-values.
- Developments in electrophysiology require advanced imaging techniques in order to improve safety, accuracy and efficacy. (This thesis)
- Real-time intracardiac echocardiography will dramatically diminish the need for fluoroscopy during electrophysiology procedures. (This thesis)
- Transseptal left heart catheterization guided by intracardiac echocardiography is a safe and effective procedure. (This thesis)
- Three-dimensional echocardiography guided interatrial septum pacing results in a more marked decrease in interatrial conduction delay than conventional fluoroscopy guided pacing. (This thesis)
- The evolution of left ventricular function following AV node ablation and right ventricular apical pacing is unpredictable. (This thesis)
- Baroreflex regulation of the peripheral circulation involves the human skin microvasculature. (Ph.D. thesis: Baroreflex regulation of the peripheral circulation by Tamas Szili-Torok, 2001)
- None of the true curative treatment modalities in electrophysiology eliminates the triggers of the arrhythmias.
- There are two types of research. One is technology driven and the other based on original ideas. The former can be done by anyone but only at very few prestigious institutions. The latter can be done everywhere but only by few gifted individuals.
- Sit tibi praecipue, quod primum est, cura salutis;
  Tempora nec culpes, cum sis tibi causa doloris. (Cato)
- The product of efficiency and bureaucracy is constant.