Objectives. The purpose of this study was to evaluate the ability of impedance cardiography to determine the change in cardiac output caused by modifications in the atrioventricular (AV) delay in DDD (dual-chamber) pacing mode while pacing the atrium and ventricle at different programmed rates.

Background. Impedance cardiography permits continuous noninvasive monitoring of hemodynamic variables on a beat to beat basis.

Methods. Eleven patients with a DDD pacemaker were evaluated by impedance cardiography. Stroke volume, cardiac output and total peripheral resistance were assessed in the supine rest position during both DDD and ventricular (VVI) pacing. Hemodynamic variables were measured during DDD pacing at rates ranging from 60 to 110 beats/min in 10-beats/min increments with programmed AV delay varying from 50 to 250 ms in 50-ms increments. When the pacemaker was reprogrammed to the VVI pacing mode, these measurements were repeated at the same pacing rates.

Results. Cardiac output measurements during programmed conditions were found to be highly reproducible. The mean coefficient of variation was 3% during DDD pacing; it was 6% in the VVI pacing mode. A large decrease in cardiac output (>30%) was found when a pacemaker was reprogrammed from the DDD to the VVI pacing mode. At DDD pacing rates between 70 to 110 beats/min, the highest cardiac output occurred at an average AV delay of <120 ms from atrial stimulus to ventricular stimulus. At an average AV delay of >200 ms, the cardiac output in the DDD and VVI pacing modes was similar.

Conclusions. 1) Impedance cardiography allows highly reproducible noninvasive assessment of cardiac output in pacemaker patients; 2) inappropriate programming of the AV interval in patients with atrial and ventricular pacing can decrease cardiac output significantly, and the extent of the decrease is similar to or less than that observed in ventricular pacing; 3) hemodynamic measurements obtained with impedance cardiography can facilitate optimal programming of pacemaker variables.

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to 73 years (average 59 ± 16). Eight patients presented with complete heart block, the remaining three with sick sinus syndrome and with various degrees of AV conduction disturbance. A primary conduction defect was the underlying disease in nine patients and coronary artery disease in the remaining two. The left ventricular ejection fraction was normal or only mildly reduced in nine patients (45% to 62%); in the other two patients it was 32% and 38%, respectively.

Impedance cardiography measurements. All patients were studied by the same operator under standardized conditions and after at least 15 min of supine rest. After routine skin preparation, four Mylar electrode strips were applied, two placed circumferentially around the neck and two around the chest (Fig. 1). Each pair of electrodes was placed ≥3 cm apart. The Minnesota Impedance Cardiograph, model 304B, which monitors displayed impedance and electrocardiographic (ECG) signals, and its dedicated computer (model 7000, Surcom) were used. The beat to beat stroke volume was computed from the Minnesota cardiogram. Two (1 and 2) electrodes and recorded by a cardiac output monitor and computer. dZ/dt = maximal rate of change of thoracic impedance.

Figure 1. Diagrammatic representation of the location of the four electrode strips for registration the impedance cardiogram. Two electrodes (1 and 2) are placed 3 cm apart circumferentially around the neck. The third is at the xiphoid level and the fourth at the level of the lowest anterior ribs. A low energy high frequency constant current (4 mA and 100 kHz) passes longitudinally through the thorax between the outer (1 and 4) electrodes. The product of this current (I) generates a voltage (Ev) that is detected by the inner (2 and 3) electrodes and recorded by a cardiac output monitor and computer. dZ/dt = maximal rate of change of thoracic impedance.

SV = \( p \cdot \left[ \frac{L}{Z_o} \right]^2 \cdot \frac{d}{dZ/dt} \cdot T \),

where \( p \) is the resistivity of blood at 100 kHz in ohms-cm, derived from the hematocrit; \( L \) is the distance between the two inner electrodes in cm; \( Z_o \) is the mean thoracic impedance in ohms; \( dZ/dt \) is the maximal rate of change of thoracic impedance during each beat in ohms-s and \( T \) is the ventricular ejection time obtained as the interval between the rapid upstroke and the nadir of the dZ/dt.

The Heather index, defined as the ratio \( (dZ/dt)/QZ \), where \( QZ \) is the interval from the start of the ECG Q wave to the onset of the dZ/dt curve, has been formulated to give an objective measure of cardiac contractility (7, 8, 13). Cardiac output was calculated from the product of the mean stroke volume, averaged over 10 consecutive beats, and the heart rate, which was derived from the ECG continuously recorded over the same period. Body surface area, in m², was computed from the patient's height and weight; the cardiac index was calculated as the product of cardiac output (CO) and body surface area. Arterial blood pressure was measured simultaneously with stroke volume by using a cuff sphygmomanometer. The mean blood pressure (mBP) was calculated from the formula

\[ mBP = DBP + \left( \frac{1}{3} \right) (SBP - DBP). \]

where DBP is the diastolic blood pressure and SBP is the systolic blood pressure. The total peripheral resistance (TPR) in dynes-s/cm² was calculated from the formula

\[ TPR = \frac{mBP}{CO} \times 80. \]

During ECG recording, the unipolar pacemaker stimulus is detected by the impedance cardiograph but the bipolar stimulus is not detected. A bipolar stimulus does not affect the measurement of cardiac output, but a unipolar stimulus may be interpreted as an R wave and thus result in an incorrect assessment of the cardiac output.

Pacemaker programming. The pacemaker was initially programmed to 60 beats/min, a rate higher than the intrinsic atrial rate, which was consequently suppressed in all 11 patients. The pacing rate was then progressively increased, in increments of 10 beats/min, to a maximal rate of 110 beats/min. At each pacing rate, the AV delay was varied from 50 to 250 ms in 50-ms increments and, at each setting, hemodynamic measurements were made. At least 3 min was also allowed to elapse between reprogramming and measurement of hemodynamic variables. No patient developed angina pectoris or arrhythmias as the pacing rate was increased.

To assess the sensitivity of stroke volume to changes in AV delay, the best and the worst AV delays, within the range of 30 to 250 ms, were defined. The best programmed AV delay was defined as the setting that produced the highest cardiac index (Clh) and, with this AV delay setting, the DDD pacing mode was defined as hemodynamically "optimal" or "highest" (DDDh). Similarly, the AV delay setting that produced the lowest cardiac index (ClL) defined the hemodynamically "worst" or "lowest" DDD setting (DDDb). After the influence of different AV delay settings in the DDD pacing mode was determined, patients were programmed to the VVI mode and the hemodynamic evaluation procedure was repeated at pacing rates that, as before, were
varied from 60 to 110 beats/min in increments of 10 beats/min.

Statistics. All results are presented as the mean value ± SD. Analysis of the variance of repeat measurements was used to evaluate changes in impedance cardiography variables resulting from changes in pacing rate, pacing mode and AV delay interval. Regression analysis, correlation analysis, paired and unpaired t tests were applied as appropriate.

To assess the degree of variability of cardiac output by using impedance cardiography, three consecutive beats at a given pacemaker setting were measured by the same examiner. The coefficients of variation and of linear correlation were calculated. Tests of hypotheses were conducted at the level of p < 0.05. Data analyses were performed with the SPSS statistical package.

Results

Hemodynamics as a function of pacing rate and pacing mode. Independent of the pacing mode, the stroke volume decreased significantly as the pacing rate was increased with the patient at rest (Table I). In the VVI mode, the stroke volume decreased 49% as the pacing rate was increased from 60 to 110 beats/min. Over the same range, the stroke volume decreased by 58% in both the DDDa and the DDDL settings. No significant systematic variation in cardiac index as a function of pacing mode was observed as the pacing rate was changed (Table I).

At a given pacing rate, the cardiac index was significantly higher (mean increase 41 ± 8%) in the DDDa setting than in the VVI mode (34 ± 8%, p < 0.01). In contrast, no significant difference (mean difference -5 ± 6%, p = 0.1) was detected between the cardiac index observed in the VVI mode (CIv) and in the DDDa setting.

At each pacing rate, the systolic blood pressure was nonsignificantly higher during DDDa pacing than during pacing in either the VVI or the DDDa mode. The systolic pressure was similar in the VVI and DDDa modes. No significant systematic variation in the diastolic blood pressure as a function of pacing mode, AV delay or pacing rate was observed. At each pacing rate, the total peripheral resistance was significantly less in the DDDa setting than in either the VVI or the DDDa mode (Table I).

Influence of AV delay on hemodynamics. At a given pacing rate, the cardiac index was significantly higher (mean increase 41 ± 8%) in the DDDa than in the DDDa setting. In Table I and Figure 2, the mean value and SD (mean ± SD of the AV delay from atrial to ventricular stimulus and the relation between AV delay and the pacing rate) are given for the highest and lowest values of the cardiac index, that is,
Clb (obtained in the DDDb setting) and Clb (obtained in the 
DDDb setting). In the DDDb mode, there is a clear tendency
for a shorter AV delay to yield superior hemodynamic values
as the pacing rate increases; in contrast, there is no systematic
variation in AV delay as the pacing rate is varied in the
DDDb setting. At all pacing rates, the Clb was greatest when
the AV delay was <200 ms whereas the AV delay was
>200 ms in patients with the lowest Clb values (Table 1, Fig.
2).

Table 2. Individual Values of Cardiac Index and Atrioventricular Delay at a Pacing Rate of 70 Beats/Min in the DDD and VVI
Pacing Modes

<table>
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<tr>
<th>Pt No.</th>
<th>DDDb</th>
<th>AVDb</th>
<th>DDDb</th>
<th>AVDb</th>
<th>VVI</th>
<th>CI</th>
<th>Rb</th>
<th>Rb Ratio</th>
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<td>3.7</td>
<td>2.5</td>
<td>1.3</td>
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<td>0.6</td>
<td>0.6</td>
<td>0.2</td>
<td>0.1</td>
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</tbody>
</table>

*Clb versus Clb, p < 0.05. *Clb versus Clb, p < 0.05. *AVDb versus AVDb, p > 0.01. *Rb versus Rb, p < 0.05. Cl = cardiac index, Clb = cardiac index and atrioventricular (AV) delay, respectively, in DDDb pacing mode; Clb = cardiac index and AV delay, respectively, in DDDb pacing mode; Clb = cardiac index in VVI pacing mode; Pt = patient; Rb = the ratio Clb/Clb; Rb = the ratio Clb/Clb; other abbreviations as in Table 1.

With every patient, in either of two pacing settings
(DDD, and DDDb) and at a pacing rate of 70 beats/min, the
greatest Clb values were achieved with an average AV delay
of 114 ± 39 ms (range 50 to 150) whereas the lowest Clb
values occurred, in all but Patient 8, at an AV delay setting
closed 200 ms (mean 232 ± 46). With the exception of Patient 8,
in the DDDb setting with the AV delay set at >200 ms, the
Clb value was the same as during VVI pacing (Table 2).
When the AV delay was ≤150 ms, cardiac index (Clb) was
always greater than during ventricular pacing (Clb). A two-
way analysis of cardiac index by heart rate and AV delay
reveals that the cardiac index is significantly influenced by
AV delay (p < 0.04).

Notwithstanding patient variability, the cardiac index
was invariably higher and the total peripheral resistance
was invariably lower in the DDDb than in the DDDb,
setting or in the VVI mode. The influence of pacing mode
is shown in Table 2, where the Rb ratio (that is, the ratio of Clb
to Clb) is invariably >1. The ratio Rb (that is, the ratio of
Clb to Clb) is generally equal to or close to but <1. The
Heather index was consistently greater (p < 0.05) in the
DDDb setting than in either the VVI or the DDDb setting
(Table 1).

Relation between Heather index and the terms in the
Nyboer-Kubicek equation. Moderate or weak but significant
correlations exist between the terms of Nyboer-Kubicek
equation: between stroke volume and dV/dt (r = 0.64, p < 0.0001); between stroke volume and L/Z and between
stroke volume and T (in both these latter cases, r = 0.2, p < 0.004).

Moderate and good correlations were observed between
the Heather index and stroke volume, 2) cardiac output and
3) total peripheral resistance with respective values of

Figure 2. Highest and lowest values of the cardiac index (Clb and
Clb, respectively) at varied atrioventricular (AV) delay intervals
and pacing rates. Open circles = mean and SD values of AV delay at the
lowest cardiac index value at each pacing rate. Closed circles = mean and SD values of AV delay at the highest cardiac index value at each pacing rate. For the highest cardiac index values, the mean AV delay was <200 ms and was shortened as the pacing rate increased. For the lowest cardiac index values, the mean AV delay was consistently >200 ms.
Table 3. Results of a Regression Analysis Among the Terms of the Nyboe-Kubicek Equation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>p Value</th>
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<tbody>
<tr>
<td>dZ/dt</td>
<td>0.64</td>
<td>0.0001</td>
</tr>
<tr>
<td>Z_m</td>
<td>0.94</td>
<td>0.0001</td>
</tr>
<tr>
<td>T</td>
<td>0.96</td>
<td>0.0001</td>
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</table>

Table 3: Results of a Regression Analysis Among the Terms of the Nyboe-Kubicek Equation

r = 0.69, r = 0.72 and r = 0.7, p < 0.0001 in all cases. A weaker but still significant correlation was found to exist between stroke volume and the QZ interval and between dZ/dt and the QZ interval with r = 0.39 and r = 0.3, respectively, p < 0.0001 in both cases. The first step of the regression analysis showed a moderate correlation between stroke volume and dZ/dt (r = 0.64, see above) and at the second step, the r value increased to 0.94, and remained virtually unaltered at the third step (Table 3).

Validity of impedance cardiography measurements. The correlation coefficient between two consecutive measurements of the cardiac index on patients with a pacemaker programmed in the DDD mode was 0.94, p < 0.0001; with the pacemaker programmed in the VVI mode, the correlation was less pronounced at 0.82, p < 0.0001. Repeated measurements of the cardiac index during DDD pacing showed a mean coefficient of variation of 3.5 ± 2.2% (95% confidence limits 1.8% to 4.9%). During VVI pacing, the mean coefficient of variation was 5.9 ± 3.5% (95% confidence limits 4.5% to 7.5%).

Discussion

Previous studies (4,7,9,10,13-20) have shown that impedance measurements of cardiac output correlate well with those obtained by standard methods (electromagnetic flowmetry, the indirect and direct Fick techniques, dye dilution, radionuclide cardiography, left ventriculography, thermodilution and Doppler echocardiography) and that impedance cardiography is a highly reliable and reproducible technique for monitoring changes in cardiac output.

Our observations confirm the finding of other investigators (21-26) who have used alternative techniques that the overall increase in cardiac index attendant on a change from the hemodynamically optimal DDD setting (DDD) to the VVI mode is -30%. This held true at all pacing rates examined. In addition, our study leads us to stress the importance of appropriate AV delay setting because a change in AV delay can result in an average change in cardiac index of 40%.

Dependence of cardiac output on AV delay values. In a normal heart, the optimal cardiac output is regulated by several physiologic factors among which is a "normal" or appropriate AV delay. Optimization of the cardiac output of patients with a DDD pacemaker requires that atrial and ventricular contraction be appropriately timed. An implanted pacemaker can provide AV intervals that can be programmed from 60 to 300 ms, a duration that can be fixed or modulated whether sensing or pacing the heart and that can be modulated as a function of the spontaneous or sensor-driven atrial rate. The contribution of a correctly timed AV delay is significant and varies from 15% to 40% of cardiac output, thus providing a hemodynamic advantage in both normal and diseased hearts (22-29).

With a given patient, the atrial contribution can be reduced significantly with an inappropriate AV delay setting. Thus, the lowest cardiac index (Cl) obtained in the DDD setting was often equal to and, on occasions, was even less than the cardiac index during ventricular pacing (Cl1) (Table 2). Too short an AV interval results in ineffective atrial contribution and may cause mild mitral regurgitation (25-31) whereas too long an AV interval can lead to diastolic mitral regurgitation referred to as "atriogenic diastolic reflux" and, in addition, reduces the atrial contribution (24-35). The importance of left atrial timing when programming DDD pacemakers has been emphasized previously (25), particular attention being directed to the deleterious influence of very short AV intervals because these cause left atrial activation and systole to occur after left ventricular contraction and mitral valve closure. The hemodynamic state resulting from DDD pacemaker function programmed to inappropriate AV interval settings can be expected to produce cardiac index values that may not be better and may even be considerably worse than those obtained in the VVI pacing mode (28). Cardiac output decreases with too long an AV delay, a factor that may present a dilemma when one is programming a DDD pacemaker implanted in a patient who has prolonged AV conduction (for example, a patient with sick sinus syndrome). Prolongation of the programmed AV delay may avoid unnecessary ventricular pacing but can result in reduced cardiac output. Conversely, programming a shorter AV delay may cause right ventricular pacing to result in retrograde ventricular depolarization and in electrophysiologic and hemodynamic distortions of left bundle branch block and even retrograde (that is, venousventricular) conduction (32-36).

Cardiac index at different pacing rates. Consistent with previous observations (37-39), the lowest cardiac index in the DDD setting (Cl1) and Cl2 and Cl3 did not change significantly during pacing at incrementally increased pacing rates between 60 and 110 beats/min (Table 1), thus reflecting a proportional reduction in stroke volume as the paced heart rate was varied in the absence of physiologic demand (all readings were obtained with the patient at rest). This finding leads us to question the common practice of setting the different pacing modes to a lower heart rate of 70 beats/min because a patient who is inactive (whether he or she is only currently at rest or generally leads an inactive life) may have...
the same cardiac index value if the pacemaker were set to a rate below 70 beats/min and reduced oxygen consumption might result.

Relation between the terms of the Nyboer-Kubicek equation and the Heather index. The correlation between stroke volume, the terms of the Nyboer-Kubicek equation and the regression analysis provided an opportunity to assess the relative importance of the terms. Individually, the terms the ratio of the distance between two electrodes to the mean thoracic impedance ($Z_0$), and $dZ/dt$ and between stroke volume and $QZ$ leads us to consider $Z_0$ as a variable and the $QZ$ interval is equivalent to a preejection period. The significant correlation that exists between the stroke index and the Heather index is a reliable indicator for the evaluation of cardiac contractility in patients at rest. The value of this index was greatest when the DDD setting was hemodynamically optimal (that is, DDD).

Variability of impedance cardiography measurements. Measurements using the impedance cardiography technique during pacing, especially in the DDD mode, are highly reproducible. In this study, each patient served as his or her own control so that relative changes in individual measurements of stroke volume observed at different pacemaker settings would be valid even if the absolute values were in error.

Limitations of this study. The following limitations are recognized: 1) In assessing cardiac output variability, we used only three consecutive beats measured by the same operator. 2) We have not compared impedance cardiography with standard methods of cardiac output estimation in order to assess its accuracy. 3) We did not require the patients to offer a subjective assessment of their sense of well-being when their pacemaker was set to DDD, DDD, and VVI. Such a comparison might well have furnished us with valuable complementary data. 4) The DDD and VVI modes were compared only with patients at rest. 5) The influence of AV delay on cardiac output was studied only after dual-chamber pacing. 6) The current limitations of the impedance cardiograph, model 304B, designed to be used with patients fitted with a unipolar pacemaker, as detailed earlier, need to be addressed by the manufacturer during future development of the device.

Conclusions. 1) Impedance cardiography enables easy, highly reproducible, serial, noninvasive assessments of the cardiac output of pacemaker patients and can detect clinically significant hemodynamic changes. 2) Hemodynamic findings obtained with impedance cardiography applied to pacemaker patients are consistent with data previously obtained using other techniques. 3) Hemodynamic measurements obtained with impedance cardiography can facilitate optimal programming in pacemaker patients. 4) Patients showing a large decrease (about 30%) in cardiac output after reprogramming from the DDD to the VVI pacing mode may display a similar or even greater decrease in cardiac output if the AV delay is incorrectly chosen after DDD pacing.

References

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