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Novel ultrasound contrast agent dilution method for the assessment of ventricular ejection fraction

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Aims Left ventricular (LV) ejection fraction is an important determinant of prognosis in heart failure. We evaluated the accuracy of a novel algorithm for LV ejection fraction quantification based on indicator dilution curve (IDC) principles using ultrasound contrast as indicator, and compared the results with contrast enhanced biplane LV ejection fraction assessment.
Method A diluted ultrasound contrast bolus (SonoVue®) was injected intravenously in 31 patients (19 male, age 65 ± 11) with known or suspected heart disease. A total of 68 recordings were made. The developed algorithm used the left atrium and LV IDC for LV ejection fraction measurement. Biplane enhanced LV ejection fraction measurements with pure ultrasound contrast (SonoVue®) were determined in multiple four- and two-chamber recordings as reference.
Results The mean LV ejection fraction measured by biplane and IDC method was 33 ± 17% and 35 ± 18%, respectively. A correlation coefficient $r = 0.93$ was observed between the two methods. Bland–Altman analysis demonstrated a slight LV ejection fraction overestimation with IDC (mean 1.9 ± 6.3%).
Conclusion A new fast method for LV ejection fraction assessment based on IDC principles is described and comparison with contrast enhanced biplane LV ejection fraction quantification shows accurate results.

Introduction

Left ventricular (LV) ejection fraction is a key determinant of prognosis in cardiac disease and is important for optimal timing of therapy and surgery.[1–6] Therefore, accuracy and reproducibility of these measurements are imperative for patient monitoring and decision making in daily cardiology.

Two-dimensional (2D) biplane echocardiography is most frequently used to obtain LV ejection fraction. However, the accuracy is highly dependent on the ability to obtain two high quality tomographic views of the heart.[7,8] To ameliorate this problem, LV opacification with ultrasound contrast agents (UCAs) is used to improve endocardial delineation.[7,9–12]

Ejection fraction can also be assessed by the interpretation of indicator dilution curves (IDCs).[13] Until now, this required the intra-ventricular injection of the indicator and subsequent analysis of the washout curve. In dogs, Rovai *et al*. found an excellent correlation with angiographic ejection fraction with this method.[14]

In this paper, we present a novel minimally invasive method for assessment of LV ejection fraction based on UCA indicator dilution curves using a peripheral intravenous injection of a small UCA bolus. An advanced dilution identification algorithm is used for the interpretation of the acoustic intensity backscattered by the UCA passages through the left atrium (LA) and LV (see Appendix).

Methods

Patients

Thirty-one patients (19 male, age 65 ± 11) referred for known or suspected heart disease were evaluated by echocardiography and UCA. Patients were randomly selected, including patients with 'normal' LV ejection fraction. A history of myocardial infarction was present in 16 patients and severe mitral regurgitation in 9 patients.

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Patients with contraindications for the UCA (SonoVue®, Bracco s.p.a., Milan, Italy) used in this study (known allergy, renal failure, unstable angina, recent myocardial infarction) and with moderate or severe aortic regurgitation were excluded from this study. Patients with NYHA class III or IV heart failure were also excluded from the time that the contraindications for SonoVue® were extended to this category of patients. The local ethics committee approved the study protocol and all patients gave informed consent.

Echocardiography

Echocardiography was performed with a Sonos 5500 and an S3 transducer (Philips Medical Systems, Andover, MA, USA). Standard transthoracic echocardiography was performed in all patients to assess LV and valve function. Nomenclature of LV segments and measurements of LV dimensions were according to the recommendations of the American Society of Echocardiography.[8] The degree of mitral regurgitation (grades I–IV) was assessed both by color jet area and by assessment of mid-systolic percentage jet area relative to LA size in the apical four-chamber view.

Automatic IDC LV ejection fraction

Measurement procedure

An ultrasound contrast bolus of 1 mL of SonoVue®was diluted 1:100 in saline solution and 10 mL of the diluted contrast was injected intravenously. The injection was performed manually and it was immediately followed by a quick saline flush. Based on previous calibration measurements in vitro, the scanner was set in power modulation mode at 1.9 MHz and low mechanical index (0.1).[15,16] The use of a contrast enhancement mode, such as power modulation, allows reducing the dose of UCA in order to obtain a linear relation between contrast concentration and measured acoustic intensity.[16,17] The use of a low mechanical index limits the collapse of UCA bubbles.[18,19] For 100 s after the intravenous antecubital injection, multiple digital loops of the apical four-chamber view were recorded for the measurement of the LA and LV UCA IDCs (*Figure 1*). These IDCs are detected by the ultrasound scanner and interpreted as the input and output of the LV dilution system, from which the proposed algorithm automatically determines the LV ejection fraction. Software Q-Lab (Philips Medical Systems, Andover, MA, USA) for acoustic quantification was used for the IDC measurement.

Further description of the automatic IDC method is presented in the Appendix.

Biplane contrast enhanced LV ejection fraction

After the IDC measurement, a bolus of 0.5 mL pure SonoVue® was administered intravenously to obtain contrast enhanced cine loops of the apical four- and two-chamber view. The loops were acquired at a frame rate of 25 Hz in the power modulation mode. Special care was taken to avoid foreshortening of the LV long axis. Three loops were digitally recorded for biplane ejection fraction estimates. In 12 patients the measurements were repeated three and/or six months after cardiac resynchronization therapy.

Statistics

Correlation analysis was performed to compare the relation between the automatic IDC method and the contrast enhanced biplane LV ejection fraction measurement. Further comparison between the two methods was performed with Bland–Altman analysis. All tests were performed using the statistical analysis program Medcalc®(Medcalc Software, Mariakerke, Belgium).

Results

Seventy-three ejection fraction measurements were performed using UCA. In five patients, IDC curves could not be obtained (14%): in two patients the UCA LV opacification failed and in three opacification was not sufficient for the automatic IDC ejection fraction assessment. Therefore, 68 measurements in 31 patients were included in this study. The clinical and echocardiographic patient characteristics are summarized in *Table 1*. The LV ejection fraction with the biplane method ranged from 10 to 75% and the LV end-diastolic volume from 80 to 510 mL. A mean LV ejection fraction of 33 $\pm$ 17% was found for the biplane enhanced contrast method in comparison to a mean LV ejection fraction of 35 $\pm$ 18% for the automatic IDC method with a correlation coefficient $r = 0.93$ (*Figure 2*). Bland–Altman analysis ($\pm$2 SD) demonstrated limits of agreement between the two methods from 14.2 to −10.6% with a mean LV ejection fraction difference of 1.8 $\pm$ 6.2% for the two methods with slightly higher estimates for the IDC method (*Figure 3*).

As expected (see Appendix), the correlation coefficient between the biplane enhanced method and the IDC method estimates was equal to 0.93 also in the two

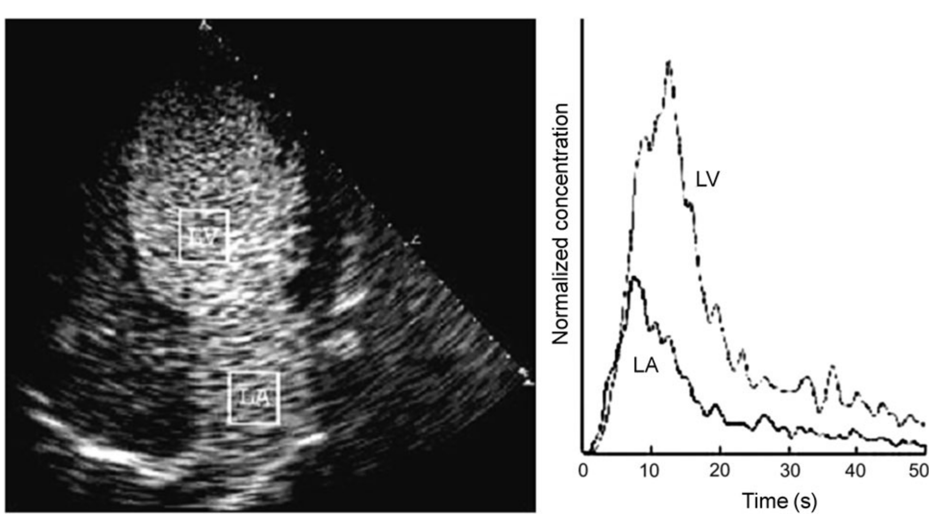

Figure 1 Left image: transthoracic four-chamber view with diluted contrast. Two regions of interest are placed in the LA and LV for IDC measurement. Right image: the LA and LV IDCs are shown.

Table 1 Patient characteristics

	All patients
Male/female	19/12
Age (years)	65 ± 11
LVEF (%, biplane)	33 ± 17
LVEF (%, IDC)	35 ± 18
LVEDV (mL, biplane)	215 ± 94
MR severity	1.8 ± 1.3
MR/LA area	0.23 ± 0.2

Abbreviations: LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; MR: mitral regurgitation; LA: left atrium.

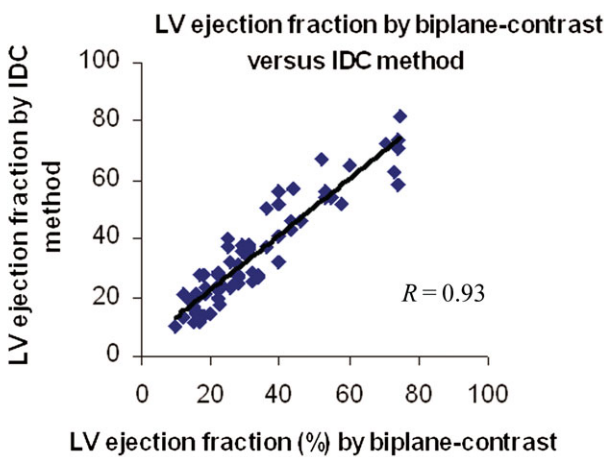

Figure 2 Scatter diagram of the LV ejection fraction assessed by biplane contrast enhanced versus the IDC method. Correlation between the two methods $r = 0.93$.

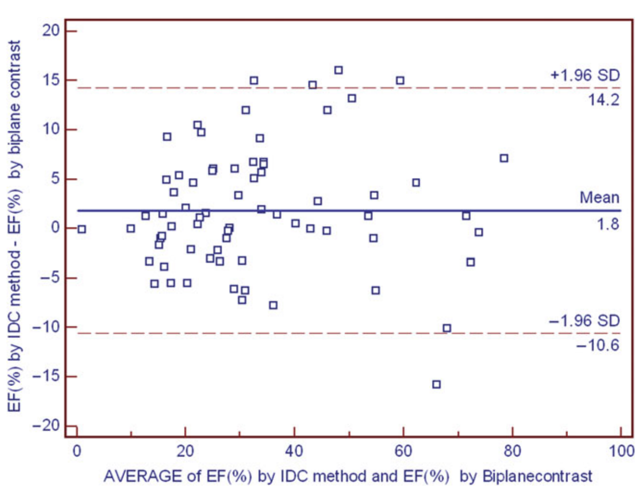

Figure 3 Bland–Altman plot of the comparison between the biplane contrast enhanced method and the IDC method.

subgroups of patients with none or mild mitral regurgitation (49 measurements) and with severe regurgitation (19 measurements; 9 patients).

The mean absolute difference between repeated measurements of the ejection fraction with the automatic IDC was 6 ± 6%. Inter- and intraobserver variability of the biplane contrast method, tested in 10 patients, was 6 ± 8% and 5 ± 6%, respectively.

Discussion

In the present study, a novel automatic IDC-based method for the assessment of LV ejection fraction by means of contrast echocardiography is presented and validated. We investigated the accuracy and reproducibility in comparison to biplane contrast enhanced LV ejection fraction measurement. An excellent correlation ($r = 0.93$) was observed between the ejection fraction estimates by the proposed method and the contrast enhanced biplane method.

The IDC method uses an intravenous injection of a small UCA bolus to produce two IDCs in the LA and LV. The amount of contrast that is needed for the IDC method is smaller than needed by a factor of 5 to obtain high quality opacification of the LV for contrast enhanced biplane ejection fraction determination.[7,11,12] These IDCs are detected by an ultrasound scanner and interpreted as the input and output of the LV dilution system, from which the proposed algorithm automatically determines the LV ejection fraction.

Currently, quantitative assessment of LV ejection fraction is most commonly obtained using 2D transthoracic echocardiography, which depends on operator technique and experience and is limited by the 'acoustic window' to obtain proper tomographic views of the heart.[8,22] Injection of UCA improves the detection of the endocardial lining by filling the intertrabecular spaces, reducing the operator-dependency and underestimation of the LV volume and ejection fraction.[7,9–12] This improvement is evident in good and bad quality images.[10,12] However, addition of a contrast agent does not eliminate the limitations of 2D transthoracic echocardiography, such as errors related to image plane positioning, determination of the proper frames, foreshortening of the LV apex, geometric assumptions of the biplane method, and cardiac translation. The proposed automatic IDC method does not require LV contour tracing and it is not limited by related problems. It is based on the concentration of a contrast agent in a sample volume of the LA and LV. After the injection of diluted contrast and acquisition of two IDCs, the automatic IDC analysis for the ejection fraction assessment takes about 1 s on a standard personal computer. Therefore, the application of the IDC method is significantly less time-consuming than the biplane method. Moreover, the automatic implementation of the IDC analysis reduces the operator-dependency.

The Bland—Altman analysis revealed slightly higher estimates of the LV ejection fraction by the proposed IDC method. However, given the LV ejection fraction underestimation of the echographic biplane method when compared to MRI as a gold standard, the automatic IDC method could effectively be closer to that gold standard.[10–12] The agreement between the IDC and the contrast enhanced biplane method (from 14.2 to −10.6%) is comparable with the agreements that are usually reported for LV ejection fraction estimates by different imaging modalities.[7,9–12,19]

In theory, by measuring the IDCs in the right atrium and right ventricle the proposed method can also be applied for assessment of the right ventricular ejection fraction. This should be clarified in future studies.

Study limitations

This single institutional study in a limited amount of patients warrants further confirmation. Signal intensity within the ultrasound field is not homogeneous, although stationary since they are relatively constant in time. Therefore, different locations of regions of interest within the left ventricular cavity may produce slightly different results. Future research is needed to study the influence of the selection of the sample volume on the measured IDCs and hence, estimated ejection fractions. There was no comparison with MRI LV ejection fraction according to the Simpson method. However, previous studies have revealed the accuracy of the biplane contrast enhanced LV ejection fraction method.[7,9–12]

Conclusion

The IDC determination of the ejection fraction is feasible and accurate, and not dependent on LV contour detection, which renders it suitable to widespread application.

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Appendix

Data analysis and ejection fraction estimation

The measured IDCs are interpreted as the input and output of the LV dilution system, which is well represented by a linear model. Therefore, a linear system identification method, such as a deconvolution, can be applied to identify the LV dilution system based on the measured IDCs.

A least mean squares (LMS) approach is employed for the identification of the LV dilution system and the assessment of the ejection fraction based on the LA and LV IDCs. The use of a system identification method based on the measurement of two IDCs from the LA and LV allows an estimation of the LV washout curve (LV dilution system impulse response) that is independent of the UCA injection function and the bolus diffusion between the injection site and the LV. In this context, the term washout curve refers to the LV IDC curve that would be measured after a fast intra-ventricular injection of the contrast bolus. The choice for an LMS approach is due to the low signal-to-noise ratios of the measured IDCs.

A mono-compartment model is adopted to represent the LV dilution system.[16] The proposed system identification method uses a Nelder–Mead simplex method to minimize the mean squared error between the measured and the estimated LV IDC.[20] This simplex algorithm is a direct search method that performs an unconstrained minimization of a multidimensional scalar function without any derivative information. For the identification of the LV dilution system the optimal parameters of the mono-compartment model that lead to the LMS solution are estimated. Therefore, the system identification is reduced to the estimation of the time constant of the mono-compartment model representing the impulse response of the LV dilution system. As a result, the influence of noise on the estimated clinical parameters is minimal.

Noise in the measured IDCs is mainly introduced by the measurement system and it is due to flow and pressure variations in the ventricles.[21] Therefore, it can be suppressed by specific filters.[17] Despite the linear relationship between the measured acoustic intensity and the UCA concentration for low mechanical index and UCA concentration, in the adopted four-chamber view the LA IDC is distorted (modulated) by the non-stationary attenuation produced by the contrast diluted in the LV. However, exploiting the linear relationship between LV contrast concentration and measured LV ultrasound intensity and the linear relationship between contrast concentration and attenuation coefficient, the LA IDC can be compensated for the LV attenuation effect.[16]

The LV dilution system identification results in the estimation of the LV impulse response, i.e. the LV IDC washout curve after a theoretical rapid injection of a contrast bolus in the LV. Therefore, the estimated impulse response fulfils the requirements for a correct ejection fraction assessment based on the Holt method which uses direct injection of contrast into the LV.[13] In particular, the estimated time constant t of the monocompartment model representing the LV impulse response can be used for the estimation of the ejection fraction (EF) as

$$\mathrm{EF} = 1 - \mathrm{e}^{\frac{-\Delta t}{T}} \quad (1)$$

where Δt is the cardiac period. Repeated measurements (within minutes) were used to assess the variability of the method.

The effect of valve regurgitation on the washout curve estimation is also considered and a distinction can be made between mitral and aortic regurgitation. In fact, since mitral insufficiency affects both the LA and LV IDCs, it does not influence the system identification (a mathematical derivation is presented further on). A similar reasoning applies to UCA re-circulation through the entire cardiovascular system. Re-circulation does not affect the measurement as it appears in both the LA and the LV. In fact, it can be simply interpreted as a component of the input (LA) IDC that is transferred to the output IDC (LV) by the LV dilution system.

Influence of valve regurgitation

A scheme of the analyzed dilution system is presented in *Figure 4*. The input $C_{in}(t)$ and the output $C_{out}(t)$ are the LA and LV IDC, respectively. The block LV represents the LV

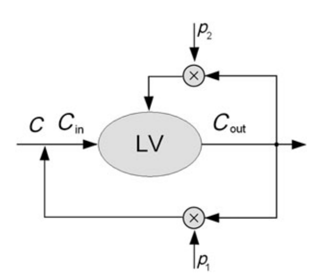

Figure 4 Scheme of the LV dilution system (LV) in the presence of mitral regurgitation (p_1) and aortic regurgitation (p_2).

dilution system. The measurement sites for the system identification correspond to the input and output of the system LV. Valve regurgitation can be interpreted as a feedback from the output $C_{out}(t)$ to the input $C_{in}(t)$.

The multiplicative factors p_1 and $p_2 \in [0, 1)$ in *Figure 4* represent the severity of the mitral and aortic insufficiency, respectively. In the presence of mitral insufficiency, $p_1 \neq 0$ and $p_2 = 0$. In this case, the effect of the feedback is a variation of the input IDC $C_{in}(t)$, which does not influence the result of the system identification method.

When aortic insufficiency is present, part of the flow goes from the aorta to the LV. In this case, $p_1 = 0$ and $p_2 \neq 0$. Therefore, only the output IDC $C_{out}(t)$ is influenced by the regurgitation. In order to show the effect of aortic regurgitation on the system identification, we consider the mono-compartment differential equation

$$\frac{\partial C_{out}}{\partial t} V + (C_{out}(t) - C_{in}(t)\Phi = 0 \qquad (2)$$

where V and Φ are the compartment volume and flow, respectively.

The system impulse response is therefore given as $\tau^{-1}e^{-t/\tau}$, with the time constant $\tau = V/\Phi$.

Including the feedback due to aortic regurgitation, Eq. (2) becomes

$$\frac{\partial C_{out}}{\partial t} V + (C_{out}(t) - (1 - p_2)C_{in}(t) - P_2 C_{out})\Phi = 0. \qquad (3)$$

As a result, the impulse response is $\tau_R^{-1}e^{-t} = \tau/\tau R$, with time constant $\tau_R = \tau/(1 - p_2) \geq \tau$.

According to Eq. (1), a larger value for the time constant τ leads to a lower ejection fraction. Therefore, in the case of aortic insufficiency, the geometric estimation of the ejection fraction, e.g. based on the biplane method, gives an overestimation with respect to the proposed dilution estimation, which is based on hemodynamics rather than volume variations.

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