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**CLINICAL RESEARCH**
*Pacing and resynchronization therapy*

# Tailoring device settings in cardiac resynchronization therapy using electrograms from pacing electrodes

**Elien B. Engels[1], Masih Mafi-Rad[2], Ben J.M. Hermans[1,3], Alfonso Aranda[4], Antonius M.W. van Stipdonk[2], Michiel Rienstra[5], Coert O.S. Scheerder[4,†], Alexander H. Maass[5], Frits W. Prinzen[1]*, and Kevin Vernooy[1,2]**

[1]Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, PO Box 616, 6200MD Maastricht, the Netherlands; [2]Department of Cardiology, Maastricht University Medical Center, PO Box 616, 6200MD Maastricht, the Netherlands; [3]Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht University, PO Box 616, 6200MD Maastricht, the Netherlands; [4]Medtronic Bakken Research Center, Endepolsdomein 5, 6229 GW Maastricht, the Netherlands; and [5]Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands

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**Aims** Left ventricular (LV) fusion pacing appears to be at least as beneficial as biventricular pacing in cardiac resynchronization therapy (CRT). Optimal LV fusion pacing critically requires adjusting the atrioventricular (AV)-delay to the delay between atrial pacing and intrinsic right ventricular (RV) activation (Ap-RV). We explored the use of electrogram (EGM)-based vectorloop (EGMV) derived from EGMs of implanted pacing leads to achieve optimal LV fusion pacing and to compare it with conventional approaches.

**Methods and results** During CRT-device implantation, 28 patients were prospectively studied. During atrial-LV pacing (Ap-LVp) at various AV-delays, LV $dP/dt_{max}$, 12-lead electrocardiogram (ECG), and unipolar EGMs were recorded. Electrocardiogram and electrogram were used to reconstruct a vectorcardiogram (VCG) and EGMV, respectively, from which the maximum QRS amplitude ($QRS_{ampl}$), was extracted. Ap-RV was determined: (i) conventionally as the longest AV-delay at which QRS morphology was visually unaltered during RV pacing at increasing AV-delays(Ap-$RV_{vis}$; reference-method); (ii) 70% of delay between atrial pacing and RV sensing (Ap-$RV_{aCRT}$); and (iii) the delay between atrial pacing and onset of QRS (Ap-$QRS_{onset}$). In both the EGMV and VCG, the longest AV-delay showing an unaltered $QRS_{ampl}$ as compared with Ap-LVp with a short AV-delay, corresponded to Ap-$RV_{vis}$. In contrast, Ap-$QRS_{onset}$ and Ap-$RV_{aCRT}$ were larger. The Ap-LVp induced increase in LV $dP/dt_{max}$ was larger at Ap-$RV_{vis}$, Ap-$RV_{EGMV}$, and Ap-$RV_{VCG}$ than at Ap-$QRS_{onset}$ (all $P < 0.05$) and Ap-$RV_{aCRT}$ ($P = 0.02$, $P = 0.13$, and $P = 0.03$, respectively).

**Conclusion** In this acute study, it is shown that the EGMV $QRS_{ampl}$ can be used to determine optimal and individual CRT-device settings for LV fusion pacing, possibly improving long-term CRT response.

**Keywords** Cardiac resynchronization therapy • Vectorcardiography • Electrogram • LV fusion pacing • AV-delay optimization

## Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure and ventricular dyssynchrony, mainly due to left bundle branch block (LBBB). Large randomized trials have shown that CRT improves both morbidity and mortality.[1] However, there is a considerable individual variability in CRT response. One of

* Corresponding author. Tel: +31 43 3881200; fax: +31 43 3884166. *E-mail address:* frits.prinzen@maastrichtuniversity.nl

† Present address. Medtronic Trading NL B.V., Larixplein 4, 5616 VB Eindhoven, the Netherlands.

## What's new?

- A two-dimensional-electrogram (EGM)-based vectorloop (EGMV) can be calculated from unpaced left ventricular (LV) quadripolar and right ventricular (RV) pacing electrodes.
- Electrogram-based vectorloop provides information that is highly comparable with the surface electrocardiogram-derived vectorcardiogram.
- The QRS amplitude as extracted from this EGMV can be used to optimize cardiac resynchronization therapy (CRT)-device settings for optimal LV fusion pacing.
- In contrast to conventional approaches, EGMV-QRS amplitude is independent of the location of the RV pacing lead and of the presence of LV latency.
- Optimizing CRT using EGMV provides similar and trended towards larger haemodynamic response as compared with other approaches for optimizing atrioventricular delay.
- EGMV-QRS amplitude can be used to optimize CRT-device settings individually, continuously and in an ambulatory fashion, possible improving CRT response.

the reasons why patients do not respond to CRT is suboptimal atrioventricular (AV) timing.[2]

Cardiac resynchronization therapy is most often employed by pacing both the right and left ventricle of the heart [biventricular (BiV) pacing]. However, acute and chronic studies have demonstrated that in patients with sinus rhythm and intact AV conduction, left ventricular (LV)-only pacing can be at least as effective as BiV pacing.[3–5] A subanalysis of the AdaptivCRT™ study even showed that a higher percentage of synchronized LV pacing was independently associated with superior clinical outcomes.[6] Furthermore, Vatasescu *et al.*[7] showed the mechanism behind fusion pacing and showed that BiV pacing with fusion may substantially increase the response rate by shortening the LV activation time. CRT using LV-only pacing has been shown to be most effective when the paced LV impulse is properly timed with respect to the intrinsically conducted activation wave fronts through the right bundle branch (RBB). Since the AV-delay impacts the amount of fusion of intrinsic conduction with the paced activation wave, timing of the AV-delay during LV-only pacing plays a crucial role.[8,9]

A few studies have shown that the 12-lead electrocardiogram (ECG) can be used to determine the optimal timing of the LV-only pacing pulse.[8,10] These methods aim to find the delay between atrial pacing and the onset of intrinsic right ventricular (RV) activation (Ap-RV). Other methods use a population-based algorithm to predict Ap-RV relative to the intrinsic AV conduction interval (the time from atrial sensing or pacing to RV sensing in unpaced beats).[11]

We aimed to investigate the possibility to create a measure that allows continuous and tailored monitoring of ventricular activation and Ap-RV. Previous research performed by our group indicated that the QRS vector extracted from a two-dimensional (2D) vectorloop or three-dimensional (3D) vectorcardiogram reflects the degree of ventricular resynchronization during various AV-delays.[12–14] The QRS vector amplitude ($QRS_{ampl}$) was shown to be able to predict the AV-delay resulting in the best haemodynamic improvement. In the present study, we explored the possibility whether $QRS_{ampl}$ from a 2D EGM-based vectorloop, obtained from the implanted pacing electrodes, can be used to determine optimal LV fusion pacing.

# Methods

## Study population

The study population consisted of 28 consecutive patients referred for CRT implantation with a class I indication according to the European society of cardiology (ESC) guidelines 2013 [New York Heart Association class II, III or ambulatory IV despite adequate medical treatment, in sinus rhythm, LV ejection fraction (LVEF) ≤35% and QRS duration >120 ms with LBBB morphology].[1] All patients were prospectively enrolled either in Maastricht University Medical Center+ (MUMC+) or in University Medical Center Groningen (UMCG). Patients presenting with ≥4 premature ventricular complexes on the 10 s 12-lead ECG or with moderate to severe aortic valve stenosis were excluded. In addition, all participants had to be between 18 and 80 years old.

This study was performed according to the principles of the Declaration of Helsinki and approved by the ethics committee of MUMC+ and UMCG. All participants gave written informed consent prior to investigation. The study was registered at clinicaltrials.gov: NCT02326493.

## Procedure

Standard digital 12-lead ECGs were recorded throughout the entire procedure. All participants underwent routine CRT-defibrillator implantation with a quadripolar LV lead (Quartet™ Model 1458Q, St. Jude Medical, St. Paul, MN, USA). The same type of quadripolar LV lead in all patients was chosen in order to achieve the same inter-electrode distance in all patients. The RV lead was routinely placed in the apical septum, the right atrial lead in the right atrial appendage, and the LV lead in a suitable vein on the postero-lateral wall. Left ventricular pacing was performed between the two middle electrodes, electrodes M2 and M3. After implantation of all leads, the pressure wire was introduced via the femoral artery into the LV cavity and unipolar electrograms (EGMs) were recorded from the unpaced electrodes during the pacing protocol (described below). To prevent blood clothing in the LV during these LV pressure measurements, one bolus of 5000 IU heparin was administered. Once the pacing protocol was completed, the leads were connected to the CRT-device and the procedure was completed.

## Pressure measurements

The acute haemodynamic response to CRT was assessed by invasive LV pressure measurements. The LV pressure measurements were performed with a 0.014-inch pressure sensor tipped transluminal guidewire (PressureWire™ Certus™, St. Jude Medical, St. Paul, MN, USA). Each ventricular pacing measurement was preceded and followed by baseline measurements (AAI pacing). After each transition, at least 10 s were used to let the pressure stabilize after which the LV pressure was measured for at least 10 s without any premature ventricular contractions. From the LV pressure measurements, the rate of LV pressure rise (LV d$P$/d$t$) curves were determined. The maximum LV d$P$/d$t$ (LV $dP/dt_{max}$) was determined per heart beat and averaged for the complete measurement period. The AAI pacing measurements (described below) just before and after each pace-setting were used to calculate relative changes in LV $dP/dt_{max}$ measurements. In order to identify the AV-delay with the largest increase in LV $dP/dt_{max}$ a parabola was fitted to the data.[15]

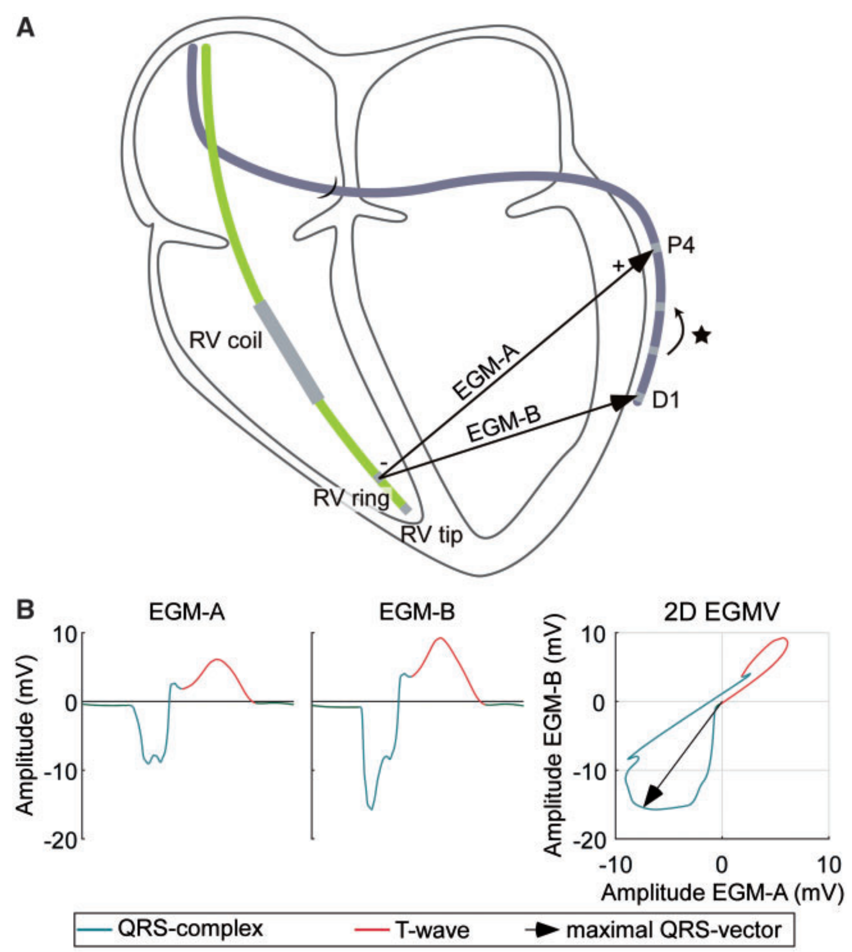


**Figure 1** (*A*) Schematic representation of the bipolar EGM-vectors A (EGM-A) and B (EGM-B). Plotting them against each other produces the 2D EGMV. The $QRS_{ampl}$ that is extracted from this 2D EGMV was defined to be negative when the vector was directed towards the RV-ring. The pacing electrodes are designated with a star. (*B*) One example of a EGM-A signal, EGM-B signal, and the accompanying EGMV. The QRS complex is represented in blue, the T-wave in red, and the maximal QRS-vector is depicted with a black arrow.

## Pacing protocol

Atrial-LV pacing (Ap-LVp) at different AV-delays was performed during atrial overdrive pacing (10 beats per minute above intrinsic heart rate), thus all settings were with atrial pacing (Ap). Programmed AV-delays were increased from a very short AV-delay (between 30 and 50 ms) to an AV-delay where the paced-QRS resembled the intrinsic QRS (pseudofusion), in steps of 30 ms. Before and after each ventricular pace setting, AAI pacing at the same heart rate was used as baseline. As already described in the previous section, after each transition at least 10 s were used for pressure stabilization after which the ECG and EGM signals were measured for at least 10 s.

## Electrograms

Twelve-lead ECG and unipolar EGM recordings were acquired at a sampling frequency of at least 1000 Hz for at least 10 s. From the 12-lead ECG, a 3D vectorcardiogram (VCG) was synthesized using the Kors matrix.

The available signals from unpaced electrodes are the unipolar EGMs of the RV ring and of the proximal (P4) and distal (D1) electrode on the quadripolar LV lead. To incorporate left-to-right information, the unipolar EGM signal from the RV ring was subtracted from both the distal LV electrode (EGM-A) and the proximal LV electrode (EGM-B; *Figure 1A* and *B*). The hereby generated two bipolar EGMs were plotted against each other to approximate a 2D electrogram-based vectorloop (EGMV; *Figure 1B*).

The VCGs and EGMVs were analysed offline using customized software programmed in MATLAB R2010b (MathWorks, Natick, MA, USA).[16] For the 3D VCG and 2D EGMV, the magnitude and direction of the maximum QRS vector in space were expressed as amplitude and angle. The $QRS_{ampl}$ was defined negative when the vector was directed towards the back (VCG) or, in the case of the EGMV, towards the RV ring electrode (*Figure 1A*).

## Determination of onset of contribution of intrinsic ventricular activation

In order to obtain adequate fusion of LV-pacing with intrinsic RV activation, it is important to properly determine the onset of contribution of intrinsic RV activation (Ap-RV). There are multiple methods to obtain Ap-RV. A conventional way to assess Ap-RV is visually observing the ECG during Ap-RV pacing at different AV-delays and look for the longest AV-delay at which QRS morphology is the same as the morphology during RV pacing at a short AV-delay (Ap-$RV_{vis}$; *Figure 2A*).[8] The idea is that at a short AV-delay the QRS morphology is determined by the site of ventricular pacing. Once this QRS morphology starts to change, the intrinsic conduction contributes to ventricular impulse conduction. Therefore, this visually determined Ap-RV was considered to be the reference method.[8] Ap-RV was also determined using the AdaptivCRT™ algorithm (Ap-$RV_{aCRT}$): the delay between atrial pacing and RV sensing (Ap-RVs) is pre-empted by 40 ms or 70% of this amount, whichever is smaller (*Figure 2B*).[11] Finally, the onset of intrinsic ventricular activation was assessed as Ap-$QRS_{onset}$: the interval between atrial pace spike and the onset of QRS (*Figure 2C*).

## Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD) whereas discrete variables are presented as counts (percentages). Different Ap-RV methods were statistically tested using a combination of the Friedman test and the Wilcoxon signed rank test with a Bonferroni correction. A two-sided *P*-value < 0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS statistics software version 24 (SPSS Inc., Chicago, IL, USA).

# Results

## Patient characteristics

Of the 28 included patients, 25 patients completed all measurements. Failure to acquire all measurements in three patients occurred due to an early stop because of back pain as a result of the prolonged procedure time in one patient, the inability to cross the aortic bioprosthesis in one patient, and technical problems with the LV pressure measurement device in one patient. Baseline characteristics of the 25 patients are presented in *Table 1*. The patient population was a typical CRT population with mostly males, half of the patients with ischaemic cardiomyopathy, and all with reduced LVEF and prolonged QRS duration. During the procedure, the LV lead was aimed at a posterolateral wall and the average total procedure time was 141 ± 22 min.

## Comparing different measures of onset of contribution of intrinsic ventricular activation

An example of the course of $QRS_{ampl}$, derived from 3D VCG or 2D EGMV with increasing AV-delay, is shown in *Figure 3*. The corresponding changes in LV d*P*/d$t_{max}$ are also shown. As can be observed, the maximal increase in LV d*P*/d$t_{max}$ was observed at an AV-delay of 150 ms. This maximal increase at an AV-delay of 150 ms corresponded to the last AV-delay at which the $QRS_{ampl}$ extracted from both the 3D VCG and 2D EGMV was the same as during Ap-LVp at an AV-delay of 30 ms. Furthermore, this moment corresponded to an Ap-$RV_{vis}$ of also 150 ms (*Figure 3*). Similar observations were made for the other patients. Therefore, Ap-RV can be extracted from the 3D VCG (Ap-$RV_{VCG}$) and 2D EGMV (Ap-$RV_{EGMV}$) by finding the longest AV-delay at which the $QRS_{ampl}$ was equal to the observed $QRS_{ampl}$ during Ap-LVp at a very short AV-delay.

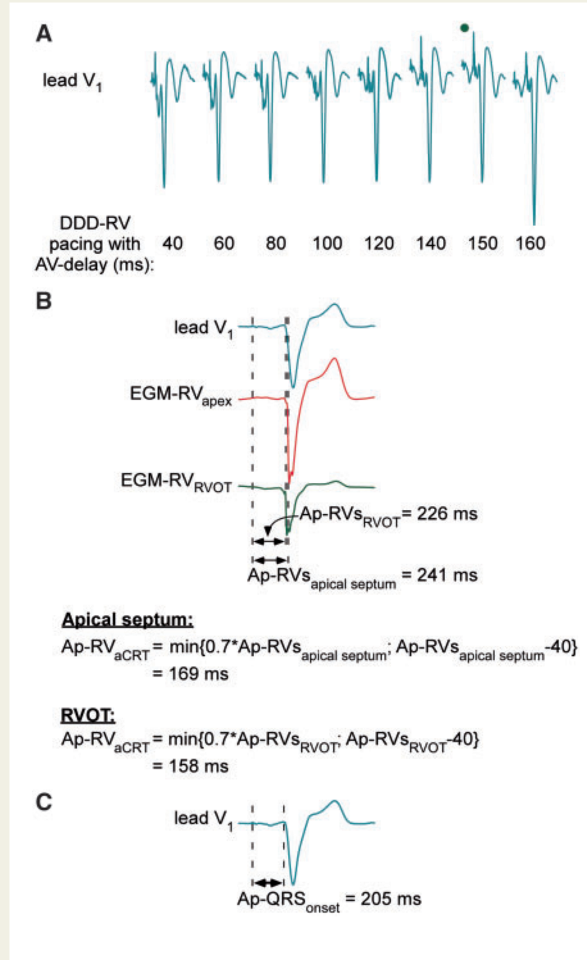


**Figure 2** Three different conventional methods to determine the onset of contribution of right ventricular activation to LV fusion pacing. To determine Ap-$RV_{vis}$, all 12-ECG leads are taken into account but for illustration purposes, only lead $V_1$ is shown in (*A*). Ap-$RV_{vis}$ (longest AV-delay at which the QRS morphology is equal to QRS morphology at the AV-delay of 40 ms) is indicated by a red dot. The S-wave at an AV-delay of 160 ms was distinctively longer than the S-wave at the previous AV-delay of 150 ms, therefore Ap-$RV_{vis}$ for this example was 150 ms. For determination of Ap-$RV_{aCRT}$ (*B*) $V_1$ is used to detect atrial pacing (Ap), and the EGM signals of the RV lead (placed in the RV apical septum or the RV outflow tract) is used to sense RV activation (Ap-RVs delay). Using the AdaptivCRT™ algorithm, Ap-$RV_{aCRT}$ was determined by pre-empting the delay between atrial activation and RV sensing by 40 ms or taking 70% of this amount, whichever is smaller. (*C*) illustrates the determination of Ap-$QRS_{onset}$. All 12-ECG leads are used to determine the location of the atrial pace-spike (Ap) as well as the onset of the QRS complex, but for illustration purposes only lead $V_1$ is displayed. RVOT, RV outflow tract.

Values for Ap-$RV_{EGMV}$, and Ap-$RV_{VCG}$, were not significantly different from the reference Ap-$RV_{vis}$ (*Table 2*). In contrast, values for Ap-$RV_{aCRT}$ were significantly larger than both Ap-$RV_{vis}$ and Ap-$RV_{VCG}$. Furthermore, Ap-$QRS_{onset}$ was significantly larger than all other indices of intrinsic RV activation (*Table 2*).

**Table 1 Patient characteristics ($n$ = 25)**

| | |
|---|---|
| **Baseline characteristics** | |
| Age (years) | 68 ± 9 |
| Male gender ($n$, %) | 15 (60) |
| Ischaemic heart disease ($n$, %) | 14 (44) |
| NYHA functional class ($n$, %) | |
| II | 21 (84) |
| III | 4 (16) |
| LVEF (%) | 26 ± 6 |
| Heart rate (BPM) | 70 ± 14 |
| PR interval (ms) | 189 ± 29 |
| QRS duration (ms) | 160 ± 15 |
| Treatment ($n$, %) | |
| Diuretics | 15 (60) |
| ACE-I/ARB | 23 (92) |
| β-blockers | 21 (84) |
| MRA | 17 (68) |
| Nitrates | 4 (16) |
| Digoxin | 0 (0) |
| Amiodarone | 1 (4) |
| **During procedure** | |
| Paced heart rate (BPM) | 83 ± 11 |
| LV lead location ($n$, %) | |
| Lateral | 15 (60) |
| Posterolateral | 9 (36) |
| Posterior | 1 (4) |
| Total procedure time (min) | 141 ± 22 |

NYHA class, New York Heart Association class; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; BPM, beats per minute.

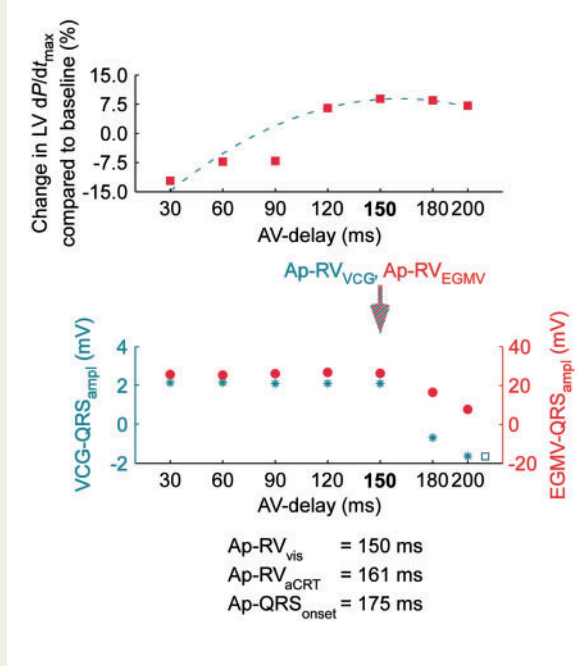


**Figure 3** Determination of the onset of contribution of ventricular contraction from the $QRS_{ampl}$ extracted from the 3D VCG (blue) or 2D EGM-based vectorloop (red). The top panel illustrates the change in LV d$P$/d$t_{max}$ compared with baseline during different AV-delays, with the dotted line representing the fitted parabola. An AV-delay of 150 ms resulted in the maximal increase in LV d$P$/d$t_{max}$. The same AV-delay was identified as Ap-$RV_{vis}$ and corresponded to the longest AV-delay at which the $QRS_{ampl}$ extracted from either the 3D VCG or 2D EGM-based vectorloop was still the same as the $QRS_{ampl}$ found at a very short AV-delay. Therefore, the longest AV-delay at which the $QRS_{ampl}$ was the same as during a very short AV-delay was identified as Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ when extracted from the 3D VCG or 2D EGM-based vectorloop, respectively.

The values for Ap-RV as presented in *Table 2* were obtained using the RV apex as site of implantation of the RV lead. In order to investigate the sensitivity of the methods for the location of the RV lead, in five patients the RV was temporarily placed at the RV outflow tract (RVOT). Ap-$RV_{vis}$, Ap-$RV_{EGMV}$, Ap-$RV_{VCG}$, and Ap-$QRS_{onset}$ were not affected by the change of location of the RV lead. However, when the RV lead was placed in the RVOT Ap-$RV_{aCRT}$ shortened in four of five cases, the difference with the RV apical septum position ranging from -27ms to +9 ms (example in *Figure 2B*).

During Ap-LVp, some patients revealed a time delay between pacing stimulus and onset of QRS complex, referred to as LV pacing latency (an example is shown in *Figure 4*). In this example, the Ap-LVp latency was 44 ms. In case of such a latency, the LV should be paced earlier compared with the onset of contribution of intrinsic RV activation to obtain optimal fusion. To determine Ap-$RV_{aCRT}$, the delay between atrial pacing or sensing and RV sensing is measured, which does not take into account whether Ap-LVp latency is present. Indeed, for the patient shown in *Figure 4*, Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ were 140ms, while Ap-$RV_{aCRT}$ was 179 ms.

Functional performance of the various algorithms was investigated by comparing the measured LV d$P$/d$t_{max}$ during Ap-LVp with an AV-delay equal to the calculated Ap-RV delays. The longer AV-delay found using Ap-$QRS_{onset}$ resulted in a significantly smaller increase in LV d$P$/d$t_{max}$ than using the other methods (*Figure 5*). Furthermore, Ap-$RV_{vis}$, Ap-$RV_{EGMV}$, and Ap-$RV_{VCG}$ resulted in a comparable increase in LV d$P$/d$t_{max}$. However, Ap-$RV_{aCRT}$ resulted in a consistently smaller increase in LV d$P$/d$t_{max}$ compared with Ap-$RV_{vis}$ ($P$ = 0.02), Ap-$RV_{VCG}$ ($P$ = 0.03), and Ap-$RV_{EGMV}$ ($P$ = 0.13).

# Discussion

The current study shows that the EGMV provides information that is highly comparable with the surface-ECG derived VCG. In the acute situation, the $QRS_{ampl}$ as determined from the EGMV determines the onset of contribution of intrinsic RV activation to LV paced activation. This results in optimal LV fusion pacing which does not depend on the position of the RV lead or on the presence of LV latency. Furthermore, optimizing CRT using the EGMV provides an equal or even larger acute haemodynamic response as compared with other algorithms. Therefore, Ap-$RV_{EGMV}$ may

**Table 2 Optimal AV-delay using different methods and the average individual difference in optimal AV-delay between the different tested methods and Ap-RV$_{vis}$. A positive difference indicates a longer optimal AV-delay than Ap-RV$_{vis}$**

| AV-delay method | Mean ± SD | Difference with Ap-RV$_{vis}$ (mean ± SD) |
|---|---|---|
| Ap-RV$_{vis}$ (ms) | 170 ± 33 | |
| Ap-RV$_{EGMV}$ (ms) | 178 ± 43 | 7 ± 25 |
| Ap-RV$_{VCG}$ (ms) | 163 ± 39$^{\#}$ | -6 ± 24 |
| Ap-RV$_{aCRT}$ (ms) | 189 ± 29* | 17 ± 25 |
| Ap-QRS$_{onset}$ (ms) | 228 ± 36$^{*\dagger\ddagger\#}$ | 56 ± 22 |

SD, standard deviation; AV, atrioventricular; RV, right ventricular.
$^{\#}P < 0.05$ compared with Ap-RV$_{aCRT}$ using the Wilcoxon signed rank test.
$^{*}P < 0.05$ compared with Ap-RV$_{vis}$ using the Wilcoxon signed rank test.
$^{\dagger}P < 0.05$ compared with Ap-RV$_{EGMV}$ using the Wilcoxon signed rank test.
$^{\ddagger}P < 0.05$ compared with Ap-RV$_{VCG}$ using the Wilcoxon signed rank test.


**Figure 4** Example of a patient with latency during Ap-LVp. The green line indicates the timing of the pace-artefact. Since the output at which was paced was as low as possible, the pace-artefact is very small. The time interval between pacemaker stimulus and the onset of the earliest paced QRS complex was ~44 ms.

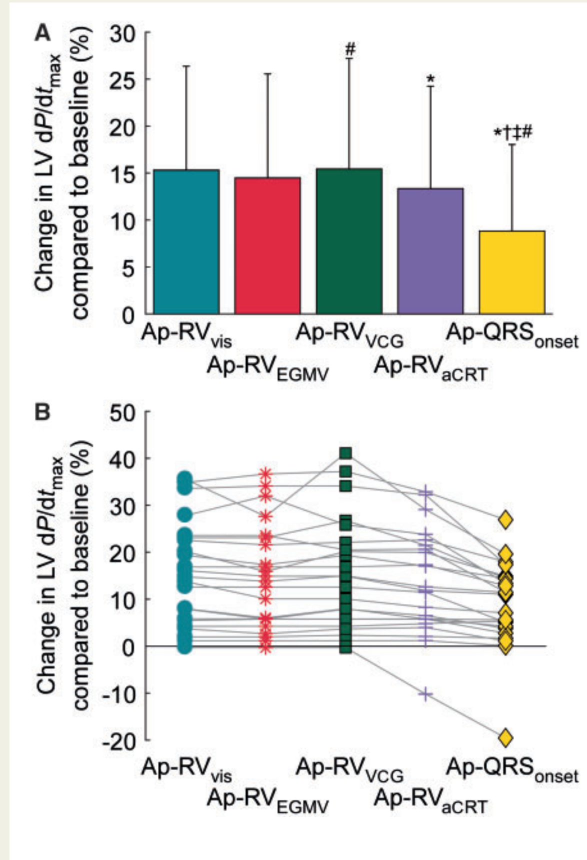


**Figure 5** (representative figure) Haemodynamic response at settings with an AV-delay equal to Ap-RV$_{vis}$ (magenta), Ap-RV$_{EGMV}$ (red), Ap-RV$_{VCG}$ (green), Ap-RV$_{aCRT}$ (pink), and Ap-QRS$_{onset}$ (yellow). Overall differences in change in haemodynamic measures are shown in (*A*), individual changes are shown in (*B*). $^{*}P < 0.05$ compared with Ap-RV$_{vis}$, $^{\dagger}P < 0.05$ compared with Ap-RV$_{EGMV}$, $^{\ddagger}P < 0.05$ compared with Ap-RV$_{VCG}$, $^{\#}P < 0.05$ compared with Ap-RV$_{aCRT}$, using the Wilcoxon signed rank test with a Bonferroni correction. Ap-RV$_{vis}$, Ap-RV as visually observed; Ap-RV$_{EGMV}$, Ap-RV according to the EGMV; Ap-RV$_{VCG}$, Ap-RV according to the VCG; Ap-RV$_{aCRT}$, Ap-RV according to AdaptivCRT$^{TM}$ algorithm; Ap-QRS$_{onset}$, time between atrial pace spike and QRS onset; SD, standard deviation.

provide a useful way to optimize LV fusion pacing individually, continuously, and in an ambulatory fashion, possibly improving long-term CRT response.

## Differences between measures of onset of intrinsic right ventricular activation

This study shows the feasibility and reliability of acute EGM vectorloop-based QRS$_{ampl}$ measurements during Ap-LVp to assess the best AV-delay for Ap-LVp to perform fusion pacing. To obtain Ap-RV$_{EGMV}$, a vectorloop was calculated from EGM signals that were recorded from unpaced electrodes. To the best of our knowledge, there is only one other case report showing vectorcardiogram reconstruction from dual chamber intracardiac cardiovertor defibrillator (ICD) electrograms.[17] However, since a dual chamber ICD was used instead of a CRT-D device, a different combination of EGM signals was used. Furthermore, the resemblance with the VCG was only shown during sinus rhythm and AAI pacing. Until now, the EGM signals are mainly being used for telemonitoring, arrhythmia detection, and as a diagnostic tool. The currently displayed method shows that the EGM signals may also be used for improvement of device therapy.

In this study, a 2D vectorloop was created by plotting two bipolar EGM vectors against each other. Doing so, the contribution of activation of both the RV and LV was taken into account and potentially disturbing influences from nearby pacing electrodes were avoided.

As shown, both the Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ approach resulted in similar AV-delays and accompanying LV $dP/dt_{max}$ values as with the visually determined Ap-RV. This latter reference method is accurate but cannot be applied during CRT, since it requires eyeballing and can only be performed during hospital visits, whereas the VCG and EMGV based methods can be applied during CRT and, potentially, in an ambulatory fashion.

Comparing the Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ with Ap-$RV_{aCRT}$, the latter one was longer in duration than the other two methods. This resulted in a haemodynamic response difference from -9.9% to 4.0% compared with using Ap-$RV_{EGMV}$. Furthermore, while Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ use measured data to find the optimal AV-delay, Ap-$RV_{aCRT}$ uses a population-based relation to find the optimal AV-delay. Moreover, to determine Ap-$RV_{aCRT}$, the delay between atrial pacing or sensing and RV sensing is measured. This delay does not take into account the presence of LV latency and therefore Ap-$RV_{aCRT}$ does not adjust for LV latency. In contrast, to determine Ap-$RV_{VCG}$ or Ap-$RV_{EGMV}$ Ap-LVp is performed and the AV-delay is gradually prolonged to detect the onset of intrinsic RV contribution. It will thus directly measure the moment of optimal fusion, whether LV latency is present or not. Finally, contrary to Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$, Ap-$RV_{aCRT}$ was dependent on lead location. Therefore, Ap-$RV_{VCG}$ and Ap-$RV_{EGMV}$ might be the more tailored and better approach for CRT optimization.

The use of Ap-$QRS_{onset}$ as the AV-delay resulted in a haemodynamic response that was -19.2% to 1.1% compared with the haemodynamic response during Ap-$RV_{EGMV}$. Ap-$QRS_{onset}$ was significantly longer in duration than all other Ap-RV methods, indicating that the onset of contribution of intrinsic RV activation is already occurring without being registered on the 12-lead ECG.

The absolute values of all Ap-RV methods may seem long (*Table 2*), but it should be noted that all measurements were performed during atrial pacing. Gold *et al.*[18] previously showed that the optimal AV-delay during atrial sensing (As) is approximately 50ms shorter than during atrial pacing. In the current study, a difference in As-V delay and Ap-V delay of 37 ± 18ms was found.

Our method of either using the EGMV or VCG for CRT-device optimization finds the optimal settings during Ap-LVp for each patient individually and has the potential to optimize in an ambulatory fashion.

## Other automatic algorithms for cardiac resynchronization therapy-device optimization

Other algorithms for automatic adjustment of CRT-device settings are the SmartDelay,[18] QuickOpt,[19] and SonR[20] algorithms. These algorithms are based on predictions of resynchronization. The SmartDelay algorithm is based on intrinsic measurements of PR interval and QRS duration, while the QuickOpt method is based on the width of atrial intrinsic depolarization (QuickOpt). The empirically derived QuickOpt algorithm resulted in an offset that depends on the actual width of the intrinsic depolarization with sharp cut-off values, resulting in a zigzag relationship of the optimal AV-delay.[19] Both the SmartDelay and QuickOpt methods optimize the delays only during in-office visits. This may not translate into full long-term clinical benefit because optimal settings may change with patient activity and disease state. The SonR algorithm has shown non-inferiority to echocardiographic optimization.[20] However, it requires a special lead in either the RV or right atrium containing the PEA sensor (SonRtip, LivaNova), an accelerometer that detects the heart sounds. The presented algorithm for Ap-$RV_{EGMV}$ can be conducted without any need of extra or different leads.

## Potential clinical implications

The demonstration of the feasibility and reliability of using EGM-based vector amplitudes to optimize LV fusion pacing is an important step towards continuous ambulatory optimization of CRT. Electrogram has the potential to find the optimal AV-delay during different levels of patient activity such as sleep, normal activity, and exercise. Until now all algorithms are based on a predicted degree of resynchronization. With aid of the QRS amplitude, the optimal resynchronization can be tracked during pacing for each patient individually and is independent of lead location and the presence of LV latency. The VCG or EGMV could be used to individualize LV fusion pacing in two ways: (i) in its simplest application a single, patient specific Ap-$RV_{VCG}$ can be determined, in-hospital at time of implant or shortly thereafter, using the regular ECG from which the $QRS_{ampl}$ can be calculated. (ii) The ultimate application of our findings would be to embed an algorithm into the CRT-device which can monitor Ap-RV using the EGMV (pseudo) continuously. It will do so by periodically testing different AV-delays and calculating the corresponding $QRS_{ampl}$. Using this data, the CRT-device will provide automated adjustment of AV-delay to diurnal or periodical changes in Ap-RV, for example during exercise of progression of heart disease.

## Limitations

The current study was a relatively small study, designed to proof the principle of electrical optimization of CRT using VCG and EGMV. The study was performed in two centres (MUMC+ and UMCG) and the patients were consecutive patients. Furthermore, as indicated by the baseline patient characteristics (*Table 1*), the patient population is representative for the CRT population. Because the acute haemodynamic response may not predict long-term outcome, a larger multicentre trial should be performed to confirm our results and to investigate the possibility to use the EGMV method to optimize LV fusion pacing continuously and in an ambulatory fashion focusing on long-term outcome.

For the EGMV method described in this study, a commercially available LV quadripolar lead was used. For the current EGMV approach, a larger inter-electrode distance may provide better results, but this requires a change in design of these leads.

In the present study, atrial overdrive pacing was used in order to keep the heart rate constant. However, the EGMV signals do not depend on the use of atrial pacing or sensing.

The current study only investigated the response in patients with a LBBB (having a Class I indication), future studies should also investigate the EGMV method in Class II patients since the response and the Ap-RV determination could be different in RBB block and intraventricular conduction delay patients.

# Conclusion

The onset of contribution of intrinsic RV activation for optimal LV fusion pacing can be determined using a 2D vectorloop derived from unipolar EGM signals measured from implanted pacing electrodes. This method can be used to objectively and easily tailor CRT-device settings. This property opens the possibility to adjust the AV-delay individually, continuously and in an ambulatory fashion, possibly improving CRT response.

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