The development of implantable technology for cardiac rhythm management remains one of the seminal achievements of the second half of the 20th century. The modern era of cardiac pacing began in 1958, when Elmqvist and Senning implanted the first cardiac pacemaker by thoracotomy in a human, and Furman and Robinson implanted the first endocardial lead.

The focus of development of cardiac pacing has changed over the last several decades. In the 1950s through 1970s, the emphasis was on the development of more reliable power sources and leads. By the end of the 1970s, the power source problems had been largely overcome, and efforts focused on mimicking the normal physiology of cardiac contraction.

In the 1980s, in the United States, the focus on normal physiology led to the nearly universal application of dual-chamber pacing to restore atrioventricular (AV) synchrony in patients with sinus rhythm. As sensor technology improved in the 1980s and 1990s, the same physiological focus spurred the advent and generalization of sensor-driven, rate-modulated pacing to restore chronotropic competence. By the early 1990s, there were lessons from physiology and an emerging body of evidence from observational epidemiological studies. Indeed, some pacemaker physicians believed that randomized trials in pacing might not be necessary to demonstrate incremental gains in prevention of clinical events and improvement of quality of life with atrial-based pacing.

It is certainly true that for many hypotheses, randomized trials are neither necessary nor desirable. For example, it would have been unethical to conduct randomized trials of cardiac pacing for the treatment of Stokes-Adams-Morgagni attacks because the benefit was so large. As a result of the evolution of progressively more sophisticated technologies, the most plausible effect sizes have become small to moderate, or between a 15% and 30% relative reduction in risk. Such effects, however, have importance clinically as well as from a public health perspective, but they are difficult to detect reliably. This is because the amount of uncontrolled and uncontrollable confounding inherent in even well-designed and well-conducted observational epidemiological studies is as large as the most plausible effects. Thus, in such circumstances the only reliable design strategy is the large-scale randomized trial.

In this article, we review emerging evidence on cardiac pacing, including basic research, primarily with a physiological focus, observational epidemiological studies, and randomized trials (Table 1). A glossary of pacing terms appears in Table 2.

**AV Synchrony, Cardiac Output, and Clinical Benefit**

Multiple studies have demonstrated the hemodynamic superiority of AV sequential pacing over ventricular pacing. A properly timed atrial systole improves stroke volume through the Frank-Starling mechanism, by providing greater left ventricular end-diastolic fiber stretch, and, consequently, enhanced end-systolic fiber shortening, all of this without an increase in average pulmonary venous pressure. Higher left ventricular end, but not average, diastolic pressures and volumes; higher systolic and mean blood pressures; and lower right atrial and pulmonary capillary wedge pressures have been reported with AV synchronous pacing compared with ventricular pacing. A variety of invasive and noninvasive hemodynamic studies have documented a 10% to 53% improvement in cardiac output with AV sequential pacing compared with single-chamber ventricular (VVI) pacing. The significance of the atrial contribution to resting cardiac output persists over a wide range of paced heart rates, in the upright and supine position and in patients with normal and impaired left ventricular function. However, noninvasive studies have failed to predict reliably which patients will derive the greatest benefit from AV synchrony. Indeed, some of the variability in the improvement in cardiac output with AV synchrony may derive from its dependence on left ventricular filling pressure. Patients with lower filling pressures appear to derive the greatest benefit because they are on the ascending limb of the Starling curve. Patients with the highest filling pressures appear to derive the least benefit, as they are on the flatter portion of the curve.

These generally consistent improvements in cardiac output led to several apparently logical conclusions—that AV se-
Sequential pacing would reduce the risk of heart failure, reduce mortality, and improve quality of life. Indeed, as dual-chamber pacing was becoming the commonest form of pacing in the United States, several large-scale observational epidemiological studies with good statistical methodology appeared that seemed to suggest that demonstrating a survival improvement would only be a formality. For example, the largest of these studies reviewed >36,000 Medicare pacemaker implants and demonstrated that dual-chamber–paced patients had a lower mortality at 1 year and 2 years than ventricular-paced patients (1-year mortality, dual-chamber 13.7% and ventricular 18.3%, \( P = 0.001 \); 2-year mortality, dual-chamber 22.3% and ventricular 28.9%, \( P = 0.001 \)). Not unexpectedly, there were many demographic and other differences between the 2 groups. However, after controlling for these differences, selection of a dual-chamber pacemaker remained as an independent predictor of survival (odds ratio for mortality

### TABLE 1. Completed and Ongoing Randomized Clinical Trials of Pacemaker Mode Selection

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Pacing Indication</th>
<th>No. of Patients</th>
<th>Modes</th>
<th>Selected Endpoints</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen 1997</td>
<td>SND</td>
<td>225</td>
<td>AAI vs VVI</td>
<td>Mortality: AAI relative risk, 0.66 (0.44–0.99); ( P = 0.045 )</td>
<td>Long-term follow up favored atrial pacing in all clinical endpoints</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thromboembolism: AAI relative risk, 0.47 (0.24–0.92); ( P = 0.023 )</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation: AAI relative risk, 0.54 (0.33–0.89); ( P = 0.012 )</td>
<td></td>
</tr>
<tr>
<td>PASE 1998</td>
<td>SND+AVB</td>
<td>407</td>
<td>DDDR vs VVIR</td>
<td>Mortality: DDDR 16%; VVIR 17%; ( P = 0.95 )</td>
<td>Quality of life was the primary endpoint and was similar between pacing modes in the overall group; subgroup analysis of SND patients suggested benefit for DDDR pacing in quality of life and atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke or death: DDDR 17%; VVIR 19%; ( P = 0.75 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation: DDDR 17%; VVIR 19%; ( P = 0.80 )</td>
<td></td>
</tr>
<tr>
<td>Mattioli 1998</td>
<td>SND+AVB</td>
<td>210</td>
<td>VVI(R) vs AAI, DDD(R) or VDD</td>
<td>Stroke: VVI(R) 19 patients; atrial-based 10 patients; ( P &lt; 0.05 )</td>
<td>Physiological pacing associated with less stroke and atrial fibrillation</td>
</tr>
<tr>
<td>PAC-A-TACH 1998</td>
<td>SND</td>
<td>200</td>
<td>DDDR vs VVIR</td>
<td>Death: DDDR 3.2%; VVIR 6.8%; ( P = 0.007 )</td>
<td>Mortality benefit for atrial-based pacing; no difference in recurrence of AF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial tachycardia: DDDR 48%; VVIR 43%; ( P = 0.09 )</td>
<td>No difference in stroke or death between pacing modalities; AF less frequent in atrial-based pacing</td>
</tr>
<tr>
<td>CTOPP 2000</td>
<td>SND+AVB</td>
<td>2568</td>
<td>DDDR(R) or AAI(R) vs VVI(R)</td>
<td>Stroke and cardiovascular mortality: reduction in relative risk, 9.4% (−10.5 to 25.7%)</td>
<td>No difference in death or stroke between pacing modalities; atrial fibrillation and heart failure less in DDDR-paced patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation: reduction in relative risk, 18% (3 to 32.6%)</td>
<td></td>
</tr>
<tr>
<td>MOST 2002</td>
<td>SND</td>
<td>2010</td>
<td>DDDR vs VVIR</td>
<td>Mortality and stroke: DDDR hazard ratio, 0.91 (0.75–1.10); ( P = 0.32 )</td>
<td>No difference in death or stroke between pacing modalities; atrial fibrillation and heart failure less in DDDR-paced patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation: DDDR hazard ratio, 0.77 (0.64–0.92); ( P = 0.004 )</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart failure hospitalization: DDDR hazard ratio, 0.73 (0.56–0.95); ( P = 0.021 )</td>
<td></td>
</tr>
<tr>
<td>UKPACE 2002</td>
<td>AVB</td>
<td>2000</td>
<td>DDD vs VVI or VVIR</td>
<td>Mortality primary endpoint</td>
<td>No difference between groups (ACC 2003 late-breaking trials presentation only)</td>
</tr>
<tr>
<td>STOP-AF RAMP 1999</td>
<td>SND</td>
<td>350</td>
<td>VVI vs AAI or DDD</td>
<td>Atrial fibrillation primary endpoint</td>
<td>Results not reported</td>
</tr>
<tr>
<td></td>
<td>SND+AVB</td>
<td>400</td>
<td>DDD vs DDDR</td>
<td>Quality of life primary endpoint</td>
<td>No difference between groups (NASPE abstract presentation only)</td>
</tr>
<tr>
<td>ADEPT 2003</td>
<td>SND+AVB+chronotropic incompetence</td>
<td>870</td>
<td>Factorial trial: DDD vs DDDR mode switch-on vs off</td>
<td>Quality of life primary endpoint</td>
<td>No difference between groups (NASPE 2003 late-breaking trials presentation only)</td>
</tr>
<tr>
<td>DANPACE</td>
<td>SND</td>
<td>2000</td>
<td>AAI vs DDD with ventricular capture</td>
<td>Mortality primary endpoint</td>
<td>Currently enrolling; results in 2004</td>
</tr>
<tr>
<td>SAVE-PACE</td>
<td>SND</td>
<td>1800</td>
<td>DDD+search AV vs DDD</td>
<td>Endpoints: reduction in %ventricular pace; atrial fibrillation; LV remodeling</td>
<td>Currently enrolling; results on % ventricular pace in 5/04; clinical results in 2005</td>
</tr>
</tbody>
</table>

ACC indicates American College of Cardiology annual scientific sessions; AF, atrial fibrillation; NASPE, North American Society of Pacing and Electrophysiology annual scientific sessions; AVB, atrioventricular block; and SND, sinus node disease.
with dual-chamber pacing 0.82, 95% confidence interval 0.77 to 0.87). Reviewers of these retrospective studies urged caution in the interpretation of these data and encouraged the performance of large-scale randomized trials. Eight years later, all the large-scale trials comparing dual-chamber with ventricular pacing have been completed, and all but 1 have been reported. The results of these trials have provided valuable hints as to the clinical physiology of ventricular contraction and cardiac pacing and are spawning another generation of pacing trials. Evidence-based recommendations for the use of dual-chamber and rate-modulated pacing systems in bradycardia patients are shown in Table 3.

In 1994, Andersen et al reported the results of the first randomized trial comparing single-chamber atrial (AAI) with VVI pacing. Patients were screened with an atrial-pacing test to assure normal AV conduction before randomization. Thus, 225 patients (mean age of 76 years) with sinus-node dysfunction, normal AV conduction, and a normal QRS complex were randomized. In the initial report with a mean follow-up of 3.3 years, there was no significant difference in survival. Longer follow-up of these trial participants to a mean of 5.5 years was subsequently published. Cardiovascular death had occurred in 19 patients from the atrial-pacing group and in 39 patients from the ventricular-pacing group ($P=0.0065$).

In 1998, a subsequent analysis showed further long-term advantages of atrial pacing in terms of heart failure and echocardiographic changes. After a mean follow-up of 5.5 years, New York Heart Association (NYHA) class was significantly lower in the atrial-pacing group (NYHA class I, 84%) compared with the ventricular-pacing group (NYHA class I, 65%). Left atrial diameter increased significantly in both groups but the increase was significantly lower in the atrial-pacing group (at end of follow-up, atrial pacing left atrial diameter was 37±7 mm; ventricular pacing left atrial diameter 41±7 mm; $P<0.0005$). Finally, left ventricular fractional shortening decreased significantly in the ventricular-pacing group but not in the atrial-pacing group.

These results have not been reproduced by any other prospective, randomized trial comparing atrial-based to ventricular pacing. For example, an intermediate-sized trial, PAcemaker Selection in the Elderly (PASE), randomized 407 patients age 65 years or older with bradycardia requiring a pacemaker to receive a dual-chamber pacemaker programmed to DDDR (rate-modulated dual-chamber pacing) versus VVIR (rate-modulated ventricular pacing) mode. No significant differences were found in clinical events including death, stroke, or hospitalization for heart failure, although some of trends compatible with benefits of dual-chamber pacing were observed, particularly in the subset of patients with sinus-node disease.

The results of the 2 largest randomized trials of atrial-based pacing compared with ventricular pacing, the Canadian Trial of Physiological Pacing (CTOPP) and the Mode Selection Trial in

<p>| TABLE 3. Evidence-Based, Guideline-Style Recommendations for the Use of Dual-Chamber and Rate-Modulated Pacing Systems in Bradycardia Patients |
|---------------------------------|---------------------------------|----------------------|</p>
<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Dual-chamber pacing is recommended over ventricular pacing to prevent atrial fibrillation, particularly in patients with SND</td>
<td>A</td>
</tr>
<tr>
<td>IIA</td>
<td>Dual-chamber pacing is preferred over ventricular pacing to prevent pacemaker syndrome</td>
<td>B</td>
</tr>
<tr>
<td>IIB</td>
<td>Dual-chamber pacing is not generally recommended over ventricular pacing to prevent heart failure</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>Dual-chamber pacing is not recommended over ventricular pacing to improve survival</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Dual-chamber pacing is not recommended over ventricular pacing to prevent stroke</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Glossary of Pacing Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terms</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>AAI</td>
</tr>
<tr>
<td>Atrial-based pacing</td>
</tr>
<tr>
<td>Chronotropic competence</td>
</tr>
<tr>
<td>DDD</td>
</tr>
<tr>
<td>Rate modulation</td>
</tr>
<tr>
<td>Physiological pacing</td>
</tr>
<tr>
<td>VVI</td>
</tr>
</tbody>
</table>
Sinus Node Dysfunction (MOST), also have failed to uncover differences in survival between groups. In 2000, Connolly et al. reported CTOPP, in which patients (mean age of 73 years) with symptomatic bradycardia requiring permanent pacing, were randomized to atrial-based (AAI, AAIR, DDD, or DDDR) or ventricular pacing (VVI or VVIR) and monitored for an average of 3 years. DDD and DDDR were used in 95% of atrial-based pacing–assigned patients. The combined primary endpoint of stroke or cardiovascular death was not significantly different between pacing modalities, with an annual rate of death or stroke of 4.9% for atrial-based pacing and 5.5% for ventricular pacing ($P = 0.33$). There were no differences in the incidence of heart failure hospitalization. More recently, the CTOPP patient population underwent extended follow-up. There were no significant differences in the rate of death or stroke after a longer follow-up of almost 8 years (reported in the May 2002 Annual Scientific Meeting of the North American Society of Pacing and Electrophysiology).

MOST, reported in 2002, was a 6-year trial comparing rate-modulated ventricular with dual-chamber pacing (VVI versus DDDR) in 2010 patients with sinus-node dysfunction. The average follow-up duration was 2.7 years. The primary endpoint was a composite of nonfatal stroke or death from any cause.

The primary endpoint occurred in 22.2% of the patients and no significant difference was found between the two treatment groups ($P = 0.32$). There were no significant differences between groups with regard to all-cause mortality or cardiovascular mortality. However, there were significantly fewer hospitalizations for heart failure in the dual-chamber–pacing group (10.3%) than in the ventricular-pacing group (12.3%, $P = 0.021$). It is an understatement that the results of these 2 trials, randomizing nearly 5000 patients, have been a surprise to pacemaker physicians and have contributed to an ongoing fundamental rethinking of physiological pacing.

This rethinking of physiology began with clinical applications in advanced heart failure, but the concepts may be applicable to bradycardia pacing as well.

AV synchrony is only a component of the physiologically normal heartbeat; ventricular activation sequence is now being appreciated as perhaps equally important. In the dog, Wiggers in 1925 reported that artificial stimulation of the right ventricle led to a less effective cardiac systole than did a normal contraction resulting from a normal cardiac depolarization. Other studies suggested that AV synchrony and right ventricular–left ventricular (V-V) synchrony were both independent and additive in contributing to pacing-dependent hemodynamic deterioration.

Although the importance of V-V synchrony in the instrumented dog is clear, its physiological and clinical importance in pacemaker patients has been overshadowed by the technical successes of providing AV synchrony and rate modulation and by the practical difficulties inherent in providing V-V synchrony.

Right ventricular (RV) apical pacing results in an asynchronous contraction whereby the electrical wavefront proceeds through slowly conducting myocardial tissue instead of through the more rapidly conducting His-Purkinje system. As such, it mimics the effect of a spontaneous left bundle-branch block, an abnormality of conduction that has been carefully studied. Grines et al. compared patients with left bundle-branch block to patients with normal conduction. Using noninvasive techniques, they found reduced septal ejection fraction (EF) leading to a reduction in global EF, as well as unfavorable alterations in diastolic filling time. Other investigators have reported similar results.

The relative importance of AV and V-V synchrony in pacemaker patients has been investigated by several groups of investigators. Rosenqvist et al. measured...
expression and ionic currents.38 Blood flow. Ventricular pacing also leads to structural abnormalities, asynchronous regional differences in myocardial work and glucose uptake, oxygen consumption, and wall motion abnormalities. These regional differences may be marked by patchy or asynchronous regional differences in myocardial work and blood flow. Ventricular pacing also leads to structural abnormalities of ventricular myocytes, including changes in protein expression and ionic currents.38–41 Thus, the abnormal contractile pattern has structural and cellular correlates as well.

Careful analyses of data in MOST are providing hints that, in the clinical arena, the benefits of AV synchrony may be mitigated by V-V dyssynchrony. Sweeney et al42 analyzed patients with a baseline, prepping QRS duration of <120 ms and determined the relationship between percentage ventricular pacing, as determined by pacer event counters, and clinical events. In the DDR- programmed patients, median cumulative percentage ventricular pacing was 90%. In the same patient group, despite maintenance of AV synchrony, percentage ventricular pacing was an independent predictor of adjudicated heart failure hospitalization (for DDR-paced patients, hazard ratio for heart failure hospitalization of cumulative percentage ventricular pacing >40% was 2.99; 95% confidence interval, 1.15 to 7.75).42

In conclusion, although AV synchrony supports an improvement in cardiac output and ventricular pressures, these favorable hemodynamics may be attenuated by ventricular dyssynchrony from RV apical pacing. This concept may explain the discrepant results when the Andersen et al22 trial is compared with MOST and CTOPP. The atrial-pacing arm of the Andersen et al22 trial could only pace atrium because the device implanted was an atrial pacemaker. In contrast, the “physiological” device implanted in CTOPP and MOST was a dual-chamber pacemaker, which paced ventricle depending on spontaneous AV conduction and programmed AV delay.

At present, at least 2 trials are ongoing that explore the benefit of reducing ventricular pacing in patients with a baseline normal QRS. The Danish Multicenter Randomized Study on Atrial Inhibited Versus Dual-Chamber Pacing in Sick Sinus Syndrome (DANPACE) compares atrial pacing (AAI) with DDD pacing programmed to have a short AV delay and obligatory ventricular capture. The Search AF Extension for Promoting Atrioventricular Conduction (SAVE-PACE) study, an industry-sponsored trial, tests whether a programmable feature that allows the AV delay to be extended up to 350 ms will reduce percentage ventricular pacing and lead to a reduction in left ventricular remodeling and atrial fibrillation (AF). Thus, the clinical significance of reducing forced ventricular desynchronization by RV pacing is being tested by the new generation of randomized trials. In time, the venerable RV apical lead may give way to the new imperative of V-V synchrony.

**Atrial Fibrillation**

Several mechanisms, both primarily electrophysiological and primarily hemodynamic, have been proposed to explain the reduction in atrial arrhythmias by a paced atrial mechanism. These include (1) suppressing atrial premature beats and preventing these atrial premature beats from initiating sustained AF; (2) prevention of dispersion of depolarization, particularly when exacerbated by bradycardia; (3) maintenance of an optimal activation sequence, minimizing areas of slow conduction in the atria; and (4) maintenance of optimal hemodynamics as compared with ventricular pacing, in particular.43 Excitation-contraction feedback, or the concept that loading conditions in the atria directly affect the electrophysiological substrate, is also a keystone in the conceptual basis for atrial pacing reducing AF. Increased atrial pressures facilitate the induction and sustaining of AF in various animal models. Unfortunately, the clinical data are less clear. Whereas Klein et al44 reported a marked increase in atrial effective refractory period in association with increased atrial pressures mediated by a short AV interval, Calkins et al45 found no meaningful change in a similar experiment. Thus, whereas AF certainly is more prevalent in patients with dilated left atria, atrial dilatation may be due to many factors, including anatomic remodeling and scarring due to chronic increases in pressures, ischemia, or neurohormonal alterations. Despite the doubts engendered by the above discussion, the clinical trials have been uniformly positive vis-à-vis the beneficial effects of atrial pacing in reduction of AF.

In 1994, Andersen et al22 reported the results of the first randomized trial comparing atrial (AAI) with ventricular (VVI) pacing. Perhaps as a result of the very small rates of events, there were no significant differences in incidence of AF (AF with atrial pacing 14% versus AF with ventricular pacing 23%; P=0.12). Three years later, longer follow-up of these trial participants to a mean of 5.5 years was published.23 The proportion of patients who remained free of incident or chronic AF was significantly higher in the atrial-pacing group as compared with the ventricular-pacing group (see Table 1 for details on effect size). Perhaps because of limited statistical power, a nonsignificant trend associated ventricular pacing with chronic AF (P=0.06). Interestingly, a later analysis reported in 1998 showed that left atrial diameter increased significantly less in the atrial-paced group (P<0.0005) than in the ventricular-paced group.24 The PASE trial, reviewed earlier, reported a marginal reduction in risk of AF in its initial publication.25 However, a more focused multivariable analysis found that DDR pacing was significantly associated with a reduced incidence of AF.46

The large pacemaker trials also have found similar results (Figure 1). For example, CTOPP reported that the annual rate of AF was lower in the atrial-based pacing group (5.3%) as compared with the ventricular-paced group (6.6%) (P=0.05). This constituted a relative risk reduction of 18% and an absolute risk reduction of 3.9% for atrial-based pacing. In MOST, perhaps because only patients with sinus-node dysfunction were included, the yearly incidence of AF was higher than in CTOPP (≈8%), but the relative risk reduction in the overall group quite similar (21%, P=0.008). A relevant observation that may explain varying results with pacing.
among different trials is that MOST patients who had never previously reported AF before pacemaker implantation had a large (50%) reduction (hazard ratio 0.50; 95% confidence interval 0.32 to 0.76; \( P = 0.0011 \)) in the incidence of AF after randomization. In contrast, dual-chamber–paced patients with a prior history of AF had a smaller, nonsignificant 14% reduction. This observation suggests that sinus-node dysfunction patients who have advanced further toward development of permanent AF, perhaps as a result of the effects of electrical and mechanical remodeling, may be less responsive to pacing modalities to prevent or treat AF. Indeed, this is a potential explanation for the sole failure to find a significant reduction in AF in a clinical trial of atrial-based compared with ventricular-based pacing in sinus-node dysfunction.47 Finally, the effects of progressive adverse atrial remodeling as described above in the ventricular-paced patients may be a reason that the incidence of AF continues to increase throughput in the ventricular-paced group.

An additional pacing technique has been used to specifically test the concept that a diminution in global atrial activation times and in the conduction delays may facilitate the initiation of AF. Dual-site atrial pacing involves pacing the right and left atria simultaneously.48,49 Although the technique showed much early promise, the most recent and largest clinical trial failed to demonstrate a conclusive benefit in reducing AF rates in comparison with single-site right atrial pacing.50 However, the trial had a small sample size (118 patients) and methodological problems, such as a crossover design, that limit the ability to exclude a small to moderate benefit.

**Stroke**

A reduction in the incidence of AF has generally been felt to be an important step toward reducing incidence of stroke, and therefore a desirable consequence of atrial-based pacing. However, the etiologies for stroke in an elderly population include not only cardiogenic emboli originating in the left atrium but also cardiogenic emboli originating in the left ventricle; spontaneous cerebral hemorrhage usually as a consequence of hypertension; hypotension with associated hypoperfusion of small arteriolar beds; increased ventricular dyssynchrony and atrial dilatation leading to a higher incidence of microemboli; and most commonly, carotid and aortic atherosclerosis. Additionally, the results of randomized trials of anticoagulation in patients with stroke may have to led to an increase in the use of these modalities in paced patients with AF, because 72% of MOST patients were taking either antiplatelet therapy or warfarin. All these considerations suggest that the most plausible magnitude of benefit of reducing stroke by preventing AF may have become quite small.

Nonetheless, 2 small trials of ventricular versus atrial-based pacing reported that atrial-based pacing reduced stroke risk.33–51 However, despite the plausible mechanisms listed above, the large trials have demonstrated that preventing stroke in pacemaker patients is as elusive a goal as preventing death. In CTOPP, the annual risk of stroke was 1.1% in the ventricular-paced group and 1.0% in the atrial-based pacing group. In MOST, the annualized incidence of stroke was 2.2%, with no clear difference based on pacing mode. Thus, whether there is a reduction in stroke risk of small (10% to 15%) magnitude will await planned meta-analyses of the published pacemaker trials. At the present time, dual-chamber pacing should not be selected to prevent stroke.

**Pacemaker Syndrome**

Pacemaker syndrome, first described in 1969,52 consists of a constellation of symptoms and signs that occur in response to ventricular pacing.53 The physiology of pacemaker syndrome is important to understand in the context of the hemodynamic discussion that preceded this section, the unexpectedly neutral results of the large trials with regard to mortality, and the small reductions in heart failure observed with dual-chamber pacing.

The symptoms and signs of pacemaker syndrome can be divided into the following 3 different types: congestive, hypotensive, and nonspecific. Congestive symptoms mimic heart failure, with dyspnea and orthopnea. Congestive signs include elevated neck veins (often with cannon A waves), rales, hepatomegaly, and pedal edema. Hypotensive symptoms and signs include near syncope or syncope at onset of pacing, associated with a drop in upright systolic blood pressure of at least 20 mm Hg. Nonspecific symptoms such as headache and fatigue have also been reported. The initial thoughts on the pathophysiology of pacemaker syndrome invoked only a drop in cardiac output in response to loss of AV synchrony. However, pacemaker syndrome is now recognized as a complex interaction of neurohumoral, autonomic, and vascular changes that ultimately lead to symptomatic hemodynamic consequences.

The presence of intact ventriculoatrial conduction has been thought to be central to the diagnosis of pacemaker syndrome; the hemodynamic effects of atrial systole against closed AV valves likely accounts for some of the congestive symptoms and signs12 (Figure 2). However, every pacemaker clinician has experienced the patient who develops profound hypotension with ventricular pacing, and it is in these patients that the role of the autonomic nervous system becomes most relevant. Hypotension during ventricular pacing is now thought to be due to individual variation in compensatory sympathetic outflow, the effects of vasodilator drugs or vascular disease, and the activation of cardioinhibitory reflexes that are brought into play by atrial distension, and that counteract the reflex increases in adrenergic tone.

Clinical trial results have shed light on the incidence and manifestations of pacemaker syndrome, although conclusions drawn from US trials are quite different from those drawn from Canadian or European trials. Earlier retrospective surveys had suggested that up to 83% of ventricular-paced patients had pacemaker syndrome.56 Ellenhorn et al57 reported on patients in the PASE trial, age 65 years or older, who had been randomized to VVIR. This trial required a DDDR pacemaker in all patients, programmed at implant to VVIR or DDDR. Of 204 patients randomized to VVIR, 26% crossed over to DDDR for “intolerance to ventricular pacing,” the operating definition of pacemaker syndrome. Most crossovers occurred early (Figure 3). In patients who had undergone quality-of-life assessments before and after cross-
over, significant improvements in quality of life were demonstrated. In MOST, pacemaker syndrome was the principal reason for crossover in 18.3% of 996 ventricular-paced patients and in 48.9% of all crossovers. Most crossovers for pacemaker syndrome occurred early (69% by 3 months and 73% by 6 months; median time to crossover 58 days). The Andersen et al22 trial and CTOPP both have reached diametrically opposite conclusions on the incidence and consequences of pacemaker syndrome. Both of these trials, in contrast to the US trials, were “hardware randomization” trials, in which the device was randomized, not the programming. Thus, crossovers required reoperation. Not unexpectedly, the rate of crossovers in both studies was low, and only 5% of the CTOPP and 1.8% of the Andersen et al22 ventricular-paced patients were crossed over to an atrial-based mode.

Our interpretation of these radically different data are that one series of studies made it inordinately hard to cross over, whereas the US trials perhaps made it too easy. Indeed, although pacemaker syndrome is a real and important diagnosis, the real incidence probably lies between the 2 extremes.

Chronotropic Incompetence and Rate-Modulated Pacing

Heart rate increase may be responsible for as much as 75% of the increment in cardiac output achievable with exercise.3 Furthermore, when performing different activities at their own rate, patients older than age 65 years demonstrated heart rate increases similar to those of younger patients.58 These data suggest that the elderly need a heart rate increase in response to exercise as much as do younger patients and imply that rate-modulated pacing should be preferable for many pacemaker recipients.

Despite convincing physiological data, clinical investigators have found an inconsistent improvement in the exercise capacity of DDDR-paced patients when compared with DDD patients.59–61 Nonetheless, unpublished data on >200 patients from the Rate Modulated Pacing and Quality of Life (RAMP) study suggest that chronotropic incompetence is an important correlate of health-related quality of life. Patients unable to reach 60% maximum predicted heart rate had worse quality of life in all dimensions than did patients who exceeded 60% maximum predicted heart rate, leaving open the question that aggressive rate-modulated pacing might improve quality of life. Furthermore, chronotropic incompetence may develop after the pacemaker has been implanted.62 Small crossover studies in highly selected patients already have suggested that DDDR pacing leads to superior quality of life.63 These small studies, however, do not provide definitive support for the concept that all or most pacemaker patients with sinus rhythm should have a DDDR pacer implanted; and indeed, it may be a realistic concern that more aggressive DDDR programming may lead to a greater frequency of ventricular pacing and more V-V dyssynchrony.

Despite the absence of convincing data showing that, in unselected populations, DDDR pacing is superior to DDD with regard to improved quality of life and reduced symptoms, 97% of all generators implanted in the United States in 2000 had rate modulation as a programmable option.64,65 The Advanced Elements of Pacing Trial (ADEPT), a well-powered trial comparing dual-sensor dual-chamber DDDR with DDD pacing will fill this important gap in knowledge.

A Clinical Interpretation of the Randomized Data: Ventricular Versus Atrial-Based Pacing

When comparing these 2 general modes of pacing, the clinician must weigh most heavily the results of the published
Figure 4. Evolving opinions on the proportional importance of the 3 principal components of physiological pacing. In the 1980s, AV synchrony was thought to be the pre-eminent component, with an appreciation that chronotropic competence also was important. By the mid-1990s, there was more literature on the importance of V-V synchrony. By the late 1990s, biventricular pacing for heart failure had been developed and thought leaders were supportive of the importance of V-V synchrony. At present, we hypothesize that an improved understanding of the critical nature of V-V synchrony is being reached, and the limitations of AV synchrony and chronotropy have become evident.

large randomized trials (MOST and CTOPP). Furthermore, the clinical applicability of the results must be segregated based on the uniformity of findings across trials, as follows.

1. Findings of benefit that are uniform across trials
   - Atrial-based pacing reduces the risk of developing persistent AF and permanent AF
2. Findings of benefit that are not uniform across trials
   - Atrial-based pacing reduces the high risk of pacemaker syndrome (MOST)
   - Atrial-based pacing reduces the risk of heart failure (MOST)
3. Findings of no benefit that are uniform across trials
   - Atrial-based pacing does not improve survival
   - Atrial-based pacing does not reduce risk of stroke

Conclusions

The treatment of bradycardia with implantable technology remains one of the great medical accomplishments of the 20th century. Many different types of devices are now available as a result of physiological discoveries and advances in engineering. However, the last decades have taught the medical community that clinical dogma and physiology have to be tested in clinical trials before decisions on the specifics of optimal therapy can be made. The results reviewed above lead us to conclude that the lessons being learned about the limits and potential of AV synchrony, V-V synchrony, and chronotropic response will lead to better care for our patients (Figure 4). These new concepts, however, must form the basis of future randomized trials.

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Evidence Base for Pacemaker Mode Selection: From Physiology to Randomized Trials
Gervasio A. Lamas, Kenneth A. Ellenbogen and With the Assistance of Charles H. Hennekens, MD, DrPH, and Alicia Montanez, MD

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