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Three-dimensional echocardiography for left ventricular quantification in heart failure

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Summary

General discussion

Heart failure can be defined as the inability of the heart to keep up with the demands of the body. Systolic heart failure can be described as failure of the pump function of the heart, as opposed to diastolic heart failure, which can be described as the failure of the ventricles to adequately relax.

Left ventricular (LV) imaging provides important diagnostic and prognostic information after myocardial infarction and in heart failure. Multiple imaging modalities are available to this goal: LV angiography, radionuclide imaging, CT, MRI and of course (2- and 3D) echocardiography.

For evaluation of LV size and function, angiography, although invasive, can be combined with coronary angiography and / or evaluation of valve function. Radionuclide imaging methods may provide additional information on myocardial perfusion and / or hibernation. Cardiac CT provides additional information about coronary and valvular anatomy. These three methods however, use ionizing radiation. Cardiac MRI does not only provide highly reproducible information on LV size and function, but also on valvular and coronary anatomy and function and (with the use of contrast) about myocardial scar. Finally, echocardiography provides information on LV size and function, valvular anatomy and function and (with the use of contrast) myocardial perfusion. Notwithstanding the advantages of other methods of LV imaging described above, echocardiography remains the first line imaging modality in patients with heart failure because of its low cost, ease of use, portability to the bedside and wide availability.

The use of three-dimensional echocardiography (3DE) for measurement of these quantitative parameters is feasible only if they can be measured reliably, serially and consistently, in a wide range of patients, irrespective of LV morphology and/or dilatation. This requires, amongst others, adequate definition of the endocardial contour. The use of intravenous ultrasound contrast significantly improves endocardial definition and reproducibility of LV volume and ejection fraction measurement, especially in the patient group with suboptimal echocardiographic image quality [1-2].

Classically, measurement of these quantitative parameters was performed by manual tracing of the endocardial contour using a computer mouse, and with the development of 3DE, the endocardial contour was simply traced in multiple image planes. Later, software was developed to semi-automatically detect the endocardial contour throughout the cardiac cycle, in three dimensions. This requires manual input of only a limited number of major anatomical landmarks, after which the software performs the analysis automatically.

With improvement of semi-automatic detection algorithms, reproducibility and comparison with cardiac MRI as a golden standard improved as well. 3DE of LV volumes and ejection fraction has an accuracy comparable to MRI [3-6]. Furthermore, analysis time decreased from over one hour to a few minutes per ventricle, greatly increasing feasibility, which is approximately 80% in studies and in real life referrals in unselected patients with heart failure.

Major clinical decisions are based on (echocardiographic) quantitation of LV function. An ejection fraction of $\leq 40\%$ is an indication for medical therapy for heart failure even in the absence of symptoms [7], an ejection fraction of $\leq 35\%$ is an indication for implantation of an implantable cardioverter/defibrillator with or without cardiac resynchronization therapy [8], an end-systolic volume index > 30 ml/m² implies worse prognosis after myocardial infarction [9], and a $\geq 15\%$ decrease in end-systolic volume serves as a marker for response to cardiac resynchronization therapy. In abnormal LVs, the impact of 3DE is of most interest especially in visual estimated ejection fractions between 25%-50%. Routine quantification of LV volumes and EF by 3DE is important in these abnormal ventricles and adds to the standard clinically indicated 2D echocardiogram [10].

Main findings

The present thesis focused on quantification of LV (dys)function in heart failure. Accurate measurement is an important aspect of prognosis, initiating and monitoring of therapy and assessment of disease progression and thus important clinical impact.

Chapter 2 provided an overview of the current state of the art in 3DE [11].

In **chapter 3**, we studied LV volume measurement in vitro and demonstrated that the position of the echo transducer does not need to be precisely aligned with the long axis of the LV using 3DE, as is necessary in 2D echocardiography [12]. Slight off-axis image acquisition in combination with tilting of the transducer, to ensure that the LV is inside the scanned volume, allows accurate volume measurement. This enables the operator to improve image quality by trying various transducer positions on the patients' chest.

In **chapter 4**, a comparison between 2D and 3DE was made of LV volume and ejection fraction measurement, using cardiac MRI as a gold standard [13]. A group of myocardial infarction patients and healthy volunteers underwent 2D and 3DE, and cardiac MRI. LV volumes and ejection fraction were measured using these three modalities. Intra- and interobserver variability and comparison to MRI was significantly better for 3D, than for 2D echocardiography.

Chapter 5 was a serial study of development of LV volumes and function after myocardial infarction in 33 patients [14]. 3DE can differentiate patients with and without subsequent development of LV remodelling accurately and early on the basis of the 3D sphericity index, a new and highly predictive variable.

In **chapter 6**, the first system for analyzing LV electromechanical dyssynchrony based on transesophageal 3DE and semi-automatic endocardial contour detection was described [15]. This generated color-coded polar maps, displaying regional LV displacement and its timing.

Ultrasound contrast agents aim to improve endocardial definition, but may delineate the outermost endocardial contour by filling up intertrabecular space. In **chapter 7**, we

demonstrated that volumes measured by 3DE indeed are significantly larger when ultrasound contrast is used [16]. However, probably because our patient group had an adequate apical acoustic window, ultrasound contrast did not improve LV volume measurement reproducibility.

Hitherto, most echocardiographic methods to describe cardiac dyssynchrony were based on measurement of timing of contraction in different segments of the LV. It was largely neglected, especially in ischemic cardiomyopathy, that a subgroup of myocardial segments show severe hypo- to akinesia. Whether they exhibit contraction delay or not, these segments hardly contribute at all to global LV function and cardiac resynchronisation therapy might not lead to improvement. Finally, in **chapters 8 and 9**, we demonstrated that correction of dyssynchrony parameters for segmental contractility improves sensitivity to changes during acute cardiac resynchronisation therapy and improves predictive value of response to cardiac resynchronisation therapy [17,18].

Methodological considerations and future perspectives

Endocardial contour detection is a key element in much of the work presented in this thesis. Although impressive progress has been made, on-line dyssynchrony assessment using full automated endocardial contour detection is still not feasible. The use of ultrasound contrast and possibly, focusing on differences between Doppler signals of blood and myocardial wall might further improve contour detection.

All methods based on contour definition suffer from one major disadvantage: they neglect all myocardial wall events that do not result in endocardial motion. From a mechanistic point of view, elucidating myocardial motion is thus very limited. However, one might reason that ultimately, the endocardial wall needs to move inward in order to eject the blood into the aorta.

Apart from endocardial contour tracing, myocardial contractility can be assessed by tissue Doppler, and by speckle tracking technology [19-23]. Their advantage over endocardial contour detection is in their use of regions of interest, in which spatial resolution may be of lesser importance. Tissue Doppler is currently available in three dimensions [24] and it is

conceivable that assessment of multiple image planes around a central LV long axis might be sufficient for clinical use. Area under curve, or, more crudely, time to peak contraction multiplied by peak contraction velocity might serve as a similar parameter to time-volume loss.

Speckle tracking technology might be even more useful than Tissue Doppler echocardiography, since it can be applied to 3DE and it is not dependent of insonification angle. Like tissue Doppler, it relies on tracing of regions of interest. Differences in longitudinal, radial and circumferential contraction patterns assessed by 3D speckle tracking may provide additional insight into cardiac dyssynchrony and individual response to biventricular pacing. It may aid in identification of the most delayed segments and optimizing lead placement. Furthermore, it might further elucidate mechanisms of papillary muscle dysfunction and mitral valve regurgitation. Minor adaptations in analysis software should be sufficient to perform similar studies as in the present thesis, but using 3D speckle tracking echocardiography.

In addition, 3DE using probes with a smaller footprint and higher temporal and spatial resolution will significantly improve feasibility and quality of acquisitions. Wider angle acquisition is indispensable for adequate visualization of the entire heart in one volume or severely enlarged ventricles often seen in patients with heart failure. Fusion of echocardiographic with cardiac MRI, (coronary) CT and / or radionuclide imaging images may facilitate studies on the complicated relationship between ischemia, scar, conduction delay and papillary dysfunction [25].

Conclusions

Three-dimensional echocardiography has moved from the research laboratory to the bedside. Feasibility of currently available real-time 3DE in unselected patients with heart failure is approximately 80% in studies and in real life referrals. Routine quantification by 3DE of LV volumes and ejection fraction is important in systolic heart failure patients and adds to the standard clinically indicated 2D echocardiogram.

Three-dimensional echocardiography provides accurate and reproducible measurements of LV volumes and ejection fraction, which may partly depend on its relative independency on transducer position. It may predict LV remodeling on the basis of 3D sphericity index, which is a new and highly predictive variable.

The use of ultrasound contrast enhancement increases end-diastolic and end-systolic volume measurements significantly compared to baseline; ejection fraction measurements remained unchanged.

This thesis was the first to demonstrate feasibility of color-coded polar maps for dyssynchrony assessment, displaying regional LV displacement and its timing. Time-volume curve analysis may be superior in prediction of response to biventricular pacing over methods based on timing alone.