

Vendor-Independent Software for Rapid Comprehensive Assessment of Changes in Left Ventricular Function During Serial Echocardiographic Studies

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Abstract

Sequential evaluation of left ventricular (LV) function is critical in patients receiving potentially cardiotoxic treatments. However, identification and interpretation of the clinical significance of subtle changes in LV function from echocardiographic images is time-consuming and requires training. The aim of this study was to develop and test a new approach aimed at addressing this issue. Dedicated semi-automated software was developed (Epsilon Imaging), which analyzes images obtained during serial examinations and provides a visual, easy-to-understand display of changes in LV ejection fraction (EF), peak systolic global longitudinal strain (GLS) or both. To test this software, 30 subjects who had 2 echocardiographic studies separated by ≥ 4 weeks were identified and their images analyzed. An expert echocardiographer reviewed EF and GLS data separately using commercial software (Philips QLab), and classified EF and/or GLS in each patient as unchanged, improved or worsened. This classification was used as a reference to test the accuracy of using a combined display of changes in EF and GLS. This was performed by an inexperienced observer with and then without the dedicated software. Image analysis and interpretation were faster using the dedicated software (27 ± 5 vs 15 ± 5 minutes). The agreement with the reference was slightly better with the software (93%; kappa=0.90) than without it (90%; kappa=0.87). Combined displays of changes in EF and GLS data from serial studies allows quick, easy and accurate interpretation of changes in LV function, promising to improve follow-up of patients undergoing potentially cardiotoxic treatments such as chemotherapy.

1. Introduction

Sequential evaluation of left ventricular (LV) function is critical in the follow-up of patients receiving potentially cardiotoxic treatments such as chemotherapy [1,2]. Current detection paradigms for chemotherapy-related LV dysfunction rely on estimation of LV ejection

fraction (EF) from sequential radionuclide ventriculographic or echocardiographic studies. However, by the time a reduction in EF becomes apparent using these modalities, significant damage may have already occurred [3]. Peak systolic global longitudinal strain (GLS) is a measure of myocardial deformation that has been shown to be a sensitive marker of LV function [4,5,6]. A reduction in GLS has been shown to precede changes in EF in patients undergoing chemotherapy [7,8,9]. Hence in such patients, GLS should ideally be considered alongside EF when interpreting longitudinal data. Simultaneous assessment of EF and GLS is not facilitated by existing software packages that are currently used for analysis of LV function. Instead, sequential changes in EF and GLS are evaluated separately, before a conclusion is reached as to whether a significant change in cardiac function has occurred. This is a cumbersome and inefficient process. In addition, strain measurements are dependent on the analysis software [10], which is usually limited to proprietary formats generated by a specific imaging system.

Accordingly, the aim of this study was to develop and test new, vendor-independent software capable of calculating myocardial strain from DICOM images, that combines changes in EF and GLS in a single, easy-to-understand display designed to facilitate rapid interpretation of serial images in patients undergoing treatments that may affect LV function.

2. Methods

We studied 30 subjects (age 51 ± 21 years) who had 2 transthoracic echocardiographic studies separated by ≥ 4 weeks, after excluding 4 patients because of inadequate image quality. The study group comprised of 14 patients with stable cardiac function, and 16 patients with significant changes in cardiac function over time, as reflected by changes in EF, GLS, or both. Echocardiographic images obtained by experienced sonographers (Philips iE33 imaging system with an S5-1 transducer) were analyzed retrospectively, including 2-, 3- and 4-chamber apical views of the left ventricle.

2.1. Reference technique

First, for each of the two sequential studies, EF and GLS were measured by an expert echocardiographer using commercial software (QLAB 9.0 Cardiac Motion Quantification, Philips). EF was calculated using modified Simpson's biplane method [11]. GLS was measured in a region of interest created by manually positioning three points of reference (one on either side of the mitral annulus and one at the apex) in each of the three apical views. Tracking was optimized using a complex, iterative, border adjustment process that is time-consuming and subjective (Figure 1).

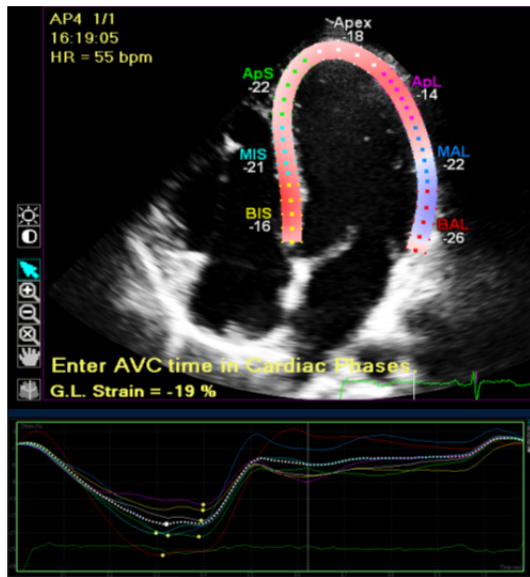


Figure 1. Commercial software for strain measurement relies on accurate tracking of speckles throughout the cardiac cycle. This relies on multiple adjustments, performed for segment boundaries, as well as the entire endocardial and epicardial borders. After tracking is completed, local strain values in the region of interest are color-encoded and superimposed on the gray-scale image (top) and strain time-curves are generated (bottom).

The resultant EF and GLS values measured in the two sequential studies were reviewed separately to determine whether significant changes had occurred in EF, GLS or both (unchanged, improved or worsened EF and/or GLS). A change of 10% in EF and a change of 12% in GLS were considered significant for the purposes of this study [12].

2.2. Alternative analysis

This classification was used as a reference to test the accuracy of interpretation of changes in LV function using a combined display of changes in EF and GLS. This interpretation was performed by an independent reader

(with minimal experience in echocardiography) with the dedicated software and then using manually generated Microsoft Excel plots displaying the same information. Time required in both cases to process data and interpret the combined displays was recorded.

Novel semi-automated vendor-independent software (EchoInsight Cardio-Oncology, Epsilon Imaging, Ann Arbor, MI) was used to load both baseline and follow-up studies and measure EF and GLS. The endocardial border was traced manually (Figure 2) and then tracked throughout the cardiac cycle using automated speckle tracking algorithm, resulting in LV volume and strain over time. For both baseline and follow-up studies, EF was calculated from the corresponding end-systolic and end-diastolic volumes (Figure 3).

Figure 2. A click-and-drag technique or interrupted mouse clicks are used to trace the LV endocardial boundary (shown during tracing). This is in contrast to the commercial software, which creates a region of interest using 3 points and assumes certain geometry. This feature results in more accurate boundary tracing, requiring less adjustment.

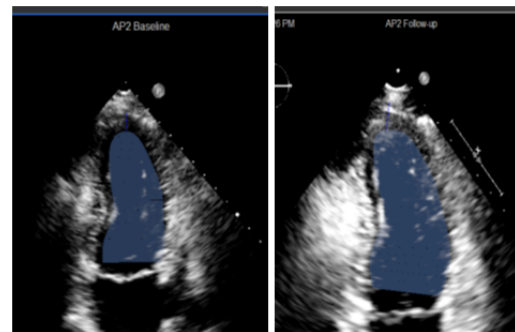


Figure 3. Side-by-side display of 2-chamber images obtained at baseline (left) and during follow-up (right) with the LV cavity shown with a color overlay.

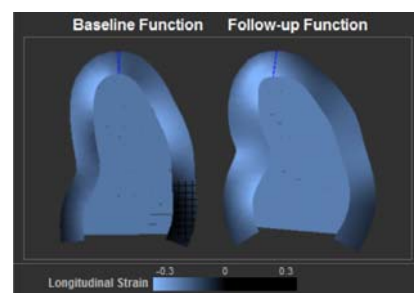
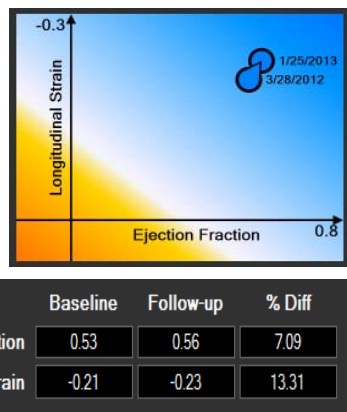


Figure 4. Side-by-side parametric displays of longitudinal strain at baseline and during follow-up.

In addition, longitudinal strain was calculated for all points along the endocardial boundary and shown in a parametric display (figure 4). GLS was calculated as a mean strain value measured in all points in the three apical views.

The software then generates an integrated display of changes in EF and GLS (Figure 5). Changes in GLS were reported as proportions of the original value, that is a change in GLS value from -20% to -10% would be reported as a 50% difference. A change of 12% in GLS (or approximately 1/8 the original GLS value) was considered significant.

Figure 5. Integrated display of changes in EF and GLS from baseline to follow-up. In this example, both EF and GLS increased slightly, as reflected by the short arrowhead pointing in the positive direction along both axes.



2.3. Statistical analysis

Agreement between the reference and the independent observer's interpretation of the change in cardiac function over time using displays generated by the dedicated software and also using Excel plots was assessed using kappa statistics.

3. Results

Analysis was feasible in all study subjects. The mean frame rate and heart rate were 54±17 fps and 76±19 bpm, respectively.

Expert interpretation using the conventional methodology identified 5 distinct patterns of changes in LV function, including: (1) stable EF and GLS, (2) increase in both parameters, (3) decrease in both parameters, (4) stable EF with increase in GLS, and (5) stable EF with decrease in GLS. Figure 6 depicts 4 of these 5 patterns as displayed by the dedicated software.

The mean EF difference in patients with significant changes in this parameter was 16±13%. This group also demonstrated a mean change in GLS of 85±57%.

Overall agreement between the reference interpretation and the inexperienced observer's classification using the commercial software was very good at 90% (kappa=0.87

with □SE=0.07, □95% CI 0.73-1.00). □ Overall agreement for the same observer's classification using the dedicated software was slightly better at 93% (kappa=0.90, □SE=0.06, □95% CI 0.78-1.03).

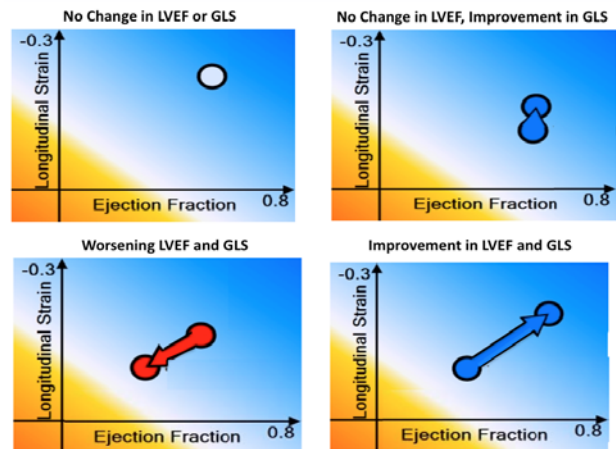


Figure 6. Typical patterns of changes in cardiac function as reflected by increase/decrease in GLS and EF.

The time from the start of processing to generation of integrated display of EF and GLS data (for two sequential studies of one patient) using the commercial software was 27±5 minutes, but only 15±5 minutes using the new dedicated software.

4. Discussion

Our goal was to address the need for improved sequential evaluation of LV function in the follow-up of patients receiving treatments such as cardiotoxic chemotherapy. The results of this initial feasibility study showed that the newly developed semi-automated software that combines EF and GLS data can be used by those without extensive training to rapidly and accurately classify subjects according to changes in cardiac function. Also, because this software is vendor-independent, it offers laboratories with equipment from different manufacturers an alternative designed to eliminate differences in strain measurements caused by the use of different vendors' images and analysis packages.

This dedicated software differs from the commercial one in that it was designed to analyze sequential echocardiographic studies in tandem and to focus on the display of changes in these parameters. Another important feature of the new software is that it utilizes a different strategy for endocardial initialization, resulting in a more accurate boundary and thus reducing the need for time-consuming adjustments.

GLS is a measure of myocardial deformation that is a sensitive marker of myocardial function and is increasingly recognized as a valuable tool in the detection of subtle changes in LV performance. Measurement of

radial and circumferential strain is also possible, but these are not considered as robust as GLS [12], and accordingly are less commonly used to detect cardiotoxic effects of chemotherapy.

The mean frame rate of 54 fps could be regarded as a potential limitation. However, recent data have demonstrated that this is unlikely to have had a significant effect on strain measurements [12].

For this novel approach to become clinically useful, it needs to be further tested and validated in a larger population of patients undergoing sequential imaging studies for the evaluation of changes in LV function as a result of various disease processes and treatments.

In summary, this study demonstrated that interpretation of displays integrating changes in EF and GLS data from serial studies is feasible and accurate. Importantly, this approach was found to provide a time-saving alternative to the conventional methodology. Incorporation of these displays into clinical practice may improve follow-up of cardiac function in patients receiving therapies such as potentially cardiotoxic chemotherapy.

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