

Pacing mode selection in patients with sick sinus syndrome

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INTRODUCTION

SICK SINUS SYNDROME

The sinus node is composed of a collection of specialised pacemaker cells embedded in a fibrous matrix that lies in the sulcus terminalis between the superior vena cava and the right atrial appendage. The sinus node serves as the primary cardiac pacemaker and controls the heart rate in normal individuals. Recent research indicates, that the sinus node is a heterogeneous tissue with multiple cell types and a complex structure (1, 2).

Keith and Flack first described the sinus node in 1907 (3). In 1915-1916, "sino-auricular heart block" was described electrocardiographically for the first time (4, 5), and the frequent coexistence of sinus brady-arrhythmia and paroxysmal atrial tachycardia was described by Short in 1954 (6). The sick sinus syndrome (SSS) was further defined in the 1960's and 1970's (7-11), and is characterised by symptoms associated with electrocardiographic findings of sinus node dysfunction. In 1972 Rubenstein et al. proposed a simple classification based on the electrocardiographic manifestations of SSS (12). According to this classification, patients with SSS can be divided into three groups:

1. Patients with sinus bradycardia,
2. Patients with sinoatrial conduction block or sinus arrest, and
3. Patients with at least one episode of documented supraventricular tachycardia in addition to sinus bradycardia or sinoatrial block/sinus arrest (brady-tachy syndrome).

Sinus bradycardia is defined as a stable sinus rate below 50 bpm. Sinus arrest occurs when there is a sudden, unexpected pause in sinus node activity. In sinoatrial conduction block, the length of the pauses between the P waves is a multiple of the PP interval. In brady-tachy syndrome, the sinus pauses tend to be particularly prolonged when the tachyarrhythmia terminates.

At the time of diagnosis, approximately half of the patients with SSS suffer from paroxysmal supraventricular tachycardia, most often atrial fibrillation. The most common clinical symptoms are syncope, dizzy spells, fatigue, and shortness of breath because of bradycardia, palpitations due to tachycardia, and exercise intolerance because of chronotropic incompetence (13). The diagnosis of SSS is most often obtained by ambulatory ECG monitoring. Exercise testing may be useful. Most of the symptoms of SSS are non-specific, and documentation of simultaneous occurrence of symptoms and arrhythmia should be aimed at before therapy is instituted. Although SSS can affect all ages, most patients are elderly and the mean age at diagnosis is approximately 75 years. There

seems to be a female preponderance among patients with SSS (I, V, VII).

The pathogenesis of SSS is unclear. Pathologically, SSS is associated with fibrosis and loss of specialised pacemaker cells in the sinus node (14). Recently SSS has been found associated with diffuse atrial remodelling characterized by changes in conduction properties, increased atrial refractoriness, and loss of the normal activation pattern in the sinus node region (15). In the majority of cases, there is no evidence of ischemia or infection (14). Ageing has been found associated with similar changes in the sinus node (16-18), and in the majority of cases SSS most probably reflects an age-related degeneration of the sinus node. In some patients, SSS is seen after cardiac surgical procedures that involve incision in the right atrium.

Despite bothersome symptoms, SSS is a relatively benign condition, not associated with any significant excess mortality as compared with the normal population (13, 19, 20). Pacemaker treatment in SSS is highly effective in relieving bradycardia related symptoms (11, 13, 21-23), and currently, there are no acceptable pharmacological alternatives; pacing is the treatment of choice for symptomatic bradycardia in SSS (23). The indications for implantation of a permanent pacemaker in SSS according to the ACC/AHA Guidelines are: "*Sinus node dysfunction with documented symptomatic bradycardia, including frequent symptomatic sinus pauses. Bradycardia may be iatrogenic and occur as a consequence of essential long-term drug therapy for which there are no acceptable alternatives*" and "*symptomatic chronotropic incompetence*" (24).

Sick sinus syndrome is the second most common reason for pacemaker implantation, comprising approximately one third of the total population undergoing primary pacemaker implantation (25, 26). In Denmark, the annual number of new patients receiving a pacemaker because of SSS is approximately 800-900 patients (25), and worldwide the number probably exceeds 200.000 each year.

PACING MODE SELECTION IN PATIENTS WITH SSS

Patients with SSS and concomitant atrioventricular (AV) block must be treated with a pacemaker system including a ventricular lead. The majority of patients with SSS have no additional atrioventricular (AV) block or bundle branch block. In those patients, the bradycardia-related symptoms can be successfully treated with any pacemaker, a single chamber pacemaker with the lead implanted in the right atrium (AAI) or in the right ventricle (VVI) or a dual chamber pacemaker with leads in both these chambers (DDD). Although effective in preventing bradycardia, the different pacing modes may be associated with different morbidity and mortality, as indicated by observational studies (27-32). Therefore, one of the most important issues in the treatment of SSS is the selection of the best pacing mode in these patients. AAI pacing preserves both the AV synchrony and the normal ventricular activation pattern, but if AV block occurs, a re-operation with implantation of a ventricular lead and a new pacemaker is necessary. DDD pacing also preserves the AV synchrony, but disrupts the ventricular activation pattern, whereas VVI pacing disrupts both the AV synchrony and the ventricular activation pattern. The main advantage of both DDD and VVI pacing is to confer protection against bradycardia if AV block occurs. The incidence of AV block in patients with SSS has been reported very differently from <1% per year to 4.5% per year in prior studies (33).

Ventricular pacing in VVI and DDD pacing modes, which disrupts the normal ventricular activation pattern, reduces both systolic and diastolic ventricular function (34, 35), and experimental studies have indicated that chronic ventricular pacing might be detrimental to the left ventricular function (36-38). The mechanisms behind this detrimental effect are not fully understood but a reduction in the regional myocardial blood flow (MBF) has been reported to play a role (36, 37, 39).

AIM OF STUDY

The present study aimed to evaluate the clinical consequences of pacing mode selection in patients with SSS.

The study includes:

1. 225 consecutive patients with SSS randomised to AAI (n = 110) or VVI pacing (I-IV).
2. 399 consecutive patients with SSS treated with an AAI/AAIR pacemaker at our institution (V).
3. 30 patients with SSS randomised to AAIR (n = 15) or DDDR pacing (VI).
4. 177 consecutive patients with SSS randomised to treatment with an AAIR pacemaker (n = 54), or a DDDR pacemaker programmed with either a dynamic, short AV delay (DDDR-s) (n = 60) or a fixed, long AV delay (DDDR-l) (n = 63) (VII).

Patients who received an AAI or an AAIR pacemaker after inclusion in the AAI/VVI trial (I) or who received an AAIR pacemaker after inclusion in the AAIR/DDDR trial at our institution (VII) were also part of the study population in Paper V. The study population presented in Paper VI was a part of the patients included in the AAIR/DDDR trial (VII).

The specific aims of the seven studies were:

- I. To investigate the long-term clinical consequences of pacing mode selection in patients with SSS randomised to AAI or VVI pacing mode.
- II. To study the evolution of congestive heart failure and elucidate the accompanying changes in left atrial and left ventricular dimensions and in left ventricular function (left ventricular fractional shortening) during long term follow-up of patients with SSS randomised to AAI or VVI pacing.
- III. To analyse whether thromboembolism in patients with SSS can be predicted by pacing mode selection, atrial fibrillation, or echocardiographic findings.
- IV. To evaluate in detail the AV conduction during long-term follow-up of patients with SSS included in a prospective trial.
- V. To analyse in detail the risk of developing AV block during long-term follow-up in a large cohort of consecutive patients with SSS who primarily received an AAI or an AAIR pacemaker in a single centre.
- VI. To quantitatively evaluate global and regional myocardial blood flow (MBF) during chronic pacing in patients with SSS randomised to long term AAIR or DDDR pacing and to study whether any such pacing-induced changes in MBF were associated with alterations in global left ventricular function.
- VII. To do a randomised comparison of AAIR and DDDR pacing in patients with SSS with respect to left atrial size and left ventricular size and function measured by echocardiography as well as clinical endpoints.

METHODOLOGICAL CONSIDERATIONS

TRIAL DESIGN

The randomised controlled trial

The randomised controlled trial has been used as a method in medicine for decades (40). In testing cardiac implantable devices, the randomised controlled trial has been used only within the last 10-15 years, the AAI/VVI trial being the first trial of pacing mode selection with a randomised controlled parallel design (41) (I). Later, the randomised controlled trial has been used also in studies of implantable defibrillators (42) and biventricular pacing devices (43).

The clinical trial or experiment is defined as “a *prospective study comparing the effect and value of intervention(s) against a control group in human subjects*” (44). The clinical trial thus is prospective, the study subjects must be followed forward in time from inclusion in the study, it employs some sort of active intervention, and it contains a control group against which the intervention group is com-

pared. It has been claimed that properly conducted clinical trials “*provide the only reliable basis for evaluating the efficacy and safety of new treatments*” (45). The ideal clinical trial is one that is randomised and double blind (44). Randomisation is the preferred way of assigning subjects to control and intervention group. There are three advantages of randomisation over other methods for selecting controls: 1) randomisation removes the potential of investigator bias in the allocation of subjects to the intervention group or to the control group, 2) randomisation tends to produce comparable groups, as both the known and the unknown prognostic factors and other characteristics of the subjects at the time of randomisation will be, on the average, evenly balanced between the intervention and control groups, and 3) randomisation guarantees the validity of statistical tests of significance (44). The major weakness of a study using a non-randomised control group, concurrent or historical, is the potential that the intervention group and the control group are not comparable.

In a double-blind trial, neither the study subjects nor the investigators following the study subjects know the intervention assignment. The advantage of a double-blind design is the reduction in bias during data collection and assessment of a trial. Bias can be defined as “*difference between the true value and that actually obtained due to all other causes than sampling variability*” (44). Trials investigating antiarrhythmic devices can however not be performed in a double-blind manner (46), and a randomised controlled trial can be successfully conducted without blinding (45). In the AAI/VVI and AAIR/DDDR trials, an un-blinded design was used. It is not realistic to withhold the actual pacemaker treatment for patients or investigators during a study period of several years with follow-up visits including ECG, echocardiography, and pacemaker check-up. The main disadvantage of an un-blinded trial is the possibility of bias. The reporting and evaluation of subjective response variables, e.g. subjective symptoms or functional class, may be influenced by conscious and subconscious factors in both study subjects and investigators. However, endpoints as death, atrial fibrillation, and thromboembolism are less prone to bias.

In both the AAI/VVI trial and the AAIR/DDDR trial we used so-called “*hardware randomisation*”. After randomisation the patients received the assigned pacemaker and lead(s). Another way to perform clinical trials in pacing mode selection is to use software randomisation, where all patients receive “universal” DDD pacemakers, which afterwards are programmed to the randomised pacing mode (47). Using software randomisation, it is possible to perform such trials in a single-blind design, as was done in the PASE and MOST trials (21, 48). An additional advantage is, that mode change easily can be done if clinically indicated during the conduct of the study or when one of the pacing modes has been found superior at the end of the study. There are however some important disadvantages using software randomisation. The easiness of crossing over from one pacing mode to another may invite to an inappropriately high crossover rate, as illustrated by the 26% and 31%, who crossed over from VVIR to DDDR in the PASE (21) and MOST trials (48), respectively. Statistical comparisons of outcome between study groups are most adequately done by the intention-to-treat principle (49), and a high crossover rate therefore will tend to decrease the differences between groups, to decrease the statistical strength of the study. Moreover, software randomisation is more expensive, as “universal” DDD pacemakers are more costly than single chamber pacemakers, and hardware randomisation allows a more reliable estimate of the total costs associated with different pacing modes.

The AAI/VVI trial was a pure single centre study, and 94% of the patients included in the AAIR/DDDR trial were recruited in the same single centre. This design is in contrast to the other trials of pacing mode selection; all performed as multi-centre studies (21, 48, 50). It may be the strength of a single-centre study, that all patients are treated and evaluated equally and by the same team. However, single-centre studies are by nature limited in population size, and

furthermore, the external validity tends to be lower than in a multi-centre study.

In the AAI/VVI and AAIR/DDDR trials, consecutive patients with SSS were included. All patients referred for primary pacemaker implantation were evaluated for inclusion, and reasons for exclusion were recorded and reported (II, VII), allowing an evaluation of the external validity. In the AAI/VVI trial, a total of 225 of 1052 (21.4%) patients were included, whereas the numbers in the AAIR/DDDR trial were 177 of 952 (18.6%). In both trials, all consecutive patients with SSS, who from a clinical point-of-view could be treated with an AAI(R) pacemaker, and who suffered from no other severe illness or awaited major surgery, were asked to participate. Only 8 and 23 eligible patients refused to participate in the AAI/VVI and AAIR/DDDR trials, respectively. The study populations therefore can be considered representative for patients with isolated SSS, thus increasing the probability that the results can be generalised to this population. However, the results are not necessarily valid for patients with SSS who suffer from other concomitant severe diseases as those mentioned in the tables presenting patients excluded from the studies (II, VII). This selection of the "less sick" patients for inclusion in randomised controlled trials is a well-described problem when extrapolating from randomised trials to the daily clinic (51).

In both the AAI/VVI trial and the AAIR/DDDR trial, all patients were followed from inclusion in the study until death or end of the study period. At that time, the survival status was known for all patients. No patients were lost to follow-up.

The retrospective observational study

The study of 399 consecutive patients with SSS treated with an AAI or AAIR pacemaker is a purely descriptive, retrospective cohort study (V). The advantage of this study design in the evaluation of the problem "AV block in patients with SSS" is, that *all* patients treated with an AAI/AAIR pacemaker within the study period were included. No patients were excluded because of co-morbidities, planned surgery or refusal. The results therefore can be generalised to the entire population treated with an AAI/AAIR pacemaker. It is well known, that outcome may differ between populations included in randomised trials and unselected cohorts, as recently shown in a study of patients with myocardial infarction (51). The most important disadvantage of such a retrospective study is the difficulties achieving the exact information needed from hospital files, which were not made for exactly that purpose. The retrospective observational cohort study does not describe the effect of an intervention in comparison to a control group, as is the case for the randomised controlled trial.

SURVIVAL ANALYSIS

Survival analysis is the most appropriate method to use in the description and statistical analysis of endpoints occurring at different points in time. The time period between inclusion in the study and occurrence of an endpoint (or the date of last follow-up if an endpoint has not occurred) is recorded for each study subject. Survival analysis is designed to accommodate also the data from patients who have not yet reached the endpoint (censored). The percentage of the population, that has still not reached the specified endpoint at a given time after inclusion is presented graphically in a Kaplan-Meier plot (Figure 1). In the AAI/VVI and AAIR/DDDR trials, survival analysis was used in the analysis and presentation of mortality as well as cause-specific mortality, thromboembolism, and atrial fibrillation, both in the total study populations and also in subgroup analysis (I-III, VII). Survival analysis includes only first-episodes of the respective endpoint: atrial fibrillation or thromboembolism. In the retrospective study of 399 consecutive patients with AAI/AAIR pacemakers, survival analysis was used to present overall survival and survival of effective AAI(R) pacing during follow-up (V). Statistical comparisons between groups were done using the log-rank test, which is more powerful for detecting late differences between

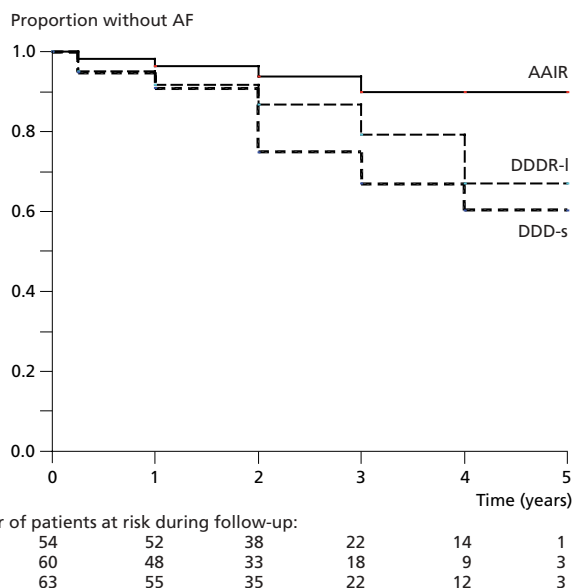


Figure 1. Kaplan-Meier plots of freedom from atrial fibrillation during follow-up in the AAIR/DDDR trial. Atrial fibrillation was diagnosed only by standard 12 lead electrocardiogram at planned follow-up visits. $p = 0.03$. For abbreviations see list on page 6.

groups. In general, statistical tests taking into account also the time to event (as the log-rank test) are more sensitive for detecting differences between groups. Relative risks associated with randomisation assignment or baseline variables were assessed using univariate and multivariate Cox proportional hazards regression analysis, and reported as relative risk with 95% confidence intervals. Relative risk is the same as risk ratio, and is sometimes called hazard ratio.

Only 12-lead electrocardiograms obtained at planned follow-up visits in the AAI/VVI and AAIR/DDDR trials were used to assess heart rhythm. Therefore, atrial fibrillation was only diagnosed at such follow-up visits. That is the explanation of the large "steps" in the Kaplan-Meier plots of freedom from atrial fibrillation in the two trials (I, III, VII) (Figure 1). Each of these steps may represent several patients with their first episode of atrial fibrillation recorded after inclusion in the study.

ECHOCARDIOGRAPHY

M-mode and 2D echocardiography

Echocardiography is the method most commonly used to obtain in vivo quantitative measures of the size and function of the cardiac chambers, also in studies of the effects of pacing on cardiac function (52-55). In echocardiography, pulses of high-frequent sound (ultrasound) are emitted from an ultrasound transducer and travels through the thoracic structures. When encountering borders between tissues with different acoustic impedance, some of the ultrasound waves are reflected. The reflected ultrasound waves returns to the transducer, where they are detected. These signals are processed for the imaging of cardiac structures.

Two-dimensional (2D) echocardiography produces a two-dimensional, real-time picture of the heart. The plane visualised depends on the location and angulation of the transducer. M-mode echocardiography, imaging the axial movement of a cross-section of the cardiac walls versus time, was guided by 2D echocardiograms. Echocardiography was done with the patient in the left lateral decubitus position. A *Toshiba SSH60* echocardiograph with a 3.5 MHz transducer was used in the AAI/VVI trial (II) and a *Vingmed CFM 750* echocardiograph (Vingmed, Horten, Norway) with a 3.25 MHz transducer was used in the AAIR/DDDR trial (VII).

We used echocardiography to measure left atrial and ventricular dimensions and left ventricular function. M-mode echocardiography

graphy was used in both the AAI/VVI trial and in the AAIR/DDDR trial. The M-mode measurements were done in accordance with the recommendations of the American Society of Echocardiography (56). The left atrial diameter was measured at end-ventricular systole and included the thickness of the posterior aortic wall. The left ventricular diameters were measured at the level of the chordae corresponding to the onset of the QRS complex (end-diastole) and to the nadir of septal motion or – in case of abnormal septal movement at the level of the chordae – peak of posterior wall motion (end-systole). The leading edge methodology was used (56).

In the AAIR/DDDR trial, 2D echocardiography was used for the determination of left ventricular end-diastolic and end-systolic volumes allowing calculation of left ventricular ejection fraction, $LVEF = (\text{end-diastolic volume} - \text{end-systolic volume})/\text{end-diastolic volume}$. At echocardiography, image frames each according to one cardiac cycle were digitally stored on optic disc and analysed off-line using *Echopac 6.0* software. We used the biplane disc summation method (modified Simpson's rule) for calculation of ventricular volumes (57, 58). The endocardium was traced in the end-diastolic and end-systolic frames in paired standard apical two- and four-chamber views (57, 58). The end-diastole was defined as the first frame in which the QRS complex appeared, and the end-systole as the frame preceding initial early diastolic mitral valve opening. The *Echopac 6.0* software calculates volume by dividing the ventricular cavity into 30 equal sections (discs) along the ventricular long axis, and summing the computed volumes in each of these 30 discs. Each left ventricular end-diastolic and end-systolic volume was averaged from three beats. As compared with other methods using mono- or biplane 2D echocardiography, the biplane disc summation method has been found the most accurate (57, 59, 60).

Variability and data quality

Both M-mode and 2D echocardiographic measurements have been found associated with a considerable variability by other authors (56, 61, 62). The variability of M-mode and 2D echocardiographic measurements obtained by the equipment described above in elderly patients with SSS and pacemaker was reported previously (63) (VII). For all echocardiographic parameters, M-mode as well as 2D, the bias was low and approximating zero for all parameters, suggesting a fairly reliable estimation of the mean echocardiographic values in groups of patients. However, the limits of agreement (64, 65) were wide in all cases. Therefore, changes over time in echocardiographic parameters should be interpreted cautiously when observed in individuals or small patient populations. In both M-mode and 2D echocardiographic studies, relative large patient populations are necessary to estimate the mean values with sufficient accuracy.

In our experience, sufficiently good quality 2D paired standard apical two- and four-chamber views are available in only 50-60% of patients with SSS and pacemaker. In half of the remaining patients, one of the two apical views is available, and can be used to calculate the left ventricular volumes, and left ventricular ejection fraction can be calculated repeatedly in approximately 75% of these patients (VII). Using single plane methods however increases the variability even further as compared with the biplane disc summation method (57, 60). The large variability of the 2D echocardiographic data in the AAIR/DDDR trial might in part explain why changes in volumes and ejection fraction did not parallel the findings from the M-mode echocardiographic results (VII). The large variability in measuring M-mode echocardiographic parameters in single patients may also add to explain why left atrial diameter was not predictive for thromboembolism in the AAI/VVI trial (III).

When the AAIR/DDDR study was planned in the early 1990's, fairly good quality 2D echocardiography had become widely accessible. Later, three-dimensional echocardiography has been developed and found associated with a much more reliable estimation of left ventricular volumes and ejection fraction than 2D echocardiography (66, 67). In a recent study of patients with good quality echo-

cardiographic images, modern 2D echocardiography was found to underestimate left ventricular volumes significantly, whereas the volumes obtained by, as well as test-retest variation of, three-dimensional echocardiography was as good as for cardiac magnetic resonance imaging (67). Therefore, at present time, three-dimensional echocardiography should be considered for measuring left ventricular volumes when planning future longitudinal studies of the effects of pacing mode selection.

Echocardiographic findings in patients with SSS

The AAI/VVI (II) and AAIR/DDDR (VII) trials report mean echocardiographic measurements in patients with SSS, at time of pacemaker implantation and during follow-up with different modes of pacemaker treatment. These data can be used as reference for future studies. Mean M-mode values were not different from normal values previously reported (68). The increase in left atrial diameter with increasing age (68) may add to explain the increase in left atrial diameter observed in all randomisation groups during follow-up. Baseline left atrial diameter was lower in the AAI/VVI trial (34 mm) (II) than in the AAIR/DDDR trial (39 mm) (VII), whereas left ventricular dimensions were similar in the two studies. No clear explanation is obvious for this difference. In a previous study, a mean left atrial diameter of 38 mm was reported in patients with a median age of 67.5 years (13), thus considerably younger than those included in the two trials.

QUANTIFICATION OF MBF USING ¹³N-LABELED AMMONIA AND PET IMAGING

A detailed discussion of the methodological and theoretical aspects of myocardial blood flow (MBF) determination using positron emission tomography (PET) and ¹³N-labeled ammonia is beyond the scope of this thesis. We used ¹³N-labeled ammonia dynamic PET imaging for quantification of MBF (VI). We chose to measure MBF not only corresponding to the three major coronary vessels, but also in the inter-ventricular septum, as the literature indicated a decreased septal perfusion during apical pacing (69).

The PET technique used for MBF measurements has been found to closely reflect the myocardial perfusion when validated against the microsphere technique (70), which is considered the "gold standard" for measuring myocardial blood flow. The microsphere technique however is not suitable for human use. Different microsphere techniques have been used in animal experiments of the changes in myocardial blood flow associated with acute and chronic pacing as described previously (69, 71, 72). The PET technique used in the present study has been found to reproducibly measure the regional myocardial perfusion (73). In contrast to different scintigraphic methods, which are qualitative, and used for the detection of myocardial perfusion defects, PET is a quantitative method, which yields the MBF as millilitres of blood per gram tissue per minute ($\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$). Currently, the PET technique is the only validated method, which can be applied to patients for the determination of quantitative MBF. The radiation associated with the present determination of MBF is approximately 4.1-6.1 mSv, corresponding to 1¹/₂-2 times the annual background radiation.

PACING MODE SELECTION OBSERVATIONAL STUDIES

Several observational studies have indicated, that VVI pacing increases atrial fibrillation, thromboembolism, heart failure, and death as compared with AAI pacing (27-30, 74). Also DDD pacing has been found superior to VVI pacing (31, 75, 76). In a large, long-term observational study comparing DDD pacing with VVI pacing in SSS, VVI pacing predicted chronic atrial fibrillation and stroke (32), but not mortality (77) or heart failure (78). One study has compared AAI (n = 95) and DDD (n = 101) pacing, and after a follow-up of 8 years, no significant differences were observed in mortality or development of atrial fibrillation between groups, although

a trend in favour of AAI pacing was seen for development of atrial fibrillation (4/95 versus 8/101 patients, $p = 0.06$) (79). In a recent observational study of very long-term survival in a cohort of 6505 patients, receiving a pacemaker between year 1971 and year 2000, survival increased significantly over the decades, SSS was associated with a better survival than high-grade AV block, and AAI or DDD pacing was associated with a better survival than VVI pacing (80). In abstract form, rate-adaptive pacing has been reported to improve survival as compared with fixed rate pacing (81). However, all these observational, non-randomised studies are potentially biased, as the decision about which pacemaker to use is likely to have been influenced by individual patient characteristics, which in turn may be important for the later outcome (82-84). Until recently, there has been a lack of randomised trials in the field of mode selection in cardiac pacing.

RANDOMISED CONTROLLED TRIALS

AAI versus VVI pacing mode

In 1994 the AAI/VVI trial, the first randomised trial comparing AAI and VVI pacing in 225 consecutive patients with SSS and normal AV conduction was reported from our institution. After a mean follow-up of 3.3 years, AAI pacing was associated with less atrial fibrillation and thromboembolism than VVI pacing, whereas no statistically significant difference in mortality or heart failure was observed between the two groups (41). In 1997, after an extended follow-up to a mean of 5.5 years, the differences between the AAI and VVI groups had enhanced substantially in favour of AAI pacing (Table 1). Total and cardiovascular mortality as well as atrial fibrillation and thromboembolism were significantly reduced in the AAI group (I). Congestive heart failure was more common in the VVI group than in the AAI group, and this finding was accompanied by a decrease in left ventricular function (left ventricular fractional shortening, LVFS) and an increased left atrial dilatation (II). Atrio-ventricular conduction was stable, and AV block occurred in only 4/110 patients in the AAI group (0.6% annual incidence) (IV). Although the second analysis done in 1997 was not protocolled when the trial was started (I), it seems conclusive, that AAI pacing is superior to VVI pacing in patients with SSS.

DDD(R) versus VVI(R) pacing mode

Three randomised controlled trials comparing DDD(R) pacing and VVI(R) pacing in patients with SSS have been reported (Table 1). In the Pacemaker Selection in the Elderly (PASE) trial a total of 407 patients were included, of whom 177 patients with SSS as the indication for pacemaker implantation. All patients received a DDDR pacemaker and were randomised by programming to VVIR or DDDR pacing mode. Median follow-up was 18 months and up to 30 months. Health-related quality of life, which was the primary end point, improved significantly after pacemaker implantation in both groups. There were no significant differences in the primary end point or in the incidences of atrial fibrillation, thromboembolism, or death between the two treatment groups. However, in the subgroup of patients with SSS, there were trends favouring DDDR pacing (21), and in an additional analysis, randomisation to VVIR pacing was an independent predictor of atrial fibrillation in patients with SSS (85). Crossover from VVIR to DDDR pacing because of pacemaker syndrome occurred in 53 patients (26%) (21, 86).

The first large-scale, randomised trial of pacing mode selection, the Canadian Trial Of Physiologic Pacing (CTOPP) was reported in year 2000 (50). In this trial ventricular pacing (VVI/VVIR) ($n = 1474$) was compared with physiological pacing (DDD/DDDR or AAI/AAIR) ($n = 1094$) in patients with symptomatic bradycardia. The indication for pacemaker implantation was SSS in 34% of the patients, AV block in 52% of the patients and both SSS and AV block in 8% of the patients. An AAI/AAIR pacemaker was implanted in 5% of the patients assigned to physiological pacing. Mean follow-up was 3 years. The primary endpoint was "stroke or cardiovascular death". No significant difference was observed in the primary end point between treatment groups during follow-up. Nor were there any differences in all cause mortality, stroke, hospitalisation for congestive heart failure, or functional capacity between groups. Atrial fibrillation was significantly reduced (relative risk reduction 18%, $p = 0.05$) in the physiological paced group. The Kaplan-Meier curves of atrial fibrillation overlapped for the first two years and then separated, indicating a delay in time before the effect of pacing mode on atrial fibrillation occurred (50). After an extended follow-up in the CTOPP trial to a mean of 6.4 years, the results were similar. There was a significantly lower rate of atrial fibrillation in the

Table 1. Randomised controlled trials in pacing mode selection.

Study	Pacing mode	N	Follow-up years	Atrial fibrillation %/year	Thromboembolism %/year	Death %/year
AAI/VVI (41)	AAI	110	3.3	4.1	1.7	5.8
	VVI	115	3.2	7.1	5.4	6.8
AAI/VVI extended (I)	AAI	110	5.7	4.1	2.1	6.2
	VVI	115	5.3	6.6	4.3	9.4
PASE (21)	DDDR	203	1.5	11.3	1.3	10.7
	VVIR	204	1.5	12.7	2.3	11.3
CTOPP (50)	DDDR	1094	3.0	5.3	1.0	6.3
	VVIR	1474	3.0	6.6	1.1	6.6
CTOPP extended (87)	DDDR	1094*	6.4	4.5	5.5#	
	VVIR	1474*	6.4	5.7	6.1#	
MOST (48)	DDDR	1014	2.8	7.6	1.4	7.0
	VVIR	996	2.8	9.7	1.8	7.3
AAIR/DDDR (VII)	AAIR	54	2.9	2.6	1.9	5.7
	DDDR-I	63	2.9	6.0	2.2	7.7
	DDDR-s	60	2.9	8.0	4.0	8.0

The annual incidences of atrial fibrillation, thromboembolism, and all-cause death are estimated on the basis of total incidences and mean follow-up times where not reported explicitly. In the PASE and MOST trials, median and not mean follow-up times are reported and used in the estimation of the annual event-rates. For explanation of trial abbreviations and pacing modes see the list on page 6.

*) A total of 7/2568 patients were lost to follow-up in the CTOPP extended study. The randomisation assignment for these 7 patients was not reported.

#) Thromboembolism or all-cause death is not reported. The annual incidence of the primary outcome event "cardiovascular death or stroke" is reported.

physiological paced group with a relative risk reduction of 20% ($p = 0.009$), but no differences between groups in the other clinical endpoints (87). At end of this extended follow-up period, 93% of patients randomised to ventricular pacing were still in VVI(R) pacing mode. For patients randomised to physiological pacing, 75% were still receiving physiological pacing (87).

The Mode Selection Trial in Sinus-Node Dysfunction (MOST) was reported in year 2002 (48). A total of 2010 patients with SSS were included, 21% of whom had AV block as well. More than 50% of the patients ($n = 1059$) had prior atrial fibrillation. All patients were implanted with a DDDR pacemaker, and afterwards the programming was randomly assigned to VVIR ($n = 996$) or DDDR ($n = 1014$) pacing mode. Mean follow-up was 33 months. The primary endpoint was death from any cause or nonfatal stroke. At the end of follow-up no differences were observed between groups in the primary endpoint or in the secondary endpoints: death, cardiovascular death, stroke, or hospitalisation for heart failure. There was a significantly lower incidence of atrial fibrillation in the group randomised to DDDR pacing (hazard ratio 0.79, $p = 0.008$). In the MOST trial a total of 313 patients (31%) crossed over from VVIR to DDDR pacing mode. The reason for cross-over was severe pacemaker syndrome in 182 patients (18%) and refractory heart failure in 39 patients (4%) (88).

In the Pacemaker Atrial Tachycardia (Pac-A-Tach) trial, 198 patients with brady-tachy syndrome were randomised to DDDR or VVIR pacing. At 2 years follow-up, there was no difference in the primary endpoint "recurrence of atrial fibrillation" between the two groups, whereas total and cardiovascular mortality and thromboembolism were reported to be less common in the DDDR group than in the VVIR group (89). However, the Pac-A-Tach trial has never been published in an article, only in abstract form in year 1998, and the data from the study therefore are not known in details.

Recently a Cochrane Database Review compared dual-chamber pacing and single chamber ventricular pacing in adults with SSS or/and AV Block. In this analysis atrial fibrillation and pacemaker syndrome were significantly less common during dual chamber pacing, whereas mortality, stroke, and congestive heart failure did not differ significantly between pacing modes (90).

AAIR versus DDDR pacing mode

The first randomised comparison of AAIR and DDDR pacing, the AAIR/DDDR trial was published in 2003 (VII). A total of 177 consecutive patients with SSS, normal AV conduction and no bundle branch block were assigned to treatment with one of three pacemaker modalities: AAIR pacemaker ($n = 54$), DDDR pacemaker programmed with a short, dynamic AV delay ($n = 60$) (DDDR-s) or DDDR pacemaker programmed with a fixed long AV delay ($n = 63$) (DDDR-l). Mean follow-up was 2.9 years. The primary endpoints were changes in left atrial diameter and left ventricular size and function (LVFS) measured by echocardiography. In the AAIR group no significant changes were observed in left atrial diameter or in LVFS from baseline to last follow-up. In both DDDR groups, left atrial diameter increased significantly, and in the DDDR-s group, with in mean 90% pacing in the ventricle, LVFS decreased significantly from baseline to last follow-up. Atrial fibrillation occurred significantly less common in the AAIR group ($p = 0.03$), also after adjusting for brady-tachy syndrome at time of randomisation (relative risk 0.27, $p = 0.02$). Mortality, thromboembolism and heart failure did not differ between groups (VII) (91).

CLINICAL OUTCOMES

Atrial fibrillation

Approximately 50% of the patients referred for pacemaker implantation because of SSS have had one or more episodes of atrial fibrillation (I, VII) (48). Prior atrial fibrillation (brady-tachy syndrome) is the strongest predictor for atrial fibrillation as well as for chronic atrial fibrillation after pacemaker implantation (I, III, VII) (85, 91,

92). Both AAIR(R) pacing (I, III) and DDDR(R) pacing (48, 50, 85, 87) reduce the incidence of atrial fibrillation as compared with VVI(R) pacing. Furthermore, the AAIR/DDDR trial indicates, that AAIR pacing reduces atrial fibrillation as compared with DDDR pacing, most likely because DDDR pacing causes atrial dilatation (VII). The finding, that ventricular pacing *per se*, also in the DDDR mode, increases the occurrence of atrial fibrillation is supported by data from the MOST trial, where an increasing cumulative percentage of ventricular pacing was associated with an increased risk of atrial fibrillation in both randomisation groups (93).

The annual incidences of atrial fibrillation in the different randomisation groups ranged from 2.6% to 12.7% in the randomised trials (Table 1). The more frequent follow-up visits – after 3, 9, and 18 months in the PASE trial and four times the first year and twice yearly thereafter in the MOST trial may have contributed to the higher incidences observed in these two trials. However, in all cases, measuring atrial fibrillation as "atrial fibrillation in an ECG at a follow-up visit" results in a conservative estimate of the occurrence of atrial fibrillation. It is well known, that patients with atrial fibrillation and no pacemaker often have asymptomatic episodes of atrial fibrillation (94). In a recent paper by Kristensen et al., the pacemaker telemetry data as well as follow-up ECG's were recorded in 109 patients with SSS treated with AAIR or DDDR pacemakers. After a mean follow-up of 1.5 year, a total of 58 patients (35% per year) had atrial fibrillation, which was diagnosed by the pacemaker telemetry exclusively in 27 patients (17% per year) (95). Similarly, in a subgroup of the patients included in the MOST trial, atrial high rate episodes exceeding 5 minutes were recorded from the pacemaker diagnostics. After a median follow-up of 27 months, atrial high rate episodes had been detected in 160/312 patients (51%) (96). There was no significant effect of pacing mode on the presence of atrial high rate episodes in that study (96).

Atrial fibrillation is known as a strong risk factor for thromboembolism in non-paced patients (97). As indicated by the AAIR/VVI trial, prior atrial fibrillation or "brady-tachy syndrome" is the strongest predictor of thromboembolism also in patients with SSS and pacemaker (I, III). Brady-tachy syndrome, present in 12 of 14 patients, was the strongest predictor of stroke also in the AAIR/DDDR trial (91). In contrast, in the MOST trial, atrial fibrillation before pacemaker implantation did not predict stroke, whereas atrial fibrillation observed after pacemaker implantation was an independent risk factor for stroke (98). This finding is surprising, and not readily explainable. In a subgroup of the MOST-population atrial high rate episodes detected by the pacemaker diagnostics were predictive of "death or non-fatal stroke", and present in 8 of 10 patients with strokes (96).

In the AAIR/VVI trial, brady-tachy syndrome was an independent predictor of all-cause mortality (relative risk 1.56) and of cardiovascular death (I). That is in accordance with recent results from the Framingham Heart Study, where atrial fibrillation was associated with a 1.5- to 1.9-fold mortality risk after adjustment for other cardiovascular risk factors (99). Surprisingly, brady-tachy syndrome had no impact on mortality in the MOST trial (100), whereas atrial high rate episodes detected during follow-up in a large subgroup of the MOST-patients were strongly predictive of all cause mortality (hazard ratio 2.48) (96).

Thromboembolism

The increased risk of thromboembolism in patients with SSS has been known for several years (22, 30, 101-103). As indicated by the AAIR/VVI trial, VVI pacing increases the risk of thromboembolism in patients with SSS (I, III), which at least in part may be explained by the increased incidence of atrial fibrillation caused by VVI pacing (III) (see above). Furthermore, VVI pacing causes left atrial dilatation (II), which is known to be a risk factor for thromboembolism in the population (104). Left atrial dimensions measured by echocardiography was not associated with thromboembolism in the

AAI/VVI trial (III), similar to the findings in a recent large trial on treatment of AF (105). It is still not clear whether VVI pacing may increase the risk of thromboembolism also by other mechanisms than causing atrial fibrillation and left atrial dilatation (106).

The reported incidences of arterial thromboembolism were higher in the AAI/VVI trial (I, III) than in the three trials of DDDR versus VVIR pacing: PASE, CTOPP, and MOST (Table 1). Two probable explanations may at least in part account for this apparent difference. First, the definitions of thromboembolism were not the same in the trials. In the two trials from our institution, thromboembolism included all cases of stroke or peripheral embolism (I, III, VII). In contrast, in the three DDDR versus VVIR trials, only strokes were reported (21, 48, 50, 98). The incidences of stroke in the AAI/VVI trial were 12/110 patients in the AAI group (1.9% per year) and 21/115 patients in the VVI group (3.4% per year) (III), similar to the incidences observed in the AAIR/DDDR trial (where no peripheral emboli occurred (VII)). Second, an increased use of antithrombotic therapy in the three DDDR versus VVIR trials may likely have reduced the occurrences of thromboembolic events significantly. These trials were conducted after trials convincingly showed the benefit of antithrombotic therapy in patients with atrial fibrillation (107). However, thromboembolism accounted for a higher proportion of the total number of deaths in the AAI/VVI trial (19/96 deaths, 20%) (I) than in the MOST trial (35/404 deaths, 8.6%) (100). Details on death causes have not been reported from the PASE or CTOPP trials.

A meta-analysis using individual patient data from five randomised trials: AAI/VVI, PASE, CTOPP, MOST and UKPACE (comparing VVI(R) and DDD(R) pacing in patients with AV block) (108) has recently been done. The pooled analysis did demonstrate a significant reduction in stroke with atrial-based pacing (HR = 0.81, 0.67-0.99, $p = 0.038$) (Healey 2005, personal communication). A finding, which is in accordance with the lower incidence of atrial fibrillation – one of the strongest risk factors for stroke – observed with atrial-based pacing (HR = 0.80, 0.72-0.89, $p = 0.00003$) (Healey 2005, personal communication).

Congestive heart failure

The AAI/VVI trial clearly demonstrated, that VVI pacing increases congestive heart failure as estimated by NYHA functional class and use of diuretics, and that these clinical findings are associated with a decrease in left ventricular function (LVFS) and an increased left atrial dilatation (II). The clinical findings became apparent only when follow-up was extended from in mean 3.3 to 5.5 years (41) (II). Echocardiographic changes identical to those observed in the AAI/VVI trial were found in the DDDR-s group in the AAIR/DDDR trial (VII), supporting that a high percentage of ventricular pacing *per se* is responsible for inducing these changes. In the AAIR/DDDR trial no differences were observed in the occurrence of congestive heart failure between groups, most likely because of the limited sample size and a mid-term follow-up period of in mean 2.9 years (VII). Most patients with SSS have a normal left ventricular function at time of pacemaker implantation (II, VII), and a longer period of ventricular pacing seems to be necessary before symptoms of heart failure occur.

In the three trials comparing DDDR and VVIR pacing, no differences in rates of “hospitalisation for congestive heart failure” were found between pacing modes. In an additional analysis of 1339 MOST patients without baseline bundle branch block, cumulative percentage of ventricular pacing was found to be a strong predictor of hospitalisation for heart failure in both randomisation groups (93). The association between ventricular pacing and congestive heart failure is furthermore supported by findings from two implantable defibrillator (ICD) trials: In the Multicenter Automatic Defibrillator Trial II (MADIT II), the development of new or worsened heart failure was more common in the ICD arm (19.9%) compared with the conventionally treated arm (14.9%) (42). The

Dual Chamber and VVI Implantable Defibrillator Trial (DAVID) compared treatment with dual-chamber ICD (DDDR pacing mode) and single chamber ICD (VVI pacing mode, 40 bpm) in patients with left ventricular ejection fraction of 40% or less. The DAVID trial was terminated prematurely after a median follow-up of 8.4 months, when a worse outcome in the primary endpoint “death or first hospitalisation for new or worsened congestive heart failure” became apparent in the DDDR-ICD group (relative hazard 1.61, $p = 0.03$). The relative hazard for “first hospitalisation for new or worsened heart failure” was 1.54 ($p = 0.07$) in the DDDR-ICD group. The mean percentage of ventricular pacing after 6 months of follow-up was 60% in the DDDR-ICD group and 1% in the VVI-ICD group (109). In a recent analysis of data from the DAVID trial, percent right ventricular pacing correlated with the primary endpoint in the trial (110).

These data support, that ventricular pacing increases the occurrence of congestive heart failure, and probably more markedly and faster in patients with impaired left ventricular function than in patients with SSS and normal left ventricular function, as indicated by the DAVID trial (109). This is also the most likely explanation, why no differences were observed in incidences of congestive heart failure between DDDR and VVIR pacing in the three trials (21, 48, 50). In mean, the percentage of ventricular pacing is higher in DDDR pacing mode than in VVIR pacing mode because in the former mode most sensed atrial beats triggers a paced ventricular beat. In the MOST trial, median percentage ventricular pacing was 90% in the DDDR group and 58% in the VVIR group (93). Therefore, any advantages of preserved AV synchrony in DDDR pacing mode may have been outweighed by the effects of a higher percentage of ventricular pacing in this mode.

Mortality

In the AAI/VVI trial, all-cause mortality was significantly higher in the VVI group than in the AAI group, the excess mortality in the VVI group was caused by cardiovascular deaths, and randomisation to VVI pacing was an independent predictor of cardiovascular (but not all-cause) mortality. In this trial, a total of 96 patients (43%) died during the course of the study, and 58 of the deaths (60%) were due to cardiovascular causes (I). The annual all-cause mortality in the AAI/VVI trial was not different from that reported in the other randomised trials (Table 1).

In the three DDDR versus VVIR trials, no significant differences or even trends have been observed in all-cause or cardiovascular death between the two pacing modes (21, 48, 50). In the CTOPP trial, follow-up was extended to in mean 6.5 years to assess a potential delayed benefit of physiological pacing, but no difference in mortality emerged between groups (87). Cause of death in the CTOPP and PASE trials has not been reported in details. In the MOST trial, a total of 404 deaths (20% of the patients) occurred, of which 44% were cardiovascular: 35% due to cardiac causes and 9% (35 patients) due to stroke or other non-cardiac, vascular causes (100). The incidence of death due to congestive heart failure was 10.6%, similar to the 10.4% found in the AAI/VVI trial (I). The apparently slightly lower proportion of cardiovascular deaths in the MOST trial as compared with the AAI/VVI trial may be associated with different death cause classifications in the two trials. Sixteen percent of the deaths in the MOST trial were classified as due to unknown causes (100).

The finding, that mortality is equal in DDDR and VVIR pacing but lower in AAI pacing than in VVI pacing indicates, that ventricular pacing *per se* may be associated with an increased risk of death. In an analysis of data from the CTOPP trial, the patients were divided into 1245 patients (55%) with an un-paced heart rate ≤ 60 bpm and 999 patients (45%) with an un-paced heart rate >60 bpm. In the former group, where patients in both *randomisation groups* probably were paced most of the time, all-cause death was significantly lower with physiological pacing than with VVIR pacing

(7.8% versus 4.6% per year, $p < 0.001$). However, in the latter group, a non-significant difference in all-cause death (5.0% versus 6.6%, $p = 0.12$) was observed *in favour of VVIR pacing*. Although non-significant, this excess mortality in the physiological paced group outweighed the counter directed difference in mortality among the patients with an un-paced heart rate ≤ 60 bpm in the analysis of the complete trial population (50). In the group of patients with an un-paced heart rate > 60 bpm, patients with VVIR pacemakers probably had a low percentage of pacing in the ventricle, whereas patients with DDDR pacemakers most likely were paced in the ventricle most of the time triggered by atrial sensed beats. The pattern was similar for cardiovascular deaths (111). These findings indicate: 1) that in patients with a high percentage of ventricular pacing, loss of AV synchrony may increase mortality, and 2) that in patients not dependent of constant pacing, mortality may be lower in those patients where ventricular pacing is avoided. One of the important limitations in this analysis is the lack of knowledge about the percentage of pacing in the ventricle in each patient. In a post-hoc subgroup analysis from the MOST trial, cumulative percentage of ventricular pacing was found to be a strong predictor of hospitalisation for heart failure and atrial fibrillation in both randomisation groups (93), events both known to be associated with an increased mortality risk. Therefore, there are several indications, that ventricular pacing may increase mortality, however, the proof is still lacking.

In the first trial comparing AAIR and DDDR pacing, no differences in mortality were observed after 2.9 years of follow-up (VII). This study included a total of 177 patients, and thus was not powered to detect any such differences in mortality.

Only a minority of the patients included in the AAI/VVI trial received rate-adaptive pacemakers (II). In contrast, all patients in the PASE (21) and MOST trials (48) and the majority of the patients in the CTOPP trial (50) had rate-adaptive pacemakers. It cannot be ruled out, that VVIR pacing is associated with a better survival than VVI pacing, as indicated by an observational study published only in abstract form (81) and by findings from the CTOPP trial, where implantation of a non rate-adaptive pacing system was found associated with an increased risk of stroke or cardiovascular death (112). That may add to explain why no differences in mortality were observed in the three DDDR versus VVIR trials although such a difference had been found in the AAI/VVI trial. Answering that question would require a randomised trial. However such a trial cannot be done as rate-adaptive pacing has been established as a standard in almost every pacemaker for several years, mimics normal physiology better than fixed rate pacing, and has been shown to increase exercise capacity and quality of life (113-116).

Pacemaker syndrome

The definition of pacemaker syndrome has been very variable, including different subjective symptoms as well as various objective findings (117, 118). Schüller and Brandt suggested the most appropriate general definition of the pacemaker syndrome as “*symptoms and signs present in the pacemaker patient which are caused by inadequate timing of atrial and ventricular contraction*” (119).

In the MOST trial pacemaker syndrome occurred in 18% of the patients treated with VVIR pacing (120). The strongest predictor of pacemaker syndrome was a higher percentage of paced beats, and all significant predictors of pacemaker syndrome were parameters promoting or strongly associated with a higher percentage of ventricular paced beats. Pacemaker syndrome caused a marked decrease in quality of life, which improved significantly after reprogramming to DDDR pacing mode. Pacemaker syndrome was strictly defined as either “*new or worsened dyspnoea, orthopnoea, elevated jugular pressure, rales, and oedema with ventriculoatrial conduction during ventricular pacing*” or “*symptoms of dizziness, weakness, presyncope, or syncope and a > 20 mmHg reduction of systolic blood pressure when the patient was ventricular paced as compared with atrial pacing or sinus rhythm*”. Both definitions included serious subjective symptoms,

which had to occur together with objective findings indicating an adverse haemodynamic effect of single lead ventricular pacing.

The incidence of pacemaker syndrome in patients treated with VVIR pacing in the MOST trial (120) was similar to the 26% found in the PASE trial (21, 86). In contrast, in the AAI/VVI trial, only 2% had pacemaker syndrome requiring change in pacing mode (I), and in the CTOPP trial, only 2.7% underwent pacing mode change because of pacemaker syndrome (50). In the two latter trials, hardware randomisation was used, and change in pacing mode to atrial based pacing required a re-operation with implantation of an atrial lead and a new pacemaker. Therefore, it is likely, that the threshold for diagnosing pacemaker syndrome was higher in these trials. A new operation not only results in an additional hospitalisation and costs, but also is associated with a risk of infection and other complications in each individual case.

Is 20% the correct incidence of pacemaker syndrome within the first years after pacemaker implantation in patients with SSS treated with VVIR pacing? In the MOST trial (120), the pacemaker programming followed usual recommendations in elderly patients with SSS, and in case of pacemaker syndrome, reprogramming of the pacemaker to reduce ventricular pacing was tried before change in pacing mode was done. Over-reporting of pacemaker syndrome cannot totally be ruled out, as the investigators were not blinded with respect to the assigned pacing mode. However, the finding of a 20% incidence probably represents the best estimate of severe pacemaker syndrome in patients with SSS treated with VVIR pacing. Four double blind, randomised crossover studies indicate the presence of a less severe form of pacemaker syndrome in an even higher proportion of the patients (121-124). Therefore, avoiding pacemaker syndrome is a strong argument to always select an atrial based pacing mode for patients with SSS.

Some authors consider the so-called “AAIR pacemaker syndrome” a concern in the use of AAIR pacing and an argument for using DDDR pacing in patients with SSS (125). The AAIR pacemaker syndrome is characterised by a paradoxical prolongation of the spike-R interval during exercise and is associated with symptoms as chest pain, dyspnoea, and light-headedness (125). This phenomenon is probably the result of an inadequate balance between the pacemaker sensor activity and the level of sympathetic tone during initial exercise, and tends to correct itself as sympathetic tone progressively increases during exercise (125, 126). Previously, it has been reported to occur only in a minority of patients (125-127), and most often during treatment with drugs depressing AV conduction. It has been found predictable from overdrive pacing at rest, and usually correctable by fine-tuning of the rate adaptive settings (126). In the study of 399 consecutive patients treated with a single lead atrial pacing system, a total of 237 patients primarily received an AAIR pacemaker. During follow-up none of these 237 patients developed symptoms of AAIR pacemaker syndrome requiring a change in pacing mode (V). Therefore, the AAIR pacemaker syndrome should not be considered a concern in the use of AAIR pacing.

Pacemaker related complications

The incidence of pacemaker related complications has been reported in different ways in the randomised trials. In the AAI/VVI trial, all complications occurring during the conduct of the trial and necessitating a re-operation were reported (AAI group: 21/110, VVI group: 14/115), and no significant difference was observed between randomisation groups (I). However, the high incidence of lead displacements in the AAI group (9/110 patients) was probably associated with a learning experience and with the use of passively fixated leads. With the present experience and the use of actively fixated leads in the atrium as standard, the incidence of lead displacements is less than 2-3%, and the incidence of any re-operation within the first 3 months after initial pacemaker implantation approximates 5% in a population-based report (25, 128). The incidences of early pacemaker related complications were reported to be

4.4% in the PASE trial (129) and 4.8% in the MOST trial (48), where all patients received DDDR pacemakers. In the CTOPP trial, the incidence of perioperative complications was significantly higher in the physiologically paced group (9%) than in the VVIR group (3.8%) (50). The AAIR/DDDR trial was not powered to detect any differences in occurrence of pacemaker related complications between AAIR and DDDR pacing modes. It is likely, that early complications are slightly more common after implantation of a DDDR pacemaker and two leads than after implantation of an AAIR pacemaker and one lead. However, after an AAIR pacemaker, approximately 2-2.5% of the patients undergo a re-operation with implantation of a ventricular lead per year (V).

RISK OF AV BLOCK IN SSS

The risk of high grade AV block has been recognized as *the major problem* in AAI pacing for decades. Two early literature reviews have summarised the results of many of the studies within this field. In 1986, Sutton and Kenny reviewed 28 studies including 1.395 patients, and reported that 8.4% of the patients developed AV block within a mean follow-up of 34 months (3% per year) (30). It was concluded that this risk was sufficient to justify use of a ventricular lead in pacemaker management. However, the definition of AV block in this review included development of P-R interval >0.24 seconds, complete bundle branch block, Wenckebach block at ≤ 120 bpm, and His-ventricular prolongation, all findings, that alone does not indicate pacing of the ventricle. Therefore, the reported 3% per year does not represent the risk of AV block necessitating change of pacing mode from AAI(R) to a pacing system including a ventricular lead. In 1989, Rosenqvist and Obel reported a review of 28 studies including in total 1.876 patients with SSS treated with AAI(R) pacing, median follow-up was 36 months (33). Only five of the studies (including 302 of the patients) reviewed were also included in the earlier survey done by Sutton and Kenny (30). The occurrence of high grade (second or third degree) AV block was in total 2.1%, equal to 0.6% per year. The annual incidence of AV block was <1% in 17 of the studies, and higher than 2% in only 4 studies (including 217 of the patients). No correlation was found between the Wenckebach block point, which was measured before pacemaker implantation and used to select patients for AAI(R) pacing in several of the studies, and later development of AV block. Brandt et al. reported the occurrence of high-grade AV block in a cohort of 213 patients with SSS treated with AAI pacing and followed for a median of 60 months (20). Overall, 18/213 patients (1.8% per year) developed high-grade AV block. The risk of AV block was 35% in patients with bundle branch block and 6.1% (equal to 1.2% per year) in patients without bundle branch block, and it was concluded, that patients with SSS and bundle branch block should initially receive a dual chamber pacemaker. In a recent observational comparison of AAI and DDD pacing with very long-term follow-up (8.7 and 7.6 years in mean in the AAI and DDD groups, respectively), the occurrence of high-grade AV block was 8/95 patients (1.1% per year) in the AAI group, and a Wenckebach block point lower than 120 bpm was found predictive of later high-grade AV block (79).

The investigation of the AV conduction in the AAI/VVI trial (IV) was the first detailed evaluation of this item in a relative large population prospectively followed for a very long period. At baseline and again at each follow-up visit, AV conduction was estimated by measuring PQ interval during sinus rhythm and atrial stimulus-Q intervals at atrial pacing rates of 100 bpm (Stim-Q100) and 120 bpm (Stim-Q120). During follow-up, mean values of these three parameters - PQ interval, Stim-Q100, and Stim-Q120 remained unchanged in the AAI group. Comparing the Wenckebach block point at baseline and at last follow-up, no significant difference was observed. Therefore, in general, a gradual deterioration of the AV conduction does not occur in patients with SSS treated with AAI pacing and followed for several years. However, a total of four patients treated with AAI pacemakers in the AAI/VVI trial developed high-grade AV

block and needed mode change to a dual chamber pacemaker (0.6% per year). The occurrence of high-grade AV block was not predictable from changes in the PQ interval, the atrial stimulus-Q intervals, or the Wenckebach block point in these four patients. Two of the four patients developing high-grade AV block had right bundle branch block at the time of primary pacemaker implantation, supporting the findings by Brandt et al (20), that such patients should receive dual chamber pacemakers initially. Changes in the Wenckebach block point during follow-up were associated with changes in medication affecting the AV conduction in a considerable proportion of cases.

The observational evaluation of 399 consecutive patients (V) treated with an AAI(R) pacemaker in our institution and followed for a mean of 4.6 years is the largest single-centre study of patients treated with AAI(R) pacing published. In this study, the risk of high-grade AV block was 1.7% per year. A total of 10 patients (0.5% per year) developed bradycardia or pauses in atrial fibrillation, and in five of these patients was the occurrence of AV conduction disturbance preceded by the initiation of medication affecting the AV conduction. Another 20 patients (1.1% per year) developed 2-3 degree AV block, only in four (20%) preceded by initiation of medication affecting the AV conduction. Bundle branch block at the time of primary pacemaker implantation was present among those who developed AV block only in the two patients also included in the AAI/VVI trial (IV). Survival of effective AAI(R) pacing was 90% at 5 years, and the incidence of AV block did not increase during very long-term follow-up.

In a recent crossover evaluation of AAIR versus DDDR pacing mode in patients with SSS and brady-tachy syndrome, second or third degree AV block was detected in ambulatory ECG monitoring during AAIR pacing in 7/19 patients (130). The authors therefore concluded, that DDDR pacing should be preferred for safety reasons. However, in that study, the basic pacing rate was programmed as high as 70-75 bpm in every patient, and all patients received antiarrhythmic drugs, in several of the patients in a quite high daily dose. None of the patients had symptoms during the ECG monitoring. The occurrence of AV block in this study most likely was caused by an inappropriately high resting pacing rate in patients treated with antiarrhythmic drugs rather than by a compromised AV conduction. In the large majority of such patients, a resting pacing rate of no more than 60 bpm is necessary, and no beneficial effects of increasing the rate to 70-75 bpm has been documented. The incidence of atrial fibrillation was 12 episodes in 2 patients with AAIR pacing and 22 episodes in 7 patients during DDDR pacing (130).

What is the incidence of AV block in patients with SSS without bundle branch block and with a Wenckebach block point of at least 100 bpm who receive an AAI(R) pacemaker? The most reliable estimate based upon present data seems to be 1.0-1.7% per year (V) (20, 33, 79). As long as DDD(R) pacing has not been shown to be equal to or superior to AAI(R) pacing with respect to patient outcome - survival, occurrence of atrial fibrillation, thromboembolism, and congestive heart failure, AAI(R) pacing should be considered first choice treatment in isolated SSS despite the risk of high-grade AV block. Special attention should be offered patients with SSS and AAI(R) pacemakers when initiating drugs affecting the AV conduction (V).

VENTRICULAR DESYNCHRONISATION

In the era of ventricular resynchronisation therapy - the treatment of patients with severe congestive heart failure, left ventricular dysfunction, and bundle branch block with biventricular or left ventricular pacing - the term *ventricular desynchronisation* has been introduced to describe the left ventricular dyssynchrony produced by single site right ventricular apical pacing (93, 131).

ACUTE CONSEQUENCES OF VENTRICULAR PACING

Wiggers reported, that artificial stimulation of the ventricles causes a prolonged electrical activation of the ventricles associated with a

less efficient mechanical performance already in the year 1925 (132). It is now well established, that single site right ventricular apical pacing causes an asynchronous and prolonged ventricular electrical activation and an abnormal mechanical contraction of the ventricles (133), which is associated with a reduced global left ventricular ejection fraction (LVEF) as compared with normal sinus rhythm or AAI pacing (34, 52, 134). Other parameters of left ventricular systolic (34, 35, 52, 135) and diastolic function (34, 35, 52, 136, 137) are also impaired during right ventricular apical pacing. The consequences of DDD pacing and VVI pacing are similar with regard to impairment of left ventricular systolic and diastolic performance (34, 52, 138). However, VVI pacing furthermore disrupts atrioventricular synchrony, and therefore reduces LVEF more than does DDD pacing (34, 52, 139, 140).

CHRONIC CONSEQUENCES OF VENTRICULAR PACING

Pathophysiological studies

Permanent pacing is a chronic therapy, for the majority of patients continued for several years, and therefore the consequences of chronic ventricular pacing are even more clinically relevant, and have attracted much interest within later years. In immature dogs, Karpawich et al. found, that chronic fixed-rate VVI pacing at the right ventricular apex was associated with right ventricular distension, elevated right atrial and pulmonary artery pressure, and histological alterations (38). If the pacing electrode was inserted into the proximal inter-ventricular septum, the ventricular activation and performance remained normal and no histological changes were induced by VVI pacing (141). Also in adult dogs with induced AV block did VVI pacing result in myofibrillar disarray in the histological samples (142). In another study on dogs with induced AV block, chronic VVI pacing resulted in myocardial perfusion abnormalities and increased myocardial catecholamine activity, but no histopathological findings were observed (37). Ono et al reported a reduction in septal myocardial blood flow and glucose uptake during single site right ventricular pacing (69). One biopsy study done in paediatric and young patients with congenital AV block reported myofiber size variation, fibrosis, fat deposition, sclerosis, and mitochondrial morphological changes after 3-12 years of chronic VVI(R) pacing (143). Histological changes have not been described in adult or elderly patients as a consequence of chronic pacing.

Prinzen and colleagues have done a large work on the pathophysiological changes induced by single site ventricular pacing. Chronic epicardial left ventricular pacing has been reported to induce redistribution of ventricular mass or ventricular remodeling characterised by thinning of the early-activated free wall close to the pacing site and thickening of the late-activated septum (144, 145). Left ventricular dilatation and increased left ventricular mass was observed in one of these studies, however, these changes were not associated with any irreversible reduction in left ventricular function (145). A similar ventricular remodeling with thinning of the earliest activated septum was observed in patients with chronic left bundle branch block (144). The myocardial work was found to be reduced by 50% in the earliest activated parts of the myocardium close to the pacing site and increased by 50% in the late-activated regions, most likely because of regional differences in effective preload (146, 147). These changes in myocardial work were accompanied by a similar redistribution in myocardial blood flow and oxygen consumption (71, 146), probably mediated by local autoregulation of the myocardial blood flow (72). The ventricular remodeling observed after chronic ventricular pacing most likely represents an adaptation to the altered workload induced by the asynchronous electrical activation during pacing (72, 145).

Clinical studies

Fewer studies have been done in patients. In a recent study, the consequences of short-term and mid-term DDD pacing on global left ventricular function were evaluated (134). A short AV delay was

used to ensure complete ventricular capture from the pacing site, and left ventricular ejection fraction (LVEF) was measured with gated cardiac blood pool imaging. After 2 hours of DDD pacing had the LVEF decreased significantly from in mean 66.5% to 60.3%. After another week of DDD pacing a further significant decrease in LVEF to a mean of 52.9% was observed. After cessation of DDD pacing, the LVEF immediately increased, however LVEF remained significantly lower than the basal LVEF for 24 hours after pacing was stopped and normal ventricular activation restored (134). This elegant study documents, that mid-term single-site right ventricular pacing causes an even more profound depression of LVEF than acute pacing. Furthermore, the persistent depression of LVEF after cessation of pacing indicates, that single-site right ventricular pacing causes functional or structural changes in the myocardium, which in turn are associated with a depressed left ventricular function. In young patients paced in the ventricle for a median of 10 years, echocardiographic indexes of left ventricular systolic and diastolic function were found impaired as compared with control subjects (54). Tse et al. reported, that long-term right ventricular apical pacing resulted in myocardial perfusion defects in patients with AV block paced in the DDDR pacing mode. These perfusion defects were associated with apical wall motion abnormalities and an impaired global left ventricular function (36).

The AAI/VVI trial was the first study of the echocardiographic changes occurring during very long-term follow-up of patients with SSS and pacemaker. As compared with AAI pacing, VVI pacing caused a decrease in left ventricular performance, which furthermore was associated with more symptomatic congestive heart failure (II). These findings are in accordance with the results from the three previously cited studies (36, 54, 134). The differences in occurrence of congestive heart failure between the two pacing modes first emerged when follow-up was extended from 3.3 to 5.5 years, indicating, that the detrimental effects of ventricular pacing takes years to become clinically important, at least in patients who have an initially normal left ventricular function. The detrimental effects of permanent ventricular pacing were confirmed by the results of the AAIR/DDDR trial, where changes identical to those observed in the VVI group in the AAI/VVI trial were found during DDDR pacing with constant ventricular pacing (VI, VII). Furthermore, chronic DDDR pacing caused a reduction in inferior, septal, and global mean myocardial blood flow (MBF) (VI). This result is in accordance with the prior findings of myocardial perfusion defects during chronic pacing (36). The most likely explanation of these pacing-induced changes in myocardial perfusion is redistribution in myocardial blood flow, adapting the changes in local myocardial workload, and probably mediated by local autoregulation (71, 72, 146). The increase in MBF during temporary AAI pacing after chronic DDDR pacing (VI) support, that the changes in MBF are mediated primarily by functional mechanisms rather than by structural changes.

A recent study of young patients with congenital complete heart block paced in the right ventricular apex for 10 years showed for the first time, that ventricular remodeling with thickening of the late activated posterior wall relative to the early activated septum occurs also in patients as a result of chronic ventricular desynchronisation (55). In that study, chronic ventricular pacing furthermore was associated with an increased left ventricular end-diastolic diameter and a decrease in cardiac output, confirming the detrimental effect of ventricular desynchronisation observed in the AAI/VVI (II) and AAIR/DDDR (VI, VII) trials. Also echocardiographic parameters of ventricular dyssynchrony were higher after 10 years of pacing (55). In the pacemaker population, almost 90% of the patients are 60 years or older when referred for their first pacemaker implantation (25), and the mean age of patients referred for pacemaker implantation due to SSS is approximately 75 years (II, VII) (48). The AAI/VVI and AAIR/DDDR trials document, that chronic ventricular desynchronisation causes ventricular dysfunction also in these elderly patients (II, VII). A longitudinal study of changes in wall thickness

or MBF during chronic pacing has never been done in this patient population.

ALTERNATIVE PACING SITES TO THE RIGHT VENTRICULAR APEX

It has been suggested, that changing the usual pacing site in the right ventricle from the apex to the outflow tract would be associated with a better function of the left ventricle because of a more “physiological” ventricular activation (148, 149). A recent meta-analysis comparing the haemodynamic effects of right ventricular outflow-tract and right ventricular apical pacing indicated a significant benefit of right ventricular outflow-tract pacing (150). In a randomised comparison between the two pacing modes in 24 patients with AV block, outflow-tract pacing was associated with less regional wall motion abnormalities, higher left ventricular ejection fraction, and a lower incidence of myocardial perfusion defects after 18 months of pacing (151). However, in a 3 months crossover study comparing haemodynamics and symptoms during right ventricular apical and right ventricular outflow tract pacing in patients with chronic atrial tachyarrhythmia, no differences were found between the two pacing modes (152). In another randomised cross-over trial of patients with chronic atrial fibrillation and left ventricular ejection fraction $\leq 40\%$, outflow-tract pacing did not improve quality of life, NYHA functional class, left ventricular ejection fraction, or 6 minute walking distance as compared with right ventricular apical pacing (153). At present time, although right ventricular outflow-tract pacing seems to improve acute and chronic haemodynamics as compared with apical pacing, no studies have demonstrated a benefit of right ventricular outflow-tract pacing on the clinical outcome of the patients.

Direct His-bundle pacing and left ventricular apical pacing has been found to improve haemodynamics in other studies (154, 155). However, no studies have demonstrated any clinically relevant improvements in patient outcome associated with changing the pacing site. For patients with severely compromised left ventricular ejection fraction, bundle branch block, and clinical heart failure, biventricular pacing has been found to improve haemodynamics as well as patient outcome (43, 156). In patients with depressed left ventricular function and chronic right ventricular apical pacing, upgrade to biventricular pacing may be beneficial (157-159), however, the data present on this problem are very limited. Any benefit of biventricular pacing in patients without left ventricular dysfunction remains to be proven.

Randomised studies with a long follow-up and sufficiently powered to evaluate the clinical outcome of the patients are needed before generally changing the clinical practice in single site right ventricular pacing.

CURRENT RECOMMENDATIONS FOR PACING MODE SELECTION IN SSS

The choice in patients with SSS is between AAIR and DDDR pacing modes. VVI(R) pacing mode should be used only for patients with chronic atrial fibrillation, and then in combination with anticoagulation. An algorithm for selecting patients for AAIR pacing is proposed in Figure 2. In case of manifest high-grade AV block, bundle branch block, pauses or bradycardia in atrial fibrillation, or concomitant carotid sinus syndrome, a DDDR pacemaker is recommended. The limits for the PQ interval as well as the intra-operatively measured Wenckebach block point ≥ 100 bpm are arbitrarily chosen, but tested in two prospective trials (I, VII).

Increasing evidence support the harmful effects of single-site right ventricular pacing (I, VII) (54, 55, 93). Therefore, in patients with SSS and without high-grade AV block who receive a DDDR pacemaker, the device should be programmed to reduce ventricular pacing, e.g. using a long AV delay or algorithms prolonging this delay. Programming a long AV delay ($>80\%$ ventricular sensing) has recently been shown to reduce the level of plasma brain natriuretic peptide (BNP) as compared with DDD pacing with a short AV delay

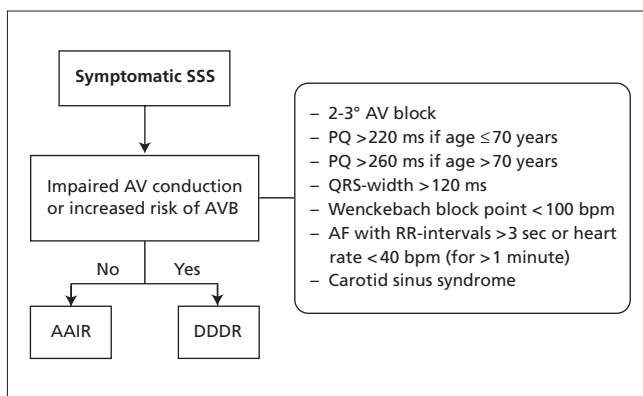


Figure 2. Current recommendations for pacing mode selection in patients with SSS. Intra-operatively, the atrium is paced at 100 bpm to ensure a Wenckebach block point ≥ 100 bpm. For abbreviations see list on page 6.

and $>80\%$ ventricular pacing in patients with SSS and concomitant hypertension or mild valvular disease (160). It should however be kept into mind, that programming a very long AV delay may increase the risk of pacemaker mediated tachycardia (161).

FUTURE STUDIES

DANPACE

A large-scale, randomised controlled multi-centre trial (DANPACE) has been initiated in Denmark to test the hypothesis “AAIR pacing is superior to DDDR pacing in patients with SSS”. The main endpoint is all-cause mortality, and more than 1.100 patients have been included at present time. The goal is inclusion of 1.900 patients, to be followed for in mean 5.5 years. Secondary endpoints are atrial fibrillation, thromboembolism, heart failure, quality of life, and development of AV block in the AAIR group. The location of lead implants in the atrium and the right ventricle as well as pacemaker telemetry data are recorded prospectively. The results of the DANPACE trial are expected to answer whether AAIR or DDDR pacing should be preferred as first choice treatment in patients with isolated SSS and to increase our present knowledge on the clinical consequences of the potential harmful effects of single-site right ventricular pacing.

PACING ALGORITHMS AND PACING SITE

New pacemaker algorithms have been suggested (74) and developed (162) and more can be expected to come aiming to minimize ventricular pacing in patients with DDDR pacemakers and preserved AV conduction. Such algorithms should basically function in the AAI(R) mode and only switch to DDD(R) mode in case of significant pauses in the ventricular action. When these algorithms are proven to be effective, the role of the AAI(R) pacemaker can be put into question. Very recently, the ability of such algorithms to reduce ventricular pacing has been reported (163). However, clinical tests of pacemakers using these new algorithms have to be performed in appropriately large and well-selected patient populations followed for a period of years before recommendations should be changed from the present. Follow-up has to include not only recording of percentage of paced beats from the pacemaker telemetry and ECG monitoring, but also clinical endpoints as atrial fibrillation and heart failure. Most appropriately should the clinical evaluations of new pacemaker algorithms include comparisons with a control group, and allocation to the two groups be randomised. In the CTOPP trial, a total of 15% and 25% of the patients randomised to physiological pacing were receiving VVI(R) pacing after 2 and 8 years, respectively (87). Are these proportions similar using pacemakers with the new algorithms to reduce ventricular pacing? In patients with SSS, primarily implanted with an AAIR pacemaker, the proportion of patients who ends up with VVI(R) pacing is lower (V).

In selected patient populations, multi-site atrial pacing has been reported effective in reducing the incidence of atrial fibrillation (164, 165). However, the benefit of multi-site atrial pacing is still controversial (166), and is not used in many centres at present time. Also the implantation of the atrial lead in the septal region has been claimed to reduce atrial fibrillation as compared with lead implantation in the right atrial appendage (167). A recent randomised controlled trial testing that hypothesis in patients with SSS receiving DDDR pacemakers found no difference in occurrence of atrial fibrillation between atrial appendage pacing and septal pacing (168). At present time, no specific implantation site of the atrial lead can be recommended to reduce the incidence of atrial fibrillation. The only pacing mode, which reproducibly has been found superior in reducing atrial fibrillation in patients with SSS, is AAI(R) pacing (I, III, VII) (130, 160). Studies of the effects of different atrial pacing sites must be performed in sufficiently powered, randomised trials before clinical consequences of their results can be taken. The pacemaker telemetry data should be used in detecting atrial fibrillation in future studies of different pacing modes (95, 96, 169, 170).

The majority of pacemaker patients need ventricular pacing. As discussed previously, any substantial benefit of implanting the ventricular lead in the right ventricular outflow tract, at the His-bundle, at the left ventricular apex, or in another location instead of in the right ventricular apex remains to be proven. Theoretically, biventricular pacing may prevent the ventricular desynchronisation caused by single-site right ventricular pacing. However, at present time no data are available supporting that. Long-term randomised studies in sufficiently large patient populations are necessary to detect clinically important differences between pacing sites. Echocardiography will still be an important tool in these studies. To increase data validity, more precise echocardiographic methods, e.g. three-dimensional echocardiography should be used in conducting such trials in the future. Furthermore, new echocardiographic techniques such as tissue-Doppler imaging may be helpful in studying the asynchrony of ventricular contraction with different pacing sites.

SUMMARY AND CONCLUSIONS

Sick sinus syndrome (SSS) is the second most common reason for pacemaker implantation, comprising approximately one third of the total population undergoing primary pacemaker implantation. The majority of patients with SSS have no additional AV block or bundle branch block. In those patients, the bradycardia-related symptoms can be successfully treated with any pacemaker, a single chamber pacemaker with the lead implanted in the right atrium (AAI) or in the right ventricle (VVI) or a dual chamber pacemaker with leads in both these chambers (DDD). Although effective in preventing bradycardia, the different pacing modes may be associated with different morbidity and mortality, as indicated by observational studies. Therefore, one of the most important issues in the treatment of SSS is selection of the best pacing mode in these patients. AAI pacing preserves both the AV synchrony and the normal ventricular activation pattern, but if AV block occurs, a re-operation with implantation of a ventricular lead and a new pacemaker is necessary. DDD pacing also preserves the AV synchrony, but disrupts the ventricular activation pattern, whereas VVI pacing disrupts both the AV synchrony and the ventricular activation pattern. The main advantage of both DDD and VVI pacing is to confer protection against bradycardia if AV block occurs. The incidence of AV block in patients with SSS has been reported very differently from <1% per year to 4.5% per year in prior studies. The present study aimed to evaluate the clinical consequences of pacing mode selection in patients with SSS.

A total of 225 consecutive patients with SSS were randomised to AAI (n = 110) or VVI pacing, and the present study presents the results of long-term follow-up to in mean 5.5 years. Total and cardiovascular mortality as well as atrial fibrillation and thromboembolism were significantly reduced in the AAI group. Congestive heart

failure was more common in the VVI group than in the AAI group, and this finding was accompanied by a decrease in left ventricular function and an increased left atrial dilatation. Atrio-ventricular conduction remained stable during long-term follow-up, and AV block occurred in only 4/110 patients in the AAI group (0.6% annual incidence). It therefore seems conclusive, that AAI pacing is superior to VVI pacing in patients with SSS. An observational study was done in 399 consecutive patients treated with AAI/AAIR pacemaker in our institution and followed for in mean 4.6 years to evaluate the incidence of AV block. The risk of high-grade AV block was found to be 30/399 patients or 1.7% per year.

In the first randomised comparison of AAIR and DDDR pacing, a total of 177 consecutive patients with SSS were assigned to treatment with one of three pacemaker modalities: AAIR pacemaker (n = 54), DDDR pacemaker programmed with a short, dynamic AV delay (n = 60) (DDDR-s) or DDDR pacemaker programmed with a fixed long AV delay (n = 63) (DDDR-l). Mean follow-up was 2.9 years. The primary endpoints were changes in left atrial diameter and left ventricular size and function (LVFS) measured by echocardiography. In the AAIR group no significant changes were observed in left atrial diameter or in LVFS from baseline to last follow-up. In both DDDR groups, left atrial diameter increased significantly, and in the DDDR-s group, LVFS decreased significantly from baseline to last follow-up. Atrial fibrillation occurred significantly less common in the AAIR group, also after adjusting for brady-tachy syndrome at time of randomisation. Mortality, thromboembolism and heart failure did not differ between groups. In a subset of patients included in the trial of AAIR versus DDDR pacing, chronic DDDR pacing was found to cause a reduction in inferior, septal, and global mean myocardial blood flow accompanied by a reduced left ventricular ejection fraction. Both the reductions in myocardial blood flow and in left ventricular ejection fraction were reversible when the normal ventricular activation and contraction was restored despite 22 months of permanent ventricular pacing. The most likely explanation of these pacing-induced changes in myocardial perfusion is redistribution in myocardial blood flow, adapting the changes in pacing-induced local myocardial workload.

Conclusions: In patients with SSS:

1. AAI pacing is superior to VVI pacing due to a significantly higher survival, less atrial fibrillation, and fewer thromboembolic events after long-term follow-up.
2. VVI pacing increases the incidence of congestive heart failure and is associated with a decrease in left ventricular function and an increased dilatation of the left atrium as compared with AAI pacing.
3. Arterial thromboembolism is common and primarily associated with atrial fibrillation and with treatment with VVI pacing.
4. Atrioventricular conduction remains stable during long-term follow-up.
5. After implantation of an AAI pacemaker, the incidence of atrio-ventricular block requiring implantation of a ventricular lead is approximately 1.7% per year.
6. Chronic DDDR pacing reduces the myocardial blood flow and the left ventricular function as compared with temporary AAI pacing.
7. DDDR pacing, but not AAIR pacing, causes left atrial dilatation and decreased left ventricular function.
8. Atrial fibrillation is significantly less common during AAIR pacing than during DDDR pacing.

Abbreviations

AAI(R)	Demand single chamber atrial pacing, (R) indicates rate-adaptive pacing
AAIR/DDDR	Danish trial of AAIR vs. DDDR pacing
AAI/VVI	Danish trial of AAI vs. VVI pacing
AV block	Atrio-ventricular block
AV delay	Programmed atrioventricular delay in a DDD pacemaker
bpm	Beats per minute
Brady-tachy syndrome	Bradycardia and at least one documented episode of supraventricular tachycardia
CTOPP	Canadian Trial of Physiologic Pacing
DAVID	The Dual Chamber and VVI Implantable Defibrillator Trial
DDD(R)	Demand dual chamber pacing, (R) indicates rate-adaptive pacing
DDDR-1	DDDR pacing with a fixed, long AV delay
DDDR-s	DDDR pacing with a dynamic, short AV delay
ICD	Implantable Cardioverter Defibrillator
LVEF	Left ventricular ejection fraction
LVFS	Left ventricular fractional shortening
MADIT II	The Multicenter Automatic Defibrillator Trial II
MBF	Myocardial blood flow
MOST	Mode Selection Trial in Sinus-Node Dysfunction
NYHA	New York Heart Association functional class
Pac-A-Tach	Pacemaker Atrial Tachycardia trial
PASE	Pacemaker Selection in the Elderly trial
PET	Positron emission tomography
SSS	Sick sinus syndrome
VVI(R)	Demand single chamber ventricular pacing, (R) indicates rate-adaptive pacing

This thesis is based on the following publications:

- I. Andersen HR, Nielsen JC, Thomsen PEB, Thuesen L, Mortensen PT, Vesterlund T & Pedersen AK. Prospective randomised trial of atrial versus ventricular pacing in sick sinus syndrome – long-term follow-up. *Lancet* 1997; 350: 1210-1216.
- II. Nielsen JC, Andersen HR, Thomsen PEB, Thuesen L, Mortensen PT, Vesterlund T & Pedersen AK. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single chamber atrial or ventricular pacing. *Circulation* 1998; 97: 987-995.
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sinus syndrome. Echocardiographic and clinical outcome. *J Am Coll Cardiol*, 2003; 42: 614-623.

Papers II and VI were included in my PhD thesis “Optimal pacing mode in patients with sick sinus syndrome, on the consequences of implanting a ventricular lead”, 2000, Aarhus University.

The papers are referred to in the text by their Roman numeral in parenthesis.

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