# 3D Echocardiographic Quantification of Ejection Fraction and Cardio-toxicity Onset

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## Abstract

*The aim of this study was to evaluate if variability in EF estimate from echocardiographic data acquired with two dimensional (2DE) and three-dimensional (3DE) systems and analyzed using different software packages could affect cardio-toxicity assessment. We analyzed 2DE and 3DE datasets in 94 patients treated for breast cancer with anthracycline and trastuzumab. EF was computed from 2DE and 3DE data using two software packages (EchoPAC, GE Healthcare and TomTec 4D LV analysis). Corresponding estimates were compared. In addition, in a subgroup of 20 patients 3DE data were re-analyzed and intra-observer and inter-observer variability by three investigators were computed, using both software packages. As expected 2DE-based estimates significantly underestimated 3DE-based estimates. Intra-observer and inter-observer variability using both analysis packages showed a huge variability, due to significant differences in end systolic volume and EF. Following clinical definition of cardio-toxicity onset, these variability results could be a confounding factor since variations in EF measurement are in the range of EF decrease due to cardiac adverse effects from cancer therapeutic drugs.*

## 1. Introduction

Ejection fraction (EF) estimate is crucial in diagnostic and therapeutic decision making in different clinical pathways, including definition of cardio-toxicity onset in oncologic patients. Cardio-toxicity is a well-known adverse effect of various chemotherapeutic agents; it is defined as a reduction of the left ventricular ejection fraction (LVEF) of >5% to <55% with symptoms of heart failure or asymptomatic reduction of the LVEF of >10% to ≤55% [1]. Following the recommendation, in cardio-toxicity conditions, chemotherapy modification or interruption should be taken into consideration [2]. Therefore, LVEF measurements should be not only accurate but also have the lowest temporal variability such that changes in LVEF truly represent cardio-toxicity.

In clinical practice, ultrasound imaging is the standard diagnostic and screening technique of choice for cardiac function assessment. Both 2D (2DE) and 3D echocardiographic (3DE) techniques can be used to assess LVEF but 3DE has already proved its superiority with respect to 2DE for LV function quantification [3-5]. Consequently, 3D echocardiography may be preferable to 2D echo also for the cardio-toxicity assessment.

Several 3DE analyzing software are available and can be used to evaluate cardiac function and compute EF. Previous studies show differences in cardiac function assessment depending on the software package used, in specific population, including patients in sinus rhythm with cardiomyopathy and in patients with ischaemic and non-ischaemic cardiomyopathy [6,7].

Therefore, the aim of this prospective study was to investigate whether variability in EF estimate due to 2DE and 3DE acquisition systems and to different analyzing programs could affect cardio-toxicity onset definition in selected patients with breast cancer treated with anthracyclines and trastuzumab.

## 2. Methods

### 2.1. Study population

Ninety-four asymptomatic patients (age 52±11yrs, 81 ductal carcinoma, 9 lobular carcinoma, 4 unknown) with histological or cytological diagnosis of breast cancer in early stage or locally advanced (stage I-IIIC) candidates for neoadjuvant therapy or treated with radical surgery, were prospectively enrolled in the study approved by the Ethical Review Board at the Romagnolo Scientific Institute for the Study and Treatment of Cancer (IRST).

Inclusion criteria consisted of having had: (1) a complete 2D and 3D echo examination; (2) neoadjuvant or adjuvant treatment program comprising an anthracycline-based regimen and trastuzumab and with any concomitant hormonal therapy; (3) adequate organ

functions (heart, bone marrow, renal, hepatic).

The exclusion criteria were: LVEF<50%, valvular or ischemic heart disease or other diseases not allowing the chemotherapy administration or conditions that compromise patient compliance.

Cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, smoking, alcohol were recorded.

All patients gave written informed consent in agreement with the local Ethics Committee.

## 2.2. Image acquisition

Acquisition was performed using a Vivid E9 (GE Healtcare, Milwaukee,WI,USA) ultrasound system equipped with a multiplanar full matrix array.

Image acquisition included apical 2- and 4-chamber and triplane views, as well as short axis views at basal, mid and apical levels.

All images were recorded with the same depth according to the recommendation for chamber quantification of the European Society of Cardiology.

## 2.3. Image processing

2DE images were analyzed by manual contouring endocardial contours. LV volumes at end diastole and end systole (EDV and ESV) were obtained applying the Simpson biplane method from apical 4- and 2- chambers views. (Figure 1a). EF was computed as:

$$EF= ((EDV-ESV)/EDV)x100$$

LV volumes and EF by 3DE were determined by manipulating the full volume dataset to derive apical 2- and 4-chamber and apical long axis views using both Tomtec and GE offline analysis software.

Quantification of 3DE LV volumes and EF was first performed using the EchoPAC software package (GE Healthcare) (Figure 1b). To detect LV endocardial border the user needs to identify two points on the 4-chamber view at end-diastole (ED) and at end-systole (ES), corresponding to the center of the mitral annulus and the LV apex. Endocardial borders were automatically detected and ED and ES volumes and EF were computed.

LV volumes and EF assessment using 4D LV Analysis (Tomtec, Unterschlessheim, Germany) (Figure 1c), required the selection of the mitral annulus plane and of the center of the mitral valve. Subsequently, the endocardial border was traced manually in the triplane view including the trabeculae and the papillary muscles at ED and ES. Finally, EDV, ESV were computed and EF was derived as previously described.
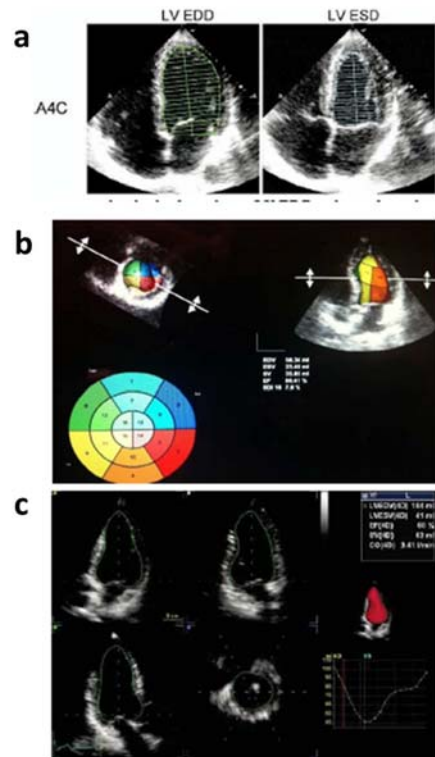


Figure 1. End diastolic and end systolic volumes computed analyzing (a) 2DE and the 3D full volume datasets using 4D LV-Function (b) and EchoPAC (c) software.

## 2.4. Statistical analysis

EDV, ESV and EF are expressed as mean ± SD.

2DE and 3DE values of EDV, ESV and EF obtained by an expert cardiologist were compared and statistical significance difference was evaluated using t-test ($p<0.05$).

In a subgroup of twenty patients randomly selected intra-observer was computed by repeating the analysis one month later as the standard deviation between the two estimates divided by their average value.

Inter-observer variability by three blinded experts was computed as the standard deviation between the three estimates divided by their average value.

All measurements were independently recorded.

## 3. Results

2DE and 3DE analyses were performed in all 94 patients.

Table 1. Results (n=94) of EDV, ESV and EF estimates from 2DE and 3DE using software package EchoPAC ($3DE_A$) and 4D LV Function ($3DE_B$); values expressed in mean±SD, *p<0.01 2DE vs $3DE_A$ and 2DE vs $3DE_B$.

|  | EDV (ml) | ESV (ml) | EF (%) |
|---|---|---|---|
| 2DE | 70±18* | 25±9* | 64±8* |
| $3DE_A$ | 85±19 | 35±10 | 59±6 |
| $3DE_B$ | 85±24 | 34±13 | 59±7 |

Table 2. Results (n=20) of variability analysis from 2DE and 3DE using software package EchoPAC ($Intra3DE_A$ and $Inter3DE_A$) and 4D LV Function ($Intra3DE_B$ and $Inter3DE_B$); values expressed in mean±SD.

|  | EDV | ESV | EF |
|---|---|---|---|
| $Intra3DE_A$ (%) | 3.4±5.3 | 5.5±6.2 | 2.2±1.8 |
| $Intra3DE_B$ (%) | 6.5±5.5 | 11.5±6.9 | 4.6±3.3 |
| $Inter3DE_A$ (%) | 3.1±3.6 | 6.4±4.9 | 3.6±2.7 |
| $Inter3DE_B$ (%) | 6.4±4.0 | 11.9±5.3 | 6.3±4.3 |

Analysis time for ED and ES frames required about 4±2 minutes for 2DE, and about 4±2 minutes with 4D LV Analysis software and about 2±1 minutes with EchoPAC, including manual corrections when necessary.

As expected 2DE-based estimates significantly underestimated 3DE-based estimates as shown in Table 1.

Intra-observer and inter-observer variability results are reported in Table 2. Both packages showed a huge variability, probably due to significant differences in ESV and EF values.

## 4. Discussion and conclusion

Cardio-toxicity onset in patients treated for breast cancer with anthracycline and trastuzumab relies on an accurate and reproducible evaluation of EF. In this study we investigated differences in EF computed from data acquired with 2DE and 3DE systems. As expected EDV, ESV and EF computed by analyzing 2DE images significantly underestimated the corresponding 3DE-based estimates. Unfortunately, missing reference values from magnetic resonance imaging (MRI) do not allow us to define which estimates are more accurate; however several studies in literature found 3DE-based estimates more accurate [4,5] and 2DE derived EDV, ESV and EF underestimated MRI-based values [4]. Therefore, our results confirmed this finding in a large population of oncologic patients. Consequently, the use 3DE is suggested for EF computation, also in this specific population. In addition, since 3DE systems are not available in many clinical settings, these results also support the research of new indexes for accurate and early identification of cardio-toxicity onset. To this aim, global strains are good candidates [8].

Intra-observer and inter-observer variability of EDV, ESV and EF assessment were lower if computed using EchoPAC software package. This result is somehow not surprising since 4D LV Function package requires more manual intervention and experience to select the correct views for the analysis with respect to EchoPAC.

Therefore 4D LV Function package suffers from operator-dependent subjectivity.

In addition, these huge differences in variability confirms different 3DE software packages for EF assessment should not be used interchangeably [9].

Our results also show changes in EF measurements are in the range of EF decrease due to cardiac adverse effects from cancer therapeutic drugs. Therefore, intra- and inter-observer variability could be a confounding factor for cardio-toxicity onset definition.

Future investigations include the assessment of EF changes by echocardiographic monitoring during anthracycline and trastuzumab therapy administration and the evaluation of the variability of additional echocardiographic parameters from strain analysis, such as myocardial deformation indexes that have been proposed to identify pre-clinical cardiac dysfunction earlier than conventional LVEF for cardio-toxicity onset.

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