

Isolated left ventricular pacing results in worse long-term clinical outcome when compared with biventricular pacing: a single-centre randomized study

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Received 31 May 2010; accepted after revision 20 July 2010; online publish-ahead-of-print 21 August 2010

Aims	The objective of this study was to compare long-term clinical effects of biventricular pacing with isolated left ventricular pacing.
Methods and results	Forty consecutive patients with idiopathic dilated cardiomyopathy and indication for cardiac resynchronization therapy were randomized to biventricular or isolated left ventricular pacing. Clinical and echocardiographic parameters were studied regularly prior to implantation and during 1 year of follow-up. Patients with atrial fibrillation were excluded from the study. A retrospective cross-sectional outcome analysis was performed 4 years after the beginning of the study. Biventricular pacing was associated with more pronounced clinical and echocardiographic benefit compared with left ventricular pacing. Biventricular pacing was associated with significantly more distinct reverse remodelling. Left ventricular ejection fraction improved by 12.5 per cent-points (95% CI 7.3–17.7) compared with 5.1 per cent-points (95% CI 1.1–9.2) ($P = 0.01$) and left ventricular end-diastolic diameter decreased by 8.69 mm (95% CI 5.2–12.2) compared with 5.1 mm (95% CI 1.5–8.7) ($P = 0.05$) in the biventricular and left-ventricular pacing group, respectively. Semi-quantitative summarization of response points revealed a greater benefit in the biventricular vs. left ventricular pacing group [mean sum of response points 3.25 (95% CI 2.62–3.88) vs. 2.35 (95% CI 1.74–2.96), respectively, $P = 0.06$]. After 3 years of follow-up, there was no cardiovascular death in the biventricular pacing group compared with three cardiovascular deaths in the left ventricular pacing group.
Conclusion	In patients with idiopathic dilated cardiomyopathy, biventricular pacing is associated with significantly more pronounced benefit in clinical outcomes and reverse remodelling. A retrospective analysis after 3 years of follow-up suggests that isolated left ventricular pacing may be associated with a higher mortality rate compared with biventricular pacing.
Keywords	Heart failure • cardiac resynchronization therapy • remodelling

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment option in patients with systolic heart failure (HF) and intraventricular conduction delay. Data from large multicenter randomized trials confirmed unanimously that CRT using biventricular

pacing (BVP) reduces mortality, improves functional capacity, and leads to reverse remodelling of a dysfunctional and dilated left ventricle.^{1–5}

Since the advent of CRT, isolated left ventricular pacing (LVP) has been evaluated as an alternative to simultaneous or sequential BVP. The rationale for such method is that isolated LVP may

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obviate the need for right ventricular pacing, or even the right ventricular lead implantation. Isolated LVP might also result in prolonged longevity of the device battery. Last but not least, proponents of LVP believe that LVP alone is capable to alleviate mechanical dyssynchrony by improving left ventricular intraventricular dyssynchrony. Indeed, early experience confirmed comparable acute haemodynamic benefit of both LVP and BVP.^{6–8} Several subsequent studies have demonstrated similar functional benefit and/or reverse remodelling of LVP when compared with BVP.^{9–11} On the other hand, other studies have suggested that BVP may result in more pronounced reverse remodelling than LVP.^{12–14} Limited data in patients with atrial fibrillation who are candidates for CRT suggest that LVP may be inferior to BVP in this subgroup of patients.¹⁵

However, the above studies were not designed to analyse differences in mortality between LVP and BVP, as they were neither adequately powered nor had a follow-up long enough to demonstrate mortality differences between the two pacing modes. The aim of this single-centre study was to provide randomized comparison of clinical efficacy between LVP and BVP in a homogeneous cohort of patients with idiopathic dilated cardiomyopathy (DCM) and conventional indication for CRT.

Methods

Study population

Between 11 March 2005 and 19 June 2007, 40 consecutive patients with DCM and indication for CRT according to the Czech National Guidelines at that time [HF in NYHA class III or IV despite optimized pharmacological therapy, left ventricular ejection fraction (EF) <35%, left ventricular end-diastolic diameter (LVEDD) \geq 55 mm, and QRS width \geq 150 ms] were randomly assigned to either LVP or BVP.

Patients were not eligible for the study in case of acute HF decompensation, the previous heart surgery, other than left bundle branch block QRS morphology, or if they had a pacemaker implanted for bradyarrhythmic indication. Seven patients with persistent or permanent atrial fibrillation were also excluded from the study. Informed consent to participate in the study was obtained from all individuals. Local institutional ethics committee approved the study protocols.

Study protocol procedures including functional capacity assessment and detailed echocardiography were performed in all patients at baseline, after implantation, at 3, 6 and 12 months, respectively. Functional capacity was evaluated by NYHA class, 6 min walking distance (6MWD), and spiroergometry. Echocardiography was performed by a single-experienced operator. Left ventricular end-diastolic diameter, interventricular septum (IVS) thickness, and posterior wall thickness (PWD) were measured according to the recommendation of the American Society of Echocardiography.¹⁶ Ejection fraction was used as a parameter of the left ventricular systolic function. Although not specifically discussed in this article, following echocardiographic measures of dyssynchrony at baseline were performed in all participants: diastolic filling time and its ratio to the length of cardiac cycle; interventricular dyssynchrony calculated as difference between pre-ejection periods in the left ventricular outflow tract (LVOT) and right ventricular outflow tract; and tissue pulse Doppler velocity assessment [tissue velocity imaging (TVI)] in six basal segments.

Positive response to CRT was defined as one or more of the following: improvement in EF \geq 5%, decrease of LVEDD \geq 5 mm, improvement in the NYHA class by \geq 1 grade, and improvement in

maximum aerobic capacity (VO_2) or 6MWD by \geq 10%. For each positive response one point was assigned, and a semi-quantitative sum of response points was calculated in every patient.

A CRT system was successfully implanted in all included patients. Available devices of major manufacturers (Medtronic, Biotronik, St Jude Medical and Boston Scientific) were allowed by the protocol. Unipolar or bipolar left ventricular leads were implanted in post-erolateral, lateral, or anterolateral veins, pre-dominantly at mid-ventricular level. In two patients (one in the LVP and one in the BVP group), transvenous left ventricular lead implantation failed and the left ventricular lead was implanted using the surgical videothoracoscopic approach. The Majority of patients was paced in a unipolar mode from their left ventricular lead. Bipolar right ventricular leads were implanted to the mid-septal position in all patients. Bipolar right atrial leads were placed in the right atrial appendage. Selection of specific type of device [biventricular pacemaker or biventricular implantable cardioverter defibrillator (ICD)] was based on valid guidelines and clinical history. True left ventricular capture without anodal capture was verified at each follow-up visit.

After implantation of a CRT device, patients were randomized to either LVP or BVP. The assigned study pacing mode was programmed before discharge from the hospital. Patients and their primary physicians and cardiologist were not informed on the pacing mode programmed. Before discharge, atrio-ventricular delay (AVD) optimization was performed in all patients using the velocity time integral (VTI) method assessment in the LVOT. An example of an ECG recording with LVP is shown in Figure 1.

After 12 months of pre-defined study follow-up, patients were followed by their physicians and electrophysiologist. A cross-sectional retrospective evaluation of major adverse events (cardiovascular or non-cardiac death, heart transplantation, or necessity of upgrade to CRT-defibrillator) was performed after a median of 3 years of follow-up in June 2009, 4 years after the beginning of the study. Data for this analysis were obtained and validated from several sources, including our clinical database, information from local hospitals, general practitioners, and occasionally directly from the families of the study participants.

Statistical analysis

Baseline demographic continuous variables were compared using t-test for independent samples and Fisher's exact test was used for categorical values. Data were expressed as the mean \pm standard deviation. Sums of response points were compared using a Wilcoxon's non-parametric test. Differences between baseline and follow-up values in outcome parameters were evaluated using the paired t-test. Linear regression was used to analyse relationship between echocardiographic values at baseline and response to CRT. For survival analysis, Kaplan–Meier curves were constructed. $P < 0.05$ was regarded statistically significant. Analyses were performed using the SPSS 13.0 and JMP IN statistical software.

Results

Forty consecutive patients with idiopathic DCM were included in the study. In all enrolled patients, a CRT device (CRT-pacemaker or CRT-defibrillator) was implanted successfully. Seven patients with persistent or permanent atrial fibrillation were excluded from the study.

Demographic characteristics of studied populations are presented in Table 1. There were no significant differences in the baseline study characteristics, including age, EF, QRS width, NYHA

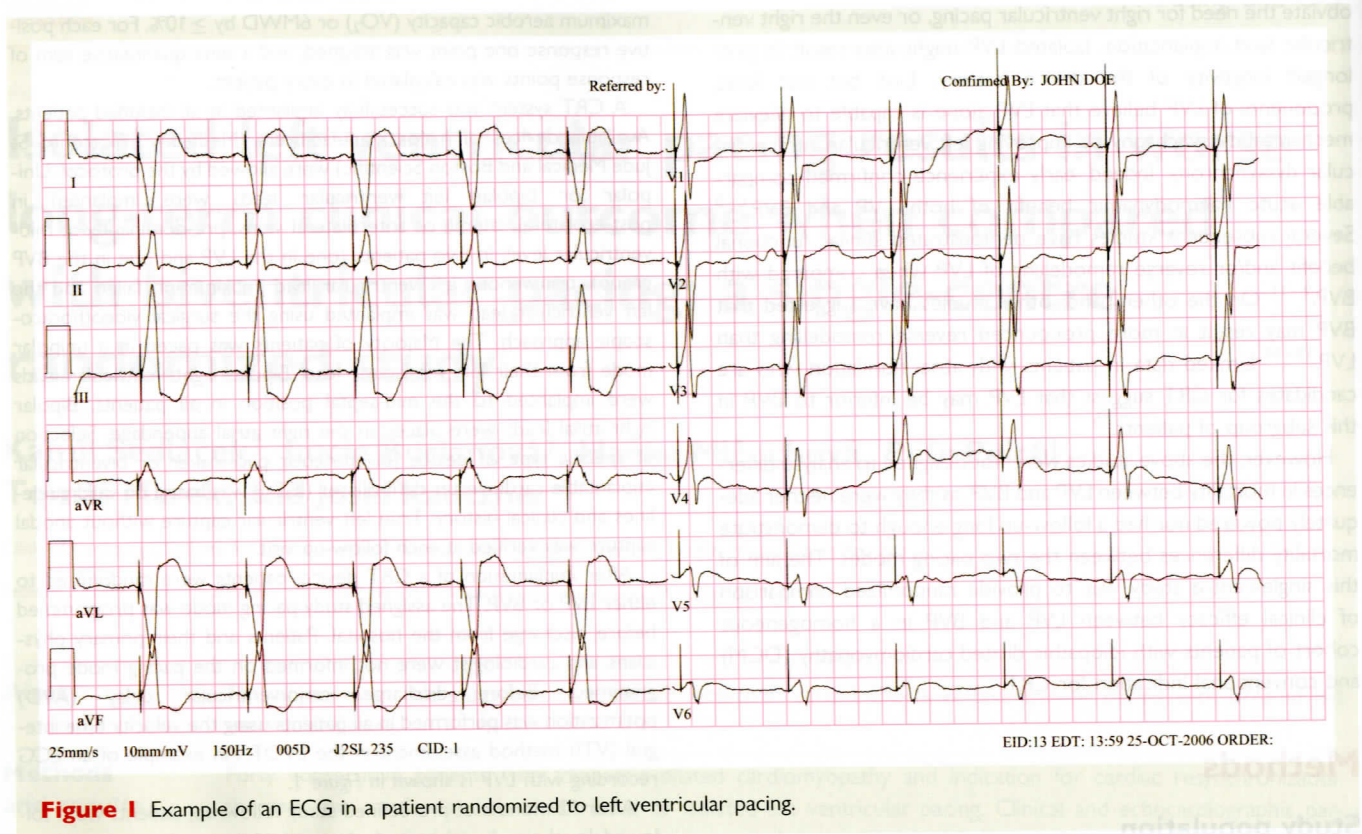


Figure 1 Example of an ECG in a patient randomized to left ventricular pacing.

class, or mitral regurgitation. Optimized AVD was similar in the BVP and LVP group. After introduction of therapeutic pacing mode, there was no statistically significant difference in paced QRS duration or percentage of ventricular pacing between the BVP and LVP group at baseline. At 12 months of follow-up, duration of paced QRS was significantly longer in the LVP group (146.1 ± 21.7 vs. 163.2 ± 21.1 ms in the BVP and LVP group, respectively; $P = 0.04$).

Functional capacity and echocardiographic parameters during the 12 month follow-up period

Changes in parameters of functional capacity and echocardiographic remodelling are shown in *Table 2*. Patients assigned to BVP improved highly significantly after 12 months of follow-up in all studied parameters (EF, LVEDD, mitral regurgitation (MR) grade, NYHA class, VO_2 , and quality of life index) with exception of 6MWD, where the improvement did not reach statistical significance. In patients who were assigned to LVP, the degree of improvement was less pronounced and reached statistical significance only for EF, LVEDD, NYHA class, and quality of life index. In a comparison between the BVP and LVP groups, the difference in magnitude of improvement of EF and LVEDD was statistically significant ($P = 0.01$ and $P = 0.05$, respectively). One parameter that improved less in BVP than in LVP after 12 months was NYHA class but the difference between the groups was not statistically significant (*Table 2*). Data shown in *Table 2* were available also at 3, 6, and 9 months of follow-up but did not contribute relevant information beyond analyses shown here.

In semi-quantitative analysis, a sum of response points was calculated and BVP was associated with a statistically significantly more pronounced response than LVP [mean of 3.25 (95% CI 2.62–3.88) response points in BVP vs. 2.35 (95% CI 1.74–2.96) response points in LVP; $P = 0.06$] (*Figure 2*).

Echocardiographic predictors of response

In the whole study cohort, none of the available echocardiographic measures of dyssynchrony predicted therapy response as measured by a sum of response points. However, there were three significant predictors of impaired response to CRT in the LVP group vs. BVP group. Patients with moderate to severe mitral regurgitation, pronounced IVD, and advanced dilatation of the left ventricle at baseline were less likely to respond to LVP when compared with BVP (*Figure 3*). Conversely, prolonged IVD was associated with a more pronounced response to CRT in the BVP group (*Figure 3*).

Cross-sectional analysis of major adverse events after 3 years of follow-up

A cross-sectional analysis was performed after 3 years (mean 1035 days, median 1011 days) of the follow-up (*Table 3*). During this period, four patients of the study cohort died. While one death in the BVP group was non-cardiovascular (a road accident not caused by the patient), all three deaths that occurred in the LVP group were cardiovascular (two of them due to progression of HF and one sudden cardiac death). Owing to a small sample size, these differences were not statistically significant (*Table 3*). In addition, LVP patients required an upgrade to a CRT-

Table 1 Demographic data and baseline characteristics of the study population

	Biventricular pacing	Left ventricular pacing	P
N	16	17	
Age	59.56 ± 6.83	62.05 ± 12.13	Ns
Body mass index	28.8 ± 1.1	28.2 ± 0.9	Ns
Heart rate (b.p.m.)	69.00 ± 5.19	74.88 ± 12.45	Ns
Men (%)	56.3	64.7	Ns
Native PQ (ms)	195.81 ± 38.43	197.93 ± 44.88	Ns
Native QRS (ms)	187.25 ± 25.26	194.6 ± 9.26	Ns
NYHA class	3.13 ± 0.39	3.21 ± 0.36	Ns
QoL (points)	35.64 ± 19.44	46.6 ± 10.47	Ns
6MWT (min)	308.93 ± 94.34	380.38 ± 88.28	0.053
VO ₂ max (l/min)	13.81 ± 3.56	13.13 ± 3.43	Ns
CRT-P (%)	93.8	70.6	Ns
Betablockers (%)	100	94.4	Ns
ACEI (%)	100	100	Ns
Diuretics (%)	87.5	94.1	Ns
LVEDD (mm)	73.25 ± 7.99	75.06 ± 9.26	Ns
EF (%)	20.69 ± 0.81	21.29 ± 0.98	Ns
Mitral regurgitation grade	2.31 ± 0.81	2.85 ± 0.98	Ns
RV-PEP (ms)	112.00 ± 23.51	107.59 ± 27.08	Ns
LV-PEP (ms)	186.93 ± 33.7	167.59 ± 28.79	Ns
IVD (ms)	74.9 ± 27.2	60.0 ± 26.4	Ns
DFT (% RR interval)	38.55 ± 4.80	40.14 ± 6.81	Ns
Sept-lat delay (ms)	75.4 ± 48.0	61.9 ± 36.7	Ns
S-AVD (ms)	105.5 ± 20.7	118.5 ± 17.2	Ns
P-AVD (ms)	139.1 ± 13.8	144.3 ± 13.4	Ns
P-QRS—baseline (ms)	147.6 ± 17.6	159.8 ± 21.6	Ns
P-QRS—12 months (ms)	146.1 ± 21.7	163.2 ± 21.1	0.04
Biv-LV pacing (%)	93.0	94.0	Ns

Data are numbers, means ± standard deviations or percentages where indicated.

Ns, not significant; b.p.m., beats per minute; QoL, quality of life; 6MWT, 6 min walking test; VO₂max, maximum aerobic oxygen consumption at spiroergometry; CRT-P, percentage of patients receiving biventricular pacemaker at baseline; ACEI, angiotensin-converting enzyme inhibitors; LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction; RV-PEP, pre-ejection period measured in the right ventricle; LV-PEP, pre-ejection period measured in the left ventricle; IVD, interventricular delay; DFT, diastolic filling time; sept-lat delay, septal to lateral left ventricular wall motion delay; S-AVD, optimized atrio-ventricular delay after atrial sense; P-AVD, optimized atrio-ventricular delay after atrial pace; P-QRS—baseline, paced QRS duration at baseline; P-QRS—12 months, paced QRS duration at 12 months; Biv-LV pacing, mean percentage of biventricular and left ventricular pacing during 1 year follow-up in the BVP and LVP group, respectively.

defibrillator (CRT-D) more often than patients in the BVP group (1 in the BVP vs. 5 in the LVP group, Table 3). All upgrades to the CRT-D system were performed after the pre-defined follow-up period of 12 months and all upgraded patients were alive at the time of this analysis.

Discussion

This single-centre randomized trial compared clinical outcomes of LVP compared with BVP in patients with advanced idiopathic DCM. Study population was a representative sample of consecutive patients with this condition who were considered for CRT in our centre at the time of enrolment. The results of this study can be summarized as follows. (i) BVP was associated with highly significant improvements after 12 months in all studied parameters with exception of 6MWD, (ii) the benefit of LVP seemed to be much less pronounced, especially in the magnitude of change

of EF and LVEDD parameters, (iii) a cross-sectional analysis after 3 years of follow-up revealed an unexpected excess of cardiovascular mortality rate in the LVP group, (iv) patients in the LVP group required more upgrades to CRT-defibrillator even though they had a higher proportion of these devices at baseline.

Between 2001 and 2010, results of several studies were published comparing LVP with BVP in patients with both ischaemic and non-ischaemic cardiomyopathy with considerable differences in study designs and numbers of enrolled patients. In some of these studies, the benefit of LVP vs. BVP as measured by functional improvement and/or reverse remodelling was similar.^{9–11} The largest of them was the BELIEVE study¹⁰ that included 66 patients and had a follow-up of 12 months. It has also been the only study so far reporting no mortality difference between the study groups during the 12 months follow-up. However, in other studies, BVP resulted in more pronounced reverse remodelling than LVP.^{12–14} The DECREASE-HF trial which comprised to date the largest

Table 2 Cardiac resynchronization therapy response parameters between baseline and follow-up at 12 months

	Biventricular pacing			Left ventricular pacing			
	Mean difference	95% CI	P	Mean difference	95% CI	P	P*
EF (%)	12.5	7.3–17.7	0.0001	5.1	1.1–9.2	0.01	0.01
LVEDD (mm) ^a	8.69	5.2–12.2	<0.0001	5.1	1.5–8.7	0.009	0.05
MR (grade) ^a	0.44	0.16–0.71	0.003	0.33	–0.10–0.77	Ns	Ns
NYHA (class)	0.9	0.7–1.1	<0.0001	1.3	1.0–1.7	<0.0001	Ns
6MWT (m)	67.5	4.5–130.4	Ns	12.7	–25.6–51.2	Ns	Ns
VO ₂ max (l/min)	2.39	0.21–4.57	0.01	0.96	–0.95–2.88	Ns	Ns
Quality of life (change)	13.29	5.9–20.7	0.005	18.5	10.1–26.8	0.002	Ns

Data are means of absolute differences between baseline and 12 months follow-up and their 95% CI. Values of statistical significance are given for comparison between baseline and 12 months follow-up and for comparisons between biventricular and left-ventricular pacing groups *, respectively. ^aAbsolute values denote decrease in LVEDD and MR grade during follow-up.

EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation grade; 6MWT, 6-minute walking test; VO₂max, maximum aerobic oxygen consumption at spirometry; ns, not significant.

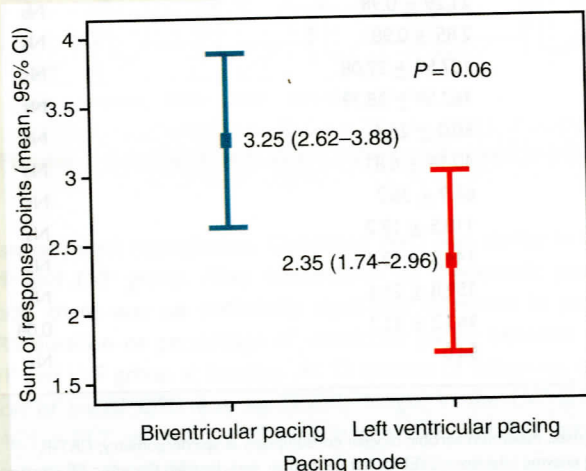


Figure 2 Comparison of sum of response points between study groups.

patient cohort in this setting demonstrated more distinct improvement in LV size and overall CRT benefit in the BVP group with no difference between simultaneous and sequential BVP. Moreover, LVP seemed to worsen mitral regurgitation in a small subset of patients in the DECREASE-HF study. Interestingly, none of the above-mentioned studies comparing LVP and BVP demonstrated a significant difference in functional capacity or quality of life. Recently, results of the B-Left HF study have been published.¹⁷ This multicenter, double-blinded study randomized 176 patients to BVP or LVP. After 6 months of follow-up, there was similar rate of response in both study groups and the authors concluded that LVP may be considered as a clinical alternative to BVP.

It has been suggested that LVP may lead to improved haemodynamic response in experimental setting provided it is associated with ventricular fusion caused by intrinsic activation.¹⁸ Optimization of CRT for fusion between native conduction and LVP remains a theoretical concept, which has not been validated

clinically. In our study, AVD optimization was performed echocardiographically using the VTI method. However, similar paced QRS duration in both study groups after exclusion of anodal capture suggests significant contribution of fusion in the LVP group. Similarly, development of high-degree atrio-ventricular (AV) conduction block was not noted in the LVP group during the pre-defined study period of 12 months.

Increased mortality in the LVP group after 3 years of follow-up was a surprising finding and forced us to switch all patients who were at that time still on LVP to BVP. The mode of cardiovascular death in LVP was progression of HF with low cardiac output or sudden cardiac death. Despite comparable baseline characteristics of the studied populations, LVP had less distinct long-term clinical effects and possibly adversely affected the outcomes in this study. Although magnitude of acute effects of BVP and LVP was similar in previous studies, LVP may worsen interventricular synchrony in the long term, probably a dominant mechanism of dyssynchrony in patients with idiopathic DCM.¹⁹ This effect is even more pronounced in patients with absent fusion due to atrial fibrillation or AV block which translates in a marked widening of the QRS complex.⁸ However, baseline paced QRS duration was similar in this study and therefore, significant fusion must have been present in most patients. In addition, it has been widely speculated in the literature that LVP might be associated with more pronounced pro-arrhythmogenic effects. This has never been proved in a larger prospective cohort. However, in our study, patients in the LVP group required more frequently an upgrade to a CRT-D that was indicated for unexplained syncope, documented ventricular tachycardias, or both. Patients with marked left ventricular dilatation and moderate to severe mitral regurgitation responded poorly to LVP. Last but not least, if LVP results in a smaller effect on conventional surrogate clinical endpoints such as reverse remodelling on echocardiography, it may translate in a long-term perspective into increased mortality risk as shown in our study.

In this context, our findings combined with previous evidence suggest that optimal response to CRT can be expected only when BVP is applied as it is capable of correcting multiple

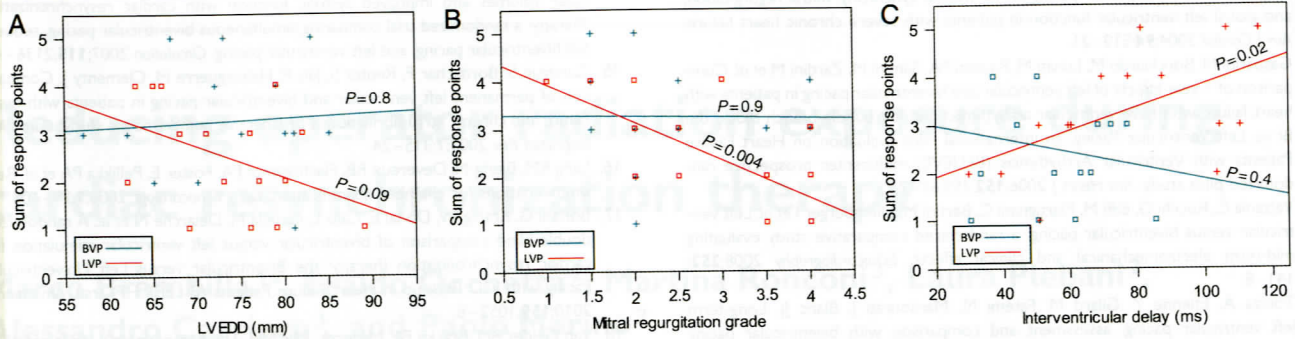


Figure 3 Principal baseline echocardiographic characteristics related to differential response to cardiac resynchronization therapy between biventricular and left ventricular pacing group. Linear regression between echocardiographic baseline findings [(A) LVEDD, (B) mitral regurgitation grade, and (C) IVD] and response to cardiac resynchronization therapy represented as a sum of response points (see Methods). BVP, biventricular pacing group (red lines and data points); LVP, left ventricular pacing group (blue lines and data points); LVEDD, left ventricular end-diastolic diameter; IVD, interventricular delay; and n.s., not significant.

Table 3 Cross-sectional analysis of major adverse events after 3 years of follow-up

Adverse event	BVP	LVP
Death	1	3
Death from cardiovascular causes	0	3
Sudden cardiac death	0	1
Death of HF progression	0	2
Non-cardiovascular death	1	0
Heart transplantation	1	1
Upgrade to CRT-D	1	5

Data are absolute numbers of specific adverse events encountered in each of the study groups. All upgrades to CRT-D took place after the pre-defined follow-up period of 12 months and all upgraded patients were alive at the time of this analysis.

HF, heart failure; CRT-D, biventricular implantable cardioverter-defibrillator; BVP, biventricular pacing study group; LVP, left ventricular pacing study group.

underlying mechanisms of dyssynchrony. Moreover, current methods to assess baseline pathophysiological dyssynchrony mechanisms are at best imperfect and not universally validated to be useful in distinguishing between potential candidates of LVP and BVP.

The main limitation of this single-centre study is the low number of recruited patients. On the other hand, it was comparable with several other studies with a similar protocol. A single-centre study design made it possible to assure a high level of homogeneity of recruitment and study procedures. Another limitation relates to the mortality analysis at 3 years of follow-up, which was not pre-specified at the beginning of the study. However, despite its cross-sectional and retrospective nature, we believe that the results carry a potential for more detailed understanding of CRT application in clinical practice. A similar long-term endpoint analysis would be of great interest in other cohorts and studies. Last but not least, our study population comprised only patients with DCM in order to reduce the heterogeneity of the sample.

Therefore, direct extrapolation of our data to the CRT population with ischaemic cardiomyopathy may be of limited value.

In conclusion, in patients with DCM, BVP is associated with significantly more pronounced benefit in clinical outcomes and reverse remodelling. A retrospective analysis after 3 years of follow-up suggests that isolated LVP may be associated with a higher mortality rate compared with BVP. This data, corroborated by substantial amount of evidence from clinical trials suggests that only BVP should be considered the treatment of choice in patients with HF who are candidates for CRT.

Conflict of interest: none declared

Funding

This study was supported by the Internal Grant Agency of the Czech Ministry of Health Care (MZ ČR NS/9698-2).

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Funding

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Assessment of left ventricular function in non-dilated and dilated hearts: Comparison of contrast-enhanced 2-dimensional echocardiography with multi-detector row CT angiography

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Objective — Multidetector-row CT (MDCT) and contrast-enhanced echocardiography (CEE) are being increasingly used for assessment of left ventricular (LV) function. Excellent spatial and contrast resolution of MDCT allows this evaluation along with coronary angiography. CEE improves the accuracy of 2D echocardiography. Data on side-by-side comparison of both techniques for assessment of LV size and function in subjects with a non-dilated or dilated left ventricle are limited.

Methods and results — Our study population included 64 patients. Group I included 31 patients with an implanted pacemaker who had a non-dilated left ventricle with preserved systolic function. Group II comprised 33 patients with dilated cardiomyopathy and severe systolic LV dysfunction. LV end-diastolic and end-systolic volumes (LVEDV, LVESV) and ejection fraction (LVEF) were assessed using both CEE and short-axis MDCT. The results obtained by both techniques were compared by linear regression and Bland-Altman analysis. Additionally, intra- and interobserver reproducibility was assessed. Both CEE and MDCT measurements highly correlated ($r = 0.61-0.94$). However, CEE significantly underestimated LVEDV and LVESV, and this bias was higher with enlarged LV volumes. LVEF was overestimated by CEE in both groups with a higher bias in the group with preserved systolic function. Both intra- and interobserver reproducibility was significantly better for MDCT, the worst reproducibility was observed for CEE in group I.

Conclusion — Despite a high correlation between MDCT and CEE measurements, CEE provides consistently lower volumes and higher LVEF. This suggests that both methods are not completely interchangeable. Reproducibility of CEE is inferior to reproducibility of MDCT, especially in non-dilated left ventricles with preserved function.

Keywords: *Echocardiography – CT angiography – left ventricular volume – left ventricular function.*

Introduction

Left ventricular (LV) diameters and volumes, ejection fraction and/or stroke volume are fundamental parameters to quantify LV function. They provide important information on prognosis, especially in chronic stable coronary artery disease or in heart failure¹⁻³.

In the past decade, magnetic resonance imaging (MRI) has become the gold standard for functional analysis of the heart due to its high temporal resolution⁴⁻⁶. However, this is an expensive technology that requires extensive training. In addition, it cannot be used in subjects with implantable devices and other metallic implants. In this respect, multidetector-row computed tomography (MDCT) provides a unique opportunity to replace MRI. Both spatial and temporal resolution have improved in new scanners with 16- to 64-slice technology, allowing quantitative analysis of functional parameters with an accuracy slightly inferior to MRI⁷. On the other hand, MDCT has several disadvantages including a relatively high radiation dose and the use of potentially nephrotoxic contrast agents.

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Received 13 February 2009; revision accepted for publication 10 June 2009.

In any case, 2D echocardiography remains the most frequently used, noninvasive and non-expensive tool for the assessment of LV function in routine clinical practice. However, the image acquisition depends on the operator and the acoustic window. The advent of novel echo-contrast agents improved feasibility, reproducibility and accuracy of echocardiographic volume measurements^{8,9}. In spite of such improvement, 2D echocardiography itself suffers from an inherent drawback, i.e. quantification of LV volumes rely on geometrical assumptions that do not apply to enlarged and remodelled left ventricles.

The purpose of our study was to compare measurements of LV function obtained by 2D contrast-enhanced echocardiography (CEE) to those obtained by retrospectively ECG-gated 64-slice MDCT angiography as the standard of reference. Both methods were compared in: (1) patients with normal LV volumes and normal or moderately depressed LV systolic function, and (2) in patients with advanced heart failure with severe LV dilatation and dysfunction.

Methods

STUDY POPULATION

Our study population consisted of 64 patients (mean age 67 ± 12 years). Patients were divided into two groups according to LV ejection fraction (LVEF) measured by conventional 2D echocardiography. Group I included 31 subjects with normal or moderately depressed LV systolic function (i.e. LVEF $> 40\%$, and non-dilated heart) who underwent pacemaker implantation for AV block. Group II comprised 33 patients with dilated cardiomyopathy with an indication to cardiac resynchronization therapy (functional class NYHA III-IV, LVEF $\leq 30\%$, QRS ≥ 120 ms). All subjects were in sinus rhythm and had an indication for CT coronary angiography. They signed an informed consent about participation in the study. The study was approved by the institutional ethics committee.

STUDY PROTOCOL

Patients were enrolled in this study between 2005 and 2007. They underwent both CEE and MDCT angiography. The time interval between both tests was 2 ± 6 days. All patients were on stable medical therapy that did not change between the two examinations.

CONTRAST-ENHANCED ECHOCARDIOGRAPHY (CEE)

CEE was performed by an experienced physician using a VIVID 7 device (GE Vingmed Ultrasound,

Horton, Norway). The subjects were lying in the left lateral recumbent position. Recordings were obtained in baseline tissue harmonic imaging with single focus. The optimal setting for defining the endocardial border was used (by modulation of transmission power, gain, focus and dynamic range in each patient). An intravenous bolus of 0.8-1 ml contrast agent, SonoVue (Bracco, Milan, Italy), was administered in 20-30 sec with a 5-ml saline solution. Recordings of standard apical four-chamber and two-chamber views were obtained. The frame rate reached about 27 frames/s. A commercially available LV opacification programme was used for CEE to minimize contrast destruction (mechanical index = 0.22, 2H – 1.7 MHz). Homogeneous LV cavity opacification without attenuation was required. Five cardiac cycles from each view were recorded and stored on hard disk in raw data format for off-line analysis.

All cine-loops were analysed blinded to the results of MDCT using the modified biplane Simpson's rule in the EchoPac PC station. According to the recommendations of the American Society of Echocardiography¹⁰, end diastole was defined as the frame after mitral valve closure, end systole as the frame preceding mitral valve opening. The inner contour of the LV cavity was then manually traced with papillary muscles and trabeculae were left within the cavity. The end-diastolic volume (LVEDV) and end-systolic volume (LVESV) from 3 cardiac cycles were averaged, avoiding extrasystolic and postextrasystolic beats. From these volumes, left ventricular ejection fraction (LVEF) was calculated.

MULTIDETECTOR-ROW CT (MDCT)

MDCT studies were performed on a 64-slice CT system (Somatom Sensation 64, Siemens, Erlangen, Germany). A pilot scan (a topogram) was acquired on which the position of the heart was selected. An axial retrospectively ECG-gated cardiac MDCT scan was acquired after intravenous bolus injection of 120 ml of non-ionic contrast media (Iomeron 400, Bracco S.p.A., Milan, Italy) at a rate of 4.3 ml/s using a power injector. Imaging was initiated after automatic detection of the contrast bolus in the ascending aorta. As soon as the contrast agent density exceeded 100 HU, volumetric data acquisition was initiated in an inspiratory breath hold. The acquisition parameters were: tube voltage 140 kV, tube current 680 mAs (with automatic dose regulation), rotation time of measuring unit 370 ms, collimation 64×0.6 mm, pitch 0.34. The time of scanning was 15 ± 3 s, depending on the scan range. Raw examination data were subsequently processed according to the evaluation software.

ECG-gated image reconstruction was performed in 10% steps through the entire cardiac cycle, yielding 10 phases. The resulting multiphase image series were

used to produce multiplanar reformations in the short-axis orientation to cover the entire LV cavity using the system's standard 3D software. The maximum systolic and diastolic phases were determined, showing the smallest and largest LV cavity area. Axial images for end-systolic and end-diastolic measurements were created by fusing the source axial image sections to thicker 8 mm axial reconstructions with no intersection gap. The images were transferred to an external workstation (Leonardo, Siemens). Global LV function analysis was performed using Argus software (SyngoVE 31 E, Siemens Medical Solutions, Erlangen, Germany). The LV boundaries of the transaxial CT in the end diastole and end systole were delineated manually. Subsequently, contours were determined automatically for all slices within the entire extent of the LV and for each particular slice. The outlined borders of the LV cavity were visually checked and manually corrected if necessary. The papillary muscles were included in the ventricular volume. The most basal slice was defined as the image closest to the mitral valve annulus. The most apical image was the last image with a detectable LV lumen. The plane connecting the anterior and posterior mitral valve annulus was used as the basal border of the LV cavity. LVEDV, LVESV, and LVEF were calculated by the software.

REPRODUCIBILITY OF VOLUMETRIC DATA

To evaluate the intraobserver variability of both CEE and MDCT, 10 randomly selected cases from each study group were re-analysed by the same specialist one week later. To assess interobserver variability, data from these patients were evaluated also by another trained specialist.

STATISTICAL ANALYSIS

All values are expressed as a mean ± SD. Agreement of CEE and MDCT was assessed using the Pearson's correlation coefficient and linear regression model. To detect differences between CEE and MDCT volumetric data, a *t*-test was performed. The Bland-Altman approach (including the 95% confidence interval) was

used to compare the quantitative data of CEE with MDCT angiography¹¹. Both intra- and interobserver variability were analysed by the intraclass correlation coefficient (ICC) provided by ANOVA analysis. A *P* value < 0.05 was considered as statistically significant.

Results

Baseline demographics of the study population are summarized in table 1. Patients in group I were older and had lower BMI than patients in group II. In addition, there was a male predominance in group I (81% vs. 57%, *P* = 0.047). There was no significant difference in the mean heart rate recorded during CEE or MDCT in the study groups.

Except of one mild allergic reaction on angiography CT contrast agent, all examinations were performed without any complication. The analysis time was approximately 30 minutes for CEE and 25 minutes for MDCT, respectively.

LV VOLUMES AND FUNCTION

Table 2 summarizes numerical results of LV volumetric data obtained by both methods. It is apparent that LV volumes were constantly lower in both study groups by CEE as compared to MDCT. For LVEF, CEE measurements were significantly higher in both groups.

Table 1. – Baseline characteristics of the study cohort

	Group I (n = 31)	Group II (n = 33)	<i>P</i> value (group I vs. group II)
Age (y)	74.1 ± 9.7	60.5 ± 10.5	< 0.001
Gender (men)	25 (81%)	19 (57%)	0.047
BSA	1.97 ± 0.26	1.98 ± 0.20	0.797
BMI	25.7 ± 3.3	28.4 ± 3.9	0.004
HR (CEE)	67 ± 10	71 ± 11	0.146
HR (MDCT)	69 ± 8	72 ± 9	0.169

BMI: body mass index, BSA: body surface area (m²), HR (CEE), and HR (MDCT): heart rate during contrast-enhanced echocardiography and multidetector-row computed tomography angiography, respectively.

Table 2. – Comparison between left ventricular volumes and ejection fraction by CEE and MDCT

	Group 1			Group 2		
	CEE	MDCT	Correlation coefficient	CEE	MDCT	Correlation coefficient
LVEDV (ml)	94 ± 24	143 ± 43	0.616	286 ± 90	374 ± 137	0.934
LVESV (ml)	34 ± 14	73 ± 29	0.650	223 ± 83	316 ± 127	0.939
LVEF (%)	65 ± 10	50 ± 9	0.640	23 ± 7	17 ± 8	0.853

MDCT vs. echocardiography: all *P* < 0.001.

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

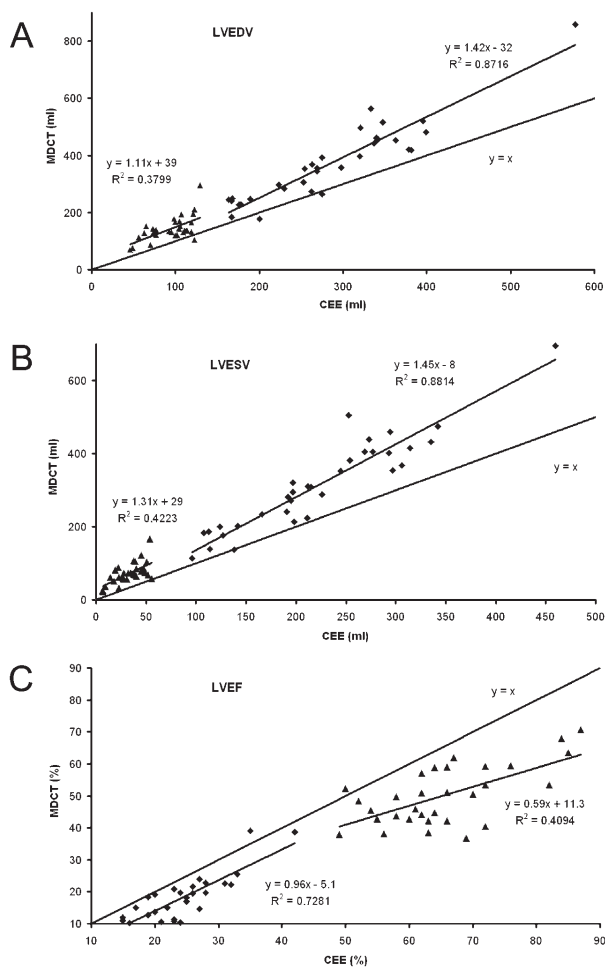


Fig. 1. – Scatter-plot diagrams showing correlation between CEE and MDCT-derived LVEDV (1A), LVESV (1B) and LVEF (1C). ▲ patients with non-dilated LV and preserved systolic function (group I), ◆ patients with dilated cardiomyopathy and systolic dysfunction (group II).

CEE: 2D contrast-enhanced echocardiography, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction LVESV: left ventricular end-systolic volume, MDCT: multidetector-row computed tomography.

The relationships between LVEDV, LVESV and LVEF measured by MDCT and by CEE are presented in scatter plot format (figure 1). The regression line by LVEDV and LVESV in group I is almost parallel with the identity line, while there is a trend to gradually more expressed underestimation by CEE with increasing values of LVEDV and LVESV in group II (figure 1 A, B). In contrast, LVEF was constantly lower when assessed by MDCT in either study group (figure 1C).

Bland-Altman plots documented better agreement between both methods for LVEDV and LVESV in group I as compared with group II (figure 2). For LVEDV, the mean difference reached 50 ± 34 ml in group I and 88 ± 62 ml in group II, the overall difference for both groups together was 67 ± 54 ml. Better agreement of both methods in group I was also

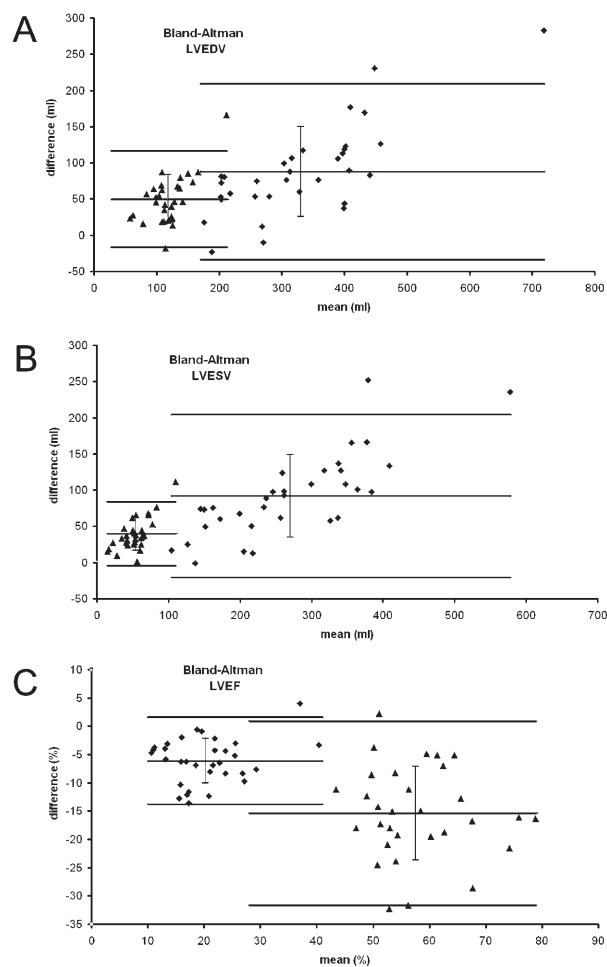


Fig. 2. – Bland Altman analysis of agreement between CEE and MDCT-derived measurements of LVEDV (2A), LVESV (2B) and LVEF (2C). ▲ patients with non-dilated LV and preserved systolic function (group I), ◆ patients with dilated cardiomyopathy and systolic dysfunction (group II).

CEE: 2D contrast-enhanced echocardiography, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction LVESV: left ventricular end-systolic volume, MDCT: multidetector-row computed tomography.

expressed by narrower 95%CI, for LVEDV it was (-16; 116) versus (-34; 210). The slope of the differences across the different values of the mean in group I is 0.69 (SE = 0.16) versus 0.43 (SE = 0.06) in group II. The same trend was observed for LVESV. The mean difference in LVESV reached 40 ± 22 ml in group I, 92 ± 57 ml in group II and 66 ± 51 ml in all patients together. The 95%CI was narrower in group I (-4; 84) versus group II (-20; 204). The slope of the differences in group I equalled 0.79 (SE = 0.15) and 0.44 (SE = 0.06) in group II. Summarizing the findings of the Bland-Altman analysis for LV volumetry, the volumes were underestimated in both groups by CEE as compared with MDCT. Furthermore, there was a significant trend to a gradually more expressed underestimation with increasing LV volumes. For LVEF, the

Bland-Altman approach (figure 2C) displayed lower values for MDCT in both groups with a narrower 95%CI in group II (-14; 2) as compared with group I (-32; 1), and a lower value of the mean difference in group II (-6 ± 4 versus -15 ± 8, respectively). So the bias was higher in the group with the preserved systolic function. The overall mean difference was 11 ± 8. In both groups, the slopes were not significantly different from 0 (0.09, SE = 0.17 in group I and 0.12, SE = 0.10 in group II). Therefore, the underestimation was constant across the values of LVEF in each study group.

INTRA- AND INTEROBSERVER VARIABILITY

For MDCT, a very high inter- and intraobserver reproducibility in the estimates of LVEDV, LVESV, and LVEF was found in both patient groups (tables 3 and 4). The mean difference in volumes ranged from 0.2 to 4.9 ml for both intra- and interobserver variability and the mean difference in LVEF was below 1%. In comparison, reproducibility of CEE measurements was lower. The lowest reproducibility was observed for non-dilated hearts, especially between two observers (the mean interobserver difference in LVESV and LVEDV reached -11.8 to 13.1 ml). The mean difference in LVEF varied between 2 and 2.8%.

Discussion

To our knowledge, this is the first study that compared LV volumes and function obtained by 2D CEE and MDCT in two well defined groups of patients – subjects with non-dilated hearts with normal or near normal LV systolic function, and subjects with severely dilated and dysfunctional left ventricles. The main findings can be summarized as follows. Despite a high correlation between CEE and MDCT, especially in patients with dilated and dysfunctional hearts, CEE-derived LV volumes were systematically lower as compared to MDCT. LVEF estimates were also significantly different between CEE and MDCT – a reflection of the fact that LVEF was significantly higher by CEE. The limits of agreement of LVEDV and LVESV were significantly narrower in non-dilated hearts together with a lower range of volumes in this group. The difference in LVEDV and LVESV between both methods increased with larger LV size. For LVEF, agreement between both methods was better in group II. Both intra- and interobserver variability was significantly better in MDCT as compared to CEE, and interobserver variability for CEE was generally the worst.

Several studies have been published that compared LV volumetry and assessment of LV systolic function obtained from echocardiography and MDCT. A good correlation between echocardiography and 16-slice

Table 3. – The intra- and interobserver variability of measurements for MDCT

	Group I			Group II		
	Intrapersonal variability		Interpersonal variability	Intrapersonal variability		Interpersonal variability
	ICC	95% CI	Mean difference	ICC	95% CI	Mean difference
LVEDV	1.00	1.00; 1.00	-0.2 ± 1.9 (ml)	0.97	0.91; 0.99	-0.9 ± 7.9 (ml)
LVESV	1.00	0.99; 1.00	-0.6 ± 3.0(ml)	0.98	0.95; 1.00	-1.7 ± 4.12 (ml)
LVEF	0.97	0.92; 0.99	0.34 ± 2.84(%)	0.96	0.86; 0.99	0.9 ± 2.64 (%)
				ICC	95% CI	Mean difference
				1.00	1.00; 1.00	2.4 ± 7.3 (ml)
				1.00	1.00; 1.00	0.29 ± 5.0 (ml)
				0.98	0.94; 0.99	0.7 ± 1.8 (%)
				0.99	0.96; 1.00	-4.9 ± 34.6 (ml)
				0.99	0.98; 1.00	-4.9 ± 22.38(ml)
				0.95	0.83; 0.98	0.9 ± 3.2 (%)

ICC: intraclass correlation coefficient, 95% CI: 95% confidence interval, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

Table 4. – The intra- and interobserver variability of measurements for CEE

	Group I			Group II		
	Intrapersonal variability		Interpersonal variability	Intrapersonal variability		Interpersonal variability
	ICC	95% CI	Mean difference	ICC	95% CI	Mean difference
LVEDV	0.72	0.30; 0.91	-4.3 ± 10.83 (ml)	0.40	-0.17; 0.77	-14.8 ± 15.9 (ml)
LVESV	0.78	0.41; 0.93	0.1 ± 5.78 (ml)	0.28	-0.31; 0.71	-8.3 ± 8.7 (ml)
LVEF	0.67	0.21; 0.89	-2.0 ± 4.7 (%)	0.23	-0.35; 0.68	2.8 ± 6.2 (%)
				ICC	95% CI	Mean difference
				0.96	0.87; 0.99	-11.9 ± 28.2 (ml)
				0.91	0.74; 0.97	-13.5 ± 33.9 (ml)
				0.59	0.07; 0.85	1.4 ± 4.5 (%)
				0.82	0.51; 0.94	-11.8 ± 40.0 (ml)
				0.78	0.42; 0.93	-13.1 ± 43.1 (ml)
				0.48	-0.07; 0.81	1.0 ± 5.5 (%)

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

MDCT for the assessment of LVEF was revealed by Salm et al.¹². Similar data were obtained in a study by Bansal et al. in a series of 52 patients with suspected coronary artery disease and normal LVEF¹³. Despite a reasonable correlation, MDCT provided consistently higher values of LV volumes. Sugeng et al.¹⁴ compared MDCT with real-time 3D echocardiographic measurements of LV size and function with cardiac MRI in 31 subjects. The study showed a good correlation of both MDCT and 3D echocardiography with MRI ($r^2 > 0.85$). However, MDCT significantly overestimated LV volumes, resulting in a small but significant bias in LVEF. Analysis of the above studies in the context of our results confirms that a good correlation between the methods does not mean that they can be used interchangeably for comparison of LV volumes and LVEF. Compared to MRI that is currently considered as a gold standard, MDCT overestimates the volumes, while echocardiography tends to underestimate. Our data suggest that this bias increases with LV dilation and dysfunction. For LVEF, the relationship is opposite and MDCT tends to underestimate it. In contrast, a study by Henneman et al.¹⁵ showed a very high agreement between 64-slice MDCT and 2D echocardiography with a tendency to underestimate MDCT-derived volumes.

Several factors may account for the above discrepancy between the results of LV volumetry obtained from CEE and MDCT. These include different temporal and spatial resolution, and LV shape and size. The lower temporal resolution of CT may cause, at least partly, an overestimation of LV volumes as compared with contrast echocardiography. Given the fact that the isovolumetric period at end systole is only 40–60 ms, high temporal resolution is mandatory for the precise assessment of functional parameters. In this respect, MRI has been considered as the gold standard for quantification of LV volumes and function. Modern MRI scanners allow a temporal resolution of 20–50 ms as well as acceptable spatial resolution. The 64-slice we used has a higher rotation speed (370 ms per rotation), and with half-scan interpolation the temporal resolution reaches approximately 185 ms. Such a limited temporal resolution is responsible for its inability to acquire the peak systolic LV volume. The lower temporal resolution of ECG-gated MDCT may lead to motion artifacts, especially during the systolic phase¹⁶. As a result, MDCT tends to overestimate predominantly LVESV and underestimate LVEF¹⁷. This has been confirmed by several MRI studies in comparison with MDCT^{18–20}. On the other hand, the reproducibility of the MDCT is superior to other imaging modalities. This is in agreement with our observation.

The reconstruction algorithms are also influenced by the heart rate of the patient during data acquisition²¹. For optimal image quality without motion artifacts, oral beta-blockers are frequently administered to

reduce heart rate. Although there was no significant difference between the heart rate during CEE versus MDCT in our study, MDCT overestimated systematically volumes compared to CEE, and underestimated the LVEF. In addition, the use of intravenous contrast injection may result in a volume overload in MDCT that could potentially lead to significant overestimation of LVEDV when compared with MRI^{20,22,23}. As a result, LVEF could be underestimated by MDCT^{22,23}.

Compared to MDCT, echocardiography is disadvantaged by the limited visualization of the heart due to a poor acoustic window and/or by reliance on geometric assumptions, especially in the presence of dilated and dysfunctional LV. With the progression of LV remodelling, the LV shape becomes more spherical and volumetry less reproducible²⁴. The echocardiographic method is also more dependent on good endocardial border definition. Although injection of contrast agent improves the accuracy of border tracing and volumetry^{8,9,25,26}, it does not eliminate underestimation of the volumes compared to MRI. This is in agreement with our results as CEE continues to underestimate LV volumes compared to MDCT. Furthermore, according to the EMEA public statement²⁷ the use of the particular contrast agent Sono Vue is contraindicated in patients with heart failure class III/IV. The FDA alert from 17 July 2008²⁸ recommends monitoring of patients with unstable cardiopulmonary status at least 30 minutes after the administration of echocardiographic contrast agent because of the risk of serious cardiopulmonary reactions. All patients included in our study were in stable condition and we did not record any complication after the administration of echocontrast agent.

In view of the rapidly growing popularity of non-invasive coronary angiography with new generations of CT scanners, MDCT has a potential for combined assessment of LV volumetry and function. MDCT provides an opportunity to evaluate LV volumes and function without some limitations of both MRI and echocardiography. It allows imaging in patients with pacemakers and other metallic implants, in obesity, chronic lung disease, and a history of prior cardiac surgery. Regarding accuracy, several studies have reported a good agreement between MRI and MDCT for the evaluation of LV function. With the rapid evaluation of non-invasive angiography with 16 and 64 slice scanners, MDCT provides an opportunity to evaluate both the coronary vessels and the LV function, without the need for additional contrast exposure. Disadvantages of MDCT include radiation exposure and the use of contrast material.

Different results of CEE and MDCT can have an important impact on the decision-making process and therapy selection in our patients, such as the indication for cardiac resynchronization therapy or to ICD implant.

Limitations of the study

This study has several limitations. One limitation is the small number of patients in both study groups. On the other hand, we compared two well-defined groups of subjects.

Since our study did not involve MRI, we cannot provide information as to which technique is more accurate. However, we could not use MRI in half of the study population because of the previous implantation of implantable devices. As previous studies have shown an excellent correlation between MDCT and MRI, we expected that MDCT measured LV volumes in this study are likely to be accurate. Nevertheless, larger comparative studies are needed in patients with non-dilated and dilated hearts to assess the agreement between MDCT, MRI and contrast echocardiography for LV volumetry and LVEF.

Conclusions

In all subjects, estimates of LVEDV, LVESV, and LVEF were significantly correlated between CEE and MDCT, especially in enlarged ventricles. However, CEE tended to underestimate LV volumes and overestimate LVEF as compared to MDCT. The difference in LVEDV and LVESV between both methods increased with larger LV size. On the contrary, the bias in LVEF was higher for non-dilated LV. This suggests that both methods are not completely interchangeable, especially in subjects with enlarged and dysfunctional LV. Reproducibility of CEE is inferior to reproducibility of MDCT, especially in non-dilated hearts with normal or near normal LV function. Therefore, MDCT could be used for the evaluation of left ventricular volumes and function in cases when MRI is contraindicated or when echocardiography cannot be successfully performed.

Acknowledgement

This study was supported in part by research grant NR8541-3/2005 and partly by research grant NR 8553-3/2005 of the Internal Grant Agency of the Ministry of Health of the Czech Republic.

Conflict of interest: none declared.

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