The Acute Effects of Changes to AV Delay on BP and Stroke Volume
Potential Implications for Design of Pacemaker Optimization Protocols
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Background—The AV delay optimization of biventricular pacemakers (cardiac resynchronization therapy) may maximize hemodynamic benefit but consumes specialist time to conduct echocardiographically. Noninvasive BP monitoring is a potentially automatable alternative, but it is unknown whether it gives the same information and similar precision (signal/noise ratio). Moreover, the immediate BP increment on optimization has been reported to decay away: it is unclear whether this is the result of an (undesirable) decrease in stroke volume or a (desirable) compensatory relief of peripheral vasoconstriction.

Methods and Results—To discriminate between these alternative mechanisms, we measured simultaneous beat-to-beat stroke volume (flow) using Doppler echocardiography, and BP using finger photoplethysmography, during and after AV delay changes from 40 to 120 ms in 19 subjects with cardiac pacemakers. BP and stroke volume both increased immediately (P<0.001, within 1 heartbeat). BP showed a clear decline a few seconds later (average rate, -0.65 mm Hg/beat; r=0.95 [95% CI, 0.86–0.98]); in contrast, stroke volume did not decline (P=0.87). The immediate BP increment correlated strongly with the stroke volume increment (r=0.74, P<0.001). The signal/noise ratio was 3-fold better for BP than stroke volume (6.8±3.5 versus 2.3±1.4; P<0.001).

Conclusions—Improving AV delay immediately increases BP, but the effect begins to decay within a few seconds. Reassuringly, this is because of compensatory vasodilatation rather than reduction in cardiac function. Pacemaker optimization will never be reliable unless there is an adequate signal/noise ratio. Using BP rather than Doppler minimizes noise. The early phase (before vascular compensation) has the richest signal lode. (Circ Arrhythm Electrophysiol. 2012;5:122-130.)

Key Words: physiology ■ BP ■ blood flow ■ pacemakers ■ hemodynamics

The increasing prevalence of devices specifically designed to improve timings within the cardiac cycle (ie, cardiac resynchronization therapy) has created a clinical need to accurately monitor the effects on cardiac performance of changes to pacing configurations.

Clinical Perspective on p 130
Optimization of pacemaker AV (and interventricular) delay settings for individual patients maximizes the hemodynamic benefit of pacing,1-4 and might be approached by monitoring stroke volume or BP, while changes are made to the settings. The most widely used quantitative approach for pacemaker optimization uses echocardiography to measure cardiac output using Doppler; however, this is time-consuming, relies on experienced operators, and has limited reproducibility.3,5

BP, whether measured invasively or noninvasively, has tracked trends in stroke volume well during pacemaker optimization6; therefore, recent studies have proposed using continuous beat-to-beat noninvasive BP as a marker during pacemaker optimization.6-10 Although potentially simple, highly sensitive, and reproducible,6,7 it is notable that the initial increment in BP that follows an AV delay change from 40 to 120 ms may not be sustained: during the course of the subsequent minute, this increment declines. A reverse phenomenon can be observed when going from the optimal to the worst configuration (Figure 1).

It is unknown whether the decline in BP increment results from decay in the stroke volume increment or is the result of reflex compensatory reduction in peripheral resistance after the stroke volume increase. This distinction is clinically important because a decline in stroke volume means that the
cardiac efficiency improvement achieved by optimization may be short-lived. Conversely, if it is caused by a decay in peripheral resistance, then the hemodynamic benefit from optimization causes an increase in cardiac output and also a reflex reduction in the chronic systemic vasoconstriction of heart failure.

In this study, we measured BP and stroke volume simultaneously to discriminate between these 2 potential hemodynamic mechanisms, to improve the protocols used in studies of the effects of pacing parameter settings optimization.

**Methods**

**Subjects**

Twenty-two consecutive outpatients with implanted pacemakers were recruited from clinics. Patients with both normal and impaired systolic function were included in the study, to ensure that any observations seen were applicable to any paced patient, rather than being limited to heart failure.

Three patients were excluded after screening because their echocardiographic windows were too poor for the reliable prolonged Doppler measurements needed for this study. Of the remaining patients, 10 had a normal systolic function and 9 had heart failure (mean left ventricular [LV] ejection fraction, 61±8% versus 30±12%; P<0.001). Patients gave informed consent for this study, which was approved by the local ethical committee.

**Data Acquisition**

Patients lay awake, recumbent in the left lateral position on a couch, having rested supine for at least 10 minutes. Systolic and diastolic BP (SBP and DBP, respectively) levels were measured noninvasively using a photoplethysmograph device (Finometer, Finapres Medical Systems; UK). This uses a cuff that is placed around the finger, a built-in photoelectric plethysmograph, and a volume-clamp circuit that dynamically follows arterial BP. The device yields a continuous beat-to-beat arterial BP waveform and has previously been extensively validated against invasive measurements for changes in BP and cardiac output.11–13 Data were acquired using Labview (National Instruments; Austin, TX) and analyzed with custom software based on the Matlab platform.

**Echocardiographic Measurement of Stroke Volume**

Stroke volume was calculated from Doppler flow velocity measurements sampled in the LV outflow tract, according to published protocols,14 using the aortic annulus leading edge method and measurements of the velocity-time integral (VTI) of pulsed-wave Doppler blood flow.15,16 Thus, cardiac output (Q) was calculated as follows:

\[
Q = VTI^*\pi(D/2)^2 \times \text{Heart Rate}
\]

Measurements were made using a Philips ATL 5500 machine with a 2.5-MHz transducer. All measurements were made by a single experienced operator (B.U.). Doppler data were transferred to the HDI Laboratory in digital format and then further analyzed off-line with custom Matlab software.

**Design of Protocol of Changes in Pacemaker Setting**

It was already known that changing a pacemaker setting causes changes in both stroke volume and BP. It was also suspected (as shown in Figure 1) that these immediate changes may not be sustained, but it was not known whether this progressive decrement in the initial change affected both stroke volume and BP and, if it did, whether it affected them to the same extent. The study was, therefore, exclusively designed to examine the temporal characteristics of secondary progressive changes in stroke volume and BP after the initial instant effect of change in AV delay. We knew that these secondary changes were likely to be smaller than the initial instant effects. To be able to confidently describe the pattern of these secondary changes, it was essential that the signal-to-noise ratio would be large enough for these response patterns to be distinguished from the spontaneous natural fluctuations that always occur in both variables. To achieve this, we required the signal to be large and the noise to be small.

To make the signal large, we designed the protocol to change the AV delay setting from one that would be far from optimal in every patient studied to another setting that would be much better in every patient studied. We settled on 40 and 120 ms, respectively, because our previous experience is that 40 ms is always far from optimal,6 whereas 120 ms is a common default setting that has frequently been used as a reference setting in our research.5,7 To make the noise (SE) small for each patient, we performed multiple replicates of each change in setting and averaged the replicates. Maximizing the number of replicate measurements per patient allowed the physiological response to be discriminated more precisely.

We have previously found, in common with other investigators,5,17,18 that the effect of changing AV delay is much larger than the effect of changing interventricular (VV) delay.6 We, therefore, chose to focus on the AV delay in this study, programming a fixed VV delay with the nominal setting of 0 ms as our standard throughout the patient group.

The paced heart rate was maintained at 120 bpm because previous data have shown that alterations in AV delay have a more pronounced effect on BP and cardiac output at higher heart rates.7 The optimal AV delay at 120 bpm correlates well with the optimal at rest,19 but the greater difference in hemodynamic parameters at the higher heart rate is because of the greater importance of LV filling characteristics when diastole is shorter. This elevated heart rate also means that a uniform protocol can be used, with all subjects being both A and V paced throughout the study.

**Experimental Protocol**

Continuous beat-to-beat BP and cardiac output were recorded using the Finometer, with simultaneous measurement of aortic Doppler
flow velocity from which stroke volume and cardiac output were calculated, during adjustment of the AV delay of the subjects’ pacemaker.

We performed continuous ECG recording and confirmed in all subjects that the QRS morphological features were consistent at both AV delay settings, thereby ensuring that there was full capture of the ventricles irrespective of the programmed AV delay.

Pacemaker reprogramming was performed via a pacemaker telemetry head positioned on the subjects’ skin over their implanted device, to enable the AV delay to be changed according to protocol. Changes to AV delay were programmed without concomitant alterations to the programmed heart rate. Finometer and Doppler data were collected for 10 beats before and 20 beats after the change in AV delay. The mean arterial pressure (MAP) was approximated using SBP and DBP in the usual way: 

$$\text{MAP} = \frac{2}{3}(\text{SBP} - \text{DBP})$$

Each AV delay change was performed in quintuplicate, and the data were averaged to minimize the effect of noise, and of variation in stroke volume caused by, for example, respiration.

In a small subset of 5 patients (3 male and 2 female), we also performed prolonged data acquisition for 1 minute (120 beats) after the AV delay change. These patients had similar characteristics to the overall patient group (3 with depressed and 2 with normal cardiac function) but were the final 5 subjects recruited because the extended recording was thought worthwhile to add as an adjunct substudy.

Calculation of Relative Change in BP and Cardiac Output Between 2 AV Delays

The baseline values for SBP, DBP, MAP, and cardiac output for each AV delay change were defined as the mean of the values for the 10 beats before the change in AV delay. We then calculated the relative change ($\Delta$) in each of the hemodynamic parameters by comparing the mean of the data from the 10 beats after a change in AV delay with the baseline value. The results of the 5 changes were then averaged.

Beat-to-Beat Data Analysis

To accurately assess whether the initial increments in BP and stroke volume after the change in AV delay from 40 to 120 ms declined after the AV delay change, we analyzed beat-to-beat data. For each beat before and after the change in AV delay, we measured SBPs and Doppler-derived stroke volume. We also calculated a baseline consisting of the mean of the final 10 beats of 40 ms before the AV delay change. All beat-to-beat data were then expressed relative to this baseline as $\Delta$SBP, $\Delta$DBP, $\Delta$MAP, and $\Delta$Q.

We then quantified the decline by applying linear regression and tested whether the slope was significantly different from 0.

Calculation of the Relevant Signal/Noise Ratio

The relevant characteristic of a variable used to detect a change is not the percentage change in response to an intervention but rather the degree of beat-to-beat variability of the baseline value.

The signal/noise ratio was calculated by dividing the signal, defined as the change in a variable ($\Delta$SBP, $\Delta$DBP, $\Delta$MAP, and $\Delta$Q), by the noise. Signal was defined as the mean of the first 10 beats after the change in AV delay (the short-term peak) minus the mean of the immediately preceding 10 beats. Noise was defined as the SEM of those preceding 10 beats.

A high signal/noise ratio for a variable means that the magnitude of the effect induced by the AV delay change is large compared with the uncertainty (arising from random beat-to-beat variation) in that measured magnitude of effect.

Statistics

Distributions are described by the mean±SD because all data met the criteria for normality. The precision of the estimate of the mean is described by the SEM. Comparisons between groups of numeric values were made using the Student t test, with 2-tailed hypothesis testing.

Correlations were measured using the Pearson correlation coefficient (with calculation of 95% CIs of r based on the Fisher r-to-z transformation), and the slope of the reduction in the BP and stroke volume data was measured using least-squares linear regression. To calculate the response across all subjects, we calculated the beat-to-beat relative change in each parameter compared with baseline, and then averaged the data across the entire subject group. $P<0.05$ was considered significant. Statistical analysis was performed using StatView software, version 5.0 (SAS Institute Inc; Cary, NC).

Results

Patient Characteristics

Of the patients, 12 were male and 7 were female (age range, 46–88 years; mean, 72 years; Table 1).

Indications for pacemaker implantation in the patients with normal systolic function comprised sinoatrial node disease (n=2), complete heart block (n=3), AV block (n=4), and syncope (n=1). Eight of the patients with heart failure had biventricular pacemakers implanted for conventional resynchronization indications, and one had a dual-chamber pacemaker implanted for complete heart block. The mean baseline sensed and paced AV delay was 120 ms (range, 80–160 ms).

In the heart failure group, most patients were New York Heart Association class II/III at the time of the study (class I, 1 patient; class II, 3 patients; and class III, 5 patients).

All patients tolerated the protocol well, without symptoms or ECG changes.

Immediate Effect of Change in AV Delay on BP and Stroke Volume

When AV delay was changed from 40 ms (unphysiologically short) to 120 ms (a more physiological value), there was an immediate increment in all hemodynamic parameters (Table 2) across all subjects, as expected. The SBP increased by an average of $19.7\pm9.5$ mm Hg (mean±SD) or, in relative
terms, 16.5±7.9% of its prior value. Cardiac output measured beat to beat by Doppler echo VTI in the LV outflow tract increased by an average of 9.7±4.8 mL/beat (20.7±10.3%) across all patients. Individual patient data are shown in Table 3.

There was a strong correlation between the initial increments in MAP and cardiac output (r=0.74, P<0.001).

Divergent Behavior of BP and Stroke Volume After the Initial Synchronous Increment

After the initial increase, the beat-to-beat BP-derived measurements showed a gradual, but distinct, decline after 5 to 10 beats (Figure 2).

All measures of increments in BP declined progressively from 5 beats after the change in AV delay. Across all subjects, SBP decreased by an average of 1.28 mm Hg/s from 5 beats after the change in AV delay. Across all patients. Individual patient data are shown in Table 3.

Table 3. Individual Patients’ Responses to a Change in Programmed AV Delay From 40 to 120 ms Across All Subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Group</th>
<th>SBP Change, %</th>
<th>DBP Change, %</th>
<th>MAP Change, %</th>
<th>Stroke Volume Change, %</th>
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<tr>
<td>1 HF</td>
<td>24.9</td>
<td>19.6</td>
<td>21.8</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>2 NHF</td>
<td>25.4</td>
<td>18.4</td>
<td>22.0</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>3 HF</td>
<td>12.1</td>
<td>9.7</td>
<td>10.3</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>4 HF</td>
<td>11.4</td>
<td>8.0</td>
<td>9.6</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td>5 NHF</td>
<td>12.2</td>
<td>3.1</td>
<td>6.0</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>6 NHF</td>
<td>20.0</td>
<td>16.2</td>
<td>18.2</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>7 HF</td>
<td>21.0</td>
<td>12.9</td>
<td>16.6</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>8 HF</td>
<td>14.3</td>
<td>8.0</td>
<td>11.1</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>9 HF</td>
<td>25.3</td>
<td>16.1</td>
<td>20.5</td>
<td>22.8</td>
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<tr>
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<td>12.7</td>
<td>15.7</td>
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</tr>
<tr>
<td>11 NHF</td>
<td>28.1</td>
<td>10.6</td>
<td>20.3</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
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<td>-0.9</td>
<td>-0.7</td>
<td>3.5</td>
<td></td>
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<tr>
<td>13 NHF</td>
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<td>8.4</td>
<td>11.1</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
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<td>15 HF</td>
<td>16.6</td>
<td>7.8</td>
<td>12.7</td>
<td>13.4</td>
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</tr>
<tr>
<td>16 HF</td>
<td>1.5</td>
<td>-1.3</td>
<td>0.1</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>17 HF</td>
<td>15.4</td>
<td>12.0</td>
<td>13.4</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
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<td>9.1</td>
<td>6.9</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td>19 NHF</td>
<td>31.7</td>
<td>28.8</td>
<td>30.0</td>
<td>41.3</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. P<0.0001.

In contrast, the beat-to-beat stroke volume measurements showed that the initial increment in cardiac stroke volume at the AV delay change was sustained throughout the recording period, with no significant decline (r=0.46; 95% CI, -0.05 to 0.78; Figure 3).

Extended Recording Substudy

In a subset of 5 patients, we used repeated experimental sequences to acquire stroke volume and BP data over a longer composite time frame than could be acquired in a single recording, to determine the pattern and time frame of change.

The first part of these extended recordings was consistent with the findings in the overall patient group. The initial BP increment then declined by ∼33% from the peak (SBP, 28%; MAP, 32%; DBP, 39%) to form a plateau after ∼30 beats. Stroke volume, however, did not decline from its initial increment (Figure 4).

Comparison of Signal/Noise Ratio for Mean Arterial BP and Cardiac Output

The signal/noise ratios of the arterial BP increment, measured using the Finometer, and cardiac output increment, measured using Doppler echocardiography, were compared to determine whether they were equivalent in terms of information quality (Figure 5). We quantified the signal/noise ratio (namely, the change in a hemodynamic parameter elicited by pacemaker reprogramming/within-patient SD in that measure in the preceding beats).

Each of the Finometer-measured indexes had a significantly higher signal/noise ratio than the gold standard noninvasive measure of cardiac output using Doppler (mean±SD signal/noise ratio for SBP versus Doppler stroke volume, 6.8±3.5 versus 2.3±1.4; P<0.001; Figure 5).

The higher signal/noise ratio for the Finometer-derived measurements compared with the Doppler-derived measurements is because of the significant beat-to-beat variability of the Doppler trace. This was seen in all of the individual patient data (Figure 6 and all individual patient data published in the Online Only Data Supplement).

Comparison of Responses Between Subjects With Heart Failure and Those With Normal Systolic Function

The magnitude of the responses in all of the variables to the change in AV delay from 40 to 120 ms was not significantly different between patients with heart failure and those with normal systolic function (mean±SD values for SBP % change, 14.7±7.3% versus 18.2±9.5% [P=0.39]; DBP % change, 9.7±5.9% versus 11.9±8.2% [P=0.50]; MAP, 12.0±6.5% versus 14.6±9.0% [P=0.48]; and stroke volume, 19.1±7.4% versus 21.5±12.5% [P=0.63]).

We compared the rate of decline of the BP and stroke volume increments in the patients with impaired systolic function with those with normal systolic function and found that the pattern of response was similar in the 2 groups. The rate of decline of SBP across the heart failure subjects was 1.29 mm Hg/s (r=0.88, P<0.001), compared with 1.28 mm Hg/s (r=0.96, P<0.001) in the subjects with a normal systolic function, with no significant difference be-
tween the groups. There was not a significant downward trend in stroke volume with time after the initial increase at the change in AV delay in either subject group.

**Discussion**

We find that, on changing AV delay, both stroke volume, measured using Doppler, and BP, measured using the Finometer device, show discernable reproducible increments and, therefore, have the potential for use as physiological markers to guide pacemaker optimization.

The effect of AV delay modification on stroke volume is immediate and persistent. However, BP, despite an initial parallel effect, subsequently partly decays back toward its prior value. We can conclude that this decay in BP is, therefore, the result of compensatory vasodilatation (which may be beneficial to the patient) rather than a loss of the increment in stroke volume.

Although the persistent nature of the stroke volume elevation permits a longer window of opportunity to measure it, this has to be balanced against the much greater operator skill needed to obtain and quantify Doppler data and its significantly poorer signal/noise ratio. If BP is to be used as a hemodynamic marker to guide pacemaker optimization to avoid the acquisition and interpretation difficulties inherent in a Doppler approach, the BP recording should be made in the initial phase after a change in pacemaker parameter when the signal is richest in information.

**Optimization of Pacemaker AV (and Interventricular) Delay Settings**

Many methods for device optimization have been proposed, including invasive hemodynamics, impedance cardiography, and implantable hemodynamic monitors. The meth-

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**Figure 2.** Beat-to-beat data for each of the hemodynamic measures during a change in AV delay from 40 to 120 ms, averaged across all subjects. Almost immediately after the change in AV delay (at beat 0), there is a sharp significant increase in all measures of BP and cardiac output. However, after a few beats, BP gradually decreases, whereas stroke volume remains elevated. Data represent the mean ± SEM. DBP indicates diastolic BP; MAP, mean arterial pressure; SBP, systolic BP.

**Figure 3.** Rate of decline of hemodynamic measures between beats 5 and 20 after the change in AV delay, averaged across all subjects. There was a clear decline in all BP-derived measures from 5 beats after the change in AV delay. In contrast, stroke volume, as measured by Doppler echocardiography, retained almost all of the increment caused by the change, throughout the recording period. Data represent mean ± SEM. DBP indicates diastolic BP; MAP, mean arterial pressure; SBP, systolic BP.
ods most commonly used are based on Doppler, using either the velocity time integral of aortic outflow\textsuperscript{23,24} or the Ritter method\textsuperscript{25} which determines the longest filling time associated with complete atrial systole uninterrupted by ventricular systole. There are, however, substantial technical difficulties with using Doppler echocardiography for pacemaker optimization in that it is time-consuming, needs skilled operators, and is difficult to perform during exercise and in nonechogenic patients.

Noninvasive beat-to-beat measurement of BP has been recently developed as an alternative approach to pacemaker optimization.\textsuperscript{6,7,9,10,19} This is significantly faster to perform, does not require skilled operators, and can, in principle, be performed on any patient, including under physiological conditions other than rest, if desired. It could also potentially be automated (further increasing the optimization process), and the data have a significantly higher signal/noise ratio.

Recently, contrary to previous individual studies\textsuperscript{4,23} SMART-AV, a carefully designed, prospectively recruited, externally monitored, randomized controlled trial has shown that neither the qualitative iterative method (whereby an echocardiogram operator qualitatively selects the visually most desirable transmitral Doppler profile) nor a proprietary ECG-based optimization (designed to match qualitative echocardiographic optimization) confer clinical benefit long-term to patients with heart failure.\textsuperscript{26} Trials of quantitative optimization are under way.

An evaluation of the clinical impact of optimization algorithms may be prolonged, expensive, and disappointing unless a rational process of selection of algorithms is applied early. First, test-retest reproducibility of the optimum delay should be evaluated in dispassionate blinded hands. Poor test-retest reproducibility disqualifies an optimization method early (and cheaply), although good reproducibility is no guarantee of suitability (and good between- and within-observer remeasurability on identical preacquired data sets gives no reassurance). Second, within the set of algorithms with good test-retest reproducibility, a head-to-head comparison of optima in the same patients may show clustering (some algorithms frequently agreeing with each other) on the optimum, whereas other algorithms rarely agree with the others. The clusters of test-retest reproducible algorithms...
with good mutual agreement are the most plausible as valid optimization methods. Because they frequently agree, any one of them might be chosen for the third stage of assessment of clinical end point impact in a prospectively recruited, randomized, controlled trial.

Mechanisms of Hemodynamic Changes During Changes in Atrioventricular Delay

Until this study, it was unclear whether the reduction in the BP increment after a change in AV delay was purely the result of compensatory vasodilatation or whether there was a significant contribution from decay in the stroke volume increment, which would clearly be deleterious in the heart failure population, in whom BP is such a significant prognostic marker.27

We found that during the 20 to 30 beats after the initial peak increment in BP, ≈33% of that increment was lost; after that time, there was no further loss up to 120 beats. In contrast, stroke volume maintained its increment, with no sign of decay. This indicates that the important benefit of increased cardiac function (namely, increased stroke volume) is preserved, and that the decline in BP is the result of compensatory vasodilatation and the increase in the Windkessel charging. The Windkessel effect is the mechanical capacitor effect of the great vessels in response to cardiac ejection, that “cushions” the peripheral vasculature from changes in stroke volume.28

We speculate that there are 4 phases to the short-term hemodynamic response to a change in AV delay. First, the improved LV filling increases stroke volume, and this partly goes toward progressively charging the Windkessel and partly toward increasing the BP. Second, the Windkessel capacitor is fully charged, and BP is maximal. Third, reflexes stimulate peripheral vasodilatation, meaning that the overall BP increment declines: in our data, this seems to start ≈10 beats (≈5 s) after the increase in stroke volume, consistent with the response time of the baroreflex.29 Fourth, a steady state is reached and BP joins the stroke volume in a plateau phase.

In summary, although the first few beats after a change in AV delays reflect the changes in cardiac output, the subsequent beats reflect reflex changes in systemic vascular resistance.

We also found that there was no difference between the subjects with heart failure and those with preserved systolic function in the patterns of response after a change in AV delay and, specifically, that the rate of decline in the BP increment was similar in the 2 groups. The implication is that, despite the likely differences in physiological responses between these groups, the phenomenon of secondary decline in pressure is conserved.

Implications for Hemodynamic Optimization

These results have importance for measurement during the clinical optimization of AV and interventricular delay of biventricular pacemakers. We found that, despite a decrease in the noninvasive BP measured, there is no concomitant decrease in stroke volume, meaning that if measurements are taken in the initial phase after a change in AV delay, noninvasive BP is a suitable surrogate marker for stroke volume and, hence, cardiac output.

Although stroke volume, measured using Doppler echocardiography, is a direct measure of cardiac function after a change in AV delay, the signal/noise ratio is 3-fold poorer than that of noninvasive BP measurements. The physiological sensitivity of Doppler stroke volume measurements is greater than that of the BP measurements because of the influence of respiration; however, these fluctuations reduce the detection of “genuine” changes in stroke volume that result from a change in pacing parameters. There is also more measurement error contributing to the Doppler data, because of the practical difficulties with maintaining a constant Doppler angle and position for repeated and prolonged measurements during optimization. Because of the 3-fold poorer signal/noise ratio with the Doppler data, it would take 9 (3^2) times as many beats to obtain the same discriminatory power using stroke volume rather than BP.

The fact that the BP increment partially declines after optimization has created a quandary for investigators designing a protocol based on BP for hemodynamic optimization, because it is unclear when the BP increment should be measured. Some investigators have elected to omit the first few beats after an AV delay change.9,20 However, they are then measuring the change in stroke volume resulting from a change in AV delay and incorporating a function of the subject’s vasomotor tone and reactivity, a variable that

![Figure 6. Individual example beat-to-beat data for systolic BP (SBP) and stroke volume](http://circep.ahajournals.org/). Data shown are the mean±SE beat-to-beat BP and stroke volume data for 5 replicate transitions in AV delay from 40 to 120 ms in 1 subject. Systolic BP had significantly less beat-to-beat variability than the Doppler-derived stroke volume data. This resulted in a much larger “noise” denominator of the signal/noise ratio calculation for the Doppler stroke volume than for BP. All other individual patient data can be found in the Online Only Data Supplement.
changes even within an individual subject with time. Our data indicate that it would be preferable to focus on the initial BP change and that it may be counterproductive to “skip” beats after the AV delay change because those skipped beats would have been the richest source of information about cardiac output changes.

An easy, time-efficient, noninvasive, rapid, and potentially reproducible method for optimization of biventricular pacemakers may, therefore, be to measure beat-by-beat BP averaged over the first 10 beats after a change to the tested setting, compared with the beats before the transition (in a common reference state used for all the tested settings). The relative status of each AV and/or interventricular delay can then be compared with the common reference, and along a common scale. It would be important to perform each test in enough replicates within the patient and average them to ensure that the inevitable chance variation is not mistaken for optimization.7,30

**Study Limitations**

In this study, we aimed to assess the cardiovascular mechanisms behind the short-term hemodynamic responses to a change in AV delay, which could later be exploited for scientific development of pacemaker optimization. This was not itself a study of optimization, and we were not assessing long-term clinical outcomes. We did not attempt to determine the optimal delay for each subject, to assess which method is the most sensitive for determining the optimal AV delay, or to draw conclusions concerning the long-term effects of optimization.

We performed elaborate beat-to-beat VTI measurements in an experimental protocol that focused on a single and consistent type of AV delay change. We designed the study to use the change in AV delay from 40 to 120 ms because our experience7 has shown that this change is likely to cause an increase in BP in all subjects and, therefore, would be suitable to use to explore the hemodynamic mechanisms. We did not assess the short-term beat-to-beat effects of each potential AV delay change because of the many measurements that would be needed to do this adequately. For example, suppose we had chosen to test, in addition to 40 ms, another setting twice as close to 120 ms (ie, 80 ms). Because of the parabolic shape of hemodynamic responses, we would expect its hemodynamics to be 4 times closer to those of 120 ms (ie, the signal would be ¼ the size of the signal for 40 to 120 ms). To preserve the signal/noise ratio so that the time course can be studied, because shrinkage of noise is proportional to the square root of the number of replicates, we would need 16 times more replicate measurements per setting tested, or 16 times more patients. In general, studying the region N times closer to the optimum requires ≈N^2 more data to be acquired per setting.

Our study was limited to noninvasive measurements; conceivably, invasive measurements might show different findings because of the ability to make more central measures of beat-by-beat pressure directly.

This study included both healthy subjects and subjects with heart failure. Although these are 2 groups with different clinical characteristics, we found that the pattern of hemodynamic responses to changes in AV delay was similar, irrespective of clinical group. This showed that the responses were not limited to heart failure subjects but were a phenomenon of any paced patient.

**Conclusions**

The early increase in BP is a valid marker of cardiac performance for optimization of pacemaker settings. Although it declines slightly after a few beats, this is not accompanied by any decline in stroke volume. The partial decline in BP is the result of compensatory vasodilatation, which is clinically desirable, rather than any reduction of cardiac performance.

If economy of time is a concern, the 3-fold higher signal/noise ratio for BP should translate into a 9-fold shorter time to deliver an optimum of the same precision versus quantitative Doppler optimization. Moreover, rather than prolonged BP recording after the signal attenuates, replicating the transition in pacemaker setting and remeasuring the signal at full strength may be wiser.

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**Disclosures**

None.

**References**


Optimization of the AV and VV delay settings of cardiac resynchronization devices is increasingly being performed clinically to maximize their potential therapeutic benefit. There is no universally accepted method for performing such optimization, although noninvasive blood pressure measurement is rapidly gaining recognition as a potential guide. Previous studies have shown, however, that the initial blood pressure increment obtained on optimization decays somewhat over the initial minutes after the transition in pacemaker settings. This decline could represent a (detrimental) decrease in cardiac output, or be the result of (desirable) compensatory changes in peripheral vascular tone. This study demonstrates that the cardiac output improvement is maintained after AV delay optimization, and that the reduction in blood pressure readings is secondary to compensatory vasodilatation. This differential pattern of response in pressure and flow to changes in pacemaker AV delay is important for understanding the physiological characteristics and critical for improving the design of quantitative pacemaker optimization protocols. This study also investigates the suitability of both noninvasive blood pressure and conventional Doppler echocardiography as markers to guide pacemaker optimization. It is important to develop optimization protocols that deliver reliable, reproducible, optimum delay settings, and understanding the relative temporal behavior of signal and noise, in pressure and flow, is critical to this understanding. Noninvasive blood pressure is easier to measure and interpret (by nonskilled operators), with significantly less noise, and the latest phase (before vascular compensation) has the greatest signal information content.

CLINICAL PERSPECTIVE
The Acute Effects of Changes to AV Delay on BP and Stroke Volume: Potential Implications for Design of Pacemaker Optimization Protocols


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Figure – Beat-by-beat blood pressure and stroke volume data for every individual subject during a change in AV delay from 40-120ms (averaged across 5 cycles)

There was an acute increase in stroke volume and systolic blood pressure when the AV delay was re-programmed from 40-120ms. The increment in stroke volume was maintained, whilst the increment in blood pressure gradually declined over the subsequent 20 heart beats. This response pattern was consistent across the subject group, with no differences noted between patients with heart failure and those without.