Comparison of a non-invasive arterial pulse contour technique and echo Doppler aorta velocity-time integral on stroke volume changes in optimization of cardiac resynchronization therapy

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Aims
We investigated the accuracy and feasibility of a non-invasive arterial pulse contour technique for continuous measurement of stroke volume (SV) in optimization of atrioventricular (AV) delay in cardiac resynchronization therapy (CRT), by comparing SV changes assessed by Nexfin CO-Trek® (Nexfin) and echo Doppler aortic velocity-time integral (VTIao). Furthermore, we investigated whether AV-delay optimization increases the effect of CRT when compared with a default AV delay (120 ms).

Methods and results
In 23 CRT patients, biventricular pacing (BiVP) was applied at various AV delays, while recording 10 beats preceding BiVP (baseline) and the first 10 BiVP beats, for both methods in parallel. Agreement between Nexfin and VTIao measurements was evaluated (Bland–Altman) on beat-to-beat changes in SV, as well as on effects of BiVP (averaged over 8 beats) at various AV delays. Individual optimal AV delays, for Nexfin (AVopt-n) and VTIao (AVopt-ao), were derived from the second-order polynomial fitted to the effect measurements of 20 patients. In 252 episodes assessed, the difference between measurements (=Nexfin − VTIao) was −0.6 ± 8.1% for beat-to-beat SV changes and −1.3 ± 7.3% for effects of BiVP. Optimal AV delays for Nexfin were well related to AVopt-ao (R² = 0.69). The effect (%) of BiVP at the optimal AV delay was significantly larger than at the default AV delay: median difference (range) being +6.3% (0.1–14.4%; P < 0.001) for VTIao and +4.7% (0.0–14.0%; P < 0.001) for Nexfin.

Conclusion
Individual AV optimization increases the effect of CRT. Nexfin is a promising tool in individual CRT optimization, as Nexfin agrees with VTIao on measuring beat-to-beat SV changes and on assessing relative effects of BiVP on SV at various AV delays.

Keywords
Pacing • CRT • Optimization • Haemodynamic • Stroke volume • Non-invasive
Introduction

Cardiac resynchronization therapy (CRT) improves left ventricular (LV) pump function and reverses LV remodelling through the restoration of synchrony in LV electrical activation in patients in a wide spectrum of mild to severe heart failure and prolonged QRS duration. The substantial evidence that CRT improves clinical status and that it reduces morbidity as well as mortality has resulted in the incorporation of CRT in the management of dyssynchrony-associated heart failure. Devices for CRT have become significantly more sophisticated, including the capability to independently program atrioventricular (AV) and interventricular (VV) stimulation timing intervals, which has been shown to acutely significantly influence cardiac function.\(^1\)\(^–\)\(^4\) Although tailoring the AV delay and VV interval to the individual patient could further increase the haemodynamic improvement and long-term benefits brought by CRT, the best way to guide the optimization of these device settings is still under debate. Since CRT has been shown to acutely improve haemodynamic status,\(^5\) AV delay and VV interval might be optimized by haemodynamic monitoring. Gold standards for the measurement of haemodynamic status are the estimation of LV contractility by measuring the maximum rate of rise of LV pressure and the measurement of cardiac output by thermodilution or conductance catheter. These invasive methods, however, are not suitable for routine use in CRT optimization as they require cardiac catheterization, and thus impose significant biological and interventional risk to patient as well as add significant financial and human resource burden. Although echocardiographic assessment of the velocity-time integral of the aorta (VTIao) has been shown to be a good surrogate for stroke volume (SV),\(^5\)\(^,\)\(^6\) this measurement may be challenging in some patients due to limited or poor acoustic window. Furthermore, it is very time-consuming to obtain a reliable set of data over a series of heart beats for device optimization. Summarizing, there is great clinical need for a harmless, patient friendly, and easy to use technique for (continuous) haemodynamic monitoring, suitable for being applied in individual optimization of CRT. A non-invasive method to continuously monitor haemodynamics, using a finger sensor, is provided by Nexfin\(^6\) (BMEYE B.V., Amsterdam, The Netherlands). We investigated whether Nexfin reliably measures beat-to-beat changes as well as immediate relative effects on SV induced by CRT at various AV delays and, hence, whether the use of Nexfin is feasible in the individual optimization of CRT. The second aim was to investigate whether benefit of CRT is increased with AV-delay optimization when compared with a default AV delay.

Methods

Subjects

From the cardiology departments of Maastricht and Lugano, 23 outpatients (5 females; 22\%) were enrolled 2.9 ± 2.6 years after implantation of a biventricular pacemaker or biventricular defibrillator for refractory heart failure and left bundle branch block (LV ejection fraction (LVEF) <35\% and QRS >130 ms). Patient characteristics at implantation: QRS duration 161 ± 25 ms; LVEF 25 ± 7; median NYHA functional class 3 (range: 2–4); heart failure aetiology: ischaemic n = 11, non-ischaemic n = 12. Exclusion criteria for the current study were atrial fibrillation, non-optimal echocardiographic image quality of the LV outflow tract which did not permit to assess VTIao (known from previous examinations), as well as the presence of moderate to severe aortic valve stenosis or regurgitation. At inclusion in the study, patient characteristics were: age 69 ± 8 years; paced QRS duration 137 ± 31 ms; LVEF 35 ± 11\%; median NYHA classification 2 (range: 1–3). Patients gave informed consent for this study, which was approved by the institutional review boards of both centres.

Study protocol

In order to investigate the reliability of Nexfin CO-Trek in measuring SV changes, we compared relative SV changes assessed by Nexfin with relative changes in VTIao on the same beats. Stroke volume changes were induced by biventricular pacing (BiVP) at various AV delays. The pacing protocol was initiated after the patient being in supine position for 15 min. To exclude haemodynamic variability induced by spontaneous changes in heart rate and to increase the probability of a more pronounced peak in the immediate haemodynamic responses to CRT at the various AV delays at higher heart rates,\(^7\) we enforced a constant heart rate by atrial override pacing (90 b.p.m.). The protocol consisted of a baseline without ventricular pacing, alternated with atrial-based BiVP at various AV delays in episodes of ~30 s (Figure 1). Starting at an AV delay of 60 ms for the first BiVP intervention, the AV delay was increased in 20 ms steps until either complete ventricular sensing occurred or until a maximum AV delay of 340 ms.

Measurements and data acquisition

During the entire protocol, arterial pressure and SV were continuously and non-invasively recorded by Nexfin. Nexfin uses an inflatable cuff that is placed around the mid-phalanx of the middle finger, which contains a built-in photo-electric plethysmograph. By a volume-clamp circuit combined with the Physiocal\(^8\) method,\(^8\)\(^,\)\(^9\) the finger arteries under the cuff are dynamically clamped to their unloaded volume, and the pressure used is determined and tracked over time, resulting in a dynamic and calibrated measurement of finger arterial pressure. The finger arterial pressure is automatically reconstructed into the brachial arterial pressure waveform.\(^8\)\(^–\)\(^10\) Stroke volume is automatically computed from the systolic area under the brachial arterial pressure pulse contour. Patient’s age, gender, height, and weight are important input parameters for the patient individualization of the SV measurement using the Nexfin CO-Trek\(^6\) algorithm.\(^10\) Simultaneously, ECG signal was recorded with the ECG module of Nexfin. Offline, data on SV as measured by Nexfin from the last 10 individual heartbeats preceding BiVP (baseline beats) and the first 10 beats during BiVP (registration in black, Figure 1) were selected and exported using customized software based on the Matlab platform (MathWorks, Natick, MA, USA) after conversion by Framel inspector (version 1.22.0.0, BMEYE) to a format compatible with Matlab (.bin).

In parallel with the Nexfin recordings, continuous wave Doppler echocardiography (Vivid 7, General Electric, Milwaukee, WI, USA) of the aorta was performed on the same beats (10 baseline beats + 10 BiVP beats). The echo Doppler recordings were stored and the VTIao was manually measured offline using EchoPAC post-processing software (Dimension BT08, General Electric). Stroke volume can directly be derived from the VTIao, by multiplying the VTIao with the aortic cross-sectional area. Though, since this study focuses on the comparison of relative changes in SV, we did not calculate absolute SV for echo measurements.
Statistical methods

Comparison of Nexfin and echo Doppler: on the assessment of beat-to-beat stroke volume changes and on the estimation of the effect on stroke volume as induced by biventricular pacing

To allow pooling of the data of the various episodes and different patients, the mean values of each of the baselines, for both Nexfin and VTIao, served as a reference (0% level in Figure 2, upper panel). Then, the relative deviation (RD, %) from the reference of the episode was calculated for each of the 20 beats in that episode, for both Nexfin and VTIao (RDSVn and RDSVao, respectively; Figure 2, upper panel).

The first objective was to identify the agreement of Nexfin and echo Doppler on the measurement of beat-to-beat SV changes due to either spontaneous variability or artificially induced variability by BiVP. For this purpose, the differences between the measurements of Nexfin and VTIao on relative beat-to-beat SV changes were calculated (Figure 2, lower panel) and evaluated according to the suggested method of analysis by Bland and Altman.11 In this method, the mean difference between the methods is defined as ‘bias’. The upper and lower limits of agreement are defined as ‘bias + 1.96 × SD of the difference between the methods’.

The second step in the comparison of Nexfin and echo Doppler was to investigate the agreement of the methods on the assessment of the effect on SV as induced by BiVP at the various AV delays. Because SV is strongly affected by changes in RR intervals due to either lengthening or shortening of the AV delay (see also the example given in Figure 1), premature and post-premature beats, as well as the first and the second beats after transition were excluded. Subsequently, we assessed the relative effect of BiVP on SV for each AV delay by calculating the mean relative SV increase or decrease over the BiVP beats (=mean RDSVao and RDSVn over BiVP beats) and defined these as ‘effect Svao’ and ‘effect Svn’, for echo Doppler VTIao and Nexfin, respectively (Figure 2, upper panel). The Bland–Altman analysis was performed on effect Svao and effect Svn, to identify the agreement between Nexfin and echo Doppler on the assessment of the relative effects on SV induced by BiVP at various AV delays.

Atrioventricular-optimization curves for Nexfin and echo Doppler

Individual optimization curves for echo Doppler and Nexfin were obtained by a second-order polynomial curve fitted to the data on the relative effects, effect Svao and effect Svn, respectively (Figure 4). The AV delay at the location of the maximal effect (peak of the curve) was defined as the optimal AV delay (AVOpt-ao and AVOpt-n, for echo Doppler and Nexfin, respectively). The difference in effect Svao at AVOpt-n and at AVOpt-ao or AVOpt-ao was used as a measure of the haemodynamic relevance of the discrepancy between AVOpt-n and AVOpt-ao. For both echo Doppler and Nexfin, the range of optimal AV delays was defined as the part of the curve where the relative effect was less than 2%-points lower than the effect at the optimal AV delay. Lastly, the maximal relative effect was compared with the relative effect at a default AV delay of 120 ms to investigate whether individual AV-delay optimization is beneficial.

Figure 1 Study design. Along a baseline (BL) of constant heart rate enforced by atrial overdrive pacing without ventricular pacing, SV changes were induced by episodes of BiVP at various AV delays in the range 60–340 ms (AV xx). Nexfin continuously recorded ECG and blood pressure and computed beat-to-beat SV. In parallel, for each intervention echo Doppler investigation of the LV outflow tract was performed on at least the final 10 baseline beats and the first 10 BiVP beats. Offline the velocity-time integral was manually estimated (for this example, SV was calculated from the velocity-time integral and cross-sectional area of the aorta).
Results

Protocol complications

In 23 patients, a total of 252 BiVP episodes at various AV delays was assessed with an average of 11 ± 3 interventions for each individual patient. In one patient, from an AV delay of 200 ms onwards, the device (St Jude Medical Systems; Promote RF 3213-36) could not be programmed in 20 ms steps; therefore, the AV delays tested were subsequently 225, 250, 275, 300, and 350 ms. In three patients, the protocol was performed using overdrive pacing at a rate of 75 b.p.m. (n = 1) or 80 b.p.m. (n = 2), since progressive AV-conduction disturbances occurred at higher rates.

Agreement between Nexfin and echo Doppler: on the assessment of relative beat-to-beat stroke volume changes and on the estimation of the effect on stroke volume as induced by biventricular pacing

For a total of 5028 beats, measurements by both Nexfin and echo Doppler were available. From the Bland–Altman analysis on the beat-to-beat RDs (Step 1), the observed variance (SD) on the measurement differences between the methods (=RDSVn – RDSVao) was ±8.1% around a mean bias of −0.6% (limits of agreement: ±15.9%).

The inter-beat variability on baseline beats (n = 2422 after exclusion of premature and post-premature beats) was ±4.7% for RDSVn and ±6.3% for RDSVao.

The second step in the comparison of Nexfin with echo Doppler was the use of the Bland–Altman analysis for evaluation of the agreement between the methods on the assessment of the relative effect of BiVP on SV in comparison with baseline (‘effect SVn’ and ‘effect SVao’, as visualized in Figure 3). By means of the Bland–Altman analysis, the difference between Nexfin and echo Doppler (effect SVn – effect SVao) was −1.3 ± 7.3% (limits of agreement: ±14.3%).

The variances (SD) observed on the measurement differences between the methods, as well as the limits of agreement (bias ±1.96 × SD), are indicative for a good agreement between the methods and suggest that Nexfin CO-Trek is reliable in the measurement of SV changes (the reliability of Nexfin is further exemplified in the ‘Discussion’ section).

Atrioventricular-optimization curves for Nexfin and echo Doppler

In the third step of the comparison of Nexfin and echo Doppler in CRT optimization, optimization curves for both Nexfin and echo Doppler could be obtained for 20 individual patients. (One patient
was excluded for this analysis because the occurrence of multiple premature beats in each episode implicated that the measurements on relative effects were not representative and thus not useful for optimization. In two patients, optimization curves could not be fitted to the individual data because of a large 'back and forth variation' between the settings.) Regarding the shape of the curves and their fit to the individual effect measurements, variation between patients was observed. Figure 4 demonstrates four different explanatory examples, all with a good agreement between Nexfin and echo Doppler on the individual effect values (limits of agreement for the individual patients are: A, ā 17.6%; B, ā 11.0%; C, ā 13.9%; and D, ā 11.8%). The optimization curves in Figure 4A show a positive effect of BiVP for all AV delays tested. The curves well fit the individual effect values (echo: $R^2 = 0.93$ and Nexfin: $R^2 = 0.80$), and

AVopt-n (258 ms) is close to AVopt-ao (270 ms). In the example shown in Figure 4B, the optimization curve for echo Doppler fits the individual points only moderately ($R^2 = 0.51$). Nevertheless, AVopt-ao (260 ms) and AVopt-n (257 ms) are almost similar. In the patient presented in Figure 4C optimization curves have a good fit to the individual data points (echo: $R^2 = 0.84$ and Nexfin: $R^2 = 0.82$), but there is less agreement between Nexfin and echo Doppler on the optimal AV delay (186 and 260 ms for AVopt-n and AVopt-ao, respectively). In the patient presented in Figure 4D, the accordance of the curves with the individual data and consensus of the optimal AV delay derived from Nexfin and echo Doppler are poor (281 and 211 ms for AVopt-n and AVopt-ao, respectively).

On average, the correlation of the fitted optimization curves and the individual effect data was similar for Nexfin ($R^2 = 0.63 \pm 0.24$)
and echo Doppler ($R^2 = 0.68 \pm 0.27$). The averaged maximum effect as derived from the Nexfin optimization curves was $4.3 \pm 5.4\%$, which was significantly smaller than the maximal effect as derived from the echo curves ($7.2 \pm 7.7\%; P = 0.008$). Optimal AV delay for Nexfin and AVopt-ao were well correlated, as is shown in Figure 5 (Patients A–D are corresponding to the patients in Figure 4). The absolute difference in AV delay (ms) between AVopt-n and AVopt-ao was $\leq 20$ ms for 13 out of 20 patients (65%), indicating (almost) similarity of AVopt-n and AVopt-ao in these patients (Figure 5). In the majority of the patients (80%; $n = 16$), the difference in relative effect by BiVP as measured with echo at the AVopt-ao and at AVopt-n was $< 1\%$-points (difference in the effect of total population: median 0.2%-points; range 0.0–5.2%-points). This might be clinically even more important than an exact similarity of AVopt-n and AVopt-ao, as the small difference in effect indicates just only a minimal haemodynamic relevance of the discrepancy between AVopt-n and AVopt-ao. For both echo Doppler and Nexfin, a range of optimal AV delays was defined as the part of the curve where the relative effect was $< 2\%$-points lower than the effect (%) at the optimal AV delay. The width of this range of optimal AV delays was $110 \pm 34$ ms for Nexfin and $97 \pm 47$ ms for echo, suggesting that there may be a broad range of AV delays leading to (almost) optimal effects. Furthermore, there was a great similarity for Nexfin and echo Doppler in this optimal range, as indicated by 73$\pm$21% overlap of the Nexfin optimal range with the optimal range of echo Doppler. The relative effect as achieved by optimizing the AV delay was significantly larger than the effect using a default (‘out-of-the-box’) AV delay of 120 ms: $7.2 \pm 7.7\%$ vs. $0.6 \pm 9.4\%$ (median difference in effect $+6.3\%$; range 0.1–14.4%; $P < 0.001$) as estimated by echo Doppler and $4.3 \pm 5.4\%$ vs. $-0.6 \pm 7.2\%$ (median difference $+4.7\%$; range 0.0–14.0%; $P < 0.001$) by Nexfin.

**Discussion**

In the current study, we investigated the accuracy and feasibility of continuous non-invasive SV measurements by Nexfin CO-Trek in CRT optimization, by comparing Nexfin with echo Doppler at three levels: the measurement of beat-to-beat changes in SV, the assessment of relative effects of BiVP at various AV delays, and the determination of the optimal AV delay. The most important findings are that Nexfin has a good agreement with VTIao by echo Doppler on the measurement of changes in SV due to either physiological beat-to-beat alterations or to changes induced by BiVP and that in individual optimization both methods Nexfin and VTIao determine similar AV delays as the optimal AV delay. Additionally, our data suggest that individual optimization of the AV delay leads to better haemodynamic improvement of CRT than programming a default AV delay of 120 ms.

**Reliability of Nexfin in the assessment of acute haemodynamic changes**

To investigate the reliability of Nexfin CO-Trek on the assessment of acute haemodynamic changes, we used the VTIao assessed by echo Doppler to compare Nexfin CO-Trek with, as this method provides a validated non-invasive measurement of (changes in) SV. Optimizing the VTIao is also one of the recognized and accurate methods for CRT optimization.12
The variance (± SD) on the measurement differences between Nexfin and echo Doppler was ± 8.1% for the measurement of beat-to-beat changes. This observed variance can be entirely explained by the summation of the variability in each of the methods, since by analysing exactly the same beats for both methods, physiological variability is excluded as a confounding factor. The measurement variability for each method separately can be hypothesized from the equation for combined variances [combined variance = \sqrt{(\text{variance A}^2 + \text{variance B}^2)}]. If the measurement variabilities on SV changes of echo Doppler and Nexfin are assumed to be equal, these variabilities would be 5.7% [\sqrt{(5.7^2 + 5.7^2)} = 8.1]. If the measurement variability of echo Doppler is assumed to be higher, the precision of Nexfin would even be better: for the theoretical example that the measurement variability of echo Doppler is 7.0%, the variability of Nexfin would be 4.1% [\sqrt{(7.0^2 + 4.1^2)} = 8.1]. When compared with the available haemodynamic measurements, a method with a ~5% inconsistency in the assessment of beat-to-beat SV changes may be considered to be very precise.\cite{14-16}

In clinical practice, haemodynamic measurements are usually performed on multiple beats. Therefore, it seems more appropriate to judge the reliability of Nexfin based on the variance on the difference between the effect measurements of Nexfin and echo Doppler (derived from averages of multiple beats), which was the second step in our comparison. The variance on these measurement differences was ± 7.3%. Consequently, if the measurement variability on the assessment of the effect on SV by BiVP are assumed to be equal for echo Doppler and Nexfin, these variabilities would be 5.2% [\sqrt{(5.2^2 + 5.2^2)} = 7.3].

From Figure 3A and B (trendline), as well as from the finding that the optimal effect was smaller when measured with Nexfin (4.3 ± 5.4%) when compared with echo Doppler (7.2 ± 7.7%), it can be deduced that using Nexfin, changes in SV are estimated to be smaller than that using echo Doppler. This may also explain the smaller inter-beat variance on baseline beats for Nexfin (± 4.7%) when compared with echo Doppler (± 6.3%). These findings appear to be in keeping with observations of Butter et al.\cite{17} that finger blood pressure measurements underestimate haemodynamic changes, but also that these measurements provide highly specific predictions of positive and negative changes in aortic pulse pressure.

Moreover, the reliability of an effect measurement is influenced by the size of the effect and the standard error of the mean effect (SEM). In the current study, the SEM can be derived from the inter-beat variance (combination of physiological inter-beat variability and measurement error on each beat), divided by the square root of the number of beats on which the effect is determined (n = 8). The ratio between the effect and SEM may be used as a measure for reliability of the effect measured [averaged optimal effect/SEM]. For the averaged optimal effect on SV by BiVP, this ratio was 2.6 [4.3%/20%/\sqrt{8}] = 2.6] for Nexfin, and even a little better for echo Doppler [7.2%/3%/\sqrt{8}] = 3.2]. However, it should be kept in mind that for the effect measurements in the present study, VTao tracing was performed using careful off-line analysis of 8 paced heart beats (in comparison with 10 baseline beats), whereas in clinical practice, often only 1–3 beats are used. By virtue of this lower number, SEM will increase and reliability will therefore decrease and will decrease even more if the beats are not randomly spread over the respiratory cycle.

Defining the optimal atrioventricular delay using individual optimization curves

There was no clinically relevant difference between the AV delays corresponding to the peaks of the individual optimization curves of Nexfin and echo Doppler, since there was a good correlation between the optimal AV delays and a great overlap of the ranges of optimal AV delays (where the effect of BiVP was not relevantly different from the effect of BiVP at the optimal AV delay). These findings suggest that Nexfin reliably defines the best AV delay setting in accordance with echo Doppler VTao. These optimal AV delays were identified from individual optimization curves for echo Doppler and Nexfin as obtained by a second-order polynomial fitted to the data on effect SVao and effect SVn (Figure 4). Whinnett et al.\cite{3} demonstrated that the curve of response to BiVP at various AV delays fits closely to a second-order polynomial. In our study, the fit of the optimization curves with the data was not as good as in the study by Whinnett et al., as reflected by lower mean R-values for both Nexfin and echo Doppler. This discrepancy may be explained by the inclusion of shorter AV delays (40 ms) by Whinnett et al., resulting in extreme worsening of haemodynamics, and therefore improving the correlation coefficient. An additional explanation may be that Whinnett et al. used repeated measurements on the effect of BiVP for each AV setting. This was not practical in our study, because this was not the first aim of our study and would have increased the duration of the patient protocol significantly, due to the time-consuming echo Doppler measurements. If only
Nexfin would be used, measurements can be performed repeatedly in order to achieve more accurate optimization curves.

Clinical implications
Cardiac resynchronization therapy is shown to be beneficial and is broadly applied in heart failure patients, though up to 30% of the patients are not fully responding to CRT. Some of the under-responders may turn into responders by better application of CRT. Despite proven acute haemodynamic benefits of individual optimization of AV delay and VV intervals, it is not yet proven whether or not CRT optimization significantly reduces the number of non-responders or has important impact on patient prognosis. Interestingly, preliminary results of the CLEAR study report that AV-delay optimization using an accelerometer substantially increases the number of patients responding to CRT and reduces the number of major clinical events including hospitalization for heart failure and death. The benefit of individual optimization of the AV delay is also indicated by our data as the optimal AV delay varied between patients and as the relative effect on SV was significantly better at the optimal AV delay than at a default AV delay of 120 ms.

Long-term effects of CRT cannot be directly predicted from the immediate haemodynamic effects achieved in optimization procedures. Nevertheless, improvements in haemodynamics have been shown to persist over time and have been associated with diminished energy costs, indicating improvement of mechanical efficiency which may last on the long term and may increase cardiac reserve. Additionally, in a recent study using invasive pulse contour measurements, patients in whom an acute SV increase of >5% by optimized CRT was achieved showed a better clinical as well as echocardiographic response at 6–8 weeks follow-up, when compared with patients in whom <5% acute SV increase was achieved. Nexfin immediately and automatically computes SV and, as shown in our study, is reliable in the assessment of SV changes. In contrast to other haemodynamic measurement techniques in CRT-optimization procedures, Nexfin is non-invasive, patient friendly, and does not require great skill.

As the main purpose of this study was to evaluate the reliability of Nexfin in the optimization of CRT and, hence, a steady and high heart rate was preferred, we performed (overdrive)pacing. In clinical practice, however, it would be important to also determine the optimal AV delay for atrial sensed ventricular pacing, as this may better reflect physiological circumstances. Moreover, it would be interesting to optimize even at various heart rates and during exercise. One of the major advantages of using Nexfin above using echocardiography is that it can easily be applied in different body positions and even during exercise. Another advantage of the simple application of Nexfin is that optimization procedures can easily be repeated multiple times over longer time course, as it is likely that on the long term and/or in real life, the optimal CRT settings will change.

Prospective randomized studies are needed to clarify the real clinical impact of CRT optimization on the patients course. In this regard, the method for optimization may be of critical importance.

Echocardiography is the most common approach to optimize AV and VV timing, yet it is a time-consuming approach and uses significant human resources. Thus, there is the quest for an alternative, inexpensive, and highly reliable method which can be included as part of routine device follow-up. With the easy and relatively inexpensive use of Nexfin, all patients could undergo individual optimization.

Study limitations
The Bland–Altman evaluation of agreement assumes independent observations. Contrary to this assumption, we used multiple measurements on SV within each subject, where the true value varies due to (spontaneous or artificially induced) changes in haemodynamics. Variances on the biases and intervals within the limits of agreement were observed between the subjects (mean interval within the limits of agreement: 15.6 ± 5.5%; mean bias −0.6 ± 2.6%) which may implicate that the interval between the observed limits of agreement for the total study group might be narrower than it should be, but probably only slightly.

Measurements on the effect of BiVP were performed once for each AV delay, since repetition was not feasible in our protocol with the parallel echocardiographic data acquisition. Nevertheless, for each AV-delay effect measurements should be performed repeatedly to define the individual optimal AV delay more reliably.

In the current study, it was practically not feasible to perform both AV and VV optimization (due to the parallel assessment of SV changes by Nexfin and VTao). Because the results of our study indicate that Nexfin is reliable in the assessment of SV changes, we feel that parallel assessment of VTao, next to Nexfin, is not longer necessary in subsequent studies.

Conclusions
Individual optimization of the AV delay may increase the beneficial response to CRT. Nexfin CO-Trek provides an easy, non-invasive, and patient-friendly method to evaluate changes in SV due to either beat-to-beat alterations or different settings of AV delays. As Nexfin has a good precision on the measurement of beat-to-beat SV changes, the assessment of relative effects induced by BiVP and on the determination of the optimal AV delay, we judge Nexfin as a promising tool in the individual optimization of CRT.

Conflict of interest: A.A. is a consultant for Medtronic and Sorin and EBR Sytems; he receives speaker fee from Medtronic, Biotronik, Sorin, and St Jude Medical; his institution participates in industry-sponsored trials from Medtronic, Biotronik, Sorin, Boston Scientific, EBR Systems, and St Jude Medical. F.W.P. is a consultant to Medtronic and has received research grants from Medtronic, Boston Scientific, and EBR Systems. R.C. and B.G. are employees of Medtronic. J.J.S. is employee of BMEYE B.V.

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