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Cardiac Chamber Volumetric Assessment Using 3D Ultrasound – a Review

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Abstract: When designing clinical trials for testing novel cardiovascular therapies, it is highly relevant to understand what a given technology can provide in terms of information on the physiologic status of the heart and vessels. Ultrasound imaging has traditionally been the modality of choice to study the cardiovascular system as it has an excellent temporal resolution; it operates in real-time; it is very widespread and – not unimportant – it is cheap. Although this modality is mostly known clinically as a two-dimensional technology, it has recently matured into a true three-dimensional imaging technique. In this review paper, an overview is given of the available ultrasound technology for cardiac chamber quantification in terms of volume and function and evidence is given why these parameters are of value when testing the effect of new cardiovascular therapies.

Keywords: Cardiac function; Cardiac volume; 3D echocardiography; Segmentation; Automated analysis; Commercial solutions; Validation studies.

1. MOTIVATION

The current global status of cardiovascular diseases, accounting for more deaths than any other cause [1] and projected to remain the leading global cause of death [2], makes the assessment of cardiac volume and function a topic of extreme importance not only in the clinical field for patient diagnostic and follow-up but also in research as new therapies are developed and tested. Several cardiac imaging modalities have arisen to satisfy the demand for cardiac function assessment techniques, among which three-dimensional (3D) echocardiography seems to be especially promising. The analysis of the images to obtain the volumetric indices has also been heavily developed in order to extract the information in a fast, exact and user-independent manner.

While much research and clinical attention has been directed towards volumetric assessment of the left ventricle (LV), as detailed in the extensive review of Leung and Bosch, an increased interest in the other cardiac chambers is more recently shifting the focus towards a more comprehensive set of volumetric biomarkers [3]. Thus, this present review presents an accurate description of the current state-of-the-art on cardiac chamber volumetric assessment using three-dimensional ultrasound. The focus is set on the available technologies in clinical practice, as well as the most relevant validation efforts for each cardiac chamber.

This manuscript is organized as follows: Section 2 provides a global perspective on the importance of volumetric cardiac indices and how these can be effectively assessed. The main existing modalities for cardiac imaging are also presented and compared. A brief conceptual description of the available methods for cardiac image processing and automated volumetric assessment is then given in Section 3. Section 4 focuses then on the available software solutions in clinical practice for volumetric biomarkers of cardiac morphology and function for each chamber, while discussing their validation level and relevant clinical findings. Finally, Section 5 concludes the current manuscript with the closing remarks on this topic discussing the present and future challenges for cardiac chamber volumetric assessment.

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2. ASSESSMENT OF CARDIAC MORPHOLOGY AND FUNCTION

The fundamental cardiac pumping function arises from a sequence of electrical events which trigger the coordinated contraction of the myocardial tissue. These events form the cardiac cycle and are regularly repeated over every heartbeat, being regulated through different pacing mechanisms which control the frequency of cardiac contraction. The rhythmic contraction of the different cardiac chambers results in intrinsic volume variations of both atria and ventricles over the cardiac cycle. From these volume traces, several indices can be extracted to characterize both cardiac morphology and global function such as the end-diastolic and end-systolic volumes (EDV and ESV). In the particular case of the atria these volumes are often referred to as LAmax and LAmin and RAmax and RAmin for the left and right atrium (LA and RA) respectively. It is also common practice to use volume indices divided by body surface area, usually the LA volume index (LAVI) and the RA volume index (RAVI). Furthermore, other cardiac global functional indices can be extracted from volume traces. Stroke volume (SV=EDV-ESV) is the effective amount of blood ejected by a cavity. The left ventricular SV, when multiplied by the heart rate, gives the total cardiac output (CO). As a measure of pumping efficiency, one can estimate the ejection fraction (EF=(SV/EDV)x100%), as proposed originally by Pombo et

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al. [4], which is still probably the most widely used parameter to assess the global status of cardiac function in LV [5]. For the atria, this measure is also called emptying fraction. Some specific measures have been proposed for the function assessment in the case of the atria such as the atrial expansion index (LAEI = LASV / LAmin and RAEI = RASV / RAmin). Moreover, atrial volume measured immediately before the atrial contraction (LApreA or RApreA) can be used to derive the passive (EFpass = (EDV - preA) / preA) and active (EFact = (preA - ESV) / ESV) components of EF, the former corresponding to the passive emptying resulting from ventricle expansion (atrial conduit function) while the latter corresponds to the active emptying (atrial contractile function) [6].

2.1. Prognostic value in clinical practice

Extensive research has been directed at determining the prognostic value of volumetric indices for different illnesses and conditions. A brief review of some of these studies is presented here to illustrate the importance of cardiac volume and function assessment.

2.1.1. Left Ventricle

Patient survival after myocardial infarction and its relation to LV function has been thoroughly described in literature. It was first associated with LV ESV by White et al. [7] and Norris et al. [8]. In a study by Burns et al., it was shown that LV EF had even a superior prognostic value than LV ESV for survival after myocardial infarction [9]. Numerous other studies have given further evidence on the prognostic value of LV EF on both short- and long-term survival after myocardial infarction [10–14]. Furthermore, LV EF has been linked to cardiac arrest events [13], heart failure [15], and arrhythmia suppression and cardiac events [16] in survivors of myocardial infarction. More generally, mortality in patients with coronary artery disease has also been associated with LV EF by Buxton et al. [17].

The prognostic value of LV EF for the mortality in patients with heart failure has also been a subject of much research and discussion with different studies reaching different conclusions as to which population, preserved or reduced LV EF, represents a higher mortality risk [18,19]. More recently, two meta-analysis studies, one by Somaratne et al. and a second by a large-scale project (MAGGIC), analyzed data from 17 and 31 studies respectively demonstrating that a higher risk of death is present in patients with heart failure and reduced LV EF [20,21].

LV function has also been used as a predictor of survival in dilated cardiomyopathy [22,23]. Furthermore, LV EF has been associated to mortality in patients with LV dysfunction [24] and to mortality in end-stage renal disease patients on starting hemodialysis [25]. Some works have also been dedicated to the study of stress and post-stress LV volumes. In Sharir et al. post-exercise LV EF and ESV were associated to cardiac death [26] and in Coletta et al. dobutamine stress testing was used to link stress LV EDV to cardiac events in patients with coronary heart disease [27].

2.1.2. Left Atrium

More recently the attention has shifted towards the prognostic value of LA volume and function. LA volume has been associated with diastolic dysfunction by Tsang et al. and also with LV remodeling by Rossi et al. [28,29]. It has also been linked to the onset of cardiovascular diseases [30], future cardiovascular events [31], to the development of congestive heart failure in patients with well-preserved LV function [32] and to the occurrence of ischemic stroke in patients without atrial fibrillation [33]. In a study by Leung et al., LAVI has been associated with the risk of cardiovascular death, heart failure, atrial fibrillation, stroke and myocardial infarction [34] and Ristow et al. have associated it to heart failure hospitalization and mortality [35]. LAVI has also been linked to the survival after myocardial infarction [36,37] and to cardiovascular events in patients with lone atrial fibrillation by Osranek et al. [38]. Finally, LA volume has been shown to have a prognostic value for atrial fibrillation [39,40].

2.1.3. Right Ventricle

Some research has also been done into the prognostic value of the right heart, and especially of the right ventricle (RV). Numerous studies relate RV function, and more precisely RV EF, with patient survival in different stages of heart failure [41–45].

The prognostic value of the RV for survival in patients with pulmonary arterial hypertension has also been well explored in the studies by van Wolferen et al. [46]and van der Veerdonk et al. [47]. Furthermore, the post myocardial infarction mortality has been associated to the RV EF measured late after clinical myocardial infarction [48]. RV EF has also been associated with survival in patients with idiopathic dilated cardiomyopathy [49]. Finally, in a study by Kang et al., the early death of patients with acute pulmonary embolism has been associated to the ratio between the RV and the LV volumes [50].

2.1.4. Right Atrium

The prognostic value of RA has been substantially less explored in literature. RAVI was linked to RV systolic dysfunction in patients with chronic systolic heart failure and abnormal RV function by Sallach et al. [51].

2.2. Available Imaging Modalities

From the above, it is clear that the assessment of cardiac volumes throughout the cardiac cycle and its associated indices is a fundamental task in diagnostic cardiology routine. Furthermore, these indices can be of paramount importance in the design of studies to show the efficacy of new therapies. To this end, there is a large array of imaging modalities providing insight to cardiac chamber size and function, with some examples shown in Figure 1.

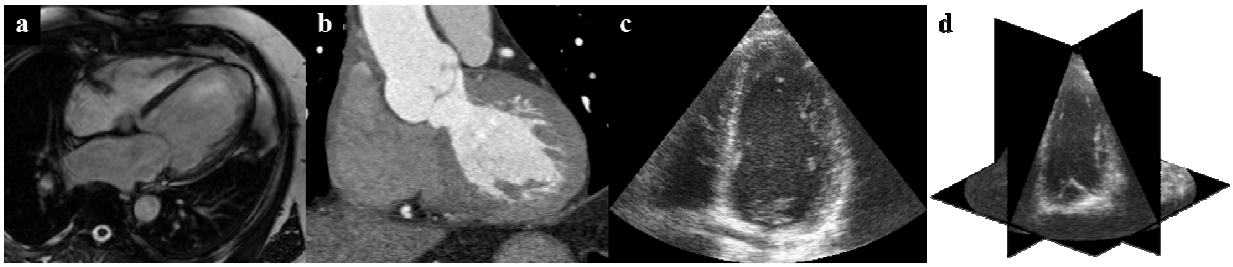

Figure 1. Examples of different cardiac imaging modalities: magnetic resonance imaging (a), computed tomography (b), 2-dimensional echocardiography (c) and 3D echocardiography (d). Computed tomography image courtesy of Walter Coudyzer, Department of Radiology, UZ Leuven, Belgium.

Magnetic resonance imaging (MRI), and more specifically cardiac MRI (cMRI), is for long considered the gold standard for assessment of cardiac anatomy and analysis of global cardiac function and shape [52]. The key limitations of cMRI are the high cost of the imaging system and the long acquisition times. This last problem is particularly relevant for cardiac imaging, given the fast dynamics of a beating heart. Computed tomography (CT) is one of the fastest evolving imaging modalities. Cardiac CT, which requires the use of contrast agents, offers superb definition of the boundary between the myocardium and the blood pool, excellent spatial resolution (<1mm) and good temporal resolution. However, it is a very technically demanding exam, involves exposure to ionizing radiation and is very expensive. Other imaging modalities used include cardiac single photon emission computed tomography (SPECT) and multiple gated imaging strategies (MUGA), also known as radionuclide ventriculography [53,54], positron emission tomography (PET) [55] and other nuclear imaging techniques [56]. However, these techniques require the injection of radioactive contrast agents, thus involving exposure to ionizing radiation, and the imaging systems are typically extremely expensive.

With the exception of standard X-ray exams, ultrasound is the leading imaging modality worldwide [57]. As key imaging advantages, the excellent temporal resolution clearly sets echocardiography apart from the remaining modalities. Other important advantages, such as its safety, good spatial resolution and low cost, also contribute to the widespread use of echocardiography as the cardiac imaging diagnostic exam of reference in daily practice. The use of echocardiography to assess cardiac chamber size and function dates to the advent of this technology. Popp et al. investigated the variation of cardiac dimensions during the cardiac cycle using M-mode echocardiography [58]. Feigenbaum et al. used these changes to assess LV function and correlated it to angiography [59]. Wyatt et al. showed that volumetric indices extracted from two-dimensional (2D) B-mode images were superior to their M-mode counterparts, especially in asymmetrical hearts [60,61]. Currently, biplane area assessment using 2D echo is the standard tool for assessment of LV volumetric indices.

2.3. Real-time 3D echocardiography

Given the considerations previously mentioned, it becomes clear why current clinical practice in cardiology typically employs 2D echocardiographic studies as the first-line and fundamental exam in the evaluation of cardiac function and morphology of patients, while cMRI is used as a second-line solution for more advanced investigation.

Nonetheless, conventional 2D presents important limitations that directly reduce its potential for accurate volumetric assessment of the different cardiac chambers. Indeed, volume estimation from 2D ultrasound images intrinsically relies on geometric assumptions, which are required to transform the planar measurements into volume estimates. Since the imaging planes may correspond to foreshortened views of the real 3D object, the geometrical assumptions can be easily violated, which in turn leads to reduced accuracy in the volume estimates. Furthermore, during the cardiac cycle, out-of-plane motion can create illusory displacement of the true boundary position, which can further reduce the volumetric assessment accuracy. Thus, the true three-dimensional nature of real-time 3D echocardiography (RT3DE) scanning enables to overcome these limitations, allowing to entirely visualize the morphology of the cardiac chambers. This directly translates into increased agreement of RT3DE against the current gold-standard method (i.e. cMRI) when compared to conventional 2D echocardiography. Summing this to the intrinsic advantages of ultrasound imaging against other modalities, RT3DE will likely become the standard echocardiographic examination of the future.

3. CARDIAC IMAGE PROCESSING METHODS

Additionally to the imaging acquisition, the extraction of the relevant information from the data by a software tool must be considered. The assessment of volumetric, functional and morphologic indices poses two main problems. First, a clear identification of the myocardial anatomy is needed, through the delineation of the endo- and epicardial surfaces at a given time point. Furthermore, the position of these boundaries throughout the cardiac cycle is needed to recover the underlying motion of the cardiac chamber and capture the volume changes. Several methods have thus been proposed to address these problems and a categorization of these methods is possible dividing into geometrical models, shape-free methods, statistical models, classification approaches and tracking [3]. Each of these categories is briefly described in this chapter. For a more comprehensive description of these methods, the interested reader can refer to the extensive review by Leung and Bosch [3].

Geometrical models are the most common border detection approaches and consist of the representation of a border in terms of a curved surface influenced by

geometrical constraints. This surface is initialized interactively or automatically and evolves iteratively according to image features such as the local intensity or edge information. Most geometrical models use energy-based optimization where a mathematical energy function is defined according to the image features and other regularization terms and optimized iteratively [62–67]. Given the surface representation that is used, the main disadvantage of these models lies in finding a balance between a surface that is too smooth and one that becomes implausible.

Shape-free methods are, as the name implies, methods with little or no dependency on the shape of the final object. As such, they are heavily dependent on low-level image information such as pixel intensity, gradients, edges and corners and motion vectors. The two main families with this category are clustering and level sets. Clustering is, simply put, a categorization of each pixel of the image into groups, for example myocardial tissue and blood pool [68–71]. Level sets are similar to geometrical models with the main difference that the shape of the object is not restricted, which can often result in multiple disconnected surfaces [72–76]. Due to the low level of shape restrictions imposed, these techniques are quite susceptible to image artifacts such as shadowing or dropouts.

Statistical models are population based methods which model the statistical variations of patient data according to borders manually contoured by experts. This is done by finding a relatively simple mathematical model with but a few parameters that can express the patient variability from an average. By varying these parameters one can then synthetize a large number of shapes. Different sources of information can be used to build such a model. Active shape models use the manual contoured borders [77–79], whereas active appearance models use a combination of the manual contoured borders and the image intensity information [80–82]. Given their origin from real examples this method can only find plausible results. However, this is also its downfall as the accuracy of the model will always be dependent on the quality of the original database and its extension throughout both healthy and pathological populations.

Classification approaches are also dependent on large sets of data contoured by experts, with however a different approach than statistical models [83–86]. According to the database information, a classifier is trained to distinguish the objects of interest into classes using appropriate features. In practice, parts of an image are then classified by selecting regions of different sizes in the image in different positions and determining its class following a coarse-to-fine scheme. Though the training procedure is extremely time consuming, the detection can be very fast. Classification approaches suffer from the same disadvantage as statistical models due to its dependency on the original database. However, even larger datasets are typically needed then for statistical models.

Finally, tracking approaches are the most different from the other approaches as they do not aim at the border detection itself but at the estimation of the motion of an object throughout time. Thus, tracking approaches have a more dynamic nature. Since tracking approaches are mostly dependent on image information such as pixel intensity, the results can be especially sensitive to the presence of artifacts. This makes the introduction of information such as cardiac motion patterns particularly interesting. The existing tracking approaches are usually based on either registration or speckle tracking. In registration approaches the spatial correspondence between sequential images is found by measuring and optimizing a measure of similarity between them [64,87–90]. Speckle tracking approaches aim at finding a correspondence between speckle patterns throughout time [91–99].

4. CARDIAC CHAMBER VOLUME ASSESSMENT USING 3D ULTRASOUND

4.1. Left Ventricle

4.1.1. Available Technology

Accurate volume measurements require precise delineation of the LV endocardial border over the entire cardiac cycle. Nonetheless, manual delineation of these boundaries in 3D data is a cumbersome and time-consuming task, making the introduction of this approach in clinical routine impractical. Hereto, several software packages have been introduced to aid the clinician in this contouring process by providing some form of automation.

Tomtec Imaging Systems (Unterschleissheim, Germany) was the first company presenting commercial tools for 3D volume quantification, taking advantage of its expertise on image processing and visualization. Their current product, TomTec 4D LV-Analysis©, performs an automatic orientation of the LV longitudinal axis to display three apical and three short axis views. If necessary, these can be adjusted by the user to avoid foreshortening and modify the aortic valve landmark orientation. The entire 3D endocardial surface of the left ventricle is then contoured by the software in end-systole and, using 3D speckle tracking, propagated throughout the heart cycle [100]. This same tool is also available under TomTec's software solution 4D LV-Function™.

Contrarily to the purely offline approach offered by TomTec, Philips Healthcare (Best, Netherlands) introduced the possibility of both offline and online analysis with their QLAB – 3DQ Advance (3DQA) software suit [101,102]. First, the longitudinal axes must be aligned in the 4-chamber and 2-chamber views at the end-diastolic phase. Five anatomical landmarks must then be marked, which are used to initialize a deformable shell model [62]. This model is afterwards deformed towards the LV boundaries, with the option for manual correction. The same process must be completed for the end-systolic phase [102]. Philips Healthcare is currently preparing to introduce a new commercial tool, HeartModel^{AI}, which will be available on their EPIQ7 system and should be released by August 2015. The HeartModel^{AI} is a fully automatic knowledge-based model which detects end-diastolic and end-systolic instances, performs localization and tracking of the four chambers and also alignment of the apical 4-, 3- and 2-chamber views [103]. Refinement of the results is also possible through manual correction of the contours. The tool returns then the LV and LA volumes at end-systole and end-diastole.

More recently, also General Electric (GE Vingmed, Horten, Norway) introduced a software package, 4D AutoLVQ, which allows both fully or semi-automated segmentation and volume quantification of the left ventricle [100]. In this product, an initial alignment of the axis is needed so as to avoid foreshortening. This can be performed either automatically or manually by pivoting and translating the planes. In the semi-automatic version, the user is required to mark the location of the apex and the mitral annulus at end-diastole and end-systole. After this, the 3D endocardial surface is automatically detected at these instances. In the fully automatic version no initialization points are required. After the conclusion of the segmentation the user is allowed to manually edit the contours.

Toshiba Medical Systems (Tokyo, Japan) has entered the RT3DE realm with its Artida™ system, which was complemented with a software tool for chamber quantification by 3D echocardiography speckle tracking, 3D Wall Motion Tracking (3D-WMT) [102,104,105]. This computational platform performs an automatic selection of apical 4-chamber and 2-chamber views, as well as 3 short-axis views at different LV levels. The user is then required to place six markers: at the edge of the mitral valve and at the apex in each of the apical planes. These points are then used to automatically segment the endocardium. The epicardial contour is defined either by a predetermined thickness or through manual contouring. The final shape of the left ventricle can then be corrected manually by the user. A 3-dimensional block matching algorithm [106] is then used to track the wall motion throughout the cardiac cycle in a fully automatic manner.

The development of a fully automatic image analysis software package has been one of the main strategic investments of Siemens Medical Solutions (Mountain View, California) while developing their Acuson SC2000™ RT3DE system, resulting in the software tool eSie LVA™ [107]. This tool is based on a comprehensive database of manually annotated RT3DE exams (over 4000) covering both healthy and typical pathological cases in clinical practice. The offline learning process was performed using a Probabilistic Boosting Tree [108] to obtain the final classifier. Given an input volume, this classifier sequentially estimates position, position-orientation and full similarity to locate the object and finally performs both an orientation according to standard planes [86] and also the contouring of the LV using boundary detectors [109] and statistical shape models. The final endocardial contours can be refined by the user through manual correction.

4.1.2. Validation Efforts

The enthusiasm generated in the medical community by 2D matrix transducers and RT3DE is well demonstrated by the numerous validation studies for this imaging modality over the past decade. Although validation on other experimental setups has been done (e.g. water balloons of known volume [110], intracavity balloon measurement in canine models [111], in vitro porcine heart models [112]), the primary and more generalized validation route for the existing software suites for volumetric measurement is to perform direct comparison of the volumetric indices extracted from RT3DE exams against reference values extracted from cMRI, which remains the generally accepted gold standard method for volumetric assessment of cardiac chamber dimensions. Alternatively, some studies report a direct comparison between automated vs. manual contouring of RT3DE data, thus providing insight on the ability of automating the contouring process. The most relevant studies are summarized in this sub-section and Table 1 provides an overview of the corresponding main results. Figure 2 shows an example of LV segmentation in 3D echocardiography data.

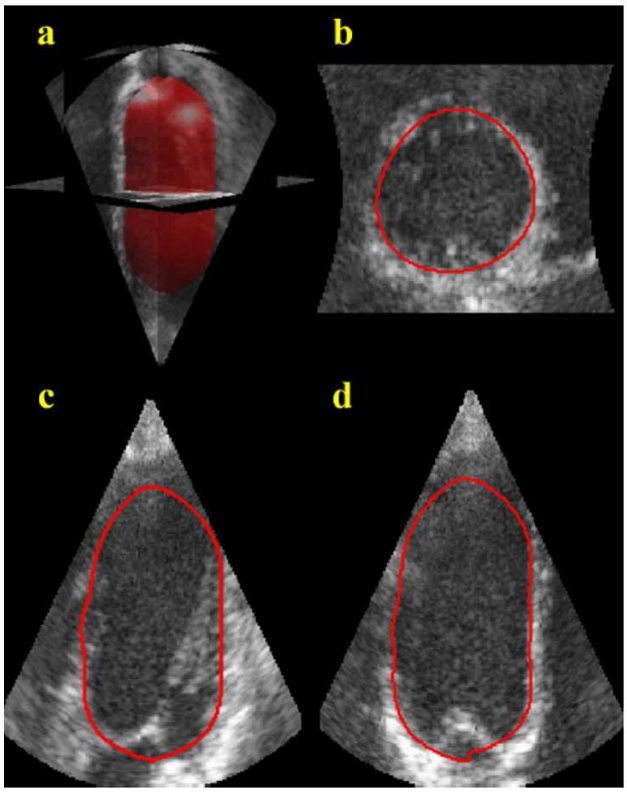

Figure 2. Example of LV segmentation in 3D echocardiography data obtained through a semi-automatic method. a: triplane-view and 3D rendering; b: short-axis view; c and d: long axis views. Reproduced from [67].

The earlier studies focused on software tools which relied mostly on a computer-assisted 3D manual contouring paradigm, either requiring manual delineation of the endocardial boundary in several long axis planes or requiring significant user input in semi-automatic segmentation algorithms. The performance of the pioneer Volumetrics system has been analyzed by both Schimdt et. al [113] and Lee et al. [114]. Both studies found excellent correlation between cMRI-derived volumetric indices and the ones extracted from RT3DE data by manually contouring in different azimuthally equidistant long axis images. Note that Kühl et al. had already demonstrated that the truly 3D nature of RT3DE data enabled long-axis contouring in contrast to the short-axis, sum-of-disk approaches initially inherited from cMRI [115]. Mannaerts et al. performed a similar study with an ATL® HDI 5000 system and manually contouring the endocardium using one of the first TomTec tools, Echo-View. Mannaerts et al. reported good correlation as well as the first evidence of a negative bias of 3D echocardiographic volumes with respect to cMRI [116]. Kühl et al. performed

the first clinical validation on the second generation of 2D (i.e. fully sampled) matrix transducers, showing excellent correlation against cMRI, in a cohort of 24 good image quality patients [117]. In this study, a manual contouring paradigm was compared against an early semi-automatic algorithm, showing that the tested semi-automated approach enabled full 4D delineation but required longer analysis times and showed larger bias and wider limits of agreement. Jenkins et al. have further validated the same system in a larger study (#=50) using a semi-automatic approach provided in an earlier version of TomTec's 4D LV-Analysis© [118]. The tool required the placement of landmarks in 12 azimuthally equidistant long axis views which were used to fit an ellipse to the endocardial borders. This was then followed by manual refinement. In addition to low bias and acceptable limits of agreement, RT3DE showed lower test-retest and intra/inter-observer variability than its 2D counterpart. The same semi-automatic approach was validated by Sugeng et al. with excellent correlation against cMRI and low bias though with wider limits of agreement [119]. Van den Bosch et al. have carried out the first clinical validation of RT3DE-derived LV volumes in congenital heart disease patients, whose challenging cardiac shapes had been previously reported as a difficulty [120]. Their results show excellent correlation/agreement for LV volumetric analysis using a fully manual contouring approach. However, when applying the same semi-automatic contouring software tool as used in [118], the results highlighted that this tool relied too much on a purely elliptical shape prior, thus having a poor performance. Despite the strong resilience of the multi-planar contouring paradigm in the early clinical validation, a more 3D-oriented vision has been introduced with the algorithm proposed by Corsi et al. [73], which was further validated by Caiani et al. in a clinical setting [76].

Jacobs et al. have been the first to validate the concept of rapid, online measurement of LV volumes from RT3DE data [101], using the tool provided by Philips, QLAB – 3DQA. Indeed, online volumetric analysis within the imaging system without the need to export data to an external computer for tracing and 3D reconstruction further reduces time load. Very strong correlation and acceptable limits of agreement were found for all volumetric indices, despite the significant bias for EDV and ESV. Additionally, the comparison between the volumetric indices extracted online correlated strongly and had good agreement against the offline semi-automatic contouring approach proposed in [117]. Nonetheless, in a study by Jenkins et al., the offline approach by TomTec was compared to Philips' QLAB – 3DQA showing that offline approaches remain superior to the online quantification of LV volumetric indices, at the expense of longer analysis times [121]. A similar study was conducted by Soliman et al. using a newer version of TomTec's 4D LV-Analysis© in which only the manual contouring of three orthogonal planes is needed and similar results as those by Jenkins et al were obtained [122]. In a different study by Soliman et al., two different versions of TomTec's 4D LV-Analysis© are compared to volumes obtained through cMRI showing strong correlation for both methods and a clear superiority of the newer version dependent on full volume reconstruction [123].

Despite the convincing results of the previous validation studies, a clearer understanding of possible sources of errors was required for optimal clinical usage. To this end, Mor-Avi et al. have studied the source of variation between volumetric indices measured with RT3DE and cMRI, showing that the fundamental difference is the inability of RT3DE to resolve the separation between trabeculae and myocardium. Indeed, including the trabecular region outside of the blood pool during cMRI contouring in the blood pool significantly reduced the RT3DE vs. cMRI bias, as well as the limits of agreement [110]. This fact sums up with the blurring effect caused by the PSF of the acquired ultrasound signal, which pushes the apparent blood-tissue interface towards the blood pool, as shown by Mor-Avi et al. in balloon phantoms.

More recently, a shift towards more advanced software suites has enabled more automated analysis of RT3DE data, allowing a more efficient workflow towards the extraction of clinically relevant information from RT3DE data. Indeed, the previously cited studies have mostly focused on semi-automatic software tools that provide at most computer-aided manual delineation of the LV cavity. Typical time of analysis ranged from around 2 min. [101] to 10 min. [76,118], although several studies report analysis times around 5 min per dataset [110,122]. Note that Jacobs et al. have shown that online LV volumetric analysis can provide accurate results in less than 2 minutes per volume [101] but they stress that manual adjustments were required in 42% of the analyzed cases using an online quantification tool, increasing the analysis time from 2 minutes to up to 5 minutes per volume.

With this in mind, strong research effort has been directed towards more efficient software packages, incorporating advanced computer algorithms enabling a faster, more efficient and more accurate processing of RT3DE volumes. Hansegard et al. [124] and Muraru et al. [125] used GE's AutoLVQ and TomTec's 4D LV-Analysis© to show that a more advanced, automated software package can reduce the average time of analysis when compared with standard semi-automated strategies, while keeping comparable accuracy. Muraru et al. [125] has equally shown that fully automated (i.e. only manual initialization on ED and ES frames, with subsequent automatic delineation) is feasible. However, their results show that a noticeable increased agreement can be achieved by manually adjusting the results from an automated method, at the cost of doubling the total analysis time. Kleijn et al. have validated another highly automated software tool, Toshiba's 3D-WMT [126]. Despite only moderately good results for the LV volume assessment, the EF results showed excellent correlation and remarkably low bias and limits of agreement, indicating that more advanced tracking methods can positively influence the quality of the extracted surfaces when compared to pure contour-extraction approaches. Similar results have been reported by Kawamura et al. [105]. To test the potential of RT3DE in a realistic clinical scenario, Miller et al. analyzed 60 consecutive patients to determine the effect of image quality in RT3DE volume quantification performance [127]. Despite reporting lower agreement with cMRI measurements than previously found, the authors stress that the degree of error is intrinsically linked with image quality.

Using Siemens' eSie LVA^{TM} tool, Thavendiranathan et al. demonstrated that fully automatic analysis of RT3DE is possible and presents extremely encouraging results [128]. Note that Thavendiranathan et al. point out that the patients undergoing RT3DE exams in the analyzed dataset were selected for good acoustical windows, thus holding good imaging quality. The authors have applied the same computational automatic analysis algorithm to the reconstructed cMRI datasets and have found slightly higher bias and limits of agreement against the manual delineation on cMRI data than when using the same software on RT3DE data (-0.8±4.7% vs. -0.3±2.5%). This seems to point towards the excellent image quality of the analyzed RT3DE dataset. Similar results have also been published by Zhang et al. [129]. Using the same tool, Chang et al. [130] reported slightly lower correlations and the Bland-Altman analysis on EF estimates revealed much larger bias and limits of agreement than reported by Thavendiranathan et al. in [128]. Nonetheless, it is important to stress that the dataset corresponded to consecutive patients, although previously selected based on 2D echo image quality and the user was allowed to manually correct the automatically detected contours. It should also be noticed that Chang et al. report that automatic results were considered excellent in 11% of the cases (i.e. not requiring any adjustment), good (i.e. five or fewer manual corrections required) in 34% of the cases and it failed completely (i.e. required manual delineation) in 10% of the cases. Regarding the influence of manual correction, Shibayama et al. have evaluated the same system, performing firstly fully automatic analysis and then allowing the user to proceed to manual corrections, in a cohort of 44 consecutive patients [131]. Their results reinforce the findings of Muraru et al. for a different system, thus highlighting that even state-of-the-art software packages are not yet able to consistently perform fully automated/automatic analysis of RT3DE data. Indeed, Shibayama et al. show that fully automatic results are significantly improved through manual interaction. Nonetheless, manual correction increased the total analysis time by a factor of 10. Using Philips' HeartModel^{AI} tool, Tsang et al. have analyzed 46 patients achieving similar results to those reported with other fully automatic approaches without performing manual correction of the contours [132].

The key summary of the literature on the clinical validation of RT3DE volumetric assessment against cMRI can also be appreciated in the recent meta-analysis studies of Shimada and Shiota [133] and by Dorosz et al. [134]. Shimada and Shiota's meta-analysis included 3055 subjects in 95 studies, focusing not only on 2D matrix transducers but also earlier systems based on mechanical steering. A key evidence is the significant underestimation bias of left ventricular volumes (both EDV and ESV) by RT3DE compared with cMRI. On the other hand, no statistically significant bias for estimation of EF was found. Sources of error included gender and presence of congenital heart disease, which were associated with more underestimation in the analysis. Semi-automatic border detection and the use of matrix-array transducers were associated with less underestimation. As key conclusion, the studied literature supports the role of RT3DE as both accurate and reproducible in assessing left ventricular volumes and EF, although it is not interchangeable with other radiologic modalities. On the meta-analysis study by Dorosz et al., also an additional perspective on how RT3DE compares with conventional 2D echocardiography is given in parallel to the central comparison of RT3DE-derived volumetric indices against cMRI. Their main conclusion is that RT3DE underestimates volumes and has wide limits of agreement, but compared with traditional 2D methods, it is more accurate (i.e. smaller bias) for volumes (EDV and ESV) and more precise (i.e. tighter limits of agreement) for EDV, ESV and EF measurements. One of the key benefits of RT3DE is the reduction in intra/interobserver variability, which is important for clinical practice, since disease progression in a patient will be most likely assessed serially by different readers. Dorosz et al. also highlight the natural influence of image quality on the estimation of LV volumetric indices. Indeed, an analysis of those studies that accepted all 3D datasets, instead of selecting patients for image quality, shows that the 95% limits of agreement against cMRI raise from ±34 to ±38ml for EDV, ±30 to ±34ml for ESV and ±12 to ±15% for EF.

At last, the first step towards effective clinical integration of 3D echo volume measurements is the population-based assessment of normal values, as acknowledged recently by Marwick in the editorial note of a leading cardiovascular imaging journal [135]. Several studies, including the work of Aune et al. [136], Kaku et al. [137], Fukuda et al. [138], Chahal et al. [139] and Muraru et al. [140], have been filling this gap, providing clinicians one of the last pieces of the path towards clinical integration of RT3DE examination in daily routine. An ongoing large-scale project (EchoNoRMAL) is aiming to define the echocardiographic normal ranges of the LV, through a collaborative effort meta-analysis approach [141,142].

4.2. Left Atrium

4.2.1. Available Technology

Given the low priority given to LA volume and function assessment, the solutions dedicated to LA segmentation are limited. TomTec was the first to commercialize a dedicated tool: 4D LA-Analysis©. Similarly to an earlier version of TomTec's 4D LV-Analysis©, the user is asked to manually contour the endocardium in three different views (2-, 3- and 4-chamber) at both ED and ES frames. A polyhedral mesh is then generated for each of those frames by volumetric interpolation of the 2D contours and temporal smoothing is performed, resulting in a smooth volume curve for the whole cardiac cycle. The mesh volume calculation excludes the mitral valve tenting volume, whose limit is that defined by the mitral valve points introduced by the user. The user can also manually adjust the segmentation results [143,144]. This same tool is also available under TomTec's software solution 4D LA-Function©.

Until recently, no other dedicated tool was available besides TomTec's. Philips' fully automatic HeartModel^{AI} tool, released on August 2015, will change that, as it also provides LA volumes besides LV (cf. Section 4.1.1.) [103].

Table 1. Literature Overview: Validation of RT3DE and commercial software tools for LV volumetric assessment (#: number of exams; Ref: reference measurements taken from cMRI or manual contouring of RT3DE data (3DM); r: correlation coefficient; BA Bland-Altman analysis).

Study	Imaging System	Analysis system	User input	#	Ref	Time (s)	r			BA (μ±2σ)		
							EDV	ESV	EF	EDV	ESV	EF
Schimdt et al., 1999 [113]	Volumetrics	-	A(NR)	25	cMRI	120-180	0.88	0.82	NR	NR	NR	NR
Lee et al., 2001 [114]	Volumetrics	-	A(7)	25	cMRI	NR	0.99	0.99	0.92	NR	NR	NR
Mannaerts et al., 2003 [116]	ATL® HDI 5000+P4	TomTec EchoView4.2	A(9)	28	cMRI	1200-1800	0.79	0.90	0.87	-27.9±45.7	-34.4±45.5	1.2±15.8
Kühl et al., 2004 [117]	Sonos 7500+X4	-	C(24.2)	24	cMRI	720±300	0.98	0.98	0.98	-13.6±37.8	-12.8±41	0.9±8.8
Kühl et al., 2004 [117]	Sonos 7500+X4	-	C(24.2)	24	3DM	720±300	0.99	0.99	0.98	-1.3±17.2	-0.2±10.8	-0.1±5.4
Jenkins et al., 2004 [118]	Sonos 7500+X4	TomTec 4DLVA	C(36.2)+R	50	cMRI	630±60	NR	NR	NR	-4±58	-3±36	0±14
Caiani et al., 2005 [76]	Sonos 7500+X4	-	B(4)+R	44	cMRI	~300	0.97	0.97	0.93	-4.1±30	-3.5±34	-0.8±14
Bosch et al., 2006 [120]	Sonos 7500+X4	TomTec EchoView5.2	A(8)	29	cMRI	1020±300	0.97	0.98	0.94	-2.9±12	0.9±9.9	-1.4±7.2
Bosch et al., 2006 [120]	Sonos 7500+X4	TomTec 4DLVA 1.2	C(24.2)	29	cMRI	360±120	0.79	0.84	0.54	NR	NR	NR
Jacobs et al., 2006 [101]	Sonos 7500+X4	QLAB - 3DQA	C(5.2)+R	50	cMRI	120-420	0.96	0.97	0.93	-14±34	-6.5±32	-1±12.8
Jenkins et al., 2006 [121]	Sonos 7500+X4	TomTec 4DLVA	C(36.2)+R	110	cMRI	630±60	0.86	0.91	0.81	-15±56	-10±44	1±16
Jenkins et al., 2006 [121]	Sonos 7500+X4	QLAB - 3DQA	C(5.2)+R	110	cMRI	240±20	0.78	0.86	0.64	-44±70	-21±56	-2±20
Sugeng et al., 2006 [119]	Sonos 7500+X4	TomTec 4DLVA	C(18.2)+R	31	cMRI	NR	0.97	0.96	0.96	-5±53	-6±53	0.3±8
Soliman et al., 2007 [122]	Sonos 7500+X4	TomTec 4DLVA 2.0	B(3)+R	41	cMRI	360±120	0.99	0.99	0.98	-9.4±8.9	-4.8±10.1	0.3±4.7
Soliman et al., 2007 [122]	Sonos 7500+X4	QLAB - 3DQA	C(5.2)+R	41	cMRI	240±20	0.99	0.98	0.97	-16.4±13.4	-8.5±14.2	0.7±6.3
Soliman et al., 2007 [123]	Sonos 7500+X4	TomTec 4DLVA 1.2	C(24.2)+R	53	cMRI	900±300	0.96	0.98	0.95	-24.0±9.4	-11.3±17.2	0.8±6.4
Soliman et al., 2007 [123]	Sonos 7500+X4	TomTec 4DLVA 2.0	B(3)+R	53	cMRI	360±120	0.99	0.99	0.98	-9.9±8.4	-5.0±9.6	0.6±4.8
Mor-Avi et al., 2008 [110]	iE33+X3-1	QLAB - 3DQA	C(5.2)+R	92	cMRI	~300	0.91	0.92	0.81	-67±92	-41±92	-3±22
Muraru et al., 2010 [125]	Vivid7+3V	4D AutoLVQ	C(9.2)	23	cMRI	48±24	0.77	0.72	0.64	-32.3±43.6	-13.9±30.7	-1.5±12.8
Muraru et al., 2010 [125]	Vivid7+3V	4D AutoLVQ	C(9.2)+R	23	cMRI	112±30	0.93	0.95	0.85	-11.0±24.2	-9.1±14.2	-2.9±8.4
Muraru et al., 2010 [125]	Vivid7+3V	TomTec 4DLVA 2.0	B(3)+R	23	cMRI	226±84	0.96	0.94	0.85	-8±19	-7±13	2.8±8.4
Chang et al., 2011 [130]	SC2000+4Z1c	eSie LVA™	D+R	91	cMRI	NR	0.91	0.94	0.91	-41.38±37.2	-7.91±33.7	-8.26±13.0
Thavendiranathan et al., 2012 [128]	SC2000+4Z1c	eSie LVA™	D	91	cMRI	30-60	0.90	0.96	0.98	-17.6±53.4	-9.8±35.8	-0.3±5.0
Kleijn et al., 2012 [126]	Artida4D+PST-25SX	3D-WMT	C(5.2)	45	cMRI	~300 (w/ acq.)	0.75	0.81	0.91	-34±50	-13±22	-0.6±2.4
Miller et al., 2012 [127]	iE33+X3-1	QLAB - 3DQA	C(5.2)+R	42	cMRI	306±60	0.83	0.84	0.77	-45±70	-11±48	-7±18
Shibayama et al., 2013 [131]	SC2000+4Z1c	eSie LVA™	D	41	cMRI	36±8	0.80	0.85	0.54	-22.2±73.0	-18±64.2	1.2±23.3
Shibayama et al., 2013 [131]	SC2000+4Z1c	eSie LVA™	D+R	41	cMRI	371±116	0.96	0.97	0.9	-4.4±34.9	-5±27.7	0.9±15.2
Tsang et al., 2013 [132]	X5-1	HeartModel^{AI}	D	46	cMRI	<5	0.89	0.94	0.93	-35.05±90.34	-24.95±86.84	0.55±11.62
Zhang et al.,2013 [129]	SC2000	eSie LVA™	D	60	cMRI	NR	0.89	0.93	0.71	-3.5±43.5	-0.07±33.2	-2.7±15.7
Kawamura et al., 2014 [105]	Artida	3D-WMT	C(5.2)+R	64	cMRI	NR	0.86	0.85	0.74	-19.0±76.5	-10.1±70.4	-0.3±13.1

User input: A(X): Computer assisted delineation of the 3D surface via manual contouring of X 2D planes; B(X): Semi-automatic segmentation, with manual initialization by contouring in X 2D planes; C(L,F): Automated segmentation, with user input of L anatomical landmarks in F time frames; D: Fully automatic segmentation without any user intervention; R: Manual refinement of segmentation results.

Apart from these tools, other LA quantification solutions still rely on the use of generic tools, primarily designed for LV volumetric quantification. With this regard, the use of QLAB – 3DQA (Philips) [102,145,146], and 3D-WMT (Toshiba) [102], and eSie LVA^{TM} (Siemens) [147] for quantification of LA volume has been reported. The description of aforementioned tools can be found in Section 4.1.1.. The current eSie LVA^{TM} fully automated solution is based on the database-driven knowledge-based approach, which relies on learned features from LV shape, appearance and motion. As such, it seems to not be suited for LA volume analysis. However, a semi-automated version was available and has been used for LA volume assessment [147].

4.2.2. Validation Efforts

The recent efforts towards clinical validation of 3D echocardiographic assessment of LA volumes have been reflected in the latest Recommendations for Chamber Quantification [148]. A summary of the validation studies found in literature are presented in this section and Table 2 presents the corresponding results. Figure 3 shows an LA segmentation example on a 3D echocardiography image.

To et al. [6] address the strengths and weaknesses of different imaging modalities (2D and 3D echocardiography, cMRI and CT) in the assessment of LA morphology and function. In this review, 3D echocardiography is considered comparable to the other modalities regarding the estimation of static dimensions, and superior in the estimation of phasic size, and LA mechanics. In addition, the authors note the current indications of echocardiography for LA assessment (first-line diagnostic evaluation and follow-up) and other potential indications (serial monitoring and detailed functional assessment of LA phasic function).

Miyasaka et al. [145] demonstrated the added value of 3D echocardiography to derive LA volumes, in a study including 57 patients, with multi-detector CT as gold-standard. The volume underestimation typically observed in echocardiographic measurements was significantly lower for LAmax volumes derived from 3D echocardiography, compared to those estimated from 2D echocardiography. Rohner et al. conducted a similar study using TomTec's 4D LA-Function© also showing good correlation between CT and RT3DE values [149]. The underestimation of volumes was in this study, however, much larger. A multicenter study (92 patients with a large range of LA volumes) conducted by Mor-Avi et al. [143] showed that LAmin and LAmax volumes from 3D echocardiography also correlate better with cMRI, compared to 2D. Moreover, statistically significant underestimation of volumes was observed on 2D and not on 3D measurements. In the same study, 3D echocardiography also improved classification of enlarged atria, while intra- and inter-observer variability was similar. The volumetric measurements reported in this study were obtained using the semi-automated 4D LA-Function© tool (Tomtec).

An extensive analysis of different techniques to derive LA volumes from echocardiography (both 2D and 3D) is presented in [146], including data from 60 patients. The 3D images were analyzed with two semi-automatic tools: TomTec's 4D LA-Analysis© and Philips' QLAB – 3DQA, which was built primarily for LV segmentation. Although all volumes derived from echocardiography were underestimated compared to cMRI, reported bias ranged from -50.5% down to -4.7% across the different techniques. The following techniques estimated LAmax and LAmin volumes with increasing accuracy (sorted from the highest to the lowest bias): 2D prolate ellipsoid method; 3D semi-automated generic tool (QLAB – 3DQA); 2D area-length method; 2D bi-plane Simpson method; 3D manual specific tool (4D LA-Analysis©). These results suggest that, despite the previously shown importance of 3D data, the accuracy may vary significantly depending on the methodology (semi-automated vs. manual or generic vs. LA-specific tools).

Another study using a generic semi-automated tool, eSie LVA^{TM}, to assess LA volumes from 3DE shows alarmingly inaccurate results [147]. It must be noted however that this study included only atrial fibrillation patients, which are typically more challenging to image and analyze, and that this tool was primarily designed for LV segmentation. Therefore, image quality played a very important role on such results (poor correlation with CT for both 2D and 3D echocardiography measurements). Nonetheless, LA volume was also significantly underestimated in a sub-group of recordings with good image quality (-44% for 2DE and -21% for 3DE).

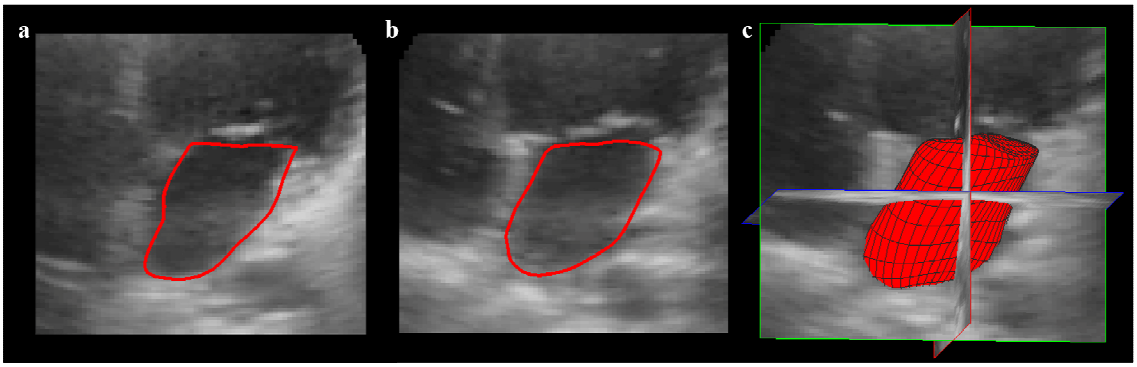

Figure 3. LA segmentation example in a 3D echocardiography image using a semi-automated algorithm [150]. a and b: long axis views; c: triplane-view and 3D rendering.

Finally, a comparison between two standard echo-analysis tools, QLAB – 3DQA (Philips) and 3D-WMT (Toshiba), was performed in a large study including 120 subjects (both unselected patients and healthy volunteers) [102]. The results were in close agreement for both LAmax and LAmin, and showed equally good inter- and intra-user reproducibility, suggesting its interchangeability. It should be noted however that this refers only to the comparison of echo-based measurements, without an independent modality as reference.

The use of LA-specific fully automatic tools has been reported in a single validation study by Tsang et al. using Philips' HeartModel^{AI} tool. The results are promising, showing good correlation with volumes obtained from cMRI though somewhat below the performance reported for other LA dedicated semi-automatic tools [132].

In summary, echocardiography is a reliable modality for LA volume assessment (albeit its typical underestimation compared to CT or cMRI). Volume measurements from 3D echocardiography are consistently more accurate and less user-dependent than those from 2D as pointed out in the recommendations by Lang et al. [148]. Image quality and LA-specificity of automated tools are important factors influencing the reliability of the measurements. LA phasic function assessment from 3D echocardiography still lacks validation, despite having been used in some clinical studies.

Table 2. Literature Overview: Validation of RT3DE and commercial software tools for LA volumetric assessment (#: number of exams; Ref: reference measurements taken from cMRI or manual contouring of RT3DE data (3DM); r: correlation coefficient; BA Bland-Altman analysis).

Study	Imaging System	Analysis system	User input	#	Ref	Time (s)	r			BA (μ±2σ)		
							LAmax	LAmin	EF	LAmax	LAmin	EF
Miyasaka et al., 2011 [145]	iE33+X3-1	QLAB - 3DQA	C(5,2)+R	57	CT	300-600	0,95	NR	NR	-2.5±3.6	NR	NR
Rohner et al., 2011 [149]	iE33+X3-1	TomTec 4DLAF	B(3)	34	CT	NR	0.92	0.95	0.82	-24.8±40.6	-25.2±39.0	8.6±18.4
Mor-Avi et al., 2012 [143]	iE33+X3-1	TomTec 4DLAF	B(3)	92	cMRI	NR	0.93	0.88	NR	-1±28	0±43	NR
Buechel et al., 2013 [144]	iE33+X3-1/X5-1	TomTec 4DLAA	B(3)	55	cMRI	NR	0.93	0.95	0.92	-7.2±21.8	-7.2±20.0	1.8±17.7
Buechel et al., 2013 [146]	iE33+X3-1/X5-1	TomTec 4DLAA	B(3)	60	cMRI	161±29	0.94	0.95	NR	-5±24	-6.5±20	NR
Buechel et al., 2013 [146]	iE33+X3-1/X5-1	QLAB - 3DQA	C(5,2)+R	60	cMRI	144±19	0.80	0.90	NR	-17±33	-11±27	NR
Tsang et al., 2013 [132]	X5-1	HeartModel^{AI}	D	46	cMRI	<5	0.91	NR	NR	-10.26±32.30	NR	NR
Heo et al., 2014 [147]	SC2000	eSie LVA^{TM}	NR	31	CT	NR	0.23	NR	NR	NR	NR	NR

User input: A(X): Computer assisted delineation of the 3D surface via manual contouring of X 2D planes; B(X): Semi-automatic segmentation, with manual initialization by contouring in X 2D planes; C(L,F): Automated segmentation, with user input of L anatomical landmarks in F time frames; D: Fully automatic segmentation without any user intervention; R: Manual refinement of segmentation results.

4.3. Right Ventricle

4.3.1. Available Technology

Recently, Tomtec Imaging Systems (Unterschleissheim, Germany) has made available an offline tool for semi-automatic RV function assessment, 4D RV-Function© [151]. Firstly, the correct anatomical axis must be defined by the user and landmarks placed in both the tricuspid and mitral valves and the apex. The end-diastolic and end-systolic phases must then be identified and the endocardial borders manually contoured on the 4-chamber, sagittal and coronal views on both phases. The software then automatically delineates the RV endocardial border along the heart cycle. The results can be refined by the user at the end of this step. A number of measurement values are then available for the user namely 3D volume measurements (RV EDV, ESV, EF and SV), strain analysis and 2D standard measurements [151]. Both GE Vingmed and Siemens Medical Solutions have recently made this tool available in their systems thanks to a strategic cooperation with TomTec Imaging Systems. Figure 4 shows an in-program screenshot of 4D RV-Function© in the contour revision step.

Ventripoint Diagnostics Ltd. (Bellevue, United States) has introduced the Ventripoint Medical System^{TM} [152]. This system relies on a 3D RV reconstruction from a freehand acquisition using a standard 2D probe with a magnetic localizing system. After acquisition of sufficient 2D planes for a good coverage of the RV (10 to 15 views) the end-diastolic phase is automatically defined according to the electrocardiographic R wave and the end-systolic phase is defined manually by the user. An offline analysis is then required, namely the identification of anatomic landmarks (ideally 17 to 23 points) after which a database of 3D RV shapes is used to define the RV shape using a piecewise smooth subdivision surface reconstruction [152].

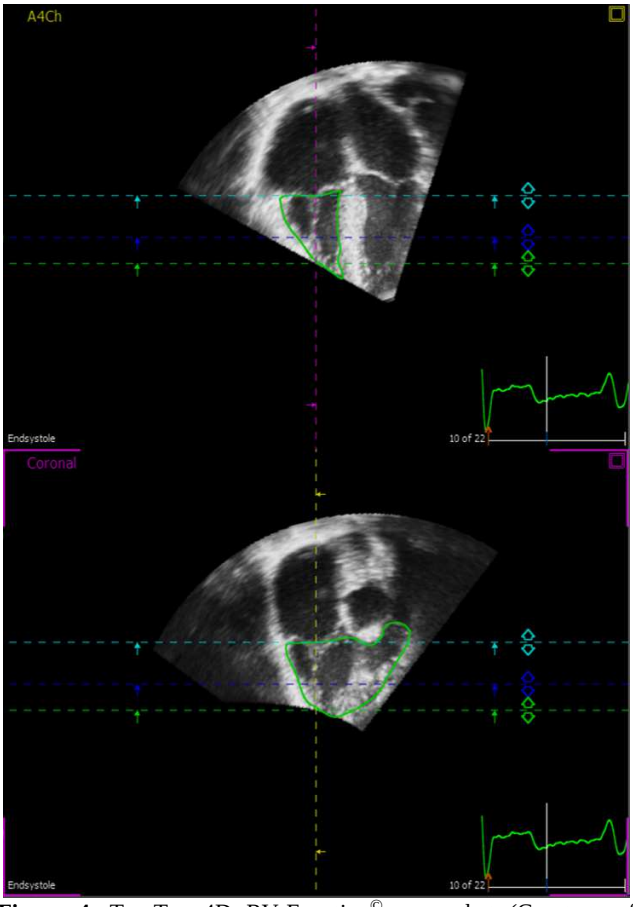

Figure 4. TomTec 4D RV-Function© screenshot (Courtesy of Guido Claessen, Laboratory on Cardiovascular Imaging and Dynamics, KU Leuven, Belgium).

4.3.2. Validation Efforts

Though the importance of assessing RV function assessment has long been recognized, the lack of literature found for RV segmentation in echocardiography is striking, especially when compared to the extensive literature found for the LV. This can be justified by a series of different factors. First of all, the very acquisition of the RV is often quite challenging in 3DTE due to its position and shape [153]. The sternum and lung tissue can shadow the imaging of the RV anterior wall and outflow tract and an attempt to avoid this shadowing frequently results in part of the anterior wall not being included in the field of view [154]. Secondly, the anatomical complexity and asymmetric shape of the RV make an automatic segmentation an extremely challenging task. The heavy trabeculation found in the RV and the thin myocardial wall can also increase the difficulty when assessing the volume [155]. Finally, the perceived greater importance of the left heart has forced most research to be directed towards LV and LA segmentation, thus demoting RV analysis to a field of study of lesser importance. In this section some of the studies focused on the validation of RV volume assessment by 3D echocardiography are summarized and Table 3 show the corresponding results.

The first efforts for RV volume/function assessment were, of course, developed for 2D echocardiography. An example of this is the tricuspid annular plane systolic excursion (TAPSE) introduced by Kaul et al. [156]. This measure extracted from a 4-chamber view is shown to correlate to RV volumes obtained from radionuclide angiography and is still common in today's clinical practice [148]. Nevertheless, Helbing et al. have shown, by comparison with cMRI volumes, that due to the asymmetrical shape of the RV, 2D echocardiography is not sufficient to assess the RV volumes [157]. Gopal et al. go a step further by comparing volumes assessed through manual contouring of 3DTE images of the RV with 2D estimated volumes and volumes determined by cMRI, concluding that 3D echocardiography is superior to 2D for RV volume assessment [158]. Two studies, by Jenkins et al. and van der Zwaan et al., compare once more 2D and 3D echocardiography to cMRI for RV volume assessment though now using 4D RV-Function© to determine the 3D RV volumes [159,160]. Both studies are in agreement that RT3DE not only is superior to the two-dimensional methods but also has a greater reproducibility. A single study by Kjaergaard et al. claims that 3D echocardiography brings no advantage from 2D when compared to cMRI assessed volumes [161]. Later studies however propose that this conclusion is merely a result of the older 3D echocardiographic platform used and the population chosen [160].

In a compromise between 2D and 3D echocardiography, some authors have used 3D reconstruction of 2D echocardiographic planes to image the whole shape of the RV. Linker et al. have used 3D reconstruction of 2D images of ex vivo hearts to manually contour the RV endocardium [162]. This was shown to correlate with the reference volume obtained by measuring the volume of water required to fill the RV. The 3D reconstruction system commercialized by Ventripoint Diagnostics Ltd. is compared in two clinical studies to RV volumes obtained by cMRI showing a good correlation between the two [152,163].

The accuracy of manual contouring of the RV in the 3D echocardiography has been validated in a number of different frameworks but the gold standard for RV volume assessment remains cMRI. Some of the approaches include models from excised animal or human hearts [37,164–168], in vivo measurement by intracavity balloon [169], thermodilution [170] and intraoperative measurements using injections of saline solution [171]. Comparisons of manual contouring of the RV in 3D echocardiography are also numerous. The first effort for validation of RV manual contouring against cMRI was conducted by Vogel et al. using a rotating one-dimensional array probe and performing manual contouring in parallel planes along the long axis [172]. Similar studies were published by Fujimoto et al. [173] and Papavassiliou et al. [174] all with good correlation values between 3D echocardiography and cMRI. Prakasa et al. performed the first validation of RV manual contouring in full matrix transducer imaging using both a Sonos 7500 and a Philips iE33 [175]. The manual contouring was performed in only two orthogonal long axes planes which accounts for the low correlation values obtained and large bias, especially for EDV. In a study by Nesser et al., RV manual contouring was compared to cMRI in both transthoracic (TTE) and transesophageal (TEE) acquisitions [176]. Manual contouring was done in this study in 10 to 12 azimuthally equidistant planes. Results highlight better correlation and

bias for the TEE approach which are explained by the better image quality. However, the TTE approach also presents very competitive values. Lu et al. have used TomTec's 4D Echo-View tool to perform manual contouring of the RV in 5mm contiguous planes and compared the volumes obtained to cMRI reference also with good results [177].

The validation of the semi-automatic method 4D RV-Function© developed by TomTec Imaging Systems has also been a subject of some attention and has been compared against cMRI RV volumes in some studies. A first effort was performed by Niemann et al. using a prototype of the 4D RV-Function© tool which depended on a single manual contouring in one plane [178]. The software then reconstructed the contours in the orthogonal planes and manual refinement could then take place. Results show good correlation for the RV volumes against manual contouring of cMRI volumes although the EF results are not so competitive. Niemann et al. also used the prototype 4D RV-Function© to contour the cMRI images obtaining excellent correlation, bias and limits of agreement. The actual 4D RV-Function© tool was validated against cMRI by Grewal et al. obtaining good correlation values [179] but also by van der Zwaan et al. [151], Leibundgut et al. [180] and Zhang et al. [181]. In spite of presenting good correlation values, the results from van der Zwaan et al. are the most striking by revealing the severe underestimation of the RV volumes by 3D echocardiography. Finally, Ostenfeld et al. have used the same commercial tool with and without performing manual refinement after the semi-automatic contouring and compared the obtained RV volumes against cMRI [154]. Besides again evidencing the volume underestimation that results from 3D echocardiography, and similarly to what was shown by Shibamaya et al. for the LV commercial approaches, Ostenfeld at al. show that manual correction is still necessary for better results to be achieved.

In regard to the reference values for RV volumes, several studies have published values in different populations. Gopal et al. [158] presented a study of the normal RV volumes performed in 71 healthy patients using manual contouring and disk summation. Tamborini et al. [182] studied 245 subjects divided by age and gender performing the contouring using TomTec's 4D RV-Function© tool. A more extensive study was conducted by Maffessanti et al. including 540 healthy adults again using the tool by TomTec for semi-automatic contouring and reporting age-, body size- and sex-specific reference values for RV volumes and RV EF [183].

4.4. Right Atrium

To the best knowledge of the authors, there is at this point no commercial solution or validation studies for automatic or semi-automatic RA volume assessment.

Table 3. Literature Overview: Validation of RT3DE and commercial software tools for RV volumetric assessment (#: number of exams; Ref: reference measurements taken from cMRI or manual contouring of RT3DE data (3DM); r: correlation coefficient; BA Bland-Altman analysis).

Study	Imaging System	Analysis system	User input	#	Ref	Time (s)	r			BA (μ±2σ)		
							EDV	ESV	EF	EDV	ESV	EF
Vogel et al., 1997 [172]	Vingmed800	-	A(2mm)	16	cMRI	NR	0.95	0.751	NR	NR	NR	NR
Fujimoto et al., 1998 [173]	SSH160A+486 CPU	-	A(2mm)	15	cMRI	NR	0.94	0.97	0.90	NR	NR	NR
Papavassiliou et al., 1998 [174]	Sonos2500	-	A(3-3.5mm)	13	cMRI	NR	0.95	0.95	0.8	-9.6±31.0	-4.3±27	-3.9±14.6
Prakasa et al., 2006 [175]	Sonos7500/iE33	TomTec	A(2)	43	cMRI	NR	0.5	0.72	0.88	-15.9±35.6	-6.8±17.8	NR
Nesser et al., 2006 [176]	CFM800 (TTE)	-	A(10-12)	20	cMRI	NR	0.85	0.86	0.86	-1.6±36.4	0.1±26.8	-2.0±18.8
Nesser et al., 2006 [176]	CFM800 (TEE)	-	A(10-12)	20	cMRI	NR	0.86	0.88	0.84	-1.3±35.6	2.8±30.4	-4.0±19.4
Niemann et al., 2007 [178]	Sonos7500	TomTec 4DRV prototype	B(1)+R	30	cMRI	600	0.93	0.92	0.68	-0.44±25.40	1.01±7.75	-1.56±13.39
Lu et al., 2008 [177]	Sonos7500+X4	TomTec 4D EchoView	A(5mm)	17	cMRI	NR	0.98	0.96	0.89	-7.0±18.0	-3.2±14.2	0.3±8.2
Grewal et al., 2010 [179]	iE33	TomTec 4DRVF	B(3)+R	25	cMRI	NR	0.88	0.89	0.89	NR	NR	NR
Leibundgut et al., 2010 [180]	iE33+X3-1	TomTec 4DRVF	B(3)+R	88	cMRI	NR	0.84	0.83	0.72	-10.2±21.6	-4.5±14.8	-0.4±7.6
Van der Zwaan et al., 2010 [151]	iE33+X3-1	TomTec 4DRVF4.0	B(3)+R	50	cMRI	126±30	0.93	0.91	0.74	-34±66	-11±56	-4±13
Ostenfeld et al., 2012 [154]	Sonos7500+X4 /iE33+X3-1	TomTec 4DRVF	B(3)	53	cMRI	NR	0.769	0.773	0.488	-32±52	-8±34	-6±18
Ostenfeld et al., 2012 [154]	Sonos7500+X4 /iE33+X3-1	TomTec 4DRVF	B(3)+R	53	cMRI	NR	0.779	0.835	0.597	-22±52	-7±32	-2±16
Zhang et al., 2013 [181]	SC2000+4Z1c	TomTec 4DRVF	B(3)+R	59	cMRI	NR	0.97	0.96	0.71	-2.16±15.40	-2.6±16.12	0.86±16.32

User input: A(X): Computer assisted delineation of the 3D surface via manual contouring, where X is the number of 2D planes contour or the distance between parallel 2D planes contoured; B(X): Semi-automatic segmentation, with manual initialization by contouring in X 2D planes; C(L,F): Automated segmentation, with user input of L anatomical landmarks in F time frames; D: Fully automatic segmentation without any user intervention; R: Manual refinement of segmentation results.

5. CLOSING REMARKS

The assessment of cardiac chamber volume is a fundamental task in both clinical and research context to obtain a unique insight into the heart function and has been shown to have a strong diagnostic and prognostic value in numerous instances. Among the different heart imaging modalities, RT3DE reveals itself as an excellent technique as it allows a true three dimensional imaging of the heart while maintaining a relatively low cost and portability and without the need for exposure to ionizing radiation. However, the nature of RT3DE make it a particularly challenging image analysis task. For these reasons, a great effort has been made towards RT3DE image analysis and retrieval of its important clinical information. Semi-automatic approaches are the most common but, recently, attention has been shifting to more automatic ones and special attention is being devoted to implementing these solutions in real-time. The use of prior information and population-based methods are particularly promising with new approaches reaching the field in the last years.

Because most attention has been directed towards the LV, the development of methods for the remaining heart chambers has been more scarce in spite of the fact that the assessment of function of these chambers is of indisputable clinical importance. Nevertheless, the advances already achieved with LV will facilitate the implementation of new methods for these chambers, with methods being transported and adapted from one chamber to the other.

Though not in the scope of this work, the advances with RT3DE image acquisition also play a powerful role in taking this field further. It is expected that, in the future, better image quality will be possible with both higher frame rates and higher spatial resolution. This will not only make cardiac function assessment through RT3DE a more accessible goal but will also give access to new information making RT3DE an even more powerful tool.

In conclusion, it can be expected that the importance of cardiac function assessment by RT3DE will continue to rise as technology evolves and novel, more sophisticated and automated approaches arise in the field making RT3DE an undeniable tool in clinical practice.

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