Author's response to reviews

Title: Novel echocardiographic techniques to assess left atrial size, anatomy and function.

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Author's response to reviews: see over
Dear Editors,

I would like to resubmit the attached manuscript, 
"Novel echocardiographic techniques to assess left atrial size, anatomy and function",

for consideration of possible publication in *Journal of Cardiovascular Ultrasound*, as a review article. I highlighted all changes made in the revised manuscript.

Point-by-point response to reviewer’s requests:

**Reviewer #1:**

1. Authors should structure the manuscript by subdividing into sub-sections focusing on the technological aspects of 3D and 2D speckle tracking.

   We have chosen to extend the part of the manuscript inherent to the technological aspects of these newer noninvasive technologies for the assessment of LA size and function, providing a methods subsection for both of these echocardiographic techniques:

   In the 3-dimensional echocardiography section:

   “LA volumes by RT3DE is collected in four-cycles full-volume during a breath hold, using a 3D matrix-array transducer. Acquisition is triggered to the electrocardiographic R wave. Particular care is taken to ensure that the entire LA is included within a pyramidal 3D data set. The pyramidal volume data is displayed in three different cross-sections that may be modified interactively by manual shifting of vertical and horizontal lines in the two orthogonal apical and the short-axis views. LA volume by 3D echocardiography is derived from semi-automated tracing of the LA endocardium, starting the measurements in the frame with the largest atrial dimension, corresponding to ventricular end-systole, just before opening of the atrio-ventricular valves, in perpendicular apical long-axis planes. This is performed by making 5 points in the atrial surfaces of the mitral annulus: at the anterior, inferior, lateral, and septal annulus, and the fifth point at the apex
of the left atrium. Following this manual identification, the program automatically identifies the endocardial surface using a deformable shell model. Then manual adjustment of the endocardial surface is performed in all examinations presented, in order to include trabeculae and to exclude atrial appendages and large veins from the cavity volumes. Then the frame with the smallest atrial dimension (at ventricular end-diastole) is selected with similar surface detection and manual editing. Atrial maximum (max) and minimum (min) volumes are obtained, and atrial EF is derived from the two volumes (Figure 1)[…].”

In the Speckle tracking section:

“Two-dimensional strain imaging is an echocardiographic technique that uses standard B-mode images for speckle tracking analysis. The speckle pattern (acoustic backscatter generated by the reflected ultrasound beam) is followed frame-by-frame, using a statistical approach based on the detection of the best matching area. The displacement of this speckled pattern is considered to follow myocardial movement and a change between speckles is assumed to represent myocardial deformation. Although this new technique was introduced for the exclusive analysis of left ventricular (LV) function, several studies have recently extended its applicability to other cardiac chamber, such as the left atrium. For speckle tracking analysis of left atrial chamber, apical four- and two-chamber views images were obtained using conventional two-dimensional gray scale echocardiography, during breath hold with a stable ECG recording. Particular attention was given to obtain an adequate gray scale image, allowing reliable delineation of myocardial tissue and extracardiac structures. Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second; these settings are recommended to combine temporal resolution with adequate spatial definition, and to enhance the feasibility of the frame-to-frame tracking technique. Recordings were processed using an acoustic-tracking software (Echo Pac, GE, USA), allowing off-line semi-automated analysis of speckle-based strain. In particular, LA endocardial surface is manually traced in both four- and two-chamber views by a point-and-click approach. An epicardial surface tracing is then automatically generated by the system, thus creating a region of interest (ROI). To trace the ROI in the discontinuity of LA wall corresponding to pulmonary veins and LA appendage, the direction of LA endocardial and epicardial surfaces at the junction with these structures was extrapolated. After manual adjustment of ROI width and shape, the software divides the ROI into 6 segments, and the resulting tracking quality for each segment is automatically scored as either acceptable or non-acceptable, with the possibility of further manual correction. Segments in which no adequate image quality can be obtained are rejected by the software and excluded from the analysis. In subjects with adequate image quality, a total of 12 segments were then analyzed. Lastly the software generates the longitudinal strain curves for each segment and a mean curve of all segments that reflect the pathophysiology of atrial function (Figure 4). During the reservoir phase, the LA fills up, stretches itself, and for this reason, the atrial strain increases, reaching a positive peak at the end of atrial filling, before the opening of the mitral valve; after the opening of the mitral valve, LA empties quickly, shortens, the strain decreases, up to a plateau corresponding to the phase of diastasis, followed by a second positive peak, but less than the first, which corresponds to the period preceding the atrial contraction, and finally a negative peak after the atrial contraction (Figure 4). This second positive deflection of the atrial strain curve, corresponding to atrial systole, is present only if the subject analyzed presents sinus rhythm. Thus, as shown in Figure 4, peak atrial longitudinal strain (PALS), measured at the end of the reservoir
phase, and peak atrial contraction strain (PACS), measured just before the start of the active atrial
contractile phase, are calculated by averaging values observed in all LA segments (global PALS
and PACS), and by separately averaging values observed in four- and two-chamber views (four-
and two-chamber average PALS and PACS, respectively). LA contraction strain index (CSI),
representing, in percentual values, the contribution of the LA active contraction to the LV filling
phase, is calculated as (global PACS/global PALS) x 100. The time to peak longitudinal strain
(TPLS) is also measured as the average of all 12 segments (global TPLS) and by separately
averaging values observed in the two apical views (four- and two-chamber average TPLS) (Figure
4).[..]

2. They should address advantages and limitations and potential use in the clinical setting when
compared to more conventional parameters. In other words authors should show if this is a
breakthrough technology that may change our approach to the study of this chamber.

Surely it is important to list the advantages and limitations of each method and to underline the
potential clinical implications of these recent technologies; for these reasons we have chosen to
include in our work brief paragraphs, entitled “advantages and limitations” and “clinical
applications” for both the two main sections.

First, in the 3D Echocardiography section:

“Advantages and Limitations

LA volume measurements by RT3DE correlate closely with those obtained on multidetector
computed tomography and on magnetic resonance imaging, showing a better diagnostic accuracy
respect to 2D methods. In particular, 3DE reconstruction overcomes 2DE limitations, avoiding
geometric assumptions for LA volume evaluation (Figure 1). The latest generation of 3D matrix-
array transducers and off-line quantification softwares, has allowed, in comparison to MRI, the
most time-efficient method of LA volume quantification, with the exception of poor image quality
or cardiac arrhythmias. Moreover, through 3DE it is possible to estimate LA ejection fraction
(LAEF) (Figure 2); despite recent guidelines did not mention any possible application, several
clinical conditions may require three-dimensional LA function analysis (Figure 3). Recent reports
have shown potential applications of LAEF in different patterns of diastolic dysfunction,
demonstrating a good correlation with the E/E’ ratio. Despite the good correlation between 3DE and
MRI in estimating LA volume, several studies show that echocardiography systematically tends to
underestimate LA volumes when compared to MRI. A probable cause of this disparity is the
difference in spatial image resolution between both 2D and 3DE compared to MRI; in fact
echocardiography presents low lateral image resolution because apical window places the left
atrium at the far field of the ultrasound beam. In addition 2D and 3D ultrasound images could not
be able to distinguish the volumes within the intratrabecular atrial areas. Moreover, as with any new
imaging technique, a learning curve exists, and recognizing and avoiding potential artifacts are
critical and most of all related to respiratory or ECG gating and/or incorrect gain settings which are
particular challenging in patients with arrhythmias or respiratory difficulties.”
Clinical applications

3D echocardiography is a safe, non-invasive imaging modality that may be a very promising tool to assess atrial size, providing important insights into LA morphologic and functional evaluations. Recently, it has been shown that LA volume provides a more accurate measure of LA size than conventional M-mode LA dimension. In fact LA enlargement occurs in all 3D directions but not in a uniform fashion and medial-lateral expansion is less prominent than longitudinal and antero-posterior expansions, so one-dimensional assessment is likely to be an insensitive assessment of any change in LA size. For these reasons, the ASE has recommended quantification of LA size by biplane 2D echocardiography. However, cyclic changes in LA volume may not be observed directly by two-dimensional echocardiography because the shape of the left atrium changes during the heart cycle and generally only maximum LA volume is routinely measured in clinical practice. The physiologic volume changes that occur in the different phases of cardiac cycle may be accurately evaluate by RT3DE; real-time acquisition of 3-dimensional views during a routine echocardiographic examination allows us to analyze the dynamic changes in LA volume and to quantify the contribution of LA to LV filling, calculating also LA ejection fraction by the 3D semi-automated software. The relative contribution of LA phasic function to LV filling is dependent upon the LV diastolic properties; with increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. Thus, LA volume increases with severity of diastolic dysfunction. The structural changes of the LA may express the chronicity of exposure to abnormal filling pressures and provide predictive information beyond that of diastolic function grade. In this way, LA volume reflects an average effect of LV filling pressures over time, rather than an instantaneous measurement at the time of study. Thus, Doppler and tissue Doppler assessment of instantaneous filling pressure is better suited for monitoring hemodynamic status in the short term, whereas LA volume is useful for monitoring long-term hemodynamic control."

Second, in the STE section:

Advantages and Limitations

STE analysis allows an excellent assessment of atrial deformation profile during an entire cardiac cycle, closely following LA physiology. Considering the limitations of classical indices of LA function, assessment of LA strain by speckle tracking may represent a relatively rapid and easy-to-perform technique to explore LA function, due to its semi-automated nature and to its off-line processing. In fact, in contrast to Doppler-derived parameters, speckle tracking has the advantage of being angle-independent, and to be less affected by reverberations, side lobes and drop out artefacts. Nonetheless, intrinsic limitations of speckle tracking include strict frame rate dependency, potential errors in epicardial/endocardial border tracing in subjects with suboptimal image quality, and need for an appropriate learning curve to achieve adequate experience in using analysis software. In fact, the potential difficulty of accurately obtaining a region of interest close enough to the effective shape of the left atrium, and the risk of contamination by signal components arising from structures surrounding the left atrium should be considered. Lastly, because a dedicated software for LA strain analysis has not yet been released, the analysis is performed using a software created for the left ventricle; for this reason, it is mandatory to be careful in the endocardial border delineation,
excluding from the analysis the auricola and the outlet of the pulmonary veins, in order to minimize the risk of artefacts caused by signals from these structures.”

“Clinical applications

The LA mechanical function studied by STE can be described by three phases, in which the atrial strain curve closely follow LV dynamics during the cardiac cycle. In fact during the period of LA reservoir, corresponding to the phases of LV isovolumic contraction, ejection, and isovolumic relaxation, LA strain increases, achieving a peak at the end of LA filling, due to the downward movement of the mitral annulus towards the apex, as a result of LV contraction. In the same way, during the conduit and LA contraction phases, the LA strain curve reflects inversely the pattern of LV myocardial deformation. Therefore LA function seems to be influenced not only by LA stiffness but also by LV compliance during ventricular filling and by contraction through the descent of the base during LV systole. It has been recently demonstrated that this new approach for the study of LA function is of potential clinical importance in a number of pathophysiologic conditions typically associated to abnormal LA function, e.g. mitral valve diseases, supraventricular arrhythmias, systemic hypertension, ischemic heart disease, heart failure, atrial stunning, and cardiomyopathies. In this overview, we have decided to focus on two of these pathologic conditions in which atrial strain imaging may be helpful in clinical management of patients.[...]

3. They should also discuss the lack of normality values, of a technological standard for speckle tracking.

In agreement with the comment of the Reviewer, we have decided to better explain this part of the manuscript at the end of the methods section of the speckle-tracking paragraph:

“Numerous methodological studies have shown the reference range values and good feasibility and reproducibility of the application of speckle tracking technique to measure LA myocardial longitudinal deformation (Table 2). Regarding the measurement of peak atrial strain, as stated in the current ASE/EAE Consensus, two techniques have been proposed to quantify atrial deformation by STE, which differ only by the choice of frame from which start processing software. The first takes as reference point the QRS onset and measures the positive peak atrial longitudinal strain, corresponding to atrial reservoir, the second uses the P wave as the reference point, enabling the measurement of a first negative peak atrial longitudinal strain, corresponding to atrial systole, a second positive peak atrial strain, corresponding to LA conduit function, and their sum.”

4. The English language should be extensively revised.

Finally, we have corrected the grammatical and spelling errors presented in the manuscript.

Reviewer #2:
1. The clinical relevance of the measurement (EF, Strain) obtained with the described new technologies is discussed with some superficiality and in terms of such measurements only. Strain and sizes are not discussed in terms of their added value in conjunction with other clinical assessment. This is particularly noticeable in the diastolic function section.
We have decided to better discuss the potential clinical applications of 3D echocardiography and of speckle tracking echocardiography in relation to other conventional echocardiographic parameters, providing to add two subsections entitled “Clinical applications” in the paragraph of 3D echocardiography and of speckle tracking echocardiography:

In the 3D echocardiography paragraph:

“Clinical applications

3D echocardiography is a safe, non-invasive imaging modality that may be a very promising tool to assess atrial size, providing important insights into LA morphologic and functional evaluations. Recently, it has been shown that LA volume provides a more accurate measure of LA size than conventional M-mode LA dimension. In fact LA enlargement occurs in all 3D directions but not in a uniform fashion and medial-lateral expansion is less prominent than longitudinal and antero-posterior expansions, so one-dimensional assessment is likely to be an insensitive assessment of any change in LA size. For these reasons, the ASE has recommended quantification of LA size by biplane 2D echocardiography. However, cyclic changes in LA volume may not be observed directly by two-dimensional echocardiography because the shape of the left atrium changes during the heart cycle and generally only maximum LA volume is routinely measured in clinical practice. The physiologic volume changes that occur in the different phases of cardiac cycle may be accurately evaluate by RT3DE; real-time acquisition of 3-dimensional views during a routine echocardiographic examination allows us to analyze the dynamic changes in LA volume and to quantify the contribution of LA to LV filling, calculating also LA ejection fraction by the 3D semi-automated software. The relative contribution of LA phasic function to LV filling is dependent upon the LV diastolic properties; with increased stiffness or noncompliance of the LV, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretch of the atrial myocardium. Thus, LA volume increases with severity of diastolic dysfunction. The structural changes of the LA may express the chronicity of exposure to abnormal filling pressures and provide predictive information beyond that of diastolic function grade. In this way, LA volume reflects an average effect of LV filling pressures over time, rather than an instantaneous measurement at the time of study. Thus, Doppler and tissue Doppler assessment of instantaneous filling pressure is better suited for monitoring hemodynamic status in the short term, whereas LA volume is useful for monitoring long-term hemodynamic control.”

And also at the end of the paragraph of Speckle Tracking Echocardiography:

“Clinical applications

The LA mechanical function studied by STE can be described by three phases, in which the atrial strain curve closely follow LV dynamics during the cardiac cycle. In fact during the period of LA reservoir, corresponding to the phases of LV isovolumic contraction, ejection, and isovolumic relaxation, LA strain increases, achieving a peak at the end of LA filling, due to the downward movement of the mitral annulus towards the apex, as a result of LV contraction. In the same way, during the conduit and LA contraction phases, the LA strain curve reflects inversely the pattern of LV myocardial deformation. Therefore LA function seems to be influenced not only by LA
2. The mechanical activity of LA is discussed like that of an independent chamber, not in relation with LV. It has not been accounted that most of LA deformations are consequent of the, normally more important, LV activity. For example the elongation (peak strain – positive in the LA) is mostly due to the downward movement of the mitral plane that is a result of LV myocardial contraction, thus mostly passive not really a LA activity. The LA deformation should be discussed in conjunction with LV dynamics. As a different perspective or a consequence of the overall cardiac dynamics.

We have chosen to explain the role of LA in the three different phases in relation to LV dynamics, therefore we have made these changes in the paragraph of speckle tracking echocardiography:

“The LA mechanical function studied by STE can be described by three phases, in which the atrial strain curve closely follow LV dynamics during the cardiac cycle. In fact during the period of LA reservoir, corresponding to the phases of LV isovolumic contraction, ejection, and isovolumic relaxation, LA strain increases, achieving a peak at the end of LA filling, due to the downward movement of the mitral annulus towards the apex, as a result of LV contraction. In the same way, during the conduit and LA contraction phases, the LA strain curve reflects inversely the pattern of LV myocardial deformation. Therefore LA function seems to be influenced not only by LA stiffness but also by LV compliance during ventricular filling and by contraction through the descent of the base during LV systole […]”.

3. The presentation is editorially poor. The reader would expect a Methods section (made of the two existing subsections 3DEcho, STE), followed by Result and Discussion sections (together or separate), and a brief Conclusion.

In complete agreement with this advice, we have decided to organize the entire manuscript in a different way, dividing the text into various sub-sections: “Background”, “Three-Dimensional Echocardiography”, “Speckle Tracking Echocardiography”, “Discussion” and “Conclusion”, providing to add, for the section of “3D Echocardiography” and of “Speckle Tracking Echocardiography”, three further sub-sections named “Methods”, “Advantages and Limitations” and finally “Clinical applications”.

I hope that the reviewing process finds the manuscript acceptable for publication in the journal.

Sincerely Yours,

Dott. Matteo Cameli,  
Cardiologia Universitaria