Fully Automatable, Reproducible, Noninvasive Simple Plethysmographic Optimization: Proof of Concept and Potential for Implantability


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**Background:** Hemodynamic optimization of cardiac resynchronization therapy (CRT) can be achieved reproducibly and—with bulky, nonimplantable equipment—noninvasively. We explored whether a simple photoplethysmogram signal might be used instead.

**Method:** Twenty patients (age 65 ± 12) with CRT underwent automatic atrioventricular (AV) delay optimization, using a multiple-transitions protocol, at two atrially paced heart rates: just above sinus rate (“slow ApVp,” 77 ± 11 beats per minute [bpm]) and 100 bpm (“fast ApVp”). We then retested to assess short-term reproducibility.

**Results:** All 80 optimizations identified an optimum (correctly oriented parabola). At 100 bpm, the simple photoplethysmogram had wider scatter between repeat optimizations than did Finometer: standard deviation of difference (SDD) 22 ms versus 14 ms, respectively, \( P = 0.028 \). The simple photoplethysmogram improved in reproducibility when slope (instead of peak) of its signal was used for optimization, becoming as reproducible as Finometer (SDD 14 ms vs 14 ms, \( P = 0.50 \)). At slow heart rate, reproducibility of simple photoplethysmogram-based optimization worsened from 14 to 22 ms (\( P = 0.028 \)), and Finometer-based optimization from 14 to 26 ms (\( P = 0.005 \)). Increasing the number of replicates averaged improved reproducibility. For example, SDD of simple photoplethysmogram optimization (using peak) fell from 62 ms with two replicates to 22 ms with eight replicates (\( P < 0.0001 \)).

At 100 bpm, the eight-replicate protocol takes ~12 minutes.

**Conclusions:** A 12-minute protocol of simple photoplethysmographic AV optimization can be processed fully automatically. Blinded test-retest reproducibility of the optimum AV is good and improves with more replicates. If benefits to some patients are not to be neutralized by harm to others, endpoint studies should first test check narrowness of “within-patient error bars.” (PACE 2012:1–13)

CRT, AV optimization, photoplethysmography

**Introduction**

Cardiac resynchronization therapy (CRT) can show an immediate improvement in hemodynamic status.\(^1\)–\(^8\) Adjusting the atrioventricular (AV) delay for an individual patient may improve acute hemodynamics further.\(^7\)–\(^9\)–\(^11\)

Beat-to-beat hemodynamics has been shown to achieve reproducible optimization of AV delay with narrow error bars for the optimum in individual patients.\(^11\) This can be conducted invasively in the catheter lab or noninvasively with beat-to-beat monitors using one of many commercial devices such as the Finometer (Finapres Medical Systems, Amsterdam, the Netherlands), Nexfin (BMEYE, Amsterdam, the Netherlands), and Task Force Monitor (APC Cardiovascular, Crewe, UK), which all operate using a similar approach to pressure measurement in the finger, first made commercially by Ohmeda (Englewood, CO, USA) in the original Finapres device. Briefly, they all measure the pressure required to be
applied externally to keep the volume of the finger constant over time despite the within-beat and between-beat fluctuations in arterial blood pressure. This permits the device to track blood pressure within the cardiac cycle and over longer periods of time. However, the equipment is not widely available to those responsible for adjusting CRT timings. Moreover, the technology could never be miniaturized for implantation with the pacemaker, which would be the ideal for any optimization technique. An automated fully implanted system might permit optimization to be conducted during sufficiently long episodes of different states, such as different postures or heart rates, and the optima stored and applied appropriately during everyday activities.

Invasive catheter lab measurements have advantages of availability and directness, but they are not practical if optimization has to be repeated. Variability between beats, which always causes test-retest variability of the optimum, can be seen by simultaneous catheter lab measurements of invasive and noninvasive pressures to be manifestations of true fluctuations in pressure and not an artifact of the measurement method (Fig. 1). In order not to limit our research to patients in the catheter lab, we have been studying other noninvasive approaches to AV optimization, which permit assessment of test-retest reproducibility—crucial for any process of optimization—without risk to the patient.

Alternative hemodynamic technologies with narrow within-patient error bars would be attractive if miniaturizable.

In this study, we evaluated the potential of a simple photoplethysmographic signal to identify the optimal AV delay. A pulse oximeter probe is simple, cheap, and miniaturizable enough to implant. We wanted to compare optima obtained by this method with optima obtained by another technique. It was essential that test-retest reproducibility of both techniques was quantifiable, because two techniques cannot agree better than they each agree with themselves.

![Figure 1. Beat-to-beat comparison of invasive and noninvasive blood pressure. Simultaneous proximal aortic, using a JR4 catheter (top panel), and Finometric noninvasive (bottom panel) blood pressure. Blood pressure variability is similar in both the invasive and noninvasive measurements. At the point of AV transition from 120 to 40 ms, the drop in blood pressure and subsequent partial recovery are evident in both the invasive and noninvasive pressure traces.](image-url)
Echocardiographic optimization, between test and retest, does not yield narrow within-patient error bars under blinded conditions and therefore was not used as the comparator. Invasive optimization can provide narrow within-patient error bars but would limit enrollment to patients undergoing invasive procedures such as implantation rather than permitting us to enroll less selected patients. We therefore used, as the comparator, the optimum obtained using a Finometer. The Finometer is not a gold standard but merely a convenient local method for estimating a physiologically optimum AV delay which is known to deliver good test-retest reproducibility.

To test how well this approach might work using equipment very familiar to us as general cardiologists, we used a pulse oximeter from our ward. Unlike the Finometer signal, however, the raw pulse oximeter signal is not a direct proxy for pressure. First, the signal output by an unmodified oximeter has already been processed by electronic filters that remove baseline trends over a few beats because these are not relevant to assessing oxygen saturation—yet these trends contain the information needed for optimization. Second, the pulse oximeter signal contains information about blood volume changes in small blood vessels, including capillaries and venules, and hence is sensitive to respiration and body movement. Accordingly, we arranged for the patient to lie still and fitted a switch to allow the built-in electronic filters to be switched off.

In this small proof of concept study, we compared the two technologies in the hemodynamic optimization of AV delay. We evaluated the relative reproducibility of optimization by each technology, head to head, and aimed to minimize bias.

Second, we assessed the utility of another measurement easily derived from the pulse oximeter, namely the peak rate of rise of the systolic upslope (maximum of first derivative), rather than simply the peak systolic value, to identify the optimal AV delay in each patient.

Third, we explored the effect of elevation of heart rate and of averaging multiple replicates of measurements on the reproducibility of optima derived by the two technologies and evaluated the clinical time taken to perform a hemodynamic optimization session using each technique.

Methods

Subjects

Twenty ambulatory patients with biventricular pacemakers or biventricular defibrillators implanted for clinical indications were enrolled in this study.

At the time of study, 3 patients were in New York Heart Association (NYHA) class I, 11 were in NYHA II, and six were in NYHA III. Eleven patients were male, age range 46–81 years (mean 65 years). Cause of heart failure was ischemic in eight, idiopathic dilated in 10, and hypertensive in two. Mean systolic blood pressure (SBP) by sphygmomanometer was 105 (standard deviation [SD] 12) mmHg. Left ventricular ejection fraction was 33 (SD 8)%.

Sixteen patients were taking angiotensin-converting enzyme inhibitors, six angiotensin-II receptor antagonists, 18 β-blockers, seven spironolactone, 12 a diuretic (loop or thiazide), and six digoxin. Patients gave written informed consent for this study which was approved by the local ethical committee.

Measurements

Simple Photoplethysmogram

We recorded the transcutaneous photoplethysmogram signal using a modified finger probe pulse oximeter (Ohmeda Biox 3700e, GE Healthcare, Waukesha, WI, USA). The pulse oximeter had to be modified slightly for use in this study. Standard clinical pulse oximeters have circuitry to rescale the detected signal continuously because of the wide dynamic range of pulse oximetry signal between patients. The continuous rescaling keeps the electrical signal in a range suitable for amplification and display on a screen. However, for the purpose of optimization, it is important for the scale to be held constant while the AV setting is changed, so that the impact of the change in AV delay is not confounded by changes in scale.

Autorescaling cannot be completely dispensed with, however, because there is still the problem of wide between-patient differences in average light absorption. We therefore fitted a switch to allow autorescaling to be switched on and off as appropriate to allow the appropriate scale for each individual patient to be established before the pacemaker optimization began.

Each patient needed one brief period of initial scaling of the signal while lying comfortably until an adequate pulsatile signal was obtained, which may take 5–10 seconds, as would be the case if the device was being used to measure oxygen...
Beat-to-Beat Continuous Noninvasive Blood Pressure Monitoring

We used a Finometer to record beat-to-beat noninvasive blood pressure. This technique, developed by Peñáz and Wesseling et al., uses a rapid servo system with a finger cuff actuator, allowing it to adjust the pressure in a finger cuff to keep a reference photoplethysmogram signal flat throughout systole and diastole. Achieving this constant blood volume within the finger means the extramural pressure being applied must be matching the intramural pressure, and therefore the time course of the pressure that the cuff has had to apply can be treated as the intrarterial pressure waveform. This process, volume-clamp photoplethysmography, is well validated for measuring instantaneous changes in blood pressure.

An electrocardiogram signal was recorded using Hewlett-Packard 78351A monitor (HP, Palo Alto, CA, USA). Analog signals were taken via a National instruments DAQ-Card AI-16E-4 (National Instruments, Austin, TX, USA) and Labview (National Instruments). They were analyzed offline with custom software based on the Matlab platform (The MathWorks, Natick, MA, USA).

Protocol of Hemodynamic AV Optimization

We carried out AV optimization using the protocol of multiple replicate transitions between a fixed-reference AV delay (AV 120 ms) and a number of prespecified tested AV delays (potentially 40, 80, 140, 160, 200, 240, 280, 320 ms but limited to the AV settings which give ventricular pacing rather than intrinsic ventricular conduction).

For each tested AV delay, we calculated the relative change in the hemodynamic signal when AV delay was transitioned from the reference (AV 120 ms) delay to the tested delay. We defined this difference as the average measurement (such as SBP) for the 10 beats after the transition minus the 10 beats before it.

We made eight replicate measurements of this difference (Fig. 2): four with “forward” transitions as described earlier and four with “backward” transitions in which case the sign of the change in signal was reversed.

The photoplethysmogram and the Finometer blood pressure waveforms were recorded simultaneously during the AV transitions. One sensor was placed on the index finger of one hand, and the other on the index finger of the other hand.

We conducted AV optimization separately at two heart rates: an atrially paced rate just above the individual patient’s resting sinus rate (averaging 77 beats per minute [bpm]), which we called “fast ApVp,” and at an atrially paced rate of 100 bpm, which we called “fast ApVp.”

To assess reproducibility, the entire process was repeated on the same day in all 20 patients, at each heart rate.

From the Finometer data, each beat was assessed by the peak SBP and the steepest rate of increase in the blood pressure (i.e. maximum first derivative). From the simple photoplethysmogram data, similarly the peak value and the steepest systolic upslope were evaluated.

All processing was conducted automatically off-line immediately after the protocol ended, not because it was complex or time-consuming but because the optimization process depended on the relative levels of the measurements at all the tested settings, which was only determinable after all settings had been tested. Processing the data took less than 30 seconds and would have been less than 1 second if pacemaker manufacturers provided real-time output of actual AV delay beat-by-beat in computer-readable form.

For each individual patient, the hemodynamic value for each tested AV delay (relative to the reference AV delay, 120 ms) was plotted and a quadratic curve was fitted. The peak of the resulting curve was taken as the optimal AV delay (Fig. 3). This was carried out separately for Finometer data and simple photoplethysmogram data.

All steps of the acquisition and analysis, including calculation of the optimum, occurred fully automatically from the data, using custom software (which is available to researchers from the authors). The only manual step required was the changing of pacemaker settings. Manufacturers do not yet allow general clinical users to do this under automatic control: in this study, a human operator changed the settings at the times indicated by the algorithm.

Statistics

We used a Bland-Altman analysis to compare between one optimization session and another, and to compare one hemodynamic technology with the other. The uncertainty of the optimum, quantified by standard deviation of difference (SDD) between test and retest, was
compared between methods using the F-test. Throughout, a P-value of <0.05 was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Scientific Integrity

All authors confirm that the study was designed to make measurements without bias, to be held jointly and severally responsible for procedural deficiency, and to retract the paper if any is suspected. We are aware of no reason why the study, if reproduced in independent hands by these described methods, should give different results. Patients were recruited only by the method described. Measurements were made blinded and uniformly. No data were deleted, nor remeasured to favor one result over another.28 The authors are committed to conducting and presenting research reliably, and without precondition welcome workers seeking to confirm, develop, or contradict these findings.

Results

Comparison of Reproducibility of Optimal AV Delay between Simple Photoplethysmogram and Finometer

The reproducibility of the optimal AV setting (for eight replicates averaged), carried out on the same day at fast ApVp, was measured using the SDD.

The SDD was 22 ms for simple photoplethysmogram and significantly better, at 14 ms, for Finometer ($P = 0.028$).

Effect of Signal Processing (Peak vs Slope of Waveform) on Reproducibility of Hemodynamic Optimization

The reproducibility of optimal AV delay identified by simple photoplethysmogram improved when, instead of the peak, the slope (maximum of first derivative) of the waveform during the cardiac cycle was used. The SDD improved significantly from 22 to 14 ms ($P = 0.028$) for the photoplethysmogram, whereas it did not change significantly ($P = 0.20$) for the Finometer (Table I).
Identification of the optimal AV delay in an example patient using the peak of the waveform (photoplethysmogram) from the pulse oximeter. The optimization is composed of a series of individual transitions between the reference AV delay (120 ms) and a tested AV delay. Example of a single transition is shown in the top left panel; the mean of 10 beats (shaded area) before and after the transition is used to calculate the relative difference (arbitrary units). Multiple replicate transitions between the reference and the tested AV delay are shown in the top right panel. All the tested AV delays and their relative change (arbitrary units) to the reference AV delay are shown in the bottom panel. The peak of the inverted parabola corresponds to the optimal AV delay.

The individual reproducibility of each of the 20 patients is shown in Figure 4 for optimization using the slope of the waveform from the photoplethysmogram. It shows that individuals had very different optima, but each individual’s optimal AV delay was reproducible between one optimization and the next.

**Effect of Number of Replicates Analyzed on Reproducibility of Hemodynamic Optimum**

The reproducibility (standard deviation of the difference of optimum, SDD), using the peak of the waveform from the photoplethysmogram, improved progressively for two, four, and eight replicates: from 62 to 34 ms (P = 0.006) to 22 ms (P = 0.032), respectively, as shown in Figure 5. The same effect was seen when using the slope of the waveform. Similar effects were seen with the Finometer data (Fig. 5).

The agreement of the optimal AV delay between the two technologies similarly improved as the number of replicates was increased from two to eight: SDD fell from 51 to 19 ms (P < 0.0001), respectively.

**Effect of Heart Rate on Reproducibility of Hemodynamic Optimization**

By comparison to the reproducibility at fast ApVp, reproducibility at slow ApVp was significantly worse. The SDD of optima using the simple photoplethysmogram slope deteriorated from 14 to 22 ms at slow heart rate (P = 0.028), and using the Finometer peak it deteriorated from 14 to 26 ms at slow heart rate (P = 0.005).

**Discussion**

In this study, we have found that a simple photoplethysmogram can be used for optimization.
Figure 4. Individual parabolic optimization curves, when using the slope of the photoplethysmogram signal from the pulse oximeter, for each of 20 patients on two separate sessions. Each pair of curves shows the optimization pattern of a single patient (black = first optimization, red = second optimization). Arrows show the peaks of the fitted parabolas, which are taken as the optima. It can be seen that different patients have different degrees of curvature of their hemodynamic response and different optimal AV delays, but the optima are consistent between optimization sessions.

Figure 5. Impact of number of replicates averaged on the reproducibility and time consumed by optimization. Reproducibility improves as the number of replicates averaged is increased. This improvement for both technologies and for both types of signals is achieved at the expense of increased time consumed by acquisition of hemodynamic data. In each case, the reproducibility for the eight-replicate process is significantly better than the two-replicate process (P < 0.05 for each pairwise comparison).
Table I. Impact of Signal Processing on Reproducibility of AV Delay: Comparison between Simple Photoplethysmogram and Finometer

<table>
<thead>
<tr>
<th>Technology</th>
<th>Reproducibility (Standard Deviation of Difference, ms)</th>
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<tr>
<td></td>
<td>Using Peak</td>
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<tr>
<td>Photoplethysmogram</td>
<td>22</td>
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<tr>
<td>Finometer</td>
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The reproducibility (standard deviation of difference, SDD) of the simple photoplethysmogram significantly improves when the maximum slope (maximum of first derivative) of the waveform is used to define the optimal AV delay. The reproducibility of the Finometer, however, remains unchanged by this alternative signal processing.

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Proprietary plethysmogram devices using specially designed hardware, firmware, and software have already been introduced into research studies of pacemaker optimization. Our study shows that it is feasible to use the photoplethysmographic signal from a standard clinically available pulse oximeter in a routine outpatient clinical setting for a 12-minute optimization, that is, that no special processing of the oximeter signal by confidential methods is necessary. In all 20 of the 20 patients, the pulse oximeter shows an inverted parabola of hemodynamic changes (Fig. 4). Within patients, this peak is reproducible in successive optimizations; between patients there are large differences.

Optimization by photoplethysmography mirrors the findings of optimization by Finometer. Although the correspondence between Finometer and simple photoplethysmogram is not perfect, it should be remembered that the correspondence cannot be any closer than the reproducibility of each technology individually.

Hemodynamic optimization by Finometer and optimization by photoplethysmography are likely to be driven by the same underlying physiological principle. Discrepancy between them, being not substantially larger than the discrepancy between each technology and itself, is not grounds to reject one or the other.

Whether optimization by either of these two techniques agrees with other techniques is unknown at present, and is important for future independent workers to evaluate, providing that those other techniques also have sufficiently good blinded test-retest reproducibility of the optimum.

Processing of the Simple Photoplethysmogram to Maximize Information Value

Using the peak of the simple photoplethysmogram signal does not produce as good reproducibility, of optimal AV delays, as the peak of the Finometer signal does. However, by using the maximum steepness of the slope, instead of the peak, the reproducibility of the photoplethysmogram improves and matches that of the Finometer. Using the steepness of the slope of the Finometer waveform does not improve its reproducibility for purposes of optimization. We speculate that these findings are related to the different ways these technologies operate.
The Finometer, a volume-clamp photoplethysmographic technology, uses a rapid servo system with a finger cuff actuator, allowing it to adjust the pressure in a finger cuff to keep a photoplethysmogram signal flat throughout systole and diastole, which means effectively a constant blood volume within the finger. The extramural pressure required to achieve this is in principle equal to the intrarterial pressure and therefore the waveform of the extramural pressure applied by the finger cuff reflects the pressure waveform of the digital artery. The extramural pressure keeps the veins and venules largely collapsed because they have much lower intramural pressures than arteries. Therefore, they have very little influence on the waveform, which is therefore almost exclusively of arterial origin.

The simple photoplethysmogram, in contrast, picks up not only the arterial pulsations but also the slow fluctuations of venous volume, such as those arising from respiration. The simple photoplethysmogram is therefore much more influenced by the relatively slow fluctuations in venous volume (for example, with respiration) than is an arterial blood pressure monitor, and is influenced by nonlinear compliance properties of all blood containing components that contribute to its signal.

The additional source of noise (respiratory venous fluctuations) gives the photoplethysmogram a lower signal-to-noise ratio for detection of arterial pressure changes during changing of AV settings, and so gives poorer reproducibility of optimization.

Using the maximum of the first derivative (steepest slope) of the signal attenuates far more dramatically the slow fluctuations (i.e. noise, such as the venous respiratory trends) than fast fluctuations (i.e. arterial volume pulsations) (Fig. 6). This relatively enriches the useful arterial information in the simple photoplethysmogram, allowing it to become comparable with the arterial blood pressure monitor.

**Trade-Off between Time and Increasing Number Replicates to Improve Reproducibility**

This study shows that attempting to minimize the time consumed in an optimization process

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**Figure 6.** Differences in the beat-to-beat variability between the peak and the steepest slope of the photoplethysmogram signal. A recording of the beat-to-beat changes of the peak of the pulse oximeter photoplethysmographic signal through a series of transition periods (marked by the shaded areas) between the reference AV delay and a tested AV delay are shown in the top left panel. Beats before and after a transition are displayed in detail in the top right panel. The same recording is shown for the slope of the photoplethysmographic signal (bottom left and right panels). The beat-to-beat variability of the peak of the photoplethysmographic signal seems to be larger (black lines in top right panel) than the variability of its slope (flatter black lines in bottom right panel).
by limiting it to just a few measurements causes optimization to be poorly reproducible. Increasing the number of replicates of measurement progressively improves the precision of the optimum.

There is no established convention on how many replicate measurements should be made at each setting during an optimization. At which stage reproducibility becomes adequate, is a matter for the individual center to decide, but it is sensible to establish this from an informed position of knowing the trade-off between time and reproducibility for that institution’s preferred optimization method. Our group has recently evaluated this trade-off mathematically.\(^\text{12}\)

Certainly, there is no need to know the optimal AV delay more precisely than the pacemaker allows AV delay to be programmed. However, it may not even be justified to spend the time needed to reach that level of precision if this would take many hours in an optimization clinic.

However, if an optimization approach has a within-patient confidence interval so wide that it spans the entire range of plausible optimal AV delays,\(^\text{12,13}\) then it may be a rational alternative to set the AV delay to an arbitrary (even random) value to save time and expense of ineffectual optimization. Of course, both approaches are equally undesirable for the patient.

An automated optimization protocol of multiple transitions using a simple photoplethysmographic device could efficiently optimize cardiac resynchronization devices in a few minutes, without heavy demands on skilled operators.

The underlying mathematics\(^\text{12}\) indicates that the fundamental limit to optimization precision comes from the ratio between beat-to-beat variability and curvature of hemodynamic response. If beat-to-beat variability in measurements is largely due to resolvable imperfections in equipment (for example, if it is electrical noise that can be filtered) then precision can be improved by technical means. If, on the other hand, the beat-to-beat variability is largely a genuine biological phenomenon then the only way to improve precision is to average more replicates, that is, spend more clinical time on the optimization. Scrutiny of Figure 1 shows that “noise” recorded by different methods at different positions in the body—invasive in the aorta and noninvasive in the finger—is concordant. This suggests that it arises from genuine biological variation and not technical imperfection, which means that general medical technology has already reached the level where the bottleneck to reliable optimization is natural biological variability. If so, 12 minutes may turn out to be an approximate lower limit on how quickly a reliable optimization can be done, improvable only on patients who have for some reason a more prominent curvature or narrower biological variability.\(^\text{12}\)

The wish for continuous ambulatory optimization is understandable but may not be realistic because real patients change state continually during everyday life over windows much shorter than 12 minutes. A more realistic aspiration may be a system that builds a table of values of AV delay that are optimal for a range of states. For example, the table may cover dimensions of atrial-sensed versus paced, heart rate (at several levels), and perhaps body posture (upright vs lying) if this is found to significantly affect AV optimum. The table could be filled progressively as opportunities arise, and updated naturally over time.

If the differences between sensed and paced optima are conserved across heart rates, as they seem to be,\(^\text{17}\) then all the sensed optima could be inferred from the respective paced optima, given a single sensed-paced difference in optimum. The sensed optimum for this would best be done at rest (which is easiest to maintain for prolonged periods) and with a very high degree of replication, because low-rate optimizations have shallow curvature that makes them need more replicates to achieve the same precision.\(^\text{12}\)

Perhaps the same is true for posture. In that case, the table of supine, atrial-paced values could be filled across a wide range of heart rates by an active algorithm during sleep, and the other values thus inferred, using a precisely obtained postural difference in optimum that would require patient co-operation such as prolonged standing or sitting. What is described here with tables could equally be achieved by a multivariate curve whose shape parameters could be progressively updated as data accumulate.

Setting aside this speculation about what might be achievable in the future, this study suggests opportunities that could immediately be tested by any reader, without new implanted technology. A clinical optimization service might use simple photoplethysmography and a systematic algorithm such as this, for setting AV delay. While this might save considerable time and uncertainty from trying to distinguish subtle echocardiographic Doppler changes, it should not eclipse the comprehensive review of the patient with CRT, which is far more extensive than AV delay alone.\(^\text{35}\)

**Potential for Harm from Unreliable Optimization**

It is unsafe to assume that something is better than nothing, i.e., that some attempt at optimization is better than leaving things at factory settings. For a patient whose true optimum is not far from the factory setting, applying an optimization protocol with poor reproducibility...
may well set the AV delay worse than factory settings in most cases. How close the optimum has to be to factory settings, for this to be the case, depends on how poor is the reproducibility of the optimization algorithm.\textsuperscript{2,13}

If a clinical trial of optimization was conducted with a method whose test-retest reproducibility was poor (or unknown), or which was reproducible but had been validated in unblinded fashion against a method with poor test-retest reproducibility, it would be quite possible that as many patients would be worsened by the intervention as benefited. In that case, the outcome of the trial may be neutral, without it meaning that the principle of optimization is useless.

**Noninvasive Hemodynamic Optimization is not a Gold Standard**

We do not make a claim that the simple photoplethysmogram or Finometer is a gold standard for optimization. Such a claim would need to be based on a series of properties which should be tested in sequence:

1. **Reproducibility**, that is, data from separate optimization sessions, analyzed with mutual blinding, give almost the same optimum.
2. **Consistency** among several independently acquired classes of measurement, that is, data acquired using separate equipment yields almost the same optimum on blinded analysis. (This criterion can only be tested between classes of measurements that are individually reproducible.)
3. **Physiological impact**, that is, ability of optimization using a measurement to consistently raise the level of some (other) variables measured independently—not from the optimization data set itself which of course will show an elevation at the selected setting even if the process is no better than random.\textsuperscript{13,36}

Hemodynamic optimization processes, because they allow large numbers of replicate measurements to be conducted and averaged to quench noise, score relatively well on reproducibility and consistency criteria. Workers in the field might easily assess reproducibility and consistency of optimization methods they are considering: having eliminated the irreproducible methods, if all the remaining methods agree with each other (within the limits of their own reproducibility) then any of them may be taken as a reasonable standard. In that case, the method which is most reproducible for a given amount of time taken might be considered as gold standard. Only when well-reproducible methods of physiological optimization disagree, beyond the expected discrepancy arising from their own imperfect reproducibility, is there any meaning to the question of which one is a better optimum. So far such a pair of reproducible-but-disagreeing methods has not yet been identified. Either our community has not looked hard enough, or all the reproducible extracardiac physiological markers agree.

**Clinical Implications**

Reproducible optimization is obtainable by a variety of hemodynamic methods, including noninvasively using blood pressure. Simple photoplethysmographic circuitry that appears to mirror this behavior, is cheap, and may even be potentially implantable, but has a slightly poorer reproducibility if the peak of the signal is used, because the simple photoplethysmogram volume signal is susceptible to venous noise. However, with no greater effort of acquisition, the steepest slope (rather than the peak of the signal) can be used, which improves its reproducibility to match that of the Finometer which is known to track beat-by-beat invasive pressures closely.

In an outpatient CRT follow-up setting, AV optimization might be achievable with little time and very little equipment cost using a modified general-purpose pulse oximeter signal.

In the further future, if it was desired to have a fully implantable system, then this first derivative of the simple photoplethysmogram signal makes it a potentially attractive solution for inbuilt pacemaker-based optimization, which has already been demonstrated to be feasible in animals.\textsuperscript{14} Unrealistic expectations should not be raised, however. There is an innate uncertainty in evaluating the AV optimum. Once equipment noise has been shrunk to much smaller than biological variability, uncertainty of the optimum can only be further reduced by making more measurements, which takes time.\textsuperscript{12} Continuous ambulatory optimization may never be attainable with narrow within-patient error bars but the ability to program AV delay according to a recorded or interpolated optimum for the patient’s current state does not appear unattainable.

**Study Limitations**

This study compared the ability of two hemodynamic beat-to-beat monitoring technologies to reproducibly identify an optimum AV. It was not designed to test the clinical benefit of hemodynamic optimization, nor to characterize differences between notional responders versus nonresponders. The reproducibility was assessed only over the very short term (same day) because when differences are found in longer term reproducibility, these might be due to changes in
underlying patient status and therefore cannot be confidently attributed to nonreproducibility of the optimization process.

There is no comparison with invasive hemodynamic measures because we wanted to conduct the study in the environment where clinical optimization is usually carried out, that is, ambulatory patients. However, the Finometer has been extensively validated for detecting changes in blood pressure using invasive pressure measurements. In addition, arterial pressure optimization is known to mirror the pattern of intracardiac pressure generation, as was demonstrated in the initial acute studies of CRT. Also, we cannot say for certain that cardiac output changes will perfectly track pressure changes but noninvasive data seem to indicate that early blood pressure increments are a usable proxy for cardiac output changes.

To minimize risk of inadvertent bias, no special steps were taken to deal with any ectopic beats that arose within the recordings. No beats were excluded. This convention makes it straightforward to evaluate the lower limit of its potential efficiency as an autonomous process.

During the study, all patients were atrially paced, either just above resting rate (slow ApVp) or at 100 bpm (fast ApVp). This differs from the conditions used in some previous studies on optimization, which have used resting rate. Our laboratory’s approach is to progressively identify steps that can be used (alone or together) to improve the reproducibility of optimization: this approach is most effective when reproducibility is already fairly good, which is the case for higher rates. As the science of optimization develops, it should be possible to apply this knowledge to make the best of any situation, even the relatively poor and in which improvements are therefore hard to detect because the large error bars themselves have large error bars.

Conclusions

1. Hemodynamic optimization, with narrow within-patient error bars, is feasible using a simple photoplethysmogram signal. Although optimization with formally calibrated blood pressure equipment is more established to be reproducible, conducting it invasively is not suitable for repeating, and conducting it noninvasively requires expensive and bulky, nonimplantable equipment. Use of the photoplethysmogram for hemodynamic optimization requires the facility to pause any autorescaling of the signal (while pacemaker settings are changed) and the peak slope of the systolic upstroke is preferable to the peak signal.

2. Regardless of the choice of monitoring technology, it is necessary to perform multiple replicate measurements, without which the reproducibility of the optimum may be so poor as to be useless or—worse—harmful. Elevating the heart rate also improves the reproducibility of hemodynamic optimization.

3. A wide variety of extracardiac hemodynamic monitoring approaches may behave in parallel fashion, differing fundamentally only in their relative susceptibility to signal versus noise. Once a family of methods with good signal-to-noise characteristics is enumerated, their narrow within-patient error bars confirmed on blinded analysis, and their information equivalence critically evaluated, cost and implantability would be criteria on which to choose between them. A photoplethysmographic signal, from a pulse oximeter in routine use in cardiology departments, provides with good test-retest reproducibility automated hemodynamic AV optimization in 12 minutes.

References
