New nonivasive method for evaluating acute response to cardiac ressynchronization therapy (NIME-CRT)

NCT ID not yet assigned
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Project management

The project will be led by senior scientist Dr. ing. Espen W. Remme. He is an expert in cardiac mechanics and has extensive experience with monitoring heart function with different devices, and with left bundle branch block (LBBB) and cardiac resynchronization therapy (CRT) studies. He has positions at the Intervention Center and Institute for Surgical Research at Oslo University Hospital, Rikshospitalet. The research groups there have long term experience in studies of LBBB and CRT studies including the patient studies CRID, IMPACT 1 and 2 among others. The research activity of the department including our group has been ranked with top grade "excellent" the last two evaluations by the international expert panel appointed by the Research Council of Norway. Head of the Section for Arrhythmias, OUS, Erik Kongsgård (Dr. med), and his team will be responsible for medical treatment of the patients at Rikshospitalet. Additional experienced clinical personnel and research fellows will be involved for organizing, collecting and analyzing the measured data.

Project design

Background

Cardiac Resynchronization Therapy (CRT) has been one of the most important advancements in the past decade for patients with dyssynchronous heart failure (left bundle branch block – LBBB), where the lateral wall of the left ventricle (LV) is late activated. Hence, the early activated region contracts while the late activated region continues to stretch in beginning of systole, causing inefficient pressure rise and ejection of blood out of the LV. LBBB can be treated with a pacemaker that paces both sides of the LV in order to restore a normal contraction. CRT is shown to cost-effectively reduce mortality and morbidity, and improve quality of life [1].

CRT is effective in selected patients for improving heart function and life expectancy, however, around 30-40% of patients who undergo this procedure do not benefit from it [2]. These patients do not respond to this therapy and their situation might even worsen, with complications occurring in up to 10% of them. If such a high percentage of these procedures are ineffective, there are a substantial amount of resources that are wasted annually worldwide and could be saved **by identifying patients that are non-responders** as **the device would not be placed**, **no CRT follow up sessions would be needed**, and there would be **no pacemaker lead-associated thrombosis and infections**.

Due to the large proportion of patients that do not respond to CRT, there is much research aiming to improve the selection criteria for whom should receive CRT, which according to current guidelines include heart failure status, ejection fraction, left bundle branch block, and ECG QRS duration [3]. This assessment is made well in advance of the CRT implantation. However, assessment of acute response during implantation may be a complimentary method. During this procedure the clinician tests several pacing lead locations using an external pacing device. The package with the expensive implantable pacemaker is not opened until the end of the procedure. Hence, if non-responders can still be identified during this procedure, unnecessary device implantation, costs, and complications can be avoided.

There is no consensus on which hemodynamic parameter should be used to identify acute response during CRT implantation [4]. Our group has been investigating methods to measure this response for several years with different sensors and parameters to assess cardiac function in both animal and clinical studies. We have found that the inefficient dyssynchronous contractions slow down the time it takes for the LV to raise pressure and open the aortic valve to start the ejection. Hence, the duration of this **preejection period (PEP)** from first electrical activation of the ventricles to aortic valve opening, is the measurement that works best as the shortening of this interval with successful CRT (all regions of the LV wall contract at the same time and the pressure raises quickly) is a more reliable marker than other indexes currently being used during procedures [5]. It is also less affected than other indexes by changes in preload (amount of filling of the ventricle) that is common with CRT [6].

We have performed a preliminary assessment of this idea in animal data recorded as part of a previous study, where the arterial pressure curve was measured invasively in the ascending aorta in addition to LV pressure by micro-tip catheters. LBBB was then induced in the animals and biventricular (BiV) pacing (i.e. CRT) was performed from different locations of the LV. From this data we measured the PEP interval from the Q wave in the ECG signal up to the upstroke of aortic pressure (AoP), as shown in Figure 1.

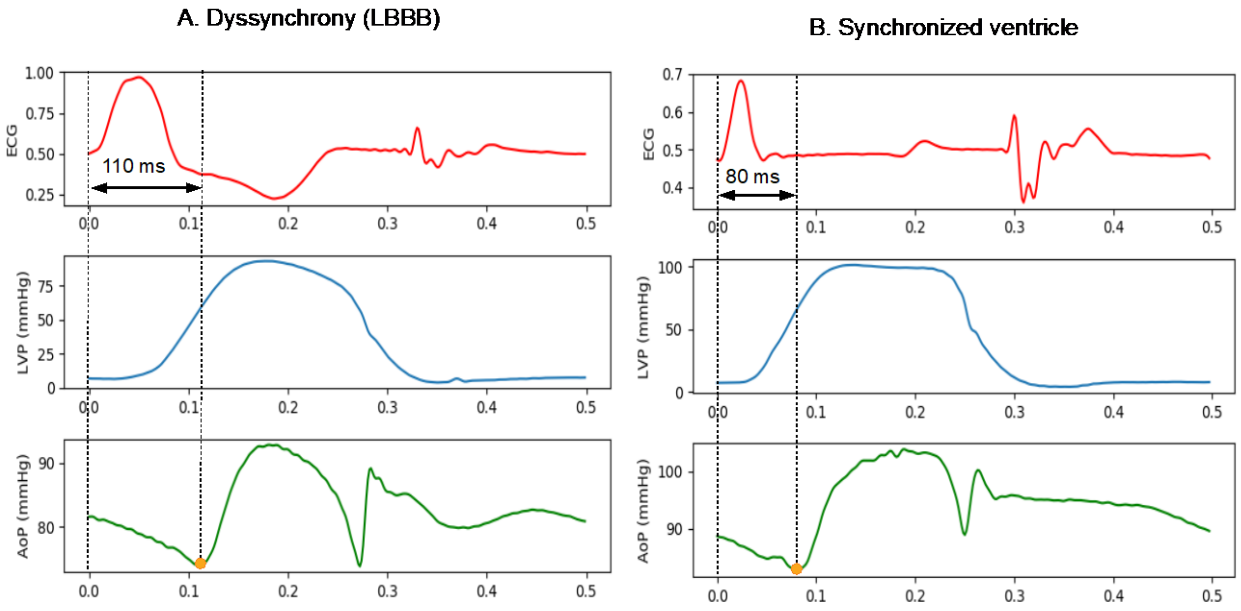

Figure 1. Data from a representative animal. In the left panel the ECG and pressure signals from a dyssynchronous heartbeat of an animal with induced LBBB. The right panel shows a heartbeat of the same animal with a synchronous contraction. The dashed vertical lines mark the PEP. The first one marks the start of electrical activation (Q wave), while the second one marks aortic valve opening (AoP upstroke, marked with an orange dot). In the dyssynchronous case the PEP is prolonged compared to the synchronous case.

Figure 2 shows data during 3 settings from the 7 animals in this preliminary study: first at baseline during normal electrical activation, then after LBBB had been induced, and during subsequent CRT to restore synchronous activation. The results show clear changes between each of them for every animal.

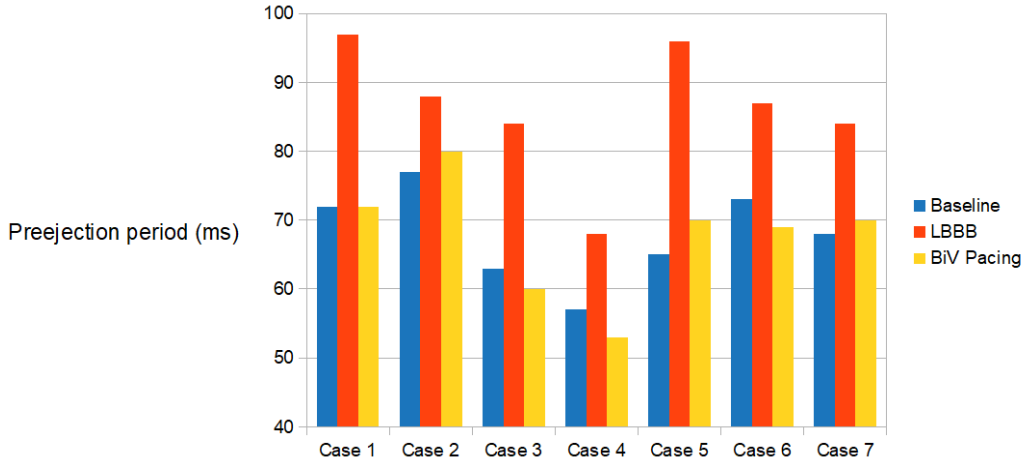

Figure 2. Preliminary results from animal study. The PEP interval was measured in 7 different animals at 3 different moments: during normal electrical activation before ablation (baseline), after ablation and induction of LBBB and with CRT (i.e. BiV pacing). It can be observed in all cases that the duration is increased in LBBB and successful CRT restores the PEP interval back to a normal value.

In our current study we propose a novel method to estimate the preejection period **noninvasively**, as the time elapsed between the Q wave of the ECG to the rise of the **peripheral arterial pulse curve** measured for example at the earlobe or in the arm or even finger. We have also done some case studies to test this concept in animals, as seen in Figure 3. In these animals a piezoelectric sensor over the skin (Figure 4B) was strapped around the lower limb ankle to measure the arterial peripheral pulse wave. This measurement is equal to the PEP plus the time required for the pulse wave to travel in the arteries to the peripheral location where the measurement is being taken. We hypothesize that this delay will remain constant for the same patient and any acute change in this time interval will therefore be a change in PEP. However, this will be tested by comparing sensors placed proximally and distally.

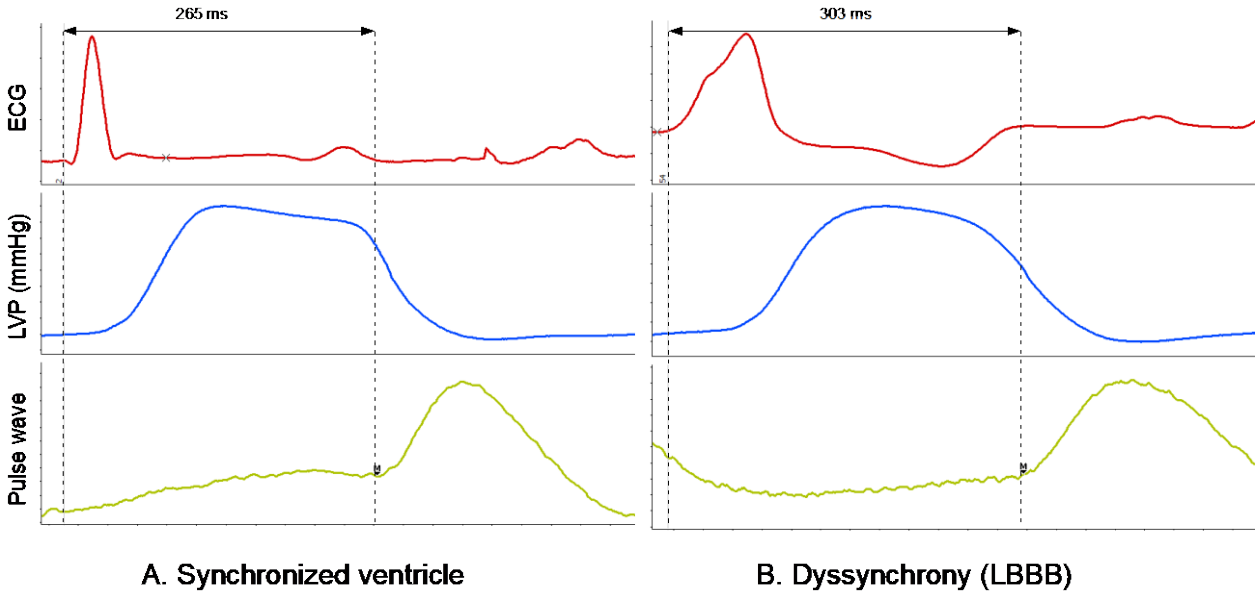

Figure 3. Data from a representative animal. In the left panel the ECG, LV pressure and pulse wave signals from a synchronous heartbeat of an animal. The right panel shows a heartbeat of the same animal with a dyssynchronous contraction after LBBB

induction. The dashed vertical lines mark the PEP, plus the time that the pulse wave takes to travel to the back limb where the measurement is being taken noninvasively by a piezoelectric sensor on the skin. The first vertical line marks the start of electrical activation (Q wave), while the second marks the upstroke of the pulse wave. In the dyssynchronous case the time interval is prolonged compared to the synchronous case.

The key aspect of our proposed methodology is to avoid invasive procedures that might entail some risk for the patient while still giving reliable feedback to the clinician. These measurements should be reliable and given during the procedure as different lead placements and pacing configurations are tested. We therefore plan to develop an auto detection algorithm that allows us to get the acute response in real time.

Aims of the study

We will investigate the capabilities of a noninvasive device to assess the cardiac function of a patient through its PEP. Different locations on the hand and arm will be tested to see which one is best to measure arterial pulse waves for this purpose, without getting in the way of clinicians or adding discomfort to the patient. The study has two different hypotheses regarding the suitability of the method for assessing acute response to CRT:

Hypothesis 1

During CRT implantation patients that are responders to the treatment will demonstrate a significantly shortening of the PEP compared to non-responders. We will perform PEP measurement during impanation while response will be defined 6 months follow up as a ≥15% reduction of LV end systolic volume (ESV) by echocardiographic examination. Fifteen percent reduction of LV ESV is a common definition of response to CRT as before CRT implantations the LV is dilated, and successful resynchronization results in systolic contraction to a lower ESV and over time reverse remodeling results in a smaller LV. Patients will also be followed after 1 and 2 years to note hard end-points such as mortality, heart transplants. This will be a proof of concept study to indicate if such non-invasive PEP measurements can be used to decide if a patient should receive CRT or not.

Hypothesis 2

Patients who have had CRT implanted at Rikshospitalet the last half a year, will be investigated at their 6 month CRT-control and response will be defined 6 months follow up as a ≥15% reduction of LV end systolic volume (ESV) by echocardiographic examination as above. We hypothesize that there will be a significant shorter PEP with CRT turned on (synchronous activation) compared to when CRT is turned off (dyssynchronous activation). Furthermore the reduction in PEP from CRT OFF to CRT ON will be larger in patients classified as responders compared to patients classified as non-responders.

Hypothesis 3 – additional echocardiographic recordings

In animals we have previously observed and published the findings that CRT acutely reduces both end systolic (ESV) and diastolic volumes (EDV). A reduction of end diastolic volume is an effective reduction of preload which according to the Frank-Starling mechanism reduces functional indices such as ejection fraction, stroke volume, strain, and more. Thus, improvements in LV function by CRT may be apparently concealed by this preload reduction. However, if the such an acute reduction in

volume as observed in our animal model, will also occur in humans is uknown. This is of importance in order to interpret potential changes in preload dependent measurements to evaluate how heart function changes when CRT is turned on. We hypothesize that there will be a reduction in ESV and EDV from CRT OFF to CRT ON as measured by volumes from echocardiography.

Furthermore, in an ongoing animal study we see that the abnormal septal motion in LBBB (CRT OFF) causes a reduced septal early diastolic lengthening velocity (septal e') which confounds the use of the E/e' index to estimate LV filling pressure (E is the velocity of the early diastolic filling wave through the mitral valve by echocardiography). CRT acutely increased septal e' in the animals while lateral e' was relatively unaltered, suggesting lateral E/e' should be used to evaluate LV filling pressure in these patients and not the average of septal and lateral e'. We want to confirm that the same observation as seen in animals is present also in patients, which will strengthen the findings in our ongoing study.

Finally, in a recent paper we showed data indicating that septal dysfunction is driving the development of heart failure in LBBB. As these patients have an echocardiographic exam the day before CRT implantation, it will allow a longitudinal study as we will perform echocardiography on the patients also after 6 months. In line with our previous paper, we hypothesize that CRT responders will have a reverse remodeling where there will be most recovery of septal function quantified by regional strain and non-invasive pressure-strain regional myocardial work indices.

Methods and material

Patients

Two different patient populations will be used in this study for the two hypotheses. On one hand, up to 40 patients admitted for CRT implantation according to current ESC/AHA guidelines at the Department of Cardiology, Rikshospitalet, Oslo University Hospital will be included in this study. While we will also include another 40 patients admitted for routine checkups of their CRT devices to test hypothesis 2. This is an observational study that will serve as proof of concept; therefore data must be registered and analyzed before a statistical calculation of the sample size can be made.

However, the rational for choosing 40 patients in each of the two substudies is as follows. Based on the animal data, we see a distinct difference in the PEP measurements between synchronous and dyssynchronous activation. Hence, we expect that we should see clear statistical differences with relatively few patients in the two groups of responders and non-responders. In order for the method to be of clinical value to ultimately decide if a patient should not receive CRT, the differences should also be so clear that few patients are needed to demonstrate this difference. We rather arbitrary believe we must have at least 10 in the group with fewest patients to have confidence in the general validity of the results in this group. Given a CRT response rate of 1/3, this would require 30 patients. In addition we estimate that 20% of patients may be excluded due to poor signal quality or unattainable data and we could have a higher response rate; therefore we have ended up with 40 patients for each of the two substudies which adds to a total of 80 patients for the whole study. However, this number may be revised during the project once we gain data to perform a proper power analysis.

Inclusion criteria hypothesis 1:

- Referred for CRT implantation at Oslo University Hospital, Rikshospitalet based on the standard guideline criteria below:
    - Sinus rhythm.
    - New York Heart Association functional class II and III heart failure on optimal medical therapy.
    - Left bundle branch block.
    - QRS duration larger than 130 ms.
    - Left ventricular ejection fraction lower than 35%.

Inclusion criteria hypothesis 2:

- Previously performed CRT implantation at Oslo University Hospital, Rikshospitalet, based on the standard guideline criteria described in the point above.

Noninvasive measurements

There are different commercial technologies that would allow us to get the needed recordings, as shown in Figure 4. We will use an IR Plethysmograph – Ear Clip II - MLT1060EC (Figure 4 A) attached to the earlobe of the patient and directly connected to a PowerLab® recording unit. In addition to that, a Finameter will be placed on the finger of the patient, which will serve as an additional, more distal, peripheral arterial pulse curve and give continuous recordings of arterial pressure. Hemodynamic recordings will also include heart rate and ECG that are standard measurements in these procedures.

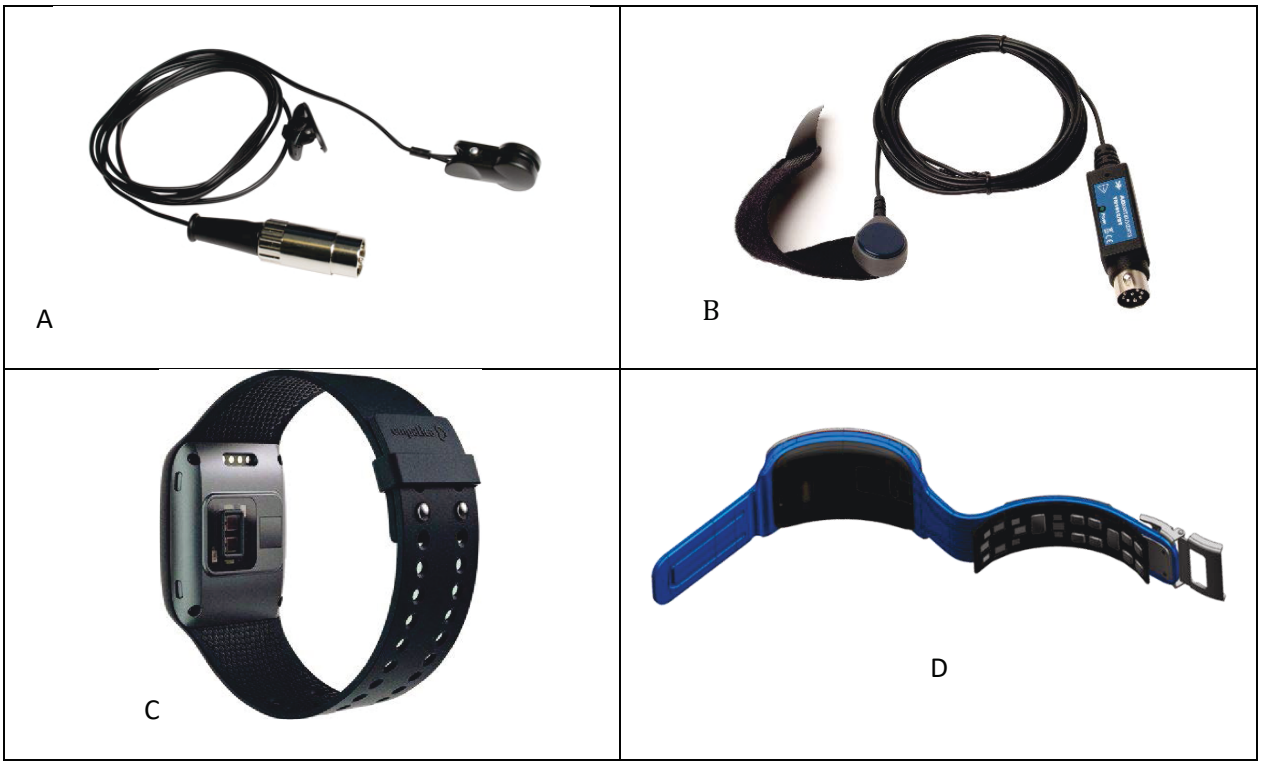

Figure 4. Different commercial technologies that could be used to measure a peripheral arterial pulse wave: Infrared photoplethysmograph which is be attached to the earlobe (ADInstruments, A). Finger pulse transducers that uses a piezo-electric sensor (ADInstruments, B). Wearable wrist cuff based on different types of sensor modules (E4 wristband, C and Simband, D).

Echocardiographic examination

A complete echocardiographic examination is performed the day before CRT implantation as part of the standard procedure at our hospital. After 6 months these patients will be called in for their standard CRT 6 months control. In addition to this standard CRT control, we will also perform another echocardiographic exam at this time which will allow us to evaluate changes in ESV to classify the patient as a responder or non-responder. Echocardiographic images will be performed both with the CRT ON and CRT OFF at this 6-months control and compared with the images acquired the day before CRT implantation.

Statistical analysis plan (SAP)

Results will be presented in mean ± standard deviation or confidence intervals (CIs). Comparison between two groups will be performed with paired Students t-tests or chi-square test as appropriate. Univariate and multivariate linear regression analyses will be used to identify predictors of reverse remodeling.

Time schedule

We aim to start inclusion of patients March 2023. We hope to include 1-2 patients per week who are going to get CRT implantation, which means we will then finish the first set of measurements in 2024. Then subsequent 6 months follow up which will then be from third quarter 2023 to 2025. The hypothesis 2 substudy we aim also to start March 2023 and include about 2 patients a week for CRT control. Inclusion should then finish by end of 2023. We will follow the patients for 2 more years (2027) to note the harder end-points. We expect several abstracts and journal papers to be written from this material. The end of registrations will be 2027, but subsequent papers may take 2 more years to finish and our experience is that such data will be included in spin-off papers not yet planned. Hence, we have set the final date for publication from this material as end of 2031.

Health information

In addition to the PEP measurements, we will note down standard echocardiographic parameters for assessment of heart function such as EF and volumes as well as heart failure relevant information such as blood pressure, type of heart disease, and heart related drugs, as well as age, gender, weight and height. Additional blood test data will be collected and registered at 6 months CRT control. Data will be handled in compliance with the rules and regulation for patient research data at Oslo University Hospital and stored in dedicated, secured servers. The patient data will be stored de-identified and the key will be stored separately in dedicated server area according to the regulations. Only project members will be able to obtain access to the key and the patient data.

Ethical considerations

This project entails very low risk as all the technology needed is noninvasive and is already in the hospital. The study involves patients who have already been referred to CRT implantation or configuration and they will undergo this procedure independently of the study. The planned clinical study is easy to carry out and will not cause any extra discomfort for the patient. The only added time to the examination time will be the time taken to place the sensors and the testing of CRT settings which entails a very small risk for the patient and will be performed by trained clinicians.

During the 6-months CRT-control, they will get an additional echocardiographic examination which has no risks. These patients will thus benefit from this extra echocardiographic investigation which can give added clinical information in exchange for the extra time it takes to perform such an examination.

Source of funding

We have received 3 year postdoc funding from the South-Eastern Norway Regional Health Authority to perform this project (HSØ grant project # 2022049).

Clinical and scientific impact

The present study may provide a novel noninvasive method for assessment of the acute response to pacing. The results of this study will be published as abstracts to scientific conferences and are expected to result in one or more journal papers which will be part of the PhD of the research fellow.

The results of the study can be of great value for researchers in addition to healthcare workers and patients as it could be used in all CRT implantation procedures and help to identify non-responders. This method would also help guide the optimal placement of the pacemaker leads during implantation. As it would detect any misplacement or if, in some patients with infarct, a scar is preventing the pulse from the pacing lead to propagate. It would therefore help identify patients who do not benefit from this therapy and avoid implanting unnecessary devices; and optimize both lead position and pacemaker settings.

Adjustment of pacemaker settings is a potential subsequent use of the method. Patients come routinely back for control of the CRT. Our method could be an easy way to give the clinician feedback on changes to the CRT settings during such controls.

Together with our technology transfer office, Inven2, we are currently looking into the possibility for patenting and commercializing the method.

Furthermore, the echocardiographic measurements can help improve our understanding acute response parameter which may be confounded by acute preload alterations, which parameters to use when estimating LV filling pressure in LBBB patients, and which mechanisms drive heart failure development in LBBB patients.

References

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