Multimodality imaging to guide cardiac interventional procedures

Tops, L.F.

1

General introduction and outline of the thesis

In the past decades, tremendous advances have been made in both the imaging and interventional field of clinical cardiology. Dedicated imaging techniques such as multi-slice computed tomography have been introduced and enable detailed non-invasive evaluation of cardiac anatomy. Furthermore, conventional techniques such as echocardiography have been improved and nowadays allow a more comprehensive assessment of cardiac morphology and function. At the same time, percutaneous interventional procedures for arrhythmias and valvular heart disease have been further explored. While conventional invasive treatment of these conditions requires open-heart surgery, nowadays it has become feasible to perform these procedures with minimal-invasive techniques.

These advances allow a more integrative approach to cardiac imaging and interventions. The combination and integration of different imaging modalities and subsequent use of these techniques during interventional procedures will further enhance the evaluation and treatment of cardiac arrhythmias and valvular heart disease. In this thesis, the role of multimodality imaging to guide cardiac interventional procedures is investigated. In particular, catheter ablation for atrial fibrillation (AF), cardiac pacing and resynchronization therapy, and percutaneous valve procedures are explored.

CATHETER ABLATION FOR ATRIAL FIBRILLATION

Atrial fibrillation is the most commonly encountered cardiac arrhythmia. It is characterized by rapid, irregular activity of the atria. In the general population, the prevalence of AF is approximately 1% (1). Since the prevalence of AF increases with age, it may become 'epidemic' in the coming decades, with an estimated 3.3 million patients in the United States in 2020 (Figure 1). Importantly, AF is associated with an increased risk of both cardiac morbidity and mortality (2).

The most important goals in the treatment of AF are: reduction of the risk of thromboembolism and control of AF-related symptoms (3). To reduce the risk of thromboembolism, a tailored anti-thrombotic regimen (e.g. anticoagulation or aspirin) should be chosen depending on clinical characteristics (4). To control symptoms of AF, both 'rate control' and 'rhythm control' strategies can be chosen. Again, an individualized approach is preferred, since the superiority of one strategy has not been proven. Large randomized trials have not demonstrated differences in mortality or quality of life between the two strategies (5,6).

If a 'rhythm control' strategy is chosen, anti-arrhythmic drugs and/or electrical cardioversion are used to restore sinus rhythm. Unfortunately, anti-arrhythmic drugs may have side-effects and often fail to maintain sinus rhythm. In the past decade, catheter ablation procedures have been introduced as a new therapeutic option in the treatment of patients with AF.

Haissaguerre et al. demonstrated that the pulmonary veins (PVs) are the main source of ectopic beats that initiate AF (7). Subsequently, it was shown that electrical isolation of these PVs with the use of (radiofrequency) catheter ablation is effective for the restoration and

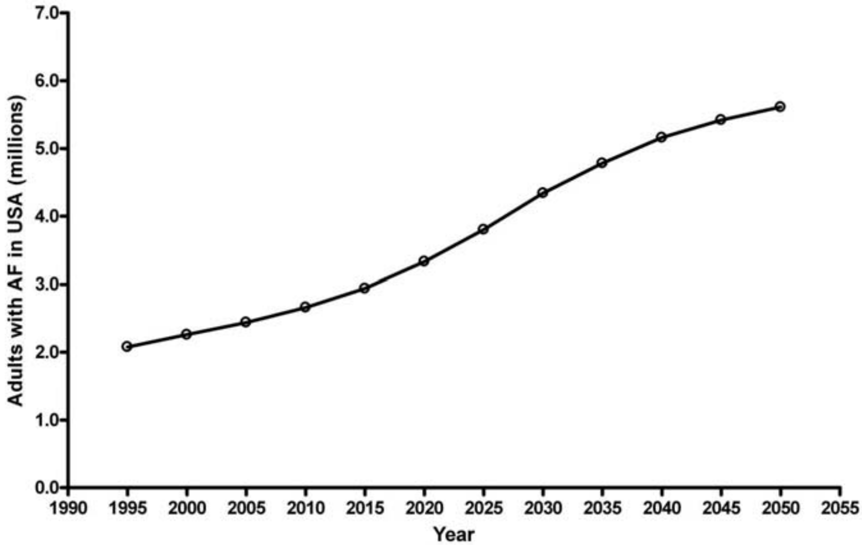

Figure 1. Estimated number of patients with atrial fibrillation (AF) in the United States of America (USA). The total number of patients may increase up to 2.5-fold in the coming 4 decades. Adapted with permission from Go AS et al., reference (1).

maintenance of sinus rhythm. During the catheter ablation procedure, the PVs are isolated from the left atrial (LA) wall by applying radiofrequency current around the PV ostia (Figure 2). Several randomized controlled trials have compared anti-arrhythmic drugs and catheter ablation procedures regarding the efficacy to maintain sinus rhythm during long-term follow-up (8-11). From these studies, it has become apparent that catheter ablation may be more effective than anti-arrhythmic drugs (Table 1). It should be noted however, that serious complications may occur in up to 5% of patients undergoing catheter ablation for AF (12). Therefore, at present catheter ablation still is considered a second-line therapy, but an excellent treatment option

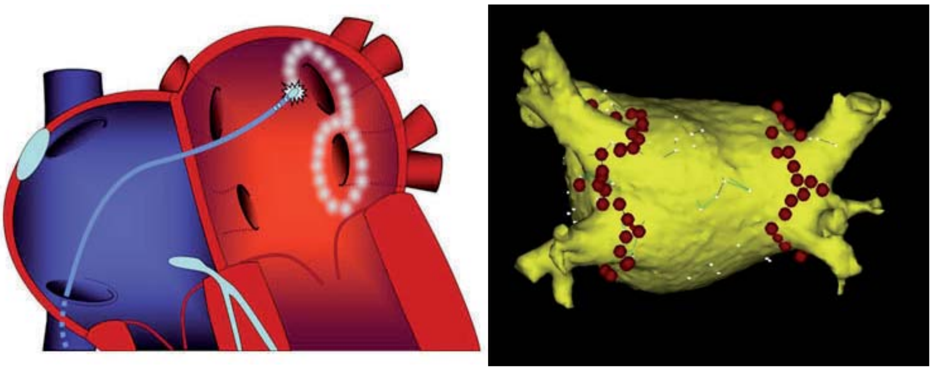

Figure 2. The left panel shows a schematic representation of a catheter ablation procedure. The ablation catheter is introduced into the left atrium (LA) through the foramen ovale. Subsequently, radiofrequency current is applied around the ostia of the pulmonary veins (PVs) (indicated with the white dots). The right panel shows a volume-rendered reconstruction of multi-slice computed tomography images of the LA and PVs that is used to guide the ablation procedure. The red dots indicate the ablation lesions.

Table 1. Randomized studies comparing catheter ablation and anti-arrhythmic drugs

Study (reference)	Number of patients	Type of AF	Follow-up	Primary endpoint: Freedom from AF (Ablation vs. AAR)	Secondary endpoints	Complications ablation
Oral et al. (9)	146	146 persistent (100%)	12 months	74% vs. 58%, p=0.05	- Decrease in LA diameter in successful ablation patients - Increase in LVEF in successful ablation patients - Improvement in symptoms in all ablation patients	None reported
Pappone et al. (10)	198	198 paroxysmal (100%)	12 months	86% vs. 22%, p<0.001	N/A	- TIA: 1 - Pericardial effusion: 1
Stabile et al. (11)	137	92 paroxysmal (67%) 45 persistent (33%)	12 months	66% vs. 9%, p<0.001	N/A	- Stroke: 1 - Transient phrenic nerve paralysis: 1 - Pericardial effusion: 1
Jais et al. (8)	112	112 paroxysmal (100%)	12 months	89% vs. 23%, p<0.001	- No differences in LA diameter and LVEF at follow-up - Greater reduction in AF burden in ablation patients - Improvement in quality of life and exercise capacity in ablation patients	- Cardiac tamponade: 2 - Hematoma: 2 - PV stenosis: 1

AF = atrial fibrillation; AAR = anti-arrhythmic drugs; LA = left atrial; LVEF = left ventricular ejection fraction; PV = pulmonary vein; TIA = transient ischemic attack

after at least one anti-arrhythmic drug has failed (3). Interestingly, an increasing number of AF patients worldwide are treated with catheter ablation (Figure 3).

The cornerstone of AF ablation procedures is electrical isolation of the PVs. However, anatomical studies have demonstrated that PV anatomy is highly variable (13). In particular, the exact number and location of the PVs has large inter-individual variation. Therefore, careful identification of the PVs is important both before and during the catheter ablation procedure. Several imaging modalities are available to evaluate the anatomy of the LA and the PVs. Multislice computed tomography and magnetic resonance imaging provide excellent images of the PVs. However, they do not provide real-time information since the images are acquired before the actual ablation procedure. On the other hand, intracardiac echocardiography and electroanatomic mapping enable online visualization of the PVs in relation with the ablation catheters. However, these techniques are limited by the two-dimensional character and the use of reconstructed anatomy, respectively. Ideally, the information of the different imaging

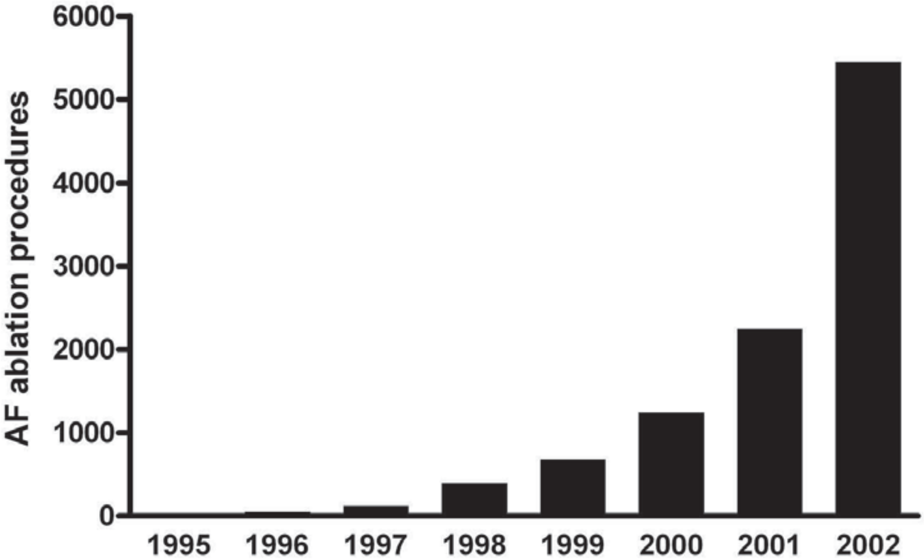

Figure 3. World-wide number of catheter ablation procedures for AF between 1995 and 2002. A clear increase in the annual number of procedures is noted. Adapted with permission from Cappato R et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100-5.

techniques is integrated, providing highly detailed on-line anatomical information during the catheter ablation procedure.

Another important issue is the effect of catheter ablation procedures for AF on cardiac size and function. It has been well recognized that there is a close relation between AF and LA size (14). After catheter ablation, the ablation lesions may result in scarring of the LA wall. This may negatively affect LA size and contractile function. On the other hand, a reduction in LA size may result in lower susceptibility to AF (15). In addition, the restoration of sinus rhythm may ultimately result in an improved LA function. Furthermore, normalization of heart rhythm may result in more efficient left ventricular (LV) function. It has been demonstrated that catheter ablation results in significant improvement in LV ejection fraction in patients with AF and systolic heart failure (16). However, the effect of catheter ablation on LV function in patients with preserved LV ejection fraction is unclear.

Multimodality imaging and image integration may enhance AF ablation procedures by improved visualization of cardiac structures, and may result in better understanding of the effects of catheter ablation on cardiac function. Accordingly, the aims of the studies described in this thesis are to test the feasibility of image integration to guide catheter ablation procedures and to assess the effects of catheter ablation procedures on LA and LV function.

VENTRICULAR PACING AND DYSSYNCHRONY

In 1958, the first pacemaker implantation was performed in a patient with high degree atrioventricular block. Since then, cardiac pacing has been an effective treatment in the management of patients with symptomatic brady- and tachy-arrhythmias. The annual number of new pacemaker implantations in the Netherlands is about 6000, and is steadily increasing (17). High degree atrioventricular block and sick sinus syndrome are the most important indications for implantation of a conventional pacemaker (Figure 4).

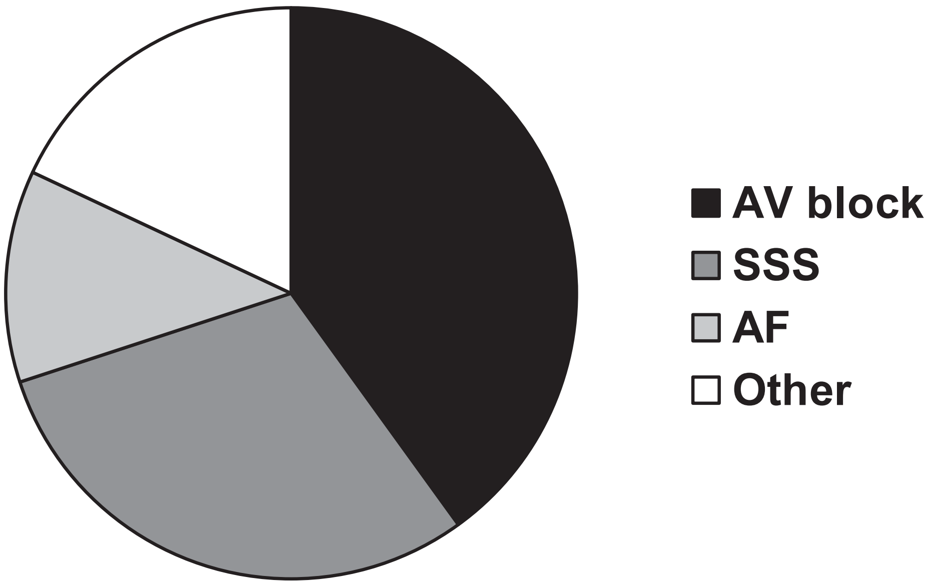

Figure 4. Indications for new pacemaker implantations in the World Survey of Cardiac Pacing and Cardioverter Defibrillators 2001. High degree atrio-ventricular (AV) block (40%) and sick sinus syndrome (SSS, 30%) remain the most important indications for pacemaker implantation. Less frequently, atrial fibrillation (AF, 12%) and other indications (e.g. bundle-branch block, cardiomyopathy) result in implantation of a pacemaker. Adapted from Mond HG et al., reference (17).

Typically, the endocardial ventricular pacing lead is positioned at the right ventricular (RV) apex. However, large randomized trials have revealed a possible association between RV apical pacing and deterioration of cardiac function (18,19). In the Mode Selection Trial (MOST), it was demonstrated that a high percentage of ventricular pacing is associated with an increased risk of heart failure hospitalization (Figure 5). Furthermore, other studies have shown that RV apical pacing results in changes in myocardial perfusion (20) and ventricular remodeling (21). At the same time, minimizing RV apical pacing with dedicated algorithms can prevent harmful effects of cardiac pacing (22).

The deleterious effects of conventional RV apical pacing may be associated with the abnormal electrical and mechanical activation pattern of the cardiac chambers. During RV apical

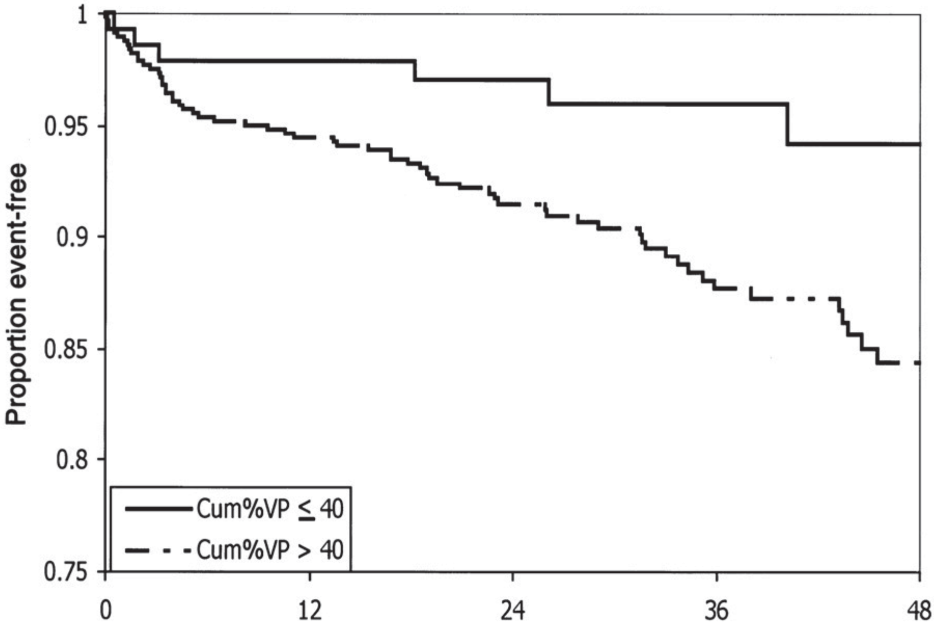

Figure 5. In the MOST trial, >40% cumulative percentage of ventricular pacing (Cum%VP) in the DDDR pacing group (n=707) significantly increased the risk of heart failure hospitalization compared with <40% pacing (hazard ratio 2.60; 95% CI 1.05 - 6.47; p<0.05). This figure demonstrates the Kaplan-Meier plots relating time to first heart failure hospitalization (event) by cumulative percentage of ventricular pacing. Reprinted with permission from Sweeney MO et al., reference (18).

pacing, the electrical wave front propagates through the myocardium, rather than through the His-Purkinje conduction system. Due to the differences in conduction velocity, heterogeneity in electrical activation of the cardiac chambers occurs (23). Simultaneously, changes in the mechanical activation pattern are noted. In particular, the onset and magnitude of mechanical contraction of various LV walls change (24). The temporal occurrence of peak strain of different ventricular segments exhibits an asynchronous pattern during RV apical pacing. This is referred to as 'ventricular mechanical dyssynchrony' (Figure 6).

Mechanical dyssynchrony can be assessed with various non-invasive imaging modalities. Already in 1977, Gomes et al. noticed the asynchronous contraction pattern of the LV during RV apical pacing with the use of transthoracic echocardiography (25). A significant delay between the (early) posterior motion of the interventricular septum and the (delayed) contraction of the posterior wall was observed immediately after onset of pacing. Nowadays, additional echocardiographic techniques are available for assessment of ventricular dyssynchrony (26). With the use of tissue Doppler imaging, myocardial velocities of different ventricular segments can be assessed throughout the cardiac cycle (Figure 6). Off-line analysis of the regional time-to-peak systolic velocity enables quantification of ventricular mechanical dyssynchrony (27). Speckle-tracking strain analysis is another echocardiographic technique that allows assessment of regional timing of peak strain (28). The assessment of myocardial strain permits differentiation

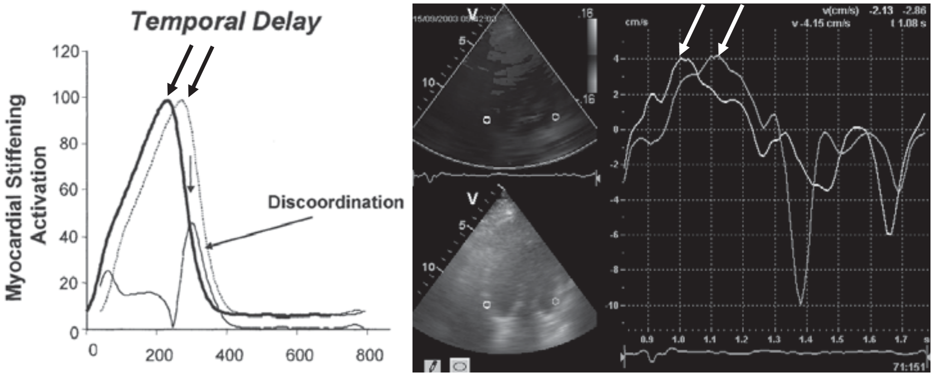

Figure 6. Mechanical dyssynchrony. The left panel is a schematic representation of mechanical dyssynchrony. Two different regions of the heart contract with similar force (myocardial stiffening), but one region has a delay in contraction relative to the other. The net difference between the two regions determines the extent of discoordination in contraction, or mechanical dyssynchrony. The right panel shows echocardiographic dyssynchrony assessment with tissue Doppler imaging. Sample areas are placed at the basal parts of the septum and lateral wall of the LV. The difference in time-to-peak systolic velocity of the two regions (indicated with white arrows) represents mechanical dyssynchrony. Left panel adapted with permission from Kass DA. An epidemic of dyssynchrony: But what does it mean? J Am Coll Cardiol 2008;51:12–7.

between active contraction and passive motion of the myocardium. Again, by calculating differences in time-to-peak systolic strain of various segments, ventricular dyssynchrony can be assessed (29).

Importantly, it has been demonstrated that the presence of mechanical dyssynchrony has prognostic value in heart failure patients (30). However, the association between mechanical dyssynchrony and the deterioration of cardiac function and functional class in pacemaker patients has not been fully elucidated yet. Furthermore, in the past decade cardiac resynchronization therapy has become a well-established therapeutic option for patients with severe drug-refractory heart failure and signs of electrical or mechanical dyssynchrony (31,32). In cardiac resynchronization therapy, an LV pacing lead is added to a conventional pacing system, allowing simultaneously pacing of the RV and LV to re-synchronize the cardiac chambers. It may well be that cardiac resynchronization therapy is able to (partly) reverse the detrimental effects of conventional RV apical pacing.

New imaging techniques may be valuable tools for the detection of mechanical dyssynchrony, and may help in monitoring patients with conventional pacemakers and selecting potential candidates for upgrade of RV pacing to biventricular pacing. Accordingly, the current studies explore the possible association between deterioration of cardiac function and ventricular mechanical dyssynchrony after onset of RV pacing, and reversal of the detrimental effects and LV dyssynchrony with cardiac resynchronization therapy.

Valvular heart disease is an important entity in clinical cardiology. Aortic stenosis (AS) and mitral regurgitation (MR) are the most common native single-valve disease. In the general population, the prevalence of AS is estimated between 2 and 7% (33). Various pathophysiologic processes can attribute to the development of AS or MR, but most frequently the etiology is degenerative (Table 2). Importantly, the presence of severe AS (34) or MR (35) is associated with a substantially increased risk of cardiac morbidity and mortality. The poor natural history of untreated AS and MR emphasizes the importance of treatment of patients with these conditions (36,37).

Surgical aortic valve replacement is the treatment of choice in severe, symptomatic AS. Operative mortality is about 3-5%, and good long-term survival has been reported (Figure 7) (38). Importantly, the severity of symptoms, LV ejection fraction and age are important predictors of good outcome after surgical aortic valve replacement (39). For MR, surgical treatment

Table 2. Results from the Euro Heart Survey on Valvular Heart Disease on the etiology and surgical treatment of aortic stenosis and mitral regurgitation.

	Aortic stenosis	Mitral regurgitation
Etiology *		
Degenerative, %	82	61
Rheumatic, %	11	14
Endocarditis, %	1	4
Inflammatory, %	0	1
Congenital, %	5	5
Ischaemic, %	0	7
Other, %	1	8
Surgical intervention †		
Mechanical prosthesis, %	49	43
Bioprosthesis, %	50	10
Valve repair, %	0	47
Other, %	1	0

* Data on etiology from 1197 patients with aortic stenosis and 877 patients with mitral regurgitation. † Data on surgical intervention from 512 patients with aortic stenosis and 155 patients with mitral regurgitation. Adapted from Iung et al., reference (42).

is more complex, due to its variety in etiologies. Mitral valve repair using undersized mitral annuloplasty is most frequently used for degenerative and ischemic MR (40). The outcome of surgical mitral valve repair depends largely on the etiology of MR, but also severity of symptoms, LV ejection fraction and age are important predictors of outcome (33). In particular for organic MR (e.g. mitral valve prolapse), good long-term results have been reported (41).

Despite the good outcome after surgical treatment of AS and MR, a large proportion of patients does not undergo surgery. The Euro Heart Survey on Valvular Heart Disease explored the characteristics, treatment and outcome of 5001 patients with valvular heart disease from 25 countries in Europe (42). From this Euro Heart Survey, it has become apparent that up to 30%

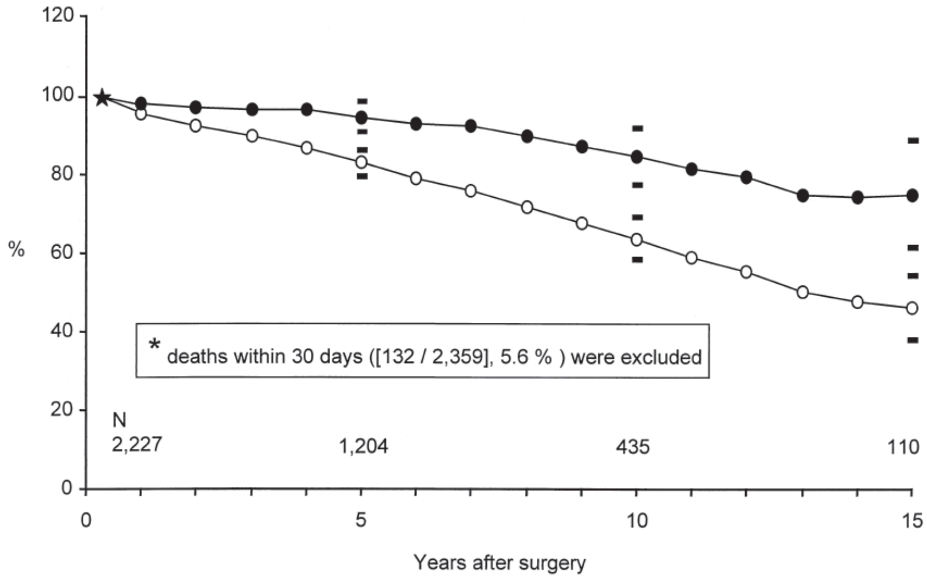

Figure 7. Long-term outcome after primary surgical aortic valve replacement in 2227 patients with severe aortic stenosis. The observed (open circles) and relative (solid circles) survival is shown in patients who survived the first postoperative month. Reprinted with permission from Kvidal P et al., reference (38).

of patients with severe symptomatic valvular disease do not undergo surgical intervention, while a clear indication exists. Most frequently, this is because of co-morbidity and age (42). Obviously, there is a need for a less invasive approach, in particular in elderly patients with co-morbidity and severe valvular heart disease.

In recent years, various new percutaneous procedures for the treatment of AS and MR have been introduced. The implantation of an aortic valve prosthesis through the femoral artery or the LV apex has become feasible (Figure 8). The feasibility of a balloon-expandable (43) and a self-expanding valve (44) for the percutaneous treatment of severe AS have been demonstrated. Importantly, large multi-center studies (45) and mid-term follow-up studies (46) have demonstrated the safety and efficacy of these procedures.

Furthermore, new percutaneous devices have been introduced for the percutaneous treatment of MR (Figure 8). The feasibility of a mitral valve clip mimicking edge-to-edge repair has been demonstrated (47), and different prostheses that target mitral annulus remodeling through the coronary sinus have been introduced (48,49). The safety and mid-term efficacy of these procedures have also been demonstrated (50,51).

However, percutaneous valve procedures still have limitations and severe complications can occur. An important issue is failure of the procedure as a result of unfavorable cardiac anatomy. For example, the close relation between the native valve leaflets, valve annulus and the coronary arteries may preclude save percutaneous implantation of a device. In the Mitral Annuloplasty Device European Union Study (AMADEUS), the coronary sinus device was recaptured because of potential coronary compromise in up to 30% of the non-implanted patients (51). Furthermore, acute coronary occlusion during percutaneous aortic valve implantation has been reported (43).

Imaging may be of great value in the percutaneous treatment of valvular heart disease. It may improve the selection of patients and may enhance real-time guidance of the procedures. In the studies described in the present thesis, the potential role of multi-slice computed tomography in the selection for candidates for new percutaneous valve procedures for AS and MR is explored.

OUTLINE OF THE PRESENT THESIS

The aim of this thesis is to evaluate the role of multimodality imaging to guide cardiac interventional procedures. In particular, catheter ablation procedures for AF, conventional pacing and cardiac resynchronization therapy, and percutaneous valve procedures are studied. Therefore, the present thesis consists of three distinct parts.

PART I: Catheter ablation for atrial fibrillation

In the first part, catheter ablation procedures for AF are studied. These procedures are considered a good treatment option in patients with drug-refractory AF, after at least one anti-arrhythmic drug has failed. Visualization of the PVs with different imaging modalities, the integration of various imaging techniques, and the effect of catheter ablation on LA and LV function are important issues in AF ablation. **Chapter 2** and **Chapter 3** provide two extensive reviews on the role of multimodality imaging in the assessment of PV and LA anatomy, and in catheter ablation procedures for AF. In **Chapter 4**, the first clinical experience with a new image integration system that allows integration of MSCT images and electroanatomic mapping is described. Subsequently, the integration of intracardiac echocardiography with electroanatomic mapping and multi-slice computed tomography is studied in **Chapter 5**. The assessment of PV anatomy with multi-slice computed tomography, and its impact on the outcome of catheter ablation procedures is explored in **Chapter 6**.

In the next chapters, the effect of catheter ablation for AF on LA and LV function is studied. In **Chapter 7**, conventional transthoracic two-dimensional echocardiography is used to assess the effect of catheter ablation on LA size. The findings of this study are further extended in the following chapters. In **Chapter 8**, real-time three-dimensional echocardiography is used to assess LA function after catheter ablation. Subsequently, the effect of catheter ablation on LA systolic and diastolic strain is investigated in **Chapter 9**. Furthermore, the predictive value of LA strain for LA reverse remodeling is studied. Finally, the effect of sinus rhythm maintenance after catheter ablation on LV function is studied in **Chapter 10**.

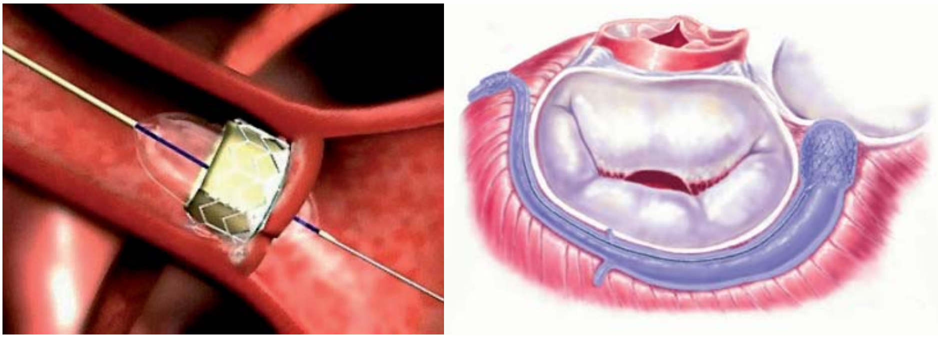

Figure 8. Percutaneous valve procedures for aortic stenosis (AS) and mitral regurgitation (MR). The left panel shows the percutaneous implantation of a balloon expandable aortic valve prosthesis. The catheter with the balloon and prosthesis is inserted retrograde through the femoral artery and aorta. The right panel shows a coronary sinus device that attempts to remodel the mitral valve annulus in severe MR. The device is inserted antegrade through the right atrium.

PART II: Ventricular pacing and dyssynchrony

In the second part, conventional RV apical pacing, cardiac resynchronization therapy and ventricular mechanical dyssynchrony are studied. In particular, the association between dyssynchrony and the deterioration of LV function after long-term RV apical pacing, and the reversal of the negative effects with cardiac resynchronization therapy are investigated. In **Chapter 11**, an extensive review of the available evidence on the effects of RV apical pacing on LV function is provided. **Chapter 12** describes the initial observation that long-term RV apical pacing can induce LV mechanical dyssynchrony assessed with conventional echocardiography and tissue Doppler imaging. Subsequently, the acute effects of RV apical pacing on ventricular dyssynchrony are studied with speckle-tracking echocardiography in **Chapter 13**. Furthermore, the effects of RV apical pacing on LV strain and LV twist are investigated in this study. Subsequently, speckle-tracking echocardiography is used to assess ventricular dyssynchrony, and in particular the site of latest activation in a cohort of patients with long-term RV apical pacing in **Chapter 14**. Importantly, the effect of upgrade to biventricular pacing is investigated in this study. In **Chapter 15**, the effect of RV apical pacing and ventricular dyssynchrony on myocardial oxidative metabolism and efficiency is studied with the use of positron emission tomography scanning. Finally, the prevalence of ventricular dyssynchrony in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy is studied in **Chapter 16**.

PART III: Percutaneous valve procedures

In the third part, the role of cardiac imaging in percutaneous valve procedures is explored. Recently, various percutaneous procedures for aortic valve and mitral valve disease have been introduced. The background of these procedures and the different prostheses are reviewed in **Chapter 17**. The relation between the mitral annulus, the LA posterior wall and the coronary arteries determines the feasibility of percutaneous mitral annuloplasty. The assessment of this critical relation with the use of multi-slice computed tomography is described in **Chapter 18**.

Subsequently, multi-slice computed tomography is used for the assessment of the mitral valve itself, and exploration of the anatomical mechanism underlying functional MR in **Chapter 19**. For percutaneous aortic valve procedures, other anatomical considerations are important. In particular, the extent and location of aortic valve calcifications, and the relation between the aortic valve annulus and the coronary arteries are important issues. The role of multimodality imaging in the selection of patients and performing percutaneous aortic valve procedures is discussed in **Chapter 20**. Furthermore, the clinical experience with percutaneous aortic valve procedures is extensively reviewed in this chapter. In **Chapter 21**, a systematic analysis with the use of multi-slice computed tomography of the aortic valve and the relation with the coronary arteries is performed in a large cohort of patients. Finally, this methodology is used in patients undergoing percutaneous aortic valve implantation in **Chapter 22**.

REFERENCES

1. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
3. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary. J Am Coll Cardiol 2006;48:854-906.
4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
5. Wyse DG, Waldo AL, DiMarco JP et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
6. Van Gelder IC, Hagens VE, Bosker HA et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.
7. Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
8. Jais P, Cauchemez B, Macle L et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 2008;118:2498-505.
9. Oral H, Pappone C, Chugh A et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med 2006;354:934-41.
10. Pappone C, Augello G, Sala S et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol 2006;48:2340-7.
11. Stabile G, Bertaglia E, Senatore G et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). Eur Heart J 2006;27:216-21.
12. Cappato R, Calkins H, Chen SA et al. Up-dated Worldwide Survey on the Methods, Efficacy and Safety of Catheter Ablation for Human Atrial Fibrillation. Circ Arrhythm Electrophysiol 2010, in press.
13. Ho SY, Cabrera JA, Tran VH, Farre J, Anderson RH, Sanchez-Quintana D. Architecture of the pulmonary veins: relevance to radiofrequency ablation. Heart 2001;86:265-70.
14. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. J Am Coll Cardiol 2008;51:1-11.
15. Chen MC, Chang JP, Guo GB, Chang HW. Atrial size reduction as a predictor of the success of radiofrequency maze procedure for chronic atrial fibrillation in patients undergoing concomitant valvular surgery. J Cardiovasc Electrophysiol 2001;12:867-74.
16. Hsu LF, Jais P, Sanders P et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373-83.
17. Mond HG, Irwin M, Morillo C, Ector H. The world survey of cardiac pacing and cardioverter defibrillators: calendar year 2001. Pacing Clin Electrophysiol 2004;27:955-64.
18. Sweeney MO, Hellkamp AS, Ellenbogen KA et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932-7.
19. Wilkoff BL, Cook JR, Epstein AE et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115-23.
20. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. J Am Coll Cardiol 1997;29:744-9.

21. van Oosterhout MF, Prinzen FW, Arts T et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998;98:588-95.
22. Sweeney MO, Bank AJ, Nsah E et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med 2007;357:1000-8.
23. Vassallo JA, Cassidy DM, Miller JM, Buxton AE, Marchlinski FE, Josephson ME. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. J Am Coll Cardiol 1986;7:1228-33.
24. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999;33:1735-42.
25. Gomes JA, Damato AN, Akhtar M et al. Ventricular septal motion and left ventriclular dimensions during abnormal ventricular activation. Am J Cardiol 1977;39:641-50.

26. Marsan NA, Breithardt OA, Delgado V, Bertini M, Tops LF. Predicting response to CRT. The value of two- and three-dimensional echocardiography. Europace 2008;10 Suppl 3:iii73-iii79.
27. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834-40.
28. Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004;17:1021-9.
29. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960-8.
30. Bader H, Garrigue S, Lafitte S et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004;43:248-56.
31. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
32. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
33. Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230-68.
34. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142-7.
35. Ling LH, Enriquez-Sarano M, Seward JB et al. Clinical outcome of mitral regurgitation due to flail leaflet. N Engl J Med 1996;335:1417-23.
36. Rosenhek R, Binder T, Porenta G et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611-7.
37. Grigioni F, Avierinos JF, Ling LH et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002;40:84-92.
38. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000;35:747-56.
39. Mihaljevic T, Nowicki ER, Rajeswaran J et al. Survival after valve replacement for aortic stenosis: implications for decision making. J Thorac Cardiovasc Surg 2008;135:1270-8.
40. Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic ischemic mitral regurgitation: repair, replace or rethink? Ann Thorac Surg 2006;81:1153-61.
41. Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. Circulation 2001;104:I1-I7.
42. Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.
43. Webb JG, Chandavimol M, Thompson CR et al. Percutaneous aortic valve implantation retrograde from the femoral artery. Circulation 2006;113:842-50.

44. Grube E, Laborde JC, Gerckens U et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation 2006;114:1616-24.
45. Piazza N, Grube E, Gerckens U et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242-9.
46. Grube E, Buellesfeld L, Mueller R et al. Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System. Circ Cardiovasc Intervent 2008;1:167-75.
47. Feldman T, Wasserman HS, Herrmann HC et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol 2005;46:2134-40.
48. Webb JG, Harnek J, Munt BI et al. Percutaneous transvenous mitral annuloplasty: initial human experience with device implantation in the coronary sinus. Circulation 2006;113:851-5.
49. Maniu CV, Patel JB, Reuter DG et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. J Am Coll Cardiol 2004;44:1652-61.
50. Herrmann HC, Kar S, Siegel R et al. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. EuroIntervention 2009;4:437-42.
51. Schofer J, Siminiak T, Haude M et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation 2009;120:326-33.