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Hemodynamic monitoring by intracardiac impedance measured by cardiac resynchronization defibrillators: Evaluation in a controlled clinical setting (BIO.Detect HF II study)

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ABSTRACT

Background: In patients with cardiac resynchronization therapy defibrillators (CRT-Ds), intracardiac impedance measured by dedicated CRT-D software may be used to monitor hemodynamic changes. We investigated the relationship of hemodynamic parameters assessed by intracardiac impedance and by echocardiography in a controlled clinical setting.
Methods: The study enrolled 68 patients (mean age, 66 ± 9 years; 74% males) at 12 investigational sites. The patients had an indication for CRT-D implantation, New York Heart Association class II/III symptoms, left ventricular ejection fraction 15%–35%, and a QRS duration ≥150 ms. Two months after a CRT-D implantation, hemodynamic changes were provoked by overdrive pacing. Intracardiac impedance was recorded at rest and at four pacing rates ranging from 10 to 40 beats/min above the resting rate. In parallel, echocardiography measurements were performed. We hypothesized that a mean intra-individual correlation coefficient (r_{mean}) between stroke impedance (difference between end-systolic and end-diastolic intracardiac impedance) measured by CRT-D and the aortic velocity time integral (i.e., stroke volume) determined by echocardiography would be significantly larger than 0.65.
Results: The hypothesis was evaluated in 40 patients with complete data sets. The r_{mean} was 0.797, with a lower confidence interval bound of 0.709. The study hypothesis was met ($p = 0.007$). A stepwise reduction of stroke impedance and stroke volume was observed with increasing heart rate.
Conclusions: Intracardiac impedance measured by implanted CRT-Ds correlated well with the aortic velocity time integral (stroke volume) determined by echocardiography. The impedance measurements

Abbreviations: Ao-VTI, aortic velocity time integral; CRT, cardiac resynchronization therapy; CRT-D, CRT defibrillator; EDZ, end-diastolic impedance; ESZ, end-systolic impedance; HF, heart failure; ICI, intracardiac impedance; ICI-MF, ICI measurement feature; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; NYHA, New York Heart Association; RV, right ventricular; SZ, stroke impedance; Z_{mean}, mean impedance.

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bear potential and are readily available technically, not requiring implantation of additional material beyond standard CRT-D system.

1. Introduction

Heart failure (HF) is a global pandemic affecting an estimated 26 million people worldwide and resulting in >2 million hospitalizations each year [1]. Despite advances in pharmacological and device therapies, the 12-month mortality and hospitalization rates remain about 17% and 44% for hospitalized HF patients, and 7% and 32% for stable, ambulatory HF patients, respectively [2]. Cardiac resynchronization therapy (CRT) can improve cardiac function and reduce morbidity and mortality of symptomatic patients with a reduced left ventricular ejection fraction (LVEF; ≤35%) and a prolonged QRS duration (≥130 msec) [2]. To terminate potentially lethal ventricular arrhythmias, most CRT devices integrate a defibrillator (CRT-D device). But the risks of progressive deterioration of HF, hospitalization (incurring high treatment costs) [3], and death remain high because of the natural history of HF and the fact that approximately 30% of patients do not respond to CRT [2,4].

Remote monitoring of CRT(-D)s has been adopted as a new standard of device and patient follow-up care where alert-driven in-person evaluations replace most of the routine device follow-ups [4–8]. Addition of a reliable hemodynamic sensor to a CRT(-D) would allow a continuous monitoring of cardiac function to reduce acute HF decompensations and achieve hemodynamic optimization by CRT(-D) self-adaptation or manual reprogramming prompted by telemonitored data. An effective implantable hemodynamic sensor is currently available as a stand-alone monitor of pulmonary artery pressure whose remote transmissions are used to optimize medication and patient management [7,9].

Hemodynamic changes may alternatively be assessed by intracardiac impedance (ICI) changes measured using 'standard' CRT-D devices with dedicated software. The principle has been explored in animals and in 14 patients by invasive methods [10–14], and in another study of 15 ischemic patients by minimally invasive methods [15]. Recently, the ICI measurement feature (ICI-MF) has been integrated for investigational purposes in the market-released Lumax 740 HF-T and the successor CRT-D device models (Biotronik SE & Co. KG; Berlin, Germany). The present study investigates the relationship of hemodynamic parameters assessed by the ICI-MF and by echocardiography in a controlled clinical setting.

2. Methods

The non-randomized Monitoring of Hemodynamics in Heart Failure Patients by Intracardiac Impedance Measurement (BIO.-Detect HF II) study was performed at 12 investigational sites in Germany, Denmark, and The Netherlands (see Appendix). The study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki, including approval of the study protocol by appropriate national and local ethics committees, and study registration with ClinicalTrials.gov, number NCT01711281. Patients provided written informed consent.

2.1. Patients

Consenting adults were enrolled if they had an accepted indication for CRT-D implantation, the New York Heart Association (NYHA) class II or III HF with ischemic or non-ischemic etiology or with dilated cardiomyopathy as the underlying disease, a left ventricular end-diastolic diameter (LVEDD) ≥55 mm, LVEF 15%–35%, and a QRS duration ≥150 msec.

Patients were excluded if they had an already implanted CRT device, persistent atrial fibrillation, aortic valve stenosis, significant aortic regurgitation (more than a trace of aortic valve insufficiency or/and vena contracta >3 mm), aortic valve prosthesis, heart transplant (or a candidate status), a planned or previous (within 3 months) heart surgery, need for chronic renal dialysis, or life expectancy ≤1 year due to a non-cardiac disease. Also those participating in another clinical trial, or who were not implanted with all components of the CRT-D system as specified below, were excluded.

2.2. CRT-D system

The Lumax 740 HF-T and its successor devices integrate the ICI-MF and Biotronik Home Monitoring® technology capable of automatic, daily transmissions of various parameters [16,17], including ICI data for investigational purposes. The ICI-MF has been market approved in Europe based on an extensive risk-benefit analysis. The benefit is currently merely hypothetical, and activation of the ICI-MF is therefore restricted to clinical trials.

While no additional material beyond standard CRT-D system needed to be implanted, the use of a true bipolar right ventricular (RV) defibrillation lead [18] and of a bipolar left ventricular (LV) lead with at least 15-mm distance between the tip and the ring electrodes is necessary for ICI-MF and was mandated by study protocol. This minimum distance was estimated based on the technical requirements needed to guarantee an adequate intracardiac impedance, given the exact measurement hardware and conditions. Originally, it was verified by numerical models but also proved to be appropriate in a previous study [15]. Right atrial and RV leads were implanted endocardially, and LV leads were implanted in a sidebranch of the coronary sinus.

2.3. Working principle of ICI measurements

Pseudo-continuous ICI curves are generated by injecting a subthreshold current between the RV lead tip and coil, and sampling voltage via the LV electrodes (Fig. 1A) [10]. After averaging ICI curves for a certain number of heart cycles, four parameters are derived:

- EDZ: End-diastolic impedance is the minimum ICI value during the heart cycle (Fig. 1B).
- ESZ: End-systolic impedance is the maximum ICI value during the heart cycle (Fig. 1C).
- SZ = ESZ - EDZ: Stroke impedance is the difference between ESZ and EDZ (Fig. 1D) [11,13]. As a rule, the larger the stroke volume, the greater the stroke impedance.
- Z_{mean}: Mean impedance is the mean value of the averaged ICI values for each heart cycle in an ICI measurement window.

ICI provides relative rather than absolute measures of hemodynamic parameters. To estimate changes in stroke volume, ICI has to be collected as serial measurements over a period of time.

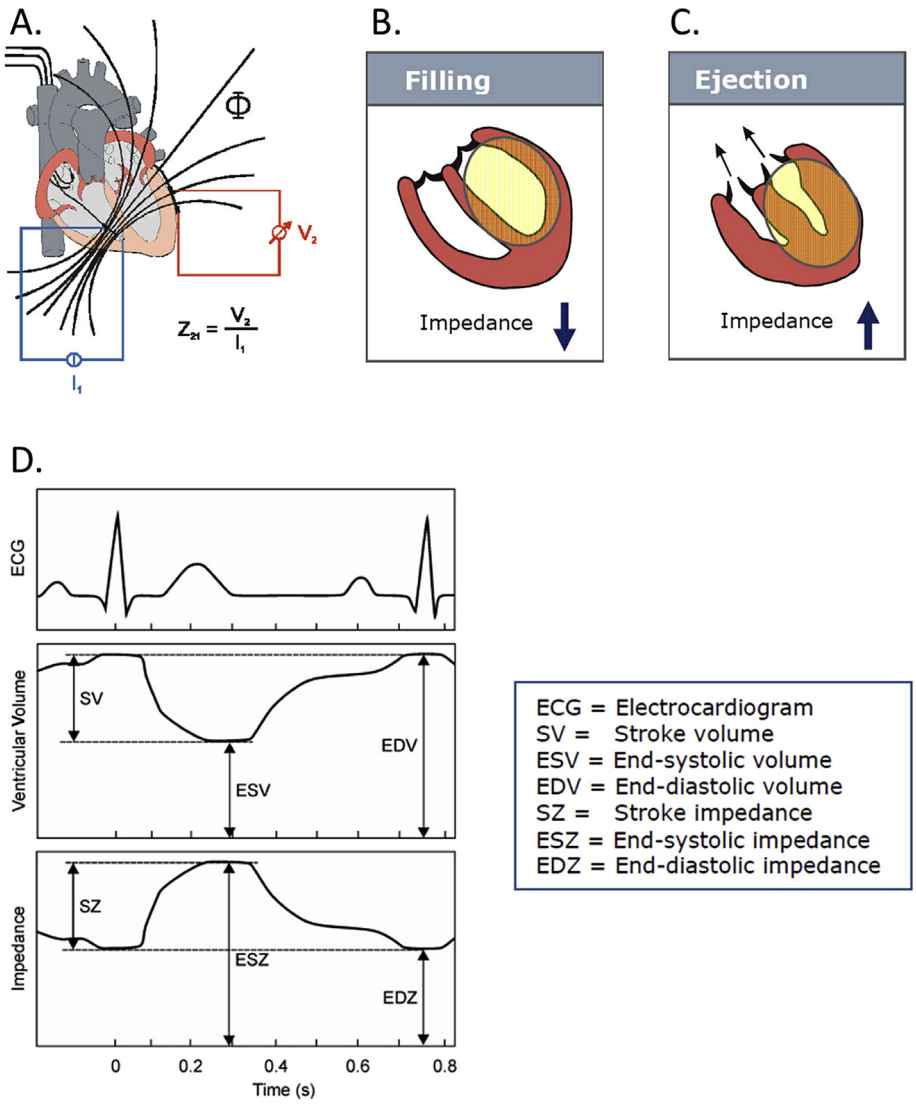

Fig. 1. Panel A: Working principle of intracardiac impedance measurements. Sub-threshold current (I_1) is injected between two electrodes on the right ventricular lead (tip and coil) and is conducted by blood and tissue. The resultant voltage (V_2) is sampled via two electrodes on the left ventricular lead (tip and ring). Current pulses of 30-μsec width per phase are delivered every 8 msec to generate impedance curve for the entire heart cycle. Panels B and C: Blood has lower electrical resistance than myocardial tissue. A maximally filled left ventricle with blood at the end of diastole is therefore associated with impedance minimum, and a maximally emptied left ventricle at the end of systole is associated with impedance maximum. Panel D: Idealized depiction of relationship between ECG, left ventricular volume, and intracardiac impedance curve during a heart cycle.

Changes in stroke volume can be provoked acutely by overdrive pacing or medications (e.g., dobutamine) and may be observed chronically as a consequence of progressive HF or cardiac remodelling.

2.4. Acute and chronic ICI measurement options

Depending on the measurement purpose, two different working options can be used: acute ICI measurement and chronic ICI measurement.

Acute ICI measurement is suited to monitor hemodynamic changes in a controlled clinical setting. ICI curves are continuously stored in the programmer memory, to be retrieved and processed later. To ensure patient safety, acute ICI measurements can be activated only if an immediate RV impedance and pacing threshold test ensures a non-capture safety margin of at least 3.5 related to 600-μA current pulses injected for the measurements. To illustrate the processing of the acute ICI data, an exemplary recording of raw impedances as measured and pre-processed by the CRT-D implant and as transmitted to the programmer via real-time telemetry is depicted along with a synchronous ECG measurement (Fig. 2).

Chronic ICI measurement is aimed at monitoring slow hemodynamic changes over time. To ensure safety of ambulatory patients under all possible conditions, the current amplitude is reduced from 600 μA to 200 μA. When chronic ICI measurement is activated, the CRT-D records ICI curves over 512 valid heart cycles (approximately 7 min) every 2 h. The curves are averaged to minimize the impact of random noise for an enhanced signal-to-noise ratio. The CRT-D device can be programmed to collect and transmit one of the twelve constructed mean ICI curves via Home Monitoring. Fig. 3 shows an exemplary ensemble of those ICI curves for one patient. From the average curve, the EDZ, ESZ, SZ, and Z_{mean} values are derived. The 12 sets of these values generated during a day are averaged per day, stored in the CRT-D memory, and transmitted via Home Monitoring. The stored ICI data can also be retrieved conventionally from the CRT-D memory during clinical

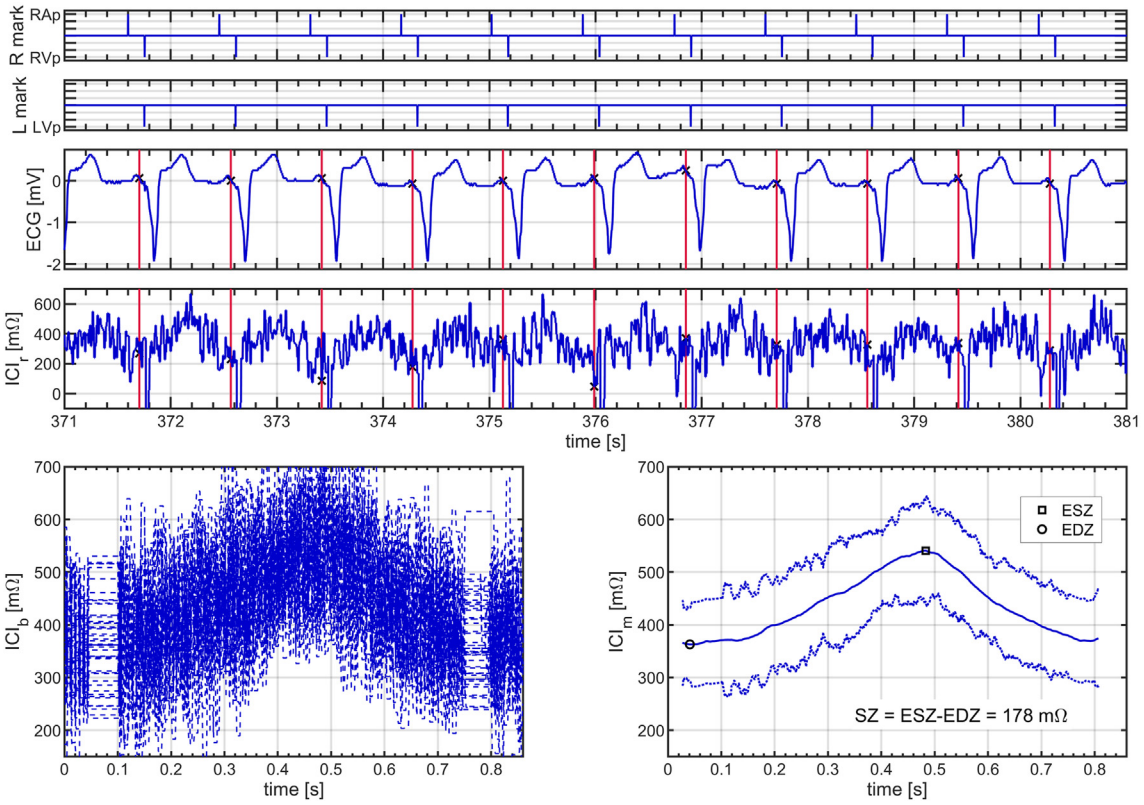

Fig. 2. Example of an ICI raw data recording during acute clinical settings where the patient was paced at a constant rate of 70 bpm. Markers at the top depict the time points of paced events in the right atrium, and right and left ventricle, respectively. ICI_r depicts the raw ICI signal sampled at 128 Hz as a result of subthreshold current injection (biphasic, 600 μA, 30 μsec) and voltage measurement after sampling, demodulation, amplification, low-pass filtering, and offset-correction. ICI_b depicts bundled ICI curves from a corresponding 1-min recording aligned by ventricular pace markers where blanked periods were used to cut out pacing artefacts. ICI_m depicts the representative ICI (mean curve, solid ± SD curves, dotted) after bundle-averaging and moving-average-smoothing. SZ is finally calculated as the difference of the maximum and minimum impedance of the mean curve. ECG, surface electrocardiogram; EDZ: end-diastolic ICI; ESZ: end-systolic ICI; ICI: intracardiac impedance; LVp: left ventricular pace; RAp: right atrial pace; RVp: right ventricular pace; SZ: stroke impedance.

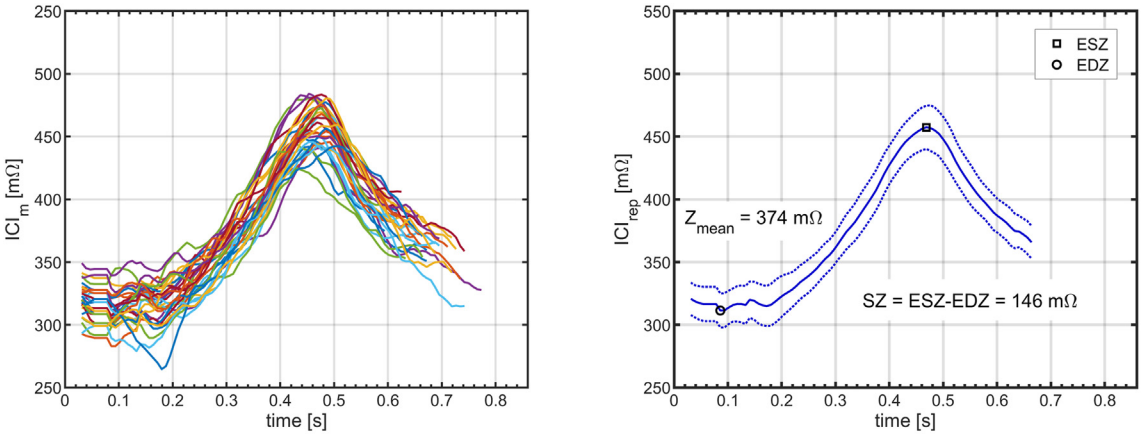

Fig. 3. Example plot of a patient's mean ICI curves (chronic measurement). Curves were collected and transmitted daily via Home Monitoring by the CRT-D device over one month (n = 31). Each of the mean curves ICI_m resulted from an averaging of 512 ICI curves taken during a night-time window. Right side depicts a representative (averaged) ICI (mean curve, solid ± SD curves, dotted) and exemplary calculated ICI parameters. CRT-D, cardiac resynchronization therapy defibrillator; EDZ: end-diastolic ICI; ESZ: end-systolic ICI; ICI: intracardiac impedance; SZ: stroke impedance; Z_{mean}: mean ICI.

visits and exported to other media for further analysis.

For safety reasons, chronic ICI measurement is temporarily terminated upon detection of ventricular tachycardia, and no valid ICI values are generated until the next measurement window of 512 heart cycles. Detection of ventricular fibrillation results in permanent deactivation of ICI measurement, with the possibility to reactivate it at a later clinical visit. The present manuscript primarily addresses study objectives related to the acute ICI measurement.

2.5. Study protocol

After CRT-D system implantation, 2 months were left for lead ingrowth and other processes that may influence lead impedance. At the 2-month follow-up visit, acute hemodynamic changes were provoked by overdrive pacing to investigate correlation of echocardiographic parameters and the ICI-based estimate of hemodynamic changes. ICI was recorded in supine patients at the resting heart rate and at four overdrive pacing rates ranging from 10 to 40 beats/min above the resting rate (Fig. 4). In parallel, echocardiography measurements were performed (Fig. 5) and later verified by a designated echo core laboratory blinded to ICI measurements and clinical data (Appendix).

Patients were excluded from the acute ICI measurement if they had any contraindication potentially increasing the risk of overdrive pacing, such as decompensated HF, symptomatic arrhythmia, unstable angina pectoris, or myocarditis. Patients excluded at 2 months were readmitted to the overdrive pacing protocol at 3 months if contraindications resolved.

For the study objectives related to the chronic ICI measurements, patients were followed for up to 9 months after implantation. Chronic ICI measurements and Home Monitoring function were activated to assess the relation of ICI towards clinical events and the potential utility of ICI for continuous monitoring of slow, persisting hemodynamic changes.

2.6. Primary hypothesis

We hypothesized that an averaged intra-individual correlation coefficient r between acutely measured SZ and the aortic velocity time integral (Ao-VTI, i.e. stroke volume) determined by continuous wave Doppler would be significantly larger than 0.65.

2.7. Statistical methods

Sample size calculation was based on experiences from previous studies, resulting in an estimated correlation coefficient of 0.75 with a variance of 0.25. Assuming a drop-out rate of 25% and a technical failure rate of 4%, a sample size of 60 enrolled patients was needed for a required threshold for the primary hypothesis of $r = 0.65$, a significance level of $\alpha = 0.05$, and a statistical power of $1-\beta = 0.8$.

The primary hypothesis was evaluated using a one-sided *t*-test. Previously, the patient-individual Pearson correlation coefficients were transformed by Fisher's z-transform to approximate a normal distribution. Normality of the distribution was assessed using Kolmogorov-Smirnov-Lilliefors and Shapiro-Wilk tests. We calculated Fisher's z-transforms by the formula $z = 0.5 \cdot \ln((1+r)/(1-r))$ to account for normalization of data. Retransformation was based on the formula $r=(\exp(2 \cdot z)-1)/(\exp(2 \cdot z)+1))$.

According to Figs. 4 and 5, up to 30 value pairs consisting of SZ and Ao-VTI were determined for each patient (6 samples x 5 heart rate stages). The statistical analysis plan pre-specified to average three subsequently measured samples at the same heart rate in order to reduce measurement noise, which cut the number of value pairs per patient from 30 to 10. A single correlation coefficient was calculated in the end from these 10 value pairs.

For descriptive statistics, categorical variables are summarized by absolute and relative frequencies, and continuous variables are summarized as mean ± standard deviation (SD). Data analysis and statistical tests were implemented in Matlab (R2013b, statistics toolbox V8.3, Math Works Inc., Natick, MA, USA). The test of the primary hypothesis was verified by means of IBM SPSS Statistics software, version 23.0 (SPSS Inc., Chicago, IL, USA).

2.8. Correction of EDZ calculation principle

Before performing the final statistical test for the primary hypothesis, we reviewed acute ICI data in a subset of patients and realized that in some patients the minimum ICI value during the heart cycle in the averaged ICI curve lied outside an expected end-diastolic time window. This implied that the true EDZ value was not always equal to the minimum of the whole ICI curve. We assume that the anomalies in the averaged signal were partly due to late pacing artefacts with too short blanking times or due to impacts of lead motions or fusion beats, in combination with the rules for filtering, smoothing, aligning and averaging the raw signals. In former studies [11–14], predefined end-systolic and end-diastolic time windows were used within which ESZ and EDZ should be found as the maximum and the minimum of ICI, respectively. Therefore, we decided to resume the previous definition of EDZ and adapt the calculation of EDZ to be determined again as the minimum within a predefined end-diastolic time window. The original test algorithm was therefore slightly modified in that EDZ was selected as the minimum impedance during an 80-msec end-diastolic window prior to biventricular pacing pulse rather than

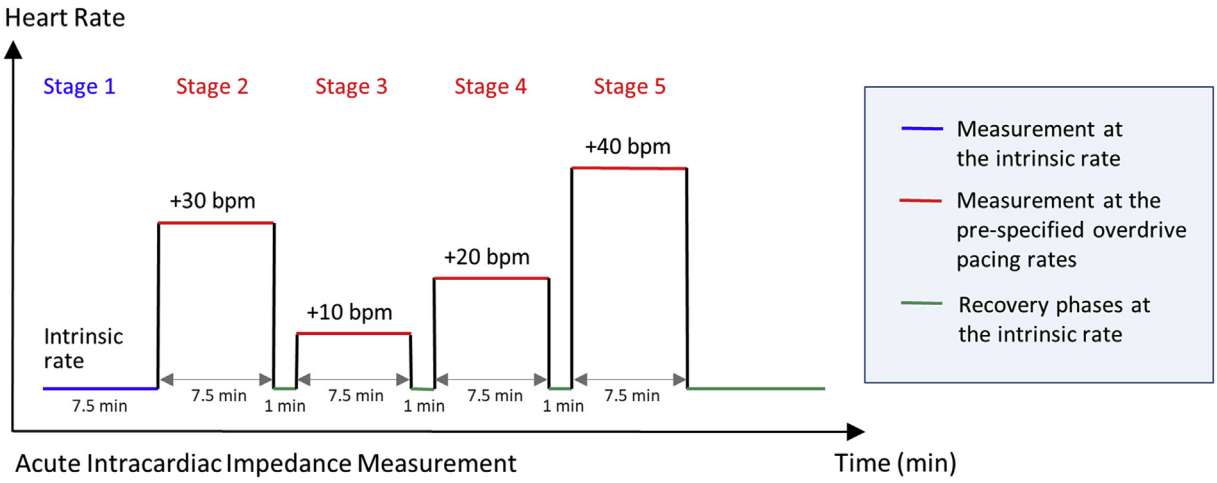

Fig. 4. Overdrive pacing protocol for acute intracardiac impedance measurements in a controlled clinical setting. Five stages of heart rates, including intrinsic atrial rate, were used always in the same order, resulting in an approximately 45-min long measurement protocol per patient. bpm: beats per minute.

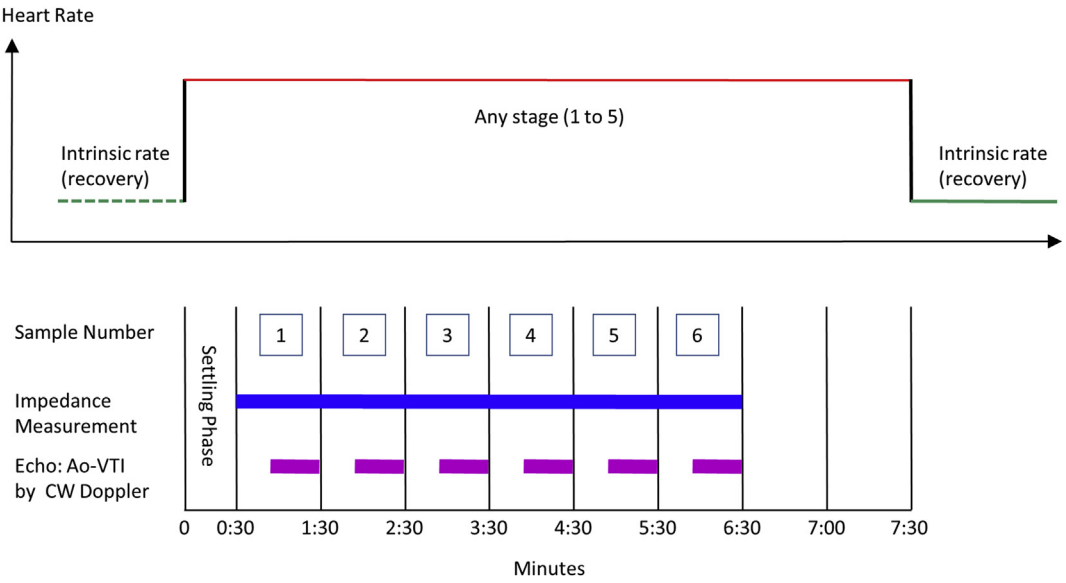

Fig. 5. The investigational scheme for each stage of heart rate from Fig. 4. After the initial settling phase at a new rate, six samples were taken of both impedance recording (1 min per sample) and Ao-VTI measurement by CW Doppler (3–4 beat captures recorded for 3 times consecutively in an apical 5-chamber view, with acquisition from the left ventricular outflow tract). Ao-VTI: Aortic Velocity Time Integral; CW: Continuous Wave.

the minimum impedance during the entire heart cycle.

3. Results

3.1. Patients and CRT-D systems

During a period of 23 months, 68 patients were enrolled in the study, and 63 of them were successfully implanted with a CRT-D system enabling ICI measurements. The implanted device models were Lumax 740 HF-T (n = 41), Iforia 7 HF-T (n = 11), Iforia 5 HF-T (n = 8), Ilesto 7 HF-T (n = 2), and Idova 7 HF-T (n = 1).

3.2. Drop-outs before completion of acute ICI measurement

In the period between implantation and the 2-month follow-up, one patient died and seven patients were excluded based on a pre-defined drop-out criterion, mainly echocardiographic one, exposed by data verification at the core laboratory. The rest of patients (n = 55) attended the 2-month follow-up, and most of them (n = 49) underwent the overdrive pacing protocol for acute ICI measurement, either at 2 months (n = 43) or at 3 months (n = 6). Six patients did not undergo acute ICI measurements, three because of late discontinuation from the study (informed consent withdrawal or a drop-out criterion) and three because we already had a sufficient number of completed acute procedures.

Of a total of 49 acute ICI data sets, 40 qualified for the test of primary hypothesis. Nine data sets did not qualify due to the missing reference echocardiographic data (n = 2), a drop-out criterion of post-implant lead revision (n = 2, discovered late), and violation of pre-defined validity rules for the acute data set (n = 5). The latter included the failure to achieve at least 4 stages of heart rate during overdrive pacing protocol (n = 3) and insufficient strength (<14%) of the heart-rate-dependent Ao-VTI trend (n = 2), which reflects the efficacy of the overdrive pacing protocol in provoking a sufficient hemodynamic change with a pre-specified minimum strength.

3.3. Analysis population

Table 1 shows baseline characteristics of the 68 enrolled patients and of 40 patients contributing to the primary hypothesis. All but one patient in the analysis population were in sinus rhythm, with a mean resting rate of 69 ± 12 beats/min. Mean QRS duration was 171 ± 13 msec, and 88% of patients had left bundle branch block. The LVEF was markedly impaired (29 ± 5%) and LVEDD increased (65±7 mm). The RV leads in the analysis population were placed in the septal area (48%) or in the apex (45%). The location of the LV lead tip along the long axis was predominantly medial (78% [40% posterolateral-medial, 30% lateral-medial]), and in other patients either basal (15%) or apical (8%).

3.4. Results of acute ICI measurements

Acute echo and ICI measurements are illustrated in Fig. 6. With increasing heart rate, a clear stepwise reduction of both Ao-VTI and SZ was observed, associated with a slight increase in EDZ and Z_{mean}, and with no clear ESZ trend. Modification of the test algorithm generated slightly different EDZ and SZ values in comparison to the original algorithm, whereas ESZ and Z_{mean} were not affected. With the modified algorithm, EDZ was commonly estimated somewhat higher compared to the original algorithm due to the introduced end-diastolic time window before biventricular paces within which EDZ was now correctly calculated as the minimum. Thus, taking EDZ as a minimum late after pace was avoided.

All 10 value pairs (SZ + Ao-VTI) were attained in 26 patients (65%), nine pairs in seven patients (18%), eight pairs in four patients (10%), and seven pairs in three patients (8%).

Inter-patient comparison tests were additionally performed for the ODP subgroups of patients with RV lead implanted in septal position (n = 19, 47.5%) versus those with RV lead in apex position (n = 18, 45.0%). Within single heart rate stages, there were no significant differences of ICI values found for any of the ICI parameters between the two subgroups.

Table 1
Baseline characteristics of the patients.

	Enrolled Patients (n = 68)	Analysis Population (n = 40)
Demographics		
Age [years]	66 ± 9	67 ± 9
Male gender	50 (74%)	29 (73%)
Height [cm]	175 ± 8	176 ± 9
Weight [kg]	85 ± 16	84 ± 17
Blood pressure		
Systolic [mmHg]	123 ± 16	125 ± 18
Diastolic [mmHg]	73 ± 10	73 ± 11
Hypertension	45 (66%)	25 (63%)
ECG diagnosis		
Sinus rhythm	66 (97%)	39 (98%)
Atrial paced rhythm	3 (4%)	1 (3%)
Heart rate at rest [beats/min]	71 ± 15	69 ± 12
QRS duration [msec]	170 ± 13	171 ± 13
Left-bundle branch block	62 (91%)	35 (88%)
Right-bundle branch block	4 (6%)	3 (8%)
Paroxysmal atrial fibrillation	6 (9%)	2 (5%)
Persistent atrial fibrillation	0 (0%)	0 (0%)
Heart failure related data		
NYHA class II	34 (50%)	23 (58%)
NYHA class III	34 (50%)	17 (43%)
LVEF [%]	26 ± 5	29 ± 5
LVEDD [mm]	65 ± 7	65 ± 7
Dilated cardiomyopathy	55 (81%)	33 (83%)
Ischemic etiology	32 (47%)	19 (48%)
Mitral regurgitation	52 (77%)	28 (70%)
Comorbidities		
Coronary artery disease	37 (54%)	22 (55%)
Myocardial infarction	28 (41%)	17 (43%)
Stroke	7 (10%)	3 (8%)
COPD	6 (9%)	5 (13%)
Diabetes mellitus	20 (29%)	11 (28%)
Renal insufficiency	12 (18%)	5 (13%)
Major medications		
Beta blocker	63 (93%)	38 (95%)
Diuretics	56 (82%)	32 (80%)
ACE inhibitor	49 (72%)	27 (68%)
Spironolactone	42 (62%)	24 (60%)
AT receptor blocker	15 (22%)	10 (25%)

Data are mean ±SD or number (percent).
ACE: Angiotensin Converting Enzyme; AT: Angiotensin; COPD: chronic obstructive pulmonary disease; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

3.5. Primary study hypothesis

The mean intra-individual correlation coefficient between SZ and Ao-VTI was $r_{mean} = 0.797$, with a lower confidence interval bound of 0.709. This is significantly larger than the hypothesized r_{mean} of 0.65 ($p = 0.007$). The primary hypothesis is therefore met. As explained above (section 2.8.), this is obtained with a modified method of EDZ calculation, in which a minimum ICI within an 80-msec end-diastolic window was taken as EDZ. With the non-modified method (EDZ equal to the minimum ICI during the entire heart cycle), a lower r_{mean} (0.688) and a lower confidence interval bound (0.574) were obtained, not fulfilling the primary hypothesis ($p = 0.272$).

Table 2 illustrates the distribution of patient-individual r values and visualizes the benefit of modified EDZ calculation. The re-introduction of an end-diastolic time window for EDZ calculation led to an improvement of the correlations in the big majority of patients (n = 38, 95%). After the modification, 29 patients (73%) had a relatively strong (r between 0.658 and 0.997) statistically significant correlation between SZ and Ao-VTI. Additional six patients (15%) exhibited an acceptable trend with $r > 0.400$ and $p \leq 0.25$. The remaining five patients (13%) showed a weak (n = 2) or reversed (n = 3) correlation. Reversed correlation was associated with an atypical LV lead tip position, other than posterolateral-medial or lateral-medial. The corresponding proportions for the original EDZ method were 22 patients (55%) with a significant correlation, seven (18%) with good trend, and 11 (28%) with a weak or reversed correlation.

4. Discussion

BIO.Detect HF II is the first non-invasive study of ICI, utilizing the novel ICI measurement feature integrated in a standard CRT-D device. After adjusting the calculation principle to ensure that EDZ lies within an expected end-diastolic window, the correlation coefficient between SZ (the pre-selected ICI parameter) and Ao-VTI (determined by echocardiography) was sufficiently strong and statistically significant, meeting the primary hypothesis.

The ICI measured 'across the heart' should not be mixed up with the intrathoracic impedance measured 'across the lung' (between RV lead and device case) to monitor lung oedema formation in HF patients, which did not have a significant effect on patient outcomes [19].

4.1. Previous research on ICI

The concept of estimating hemodynamic changes by ICI was first explored in animal studies (2006–2009) [10–12]. ICI was measured

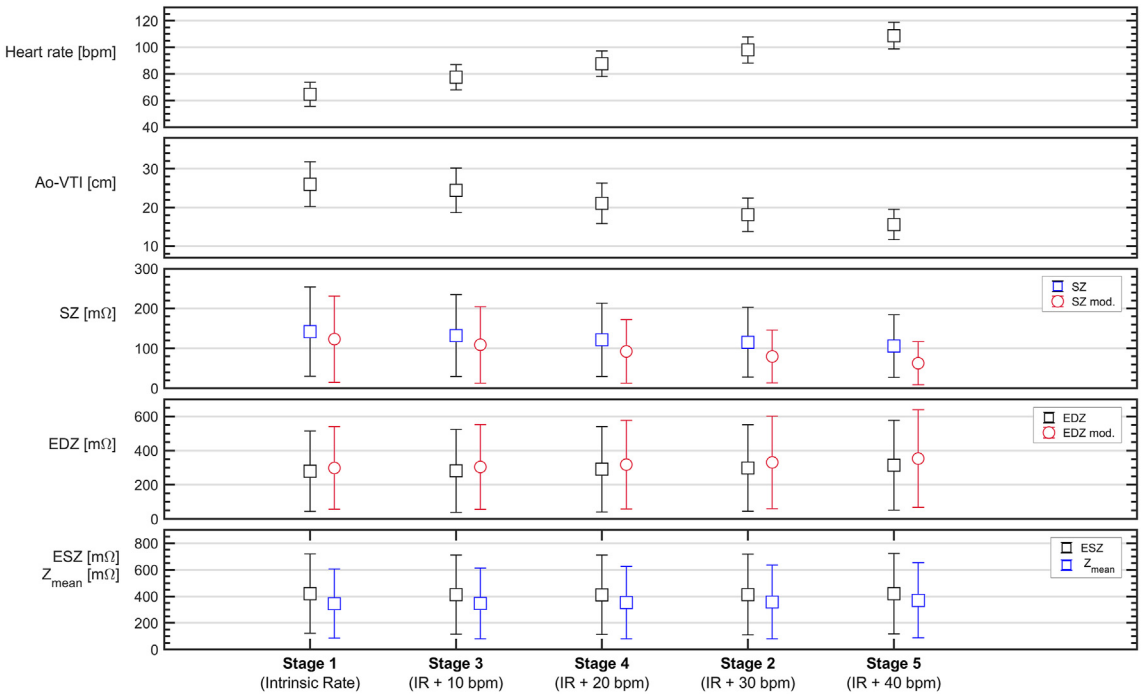

Fig. 6. Results of acute echo and ICI measurements averaged for all patients (mean ± SD). Stages 1–5 are ordered along X-axis according to increasing heart rate. The modified algorithm affected only SZ and EDZ. Ao-VTI: aortic velocity time integral measured by continuous wave Doppler; bpm: beats per minute; EDZ: end-diastolic ICI; ESZ: end-systolic ICI; ICI: intracardiac impedance; IR: intrinsic rate; mod.: modified algorithm; SZ: stroke impedance (SZ = ESZ - EDZ); Z_{mean}: mean ICI.

using two electrodes of a bipolar RV lead (for current injection) and epicardial leads screwed into the mid-lateral LV wall [10] or along a basal-apical line [11,12]. Acute hemodynamic changes were induced by overdrive pacing [10] and/or graded isoprenaline [10] or dobutamine [12] infusion. In the first study, the correlation between LV conductance and stroke volume in six healthy mongrel dogs was robust and significant (r_{mean} = 0.89 [overdrive pacing] and 0.97 [isoprenaline]) [10].

In the second study, HF was induced in nine mini-pigs by 3 weeks of high-rate pacing. The resulting hemodynamic deterioration was characterized by reduced mean LVEF (71% → 48%), increased mean end-diastolic pressure (12 → 26 mmHg), increased mean end-diastolic volume (by 20%), and a decreased mean EDZ (by 33%). EDZ correlated with end-diastolic pressure ($r_{mean} = -0.81$, $p < 0.001$) [11].

In the third study, acute hemodynamic changes were induced by dobutamine infusion in failing hearts of five mini-pigs after 3 weeks of high-rate pacing. Significant correlation was found between EDZ and end-diastolic pressure ($r_{mean} = -0.82$, $p < 0.001$) and between SZ and stroke volume ($r_{mean} = 0.88$, $p < 0.001$) [12].

After promising animal data, Bocchiardo et al. conducted an acute proof-of-concept study during CRT(-D) system implantation or electrophysiology study in 14 patients with dilated cardiomyopathy (2010) [13]. In contrast to animal studies, the defibrillation coil was predominantly used instead of the ring electrode of an RV lead. Acute hemodynamic changes were induced by overdrive pacing and measured invasively by a tip manometer catheter as stroke volume changes derived from the aortic blood pressure. The strong, stable correlation between SZ and stroke volume ($r = 0.82 \pm 0.16$) was regarded as a proof that implant-based continuous monitoring of cardiac function by ICI measurements is feasible [13]. The respiratory influence was visible in the impedance traces, necessitating an averaging of ICI curves over several minutes, as implemented in the Lumax 740 HF-T and successors devices [13]. In an additional study in the same patient cohort during the same study set-up, Bocchiardo et al. demonstrated the feasibility of optimizing LV lead site, atrioventricular delay, and interventricular delay by ICI (i.e., SZ and ESZ) [14]. Furthermore, Kühne et al. investigated ICI during CRT implantation in patients with chronic infarction and documented wall motion abnormalities. Using the arterial pulse contour method to derive hemodynamics along with ICI, they also suggested the impedance as a valid parameter to estimate stroke volume or to guide optimization of CRT timing [15].

4.2. Limitations

There is a variety of impact factors on ICI which may be suggested from the theory behind it, i.e. from the fact that the measured ICI signal in the described 4-terminal configuration depends 1) on the conductivity of the tissue between the involved electrodes, 2) on the spacing between the electrodes, and 3) on the tilt angle between the RV and LV lead. Every factor affecting this configuration may also “negatively” affect ICI, e.g. inappropriate lead positions, lead movements, changes in body position, changes in heart geometry, and changes in the conductivity of blood and tissue.

The long-lasting process of gathering a single ICI data set demonstrates the technical challenges that exist to reliably measure ICI signals at a low milli-ohm level in contrast to the larger ohm level known for other impedances like thoracic impedance. This becomes particularly obvious when looking at the elaborate (time and storage-consuming) averaging of many beat-to-beat ICI curves to a final ICI mean curve in order to enhance the overall signal-to-noise ratio.

Our study focused on the short-term correlation between SZ and echo Ao-VTI in a controlled clinical setting with the patient in supine position. During ICI data inspection, it turned out that it was necessary to slightly modify the prescribed algorithm for EDZ calculation (as the minimum of the whole ICI curve) and adapt it

Table 2
Correlation Coefficient R between SZ and Ao-VTI (Descending order of R).

Patient Rank	Modified Algorithm[a]		Original Algorithm[b]	
	R	P-value	R	P-value
1	0.997	<0.001	0.984	<0.001
2	0.982	<0.001	0.962	<0.001
3	0.977	<0.001	0.962	0.001
4	0.974	<0.001	0.952	<0.001
5	0.963	<0.001	0.940	<0.001
6	0.934	0.002	0.932	0.001
7	0.928	<0.001	0.896	<0.001
8	0.924	<0.001	0.880	0.001
9	0.909	<0.001	0.877	0.001
10	0.895	<0.001	0.867	0.001
11	0.880	0.001	0.859	0.006
12	0.876	0.004	0.857	0.002
13	0.873	0.005	0.854	0.002
14	0.853	0.002	0.851	0.004
15	0.850	0.004	0.815	0.004
16	0.849	0.002	0.803	0.009
17	0.847	0.002	0.774	0.009
18	0.841	0.002	0.706	0.023
19	0.828	0.003	0.700	0.024
20	0.825	0.022	0.688	0.028
21	0.817	0.013	0.681	0.030
22	0.808	0.015	0.679	0.031
23	0.789	0.007	0.635	0.126
24	0.789	0.011	0.631	0.050
25	0.718	0.019	0.628	0.052
26	0.707	0.022	0.627	0.052
27	0.706	0.034	0.544	0.130
28	0.700	0.024	0.506	0.135
29	0.658	0.039	0.491	0.179
30	0.572	0.108	0.339	0.338
31	0.556	0.095	0.277	0.439
32	0.543	0.105	0.223	0.564
33	0.515	0.156	0.054	0.898
34	0.462	0.178	0.034	0.937
35	0.401	0.250	−0.024	0.951
36	0.231	0.520	−0.044	0.904
37	0.145	0.756	−0.092	0.800
38	−0.088	0.822	−0.258	0.471
39	−0.401	0.250	−0.342	0.334
40	−0.768	0.009	−0.681	0.092
Mean	0.797		0.688	
SD	0.645		0.615	
CI low[c]	0.709		0.574	
P-value[d]	0.007		0.272	

Ao-VTI: aortic velocity time integral measured by continuous wave Doppler; EDZ: end-diastolic ICI; ESZ: end-systolic ICI; ICI: intracardiac impedance; SD: standard deviation; SZ: stroke impedance (SZ = ESZ - EDZ).
[a] EDZ = minimum ICI within 80-msec end-diastolic window.
[b] EDZ = minimum ICI during the entire heart cycle.
[c] The lower 95% confidence interval (CI) boundary.
[d] Significance of the mean value compared with the hypothesized mean value of 0.65.

according to previous versions where the search for a minimum was restricted to a predefined end-diastolic time window.

In the uncontrolled chronic setting, ICI sets will be measured for safety reasons by use of a lower current amplitude. Consequently, measurement times for averaging ICI must be prolonged to keep a similar signal-to-noise ratio. This might conversely lead to non-stationary measurement conditions. However, our first results showed satisfactory mean ICI curves as well for the chronic setting. This suggests that ICI-based applications may also be worth considering for a long-term monitoring of HF progression by the Home Monitoring functionality of the CRT-D device.

4.3. Device therapy and remote monitoring in heart failure

The prevalence of HF in the adult population in developed countries is 1%–2%, rising to ≥10% among people >70 years of age [2]. Although an increasing number of HF patients is treated by implantable-cardioverter defibrillator (ICD) and CRT(-D) devices capable of reducing mortality and morbidity, it remains challenging to prevent symptom worsening, decompensation, and hospital admissions in ambulatory patients [2]. Implant-based remote monitoring failed to improve hard clinical outcomes in randomized controlled trials, except for daily multi-parameter Home Monitoring (without a hemodynamic sensor) that reduced all-cause mortality but not HF hospitalization in a single trial (IN-TIME) [17,20]. The 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [2] recommend only the IN-TIME approach and a stand-alone monitor of pulmonary artery pressure (CardioMEMS, reduced HF hospitalization but not mortality) [7,9] as the remote monitoring strategies capable of improving clinical outcomes in symptomatic HF patients, with the class of recommendation IIb (may be used) and the level of evidence B (single trial evidence). Further tools are needed in the future to improve early recognition of HF progression or, even better, to shift from crisis detection to health maintenance [8]. Having this in mind, it might be of major benefit to add hemodynamic parameters to the current remote HF diagnostics.

The ICI measurement bears some potential and is readily available technically, not requiring implantation of additional material beyond that of a standard CRT(-D) system. It remains to evaluate the utility of ICI coupled with remote monitoring in guiding medical therapy and optimizing CRT. Another hemodynamic-based concept has been tested recently, the peak endocardial acceleration (PEA) sensor integrated in an RV or right atrial lead to assess cardiac contractility [21]. PEA-based algorithms can be utilized to optimize CRT automatically on a weekly basis, by adapting atrioventricular and inter-ventricular delays. However, no remote monitoring of this hemodynamic sensor is currently available [21]. Other hemodynamic sensors, such as RV pressure or left atrial pressure, are also under development [4,7].

5. Conclusions

Intracardiac impedance measured by implanted CRT-Ds correlated well with the aortic velocity time integral (stroke volume) determined by echocardiography in a controlled clinical setting. As an integral part of a standard CRT-D system capable of remote monitoring, the novel sensor has potential to continuously track changes of cardiac hemodynamics.

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Contributions of authors

P. Søgaard and S. Paule contributed to the conception and design of the study, and to the analysis and interpretation of data. The steering committee (K.-J. Gutleben, P.-P. HM Delnoy, N.E. Bruun, S.K.G. Maier) contributed to the design of the study. All authors except for S.K.G. Maier contributed to data acquisition. P.-P. HM Delnoy, P. Søgaard and S. Paule contributed to drafting the article. All authors contributed to critical reading of the article and approved the submitted version.

Declaration of competing interest

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