

## “What & How” About Implantation of AAI/R, DDD/R, and VVI/R Pacemakers

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Because of new development of active and passive fixation leads that greatly decrease the possibility of dislodgment, the transvenous approach for permanent cardiac pacing has virtually replaced thoracotomy implantation and is generally performed by cardiologists in the catheterization laboratory. This is an overview of selected topics regarding single- and dual-chamber pacemaker implantation (AAIR, VVIR, and DDDR). Transvenous implantation of a pacemaker is typically an easy and safe procedure if the cardiologist pays careful attention to perioperative considerations, which are patient preparation, venous access, site of implantation, lead configuration, alternate pacing sites in the atrium and ventricle, electrical parameter measurements, lead anchoring and final connection, site of pacemaker pocket, and potential complications. However, cardiologists have been challenged by the increasing complexity of programming of pacemakers. In particular, atrioventricular delay (AV delay), mode switch, and rate response need to be carefully programmed to maximize benefits of pacemaker therapy.

**Key Words:** Pacemaker • AV delay • Mode switch • Rate response

A permanent pacing system usually consists of the pacemaker generator and one to three leads that are attached to the endocardial or epicardial surface of the heart. The improvement of technology in leads and generators has simplified the implantation procedure so much that now cardiologists virtually perform all pacemaker implantation in the catheterization laboratory. This is an overview of selected topics regarding single- and dual-chamber pacemaker implantation (AAIR, VVIR, and DDDR) as well as complex programming of the pacemaker for bradycardia therapy.

### Patient preparation

Transvenous pacemaker implantation is usually performed in the catheterization laboratory, which should have all standard devices and equipment and should maintain aseptic standards adopted in a surgical environment. Although the implantation of a pacemaker is considered a minor surgical procedure, patients should be prepared as though they are to undergo a major surgical procedure. Because most cases of pacemaker infection are a result of perioperative contamination of skin flora bacteria, the site of incision should be thoroughly scrubbed preferably one day before the procedure as well as just before the procedure in the catheterization laboratory. Although the prophylactic use of antibiotics before and immediately after implantation remains controversial, results from one meta-analysis suggest it helps in reducing the incidence of potentially serious infection complications.<sup>1</sup> Because the veins may be less extended in the recumbent patient with normal venous pressure even after just an overnight fasting, proper

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hydration of the patient before the procedure will facilitate venous puncture.

### Venous access and site of implantation

When deciding on a site to implant the pacemaker, the cardiologist should consider the individual needs and characteristics of each patient, including his or her concomitant medical conditions, hobbies or occupation, right- or left-handedness, anomalous venous drainage, infection or skin disorders, the site of a recent or current pacer or central line and patient personal preference for the site of implantation.<sup>2</sup>

Leads are usually introduced through the subclavian, cephalic, or axillary veins but on rare occasions through the internal or external jugular and iliofemoral veins, and they are positioned to the right heart for permanent pacing. The pacemaker is generally placed near the site of venous entry just above or under the muscle layer to minimize potential erosion.

The subclavian vein approach remains popular because it is more simply performed than other approaches. However, this subclavian approach could result in lead fracture, as some have reported happening as a result of entrapment of the lead by the costoclavicular ligament and the subclavian muscle.<sup>3,4</sup> The lead should be introduced into the subclavian vein laterally because a very medial approach also predisposes the lead to crush injury between the clavicle and the first rib. A thorough understanding of the course of the subclavian and axillary

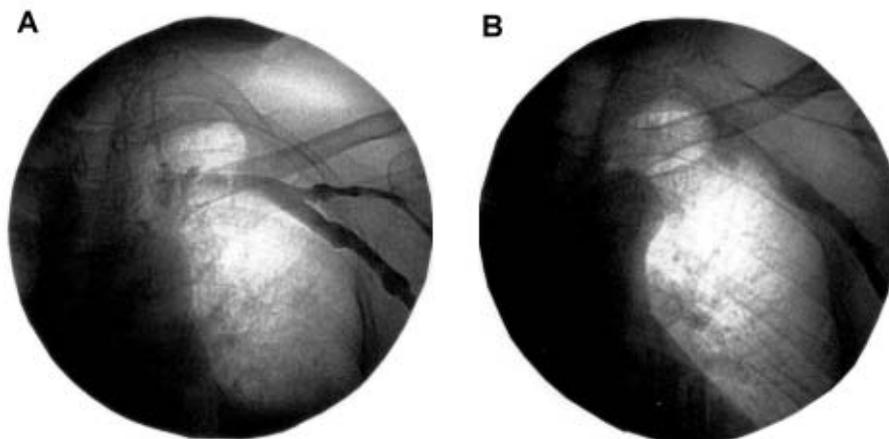
veins helps to reduce these potential complications (Figure 1).

A variation in the anatomy of subclavian vein rarely occurs but can increase the risk of complications with repeated additional blind needle punctures. Thus, venography is strongly recommended in patients, provided that they have not been found to be allergic to contrast medium, because it will show the course of subclavian and axillary and cephalic veins, and thus serve as a guidance for venous access.<sup>5</sup> Because the axillary and cephalic veins are extrathoracic, lead entry into these veins essentially avoids the potential risks of lead crush and pneumothorax or hemothorax (Figure 1).

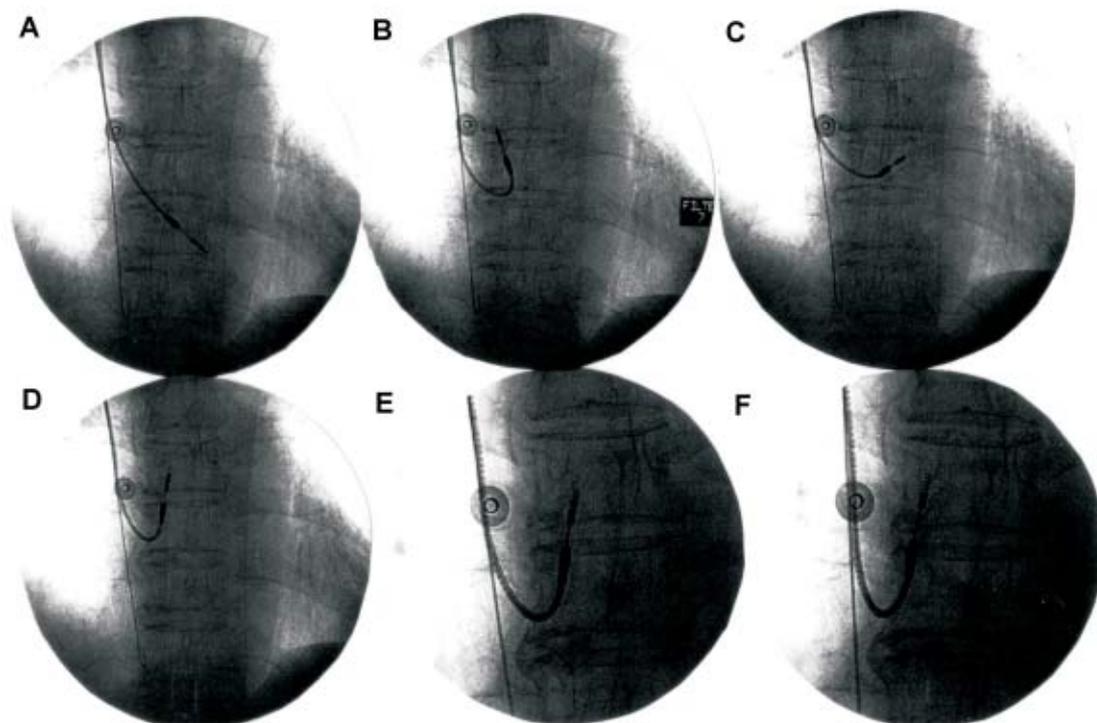
The additional benefit of contrast venography before venipuncture is to determine if the patient has a persistent left superior vena cava with drainage into the coronary sinus, which may complicate lead positioning. In patients with a persistent left superior vena cava, right-sided contrast venography should also be performed to exclude a rare coexistence of absence of the right superior vena cava. In patients without a right-sided superior vena cava, an epicardial approach may be taken as an alternative.

### Atrial lead placement

The atrial appendage is the most popular atrial-pacing site because it provides a stable lead position. Placement of the atrial lead to the appendage can be achieved easily using a passive or active fixation lead with a pre-formed



**Figure 1.** The course of the axillary and subclavian veins with the presence (A) or absence of the cephalic vein (B). The subclavian vein becomes the axillary vein at the lower margin of the first rib.



**Figure 2.** Placement of a preformed J and retractable atrial active fixation lead with a screw-in electrode. The lead should be straightened and pulled into the low right atrium first (A) and the guide wire withdrawn to form a J curve (B) and then pulled back slowly. Straightening of the J with gentle traction confirms entry into the base of the appendage (C). The lead is advanced to the tip of the appendage with further gentle manipulation (D). The view is magnified fluoroscopically (E) and the lead screw is extended out (F) successfully, as evidenced by closing the space of the electrode tip.

J configuration (Figure 2). In patients without an appropriate appendage, usually as a result of previous cardiac surgery, the cardiologist can use other positions within the right atrium, including the septum, coronary sinus, and Bachmann's bundle. Placement at these sites usually requires an active fixation electrode. Appropriate and adequate lead fixation can be confirmed by gentle traction or an increase in lead impedance after lead fixation.<sup>6</sup>

### Potential benefits of alternate atrial pacing sites

Pacing at the alternate atrial sites may shorten the total atrial conduction time and interatrial conduction delay as compared to pacing from the right atrial appendage.<sup>7-12</sup> It has been reported that recurrence of atrial fibrillation in patients with paroxysmal atrial fibrillation is less with septal pacing,<sup>11</sup> Bachmann's bundle pacing,<sup>12</sup> or with dual-site right atrial pacing (the appendage and

coronary sinus ostium)<sup>13,14</sup> when compared to high right atrial pacing used alone. Combining with antiarrhythmic drug therapy, however, high right atrial pacing and coronary sinus ostial pacing have similar efficacy in reducing recurrence of atrial fibrillation, although the prevention of atrial fibrillation can be further enhanced by pacing at both sites.<sup>14</sup> One recent study using biatrial pacing at the right atrium and distal coronary sinus demonstrated benefits in patients with drug-refractory atrial tachyarrhythmias.<sup>15</sup> Thus, permanent pacing of the left atrium at the distal coronary sinus can also be considered if needed.

### Atrial pacing algorithm for prevention of atrial tachyarrhythmias

Advanced atrial pacing algorithms to prevent paroxysmal atrial tachyarrhythmias have been developed, but studies to examine the efficacy of these algorithms have yielded inconsistent results.<sup>16,17</sup> One recent study

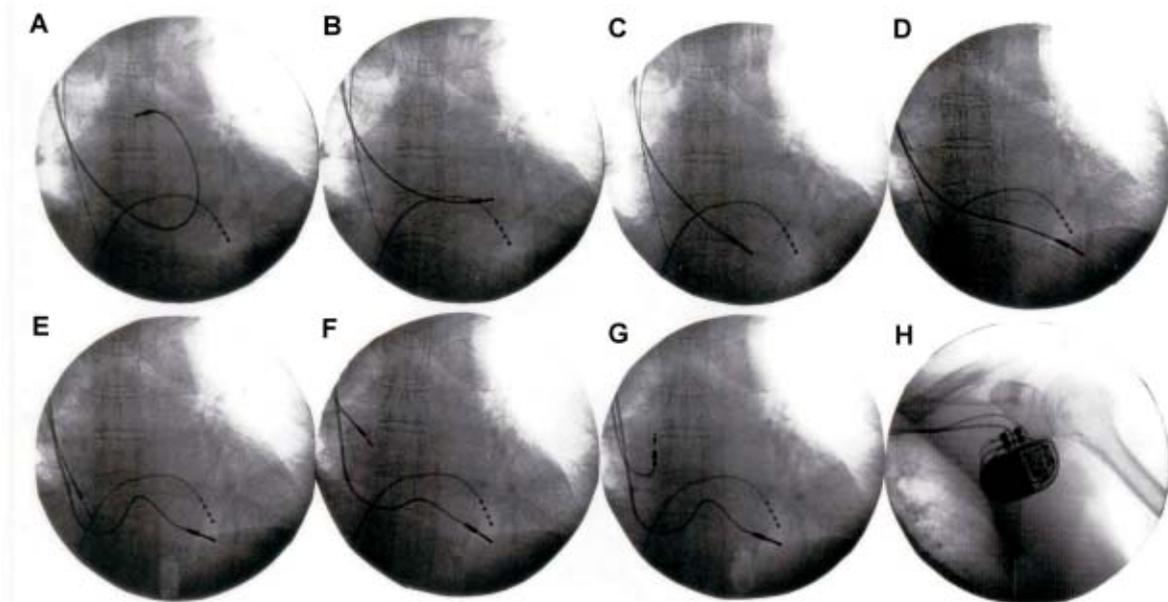
showed that combination of three atrial prevention pacing algorithms, including atrial overdrive pacing to maintain consistent atrial activation sequence, a temporary atrial overdrive mode to avoid long-short interval following a premature atrial beat, and post mode-switch transient overdrive pacing at a higher rate to inhibit early recurrence of atrial tachyarrhythmias following termination of tachycardic episode, did not decrease device-recorded atrial tachycardia/fibrillation frequency and burden in bradycardic patients with septal or nonseptal pacing.<sup>18</sup> However, patients with septal leads had fewer symptomatic atrial tachyarrhythmic episodes with algorithms on versus off. It appears that current sophisticated atrial pacing algorithms have a modest role only in the prevention of paroxysmal atrial tachyarrhythmias.

### Ventricular lead placement

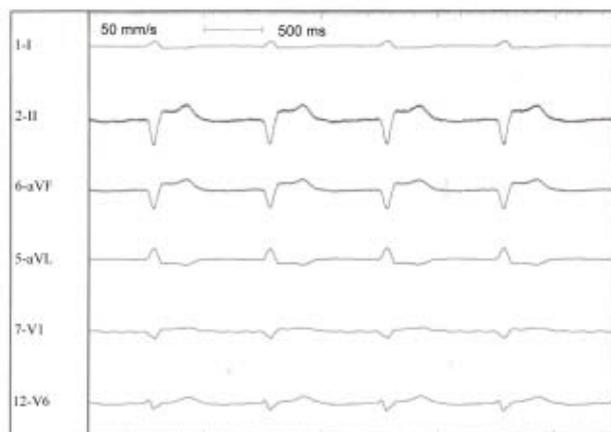
With a passive or active fixation lead, ventricular pacing leads are generally placed in the right ventricular apex, which, like the atrial appendage, provides an easy placement site with long-term stability. To ensure suc-

cessful placement in the right ventricle, the lead should be initially introduced into the right ventricular outflow tract, and then slowly withdrawn from it, allowing the lead tip to fall toward the right ventricular apex. With stylet in place, the lead can be advanced further to the apex (Figure 3). This lead advancement needs to be carried out gently because the apex could be thin and easily perforated.

To ensure that the lead is placed at the right ventricular apex and not inadvertently placed into the left ventricle, the cardiologist should check 12-lead ECG and the position of the lead with different fluoroscopic views in the catheterization laboratory after finishing pacemaker implantation procedure. It should be noted that right ventricular apex pacing usually produces a left superior axis. However, the axis may also be in the right superior quadrant, where it causes leads I, II, and III to be negative and lead aVR to show a largest positive deflection. A typical left bundle branch block pattern in the left precordial leads may not present and all leads show a QS pattern. Therefore, during implantation procedure, multilead ECG should be monitored



**Figure 3.** Placement of a ventricular lead followed by an atrial lead in the implantation of a dual-chamber pacemaker: The ventricular lead is first introduced into the pulmonary artery via the right ventricular outflow tract (A). The lead is withdrawn and falls toward the right ventricular apex (B) and then at the diaphragmatic surface with further gentle withdrawal (C). Gently advance the lead into the apex (D). A deep breath generally facilitates the advancement. The atrial lead should be positioned into the right atrial appendage without entanglement with the ventricular lead (E, F, G). Both leads are securely placed underneath the generator without acute angulations (H).



**Figure 4.** ECG monitoring during right ventricular apex pacing. Lead V6 does not have a typical R wave in left bundle block pattern, but the R waves in leads I and aVL confirm the electrode position in the right ventricle.

with ventricular apex pacing during implantation procedure (Figure 4).

### Dual chamber pacemaker implantation

Implantation of a dual-chamber pacemaker generally involves first positioning a ventricular lead followed by placement of an atrial lead, because ventricular stimulation is usually more important than atrial stimulation (Figure 3). Both leads can be introduced via the subclavian, axillary, or cephalic veins. Separation of the two leads without mechanical interference should be confirmed by examining lead positions from different fluoroscopic projections.

### Optimal right ventricular pacing site

Results from clinical trials comparing AAI versus VVI pacing in patients with sinus node dysfunction have demonstrated that ventricular pacing is significantly associated with decreased survival rate, more atrial fibrillation, higher thromboembolic events, and more heart failure than either with AAI pacing or physiological pacing.<sup>19,20</sup> DDDR pacing improves quality of life<sup>21,22</sup> and reduces the risk of atrial fibrillation<sup>21,22</sup> but provides little or no benefit in the prevention of stroke or overall cardiovascular death over VVIR pacing.<sup>22,23</sup> One recent clinical trial in patients with sick sinus syndrome and normal baseline QRS duration also showed that right ventricular apex pacing, even when AV syn-

chrony was preserved, increased the risk of heart failure hospitalization and atrial fibrillation.<sup>24</sup> Thus, right ventricular apex pacing may have a deleterious effect on ventricular function. This hazard was supported by the results of another recent randomized study comparing atrial and dual-chamber pacing in patients with sick sinus syndrome.<sup>25</sup> In that study, DDDR pacing with a short AV delay increased left atrial diameter and decreased left ventricular systolic function, but AAIR pacing did not change left atrial or ventricular diameters or left ventricular systolic function, and it resulted in a fewer instances of atrial fibrillation.

A review of these above-mentioned studies clearly suggested that the apex may be a less than ideal position for right ventricular pacing. The mechanisms of the adverse effects associated with right ventricular apex pacing are probably related to ventricular desynchronization and compromised regional and global mean myocardial blood flow, which might lead to reduced left ventricular ejection fraction.<sup>26,27</sup>

Alternate right ventricular pacing sites, such as the inlet, infundibular, ventricular outflow tract, and apical septal areas, have been attempted, but the results of pacing at these sites have been inconsistent. For example, Victor et al.<sup>28</sup> reported no systemic improvement or hemodynamic benefit after three months of right ventricular outflow pacing as compared to right ventricular apex pacing. In contrast, there are reports of acute<sup>29</sup> hemodynamic benefits and beneficial long-term<sup>30</sup> effects on myocardial perfusion and functions in patients with right ventricular outflow pacing as compared to ventricular apex pacing. On the other hand, while right ventricular outflow pacing and dual-site right ventricular pacing were found to have shortened QRS duration, they did not consistently improve quality of life or other clinical outcomes as compared with RVA pacing in patients with congestive heart failure, left ventricular dysfunction, and chronic atrial fibrillation.<sup>31</sup>

The inconsistent results and controversy over the ventricular pacing at various sites are probably related to different lead locations, physiological or non-physiological pacing, setting of AV delay, baseline ventricular function, QRS duration, and patients' underlying diseases. More studies are needed to determine the best site for right ven-

tricular pacing. Permanent and direct His-bundle pacing<sup>32</sup> has been reported but can be technically difficult and is limited to a subset of patients with normal His-Purkinje activation. Until further studies prove differently, at present, the right ventricular apex may still be considered an appropriate site for right ventricular pacing.

### **Electrical parameters and lead configuration**

Measurements of pacing and sensing thresholds and impedance with unipolar and bipolar lead configurations as well as evaluation of antegrade Wenckebach-block point should be performed during implantation.

For all practical purposes, currently available unipolar and bipolar electrodes are interchangeable in terms of stimulation threshold and electrogram sensing.<sup>33</sup> Unipolar pacing is more likely to result in extracardiac stimulation, detection of myopotentials, far-field signals, and electromagnetic interference. However, unipolar leads have smaller diameter and may be preferred in patients with a small stature. In addition, unipolar leads are simple in design and may have increased durability.

### **Generator insertion and pacemaker pocket**

After confirming the stability of lead placement by having the patient cough and do deep breathing and after tying leads to the underlying tissue, the electrical parameters and lead positions should be rechecked. The generator should be placed in the pocket with marking face up, and the redundant leads should be arranged underneath the generator without acute angulations (Figure 3). Electrical parameters and the lead course should be rechecked before and after closing the incision wound. The pacemaker pocket is usually placed in the pectoral region but may be placed in the retro-mammary area in female patients for cosmetic consideration.

### **Selected topics of pacemaker programming**

Modern pacemaker programming is increasingly complex, and appropriate programming is a challenging and time-consuming task. Preservation of normal ventricular activation and optimal AV delay are required for proper cardiac performance. Because paroxysmal atrial tachyarrhythmias frequently occur in patients with sinus node dysfunction, appropriate mode switch programming is

important to reduce inappropriate rapid ventricular tracking in dual-chamber pacing mode. Adequate rate response with rate adaptive pacing greatly benefits patients with chronotropic incompetence. The principles of programming of AV delay, mode switch, and rate adaptive pacing will be specifically discussed below. A comprehensive review of pacemaker programming is beyond the scope of this paper.

### **AV delay**

The optimal values of the AV delay vary greatly among patients and depend on several physiological and pathological factors; they cannot be determined from the surface ECG. Doppler echocardiography is the best way to determine an optimal AV delay that produces the best stroke volume and cardiac output for each individual. In patients with an implanted DDD pacemaker, the AV delay may be optimal if the end of A wave on transmitral flow coincides with complete closure of the mitral valve.<sup>34</sup>

A simple formula of optimal AV delay that predicts completion of end-diastolic filling just prior to ventricular contraction has been proposed.<sup>35</sup> The optimal AV delay setting should equal the slightly prolonged AV delay minus the interval between the end of the A wave and complete closure of the mitral valve at the AV delay setting.

The difference of AV intervals during atrial sensing and pacing and progressive shortening of the AV interval with rapid heart rate (rate adaptive AV interval) also need to be understood, and AV delay should be programmed accordingly.

For patients with intact or intermittent AV conduction, fixed AV delay may increase the chances of inappropriate ventricular pacing, resulting in reduced ventricular function and increased incidence of heart failure and atrial fibrillation.<sup>24,25</sup> The adverse outcome increases with increasing cumulative time spent in ventricular pacing. Therefore, preservation of normal ventricular activation by intrinsic conduction is desirable to maximize cardiac performance.

Facilitation of normal AV conduction can be achieved by programming AV delay hysteresis. After a set number of consecutive ventricular pacing, the AV delay can be prolonged for one cycle. The AV delay will remain prolonged or revert to the programmed value depending on whether an intrinsic event is sensed or not. Adaptive

search AV is also available in the Medtronic Kappa 900 series pacemaker. When search AV is programmed to Adaptive Mode, the pacemaker continuously monitors the AV conduction time and adjusts a shorter or longer AV delay to permit intrinsic conduction.

### Mode switch

Late models of dual-chamber pacemakers are usually equipped with a mode switch program to alleviate symptoms related to ventricular tracking of rapid atrial rate and these models have generally been preferred by most patients.<sup>36</sup> Mode switch algorithm should be programmed to have rapid detection<sup>37</sup> with appropriate sensitivity and specificity and without mode switch oscillations due to undersensing. A quick AV resynchronization after mode switch is also desirable. Accurate record of time, date and duration of arrhythmia episodes also are helpful for the fine-tuning of the programming.

### Rate adaptive pacing

Rate-adaptive pacing is very important in patients with chronotropic incompetence because heart rate increases alone can nearly triple cardiac output in response to increased metabolic demands. Activity and minute ventilation sensors are the most popular rate response sensors available on the market. The former detects physical movement and increases the rate according to the level of activity while the latter measures the changes in respiration rate and tidal volume via transthoracic impedance reading. Physicians who manage chronotropic incompetent patients need to understand the advantages and limitations of each type of sensor and adjust the programmable rate response parameters to simulate normal chronotropic responsiveness. Despite autocalibration or autoprogramming of the sensor in some pacemaker models, every patient with a pacemaker programmed to a rate-adaptive pacing mode must be assessed functionally to determine whether there is appropriate or inappropriate functional response to the sensor.<sup>38,39</sup>

Optimal rate-adaptive pacing requires exercise testing for functional assessment. For patients who are physically active, a standard chronotropic exercise protocol can be adopted and relation between expected sinus rate and metabolic demand can be reasonably predicted.<sup>40</sup> For patients

who are sedentary most of the time, a casual and/or brisk walking in the hallway can be performed with expected heart rates of 85-90 beats/min and 100-110 beats/min, respectively. These expected heart rates serve as a guide for appropriate rate responses during different level of physical activities. Trending plots and sensor histograms obtained after a patient exercises are helpful in assessing the effectiveness of rate-adaptive programming. The rate response should be reassessed as often as needed, particularly if the patient complains of exertional fatigue, chest discomfort, or sudden changes in heart rate.

### Summary

Transvenous pacemaker implantation involves a number of perioperative considerations regarding patient preparation, lead configuration, site of implantation and venous access, alternate pacing sites, electric parameter measurements, lead anchoring and final connection, site of pacemaker pocket, and potential complications. Physicians need to be familiar with the increasingly complex pacemaker programming related to single- and dual-chamber pacing, particularly those related to optimal AV delay, preservation of intrinsic ventricular activation, mode switch, and rate adaptive pacing.

### REFERENCES

1. Costa AD, Kirkorian G, Cucherat M, et al. Antibiotics prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation* 1998;97:1796-801.
2. Midei M, Brinker J. Pacemaker implantation. In: Ellenbogen KA, Ed. *Cardiac pacing*. Boston: Blackwell Scientific Publications, 1992:211-62.
3. Aggarwal RK, Connelly DT, Ray SG. Early complications of permanent pacemaker implantation: no difference between dual and single chamber systems. *Br Heart J* 1995;73:571-5.
4. Roelke M, O'Nunain SS, Osswald S, et al. Subclavian crush syndrome complicating transvenous cardioverter defibrillator systems. *PACE* 1995;18:973-9.
5. Ramza BM, Rosenthal L, Hui R, et al. Safety and effectiveness of placement of pacemaker and defibrillator leads in the axillary vein guided by contrast venography. *Am J Cardiol* 1997;80:892-6.
6. Roelke M, Bernstein AD, Parsonnet V. Serial lead impedance measurements confirm fixation of helical screw electrodes during pacemaker implantation. *PACE* 2000;23[Pt. I]:488-92.

7. Papageorgiou P, Anselme F, Kirchhof CJ, et al. Coronary sinus pacing prevents induction of atrial fibrillation. *Circulation* 1997; 96:1893-8.
8. Spencer WH, Zhu WX, Markowitz T, et al. Atrial septal pacing: a method for pacing both atria simultaneously. *PACE* 1997;20: 239-45.
9. Katsivas A, Manolis AG, Lazaris E, et al. Atrial pacing to synchronize atrial depolarization in patients with delayed interatrial conduction. *PACE* 1998;21[Pt. II]:2220-5.
10. Roithinger RX, Abou-Harb M, Pachinger O, et al. The effect of the atrial pacing site on the total atrial activation time. *PACE* 2001;24:316-22.
11. Hermida JS, Carpentier C, Kubala M, et al. Atrial septal versus atrial appendage pacing: feasibility and effects on atrial conduction, interatrial synchronization, and atrioventricular sequence. *PACE* 2003;26[Pt.I]:26-35.
12. Bailin SJ, Adler S, Giudici M. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. *J Cardiovasc Electrophysiol* 2001;12:912-7.
13. Saksena S, Prakash A, Ziegler P, et al. Improved suppression of recurrent atrial fibrillation with chronic dual-site right atrial pacing and antiarrhythmic drug therapy. *JACC* 2002;40:1140-50.
14. Delfaut P, Saksena S, Prakash A, et al. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. *JACC* 1998;32:1900-8.
15. D'Allones GR, Pavin D, Leclercq C, et al. Long-term effects of biatrial synchronous pacing to prevent drug-refractory tachycardia: a nine-year experience. *J Cardiovasc Electrophysiol* 2000;11:1081-91.
16. Carlson MD, Gold MR, Ip J, et al. Dynamic overdrive pacing decreases symptomatic atrial arrhythmia burden in patients with sinus node dysfunction. *Circ* 2001;104:II-383.
17. Israel CW, Hugl B, Unterberg C, et al. Pace-termination and pacing for prevention of atrial tachyarrhythmias: Results from a multicenter study with an implantable device for atrial therapy. *J Cardiovasc Electrophysiol* 2001;12:1121-8.
18. Padeletti L, Püferfellner H, Adler SW, et al. Combined efficacy of atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial tachyarrhythmia. *J Cardiovasc Electrophysiol* 2003;14:1189-95.
19. Andersen HR, Nielsen JC, Thomsen PEB, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;350: 1210-6.
20. Nielsen JC, Andersen HR, Thomsen PEB, et al. 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;97:987-95.
21. Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. *N Engl J Med* 1998;338:1097-104.
22. Lamas GA, Lee KL, Sweeney MO, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;346:1854-62.
23. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiological pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med* 2000;342:1385-91.
24. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circ* 2003;107:2932-7.
25. Nielsen JC, Krietensen L, Andersen HR, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome. echocardiographic and clinical outcome. *JACC* 2003;42:614-23.
26. Nielsen C, Böttcher M, Nielsen TT, et al. Regional myocardial flow in patients with sick sinus syndrome randomized to long-term single atrial or dual chamber pacing: effect of pacing mode and rate. *JACC* 2000;35:1451-61.
27. Schwaab B, Fröhlig G, Alexander C, et al. Influence of right ventricular stimulation site on left ventricular function in atrial synchronous ventricular pacing. *J Am Coll Cardiol* 1999;33: 317-23.
28. Victor F, Leclercq C, Mabo P, et al. Optimal right ventricular pacing site in chronically implanted patients: a prospective randomized crossover comparison of apical and outflow tract pacing. *J Am Coll Cardiol* 1999;33:11-9.
29. De Cock CC, Meyer A, Kemp O, et al. Hemodynamic benefits of right ventricular outflow tract pacing in comparison with right ventricular apex pacing. *PACE* 1998;21:536-41.
30. Tse HF, Yu C, Wong KK, et al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *JACC* 2002;40:1451-8.
31. Stambler BS, Ellenbogen KA, Zhang X, et al. Right ventricular outflow versus apical pacing in pacemaker patients with congestive heart failure and atrial fibrillation. *J Cardiovasc Electrophysiol* 2003;14:1180-6.
32. Deshmukh P, Casavant DA, Romanynshyn M, et al. Permanent, direct His-bundle pacing, a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; 101:869-77.
33. Furman S. Basic concepts. In: Furman S, Hayes DL, Holmes DR, eds. A practice of cardiac pacing. 3<sup>rd</sup> ed. Mount Kisco, New York: Futura Publishing Company, Inc.,1993:1-88.
34. Ritter P, Dib JC, Mahaux V, et al. New method for determining the optimal atrioventricular delay in paced in DDD mode for complete atrioventricular block [abstract]. *PACE* 1995;18:855.
35. Ishikawa T, Sumita S, Kimura K, et al. Prediction of optimal atrioventricular delay in patients with implanted DDD pacemakers. *PACE* 1999;22:1365-71.
36. Kamalvand K, Tan K, Kotsakis A, et al. Is mode switching beneficial? A randomized study in patients with paroxysmal atrial

- tachyarrhythmias. *J Am Coll Cardiol* 1997;30:496-504.
37. Kay GN, Hess M, Marshall H, et al. Effects of mode switching algorithm on patient symptoms [abstract]. *PACE* 1997;20[Pt II]: 1064.
38. Hayes DL. Rate-adaptive pacing. In: Hayes DL, Lloyd MA, Friedman PA, Ed. Cardiac pacing and defibrillation: A clinical approach. Armonk, New York: Futura Publishing Company, Inc., 2000:325-46.
39. Freedman RA, Hopper DL, Mah J, et al. Assessment of pacemaker chronotropic response: Implementation on the Wilkoff mathematical model. *PACE* 2001;24:1748-54.
40. Wilkoff BL, Corey J, Blackburn G. A mathematical model of the cardiac chronotropic response to exercise. *J Electrophysiol* 1989; 3:176-80.