Does it matter if it’s left or right?

Echocardiographic image quality in patients after breast cancer surgery

Eivind Bjørkan Orstad

Master thesis
Institute for health and society
Faculty of Medicine

UNIVERSITY OF OSLO

May 2018

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http://www.duo.uio.no/

Trykk: Reprosentralen, Universitetet i Oslo

Abstract

Purpose: It has been shown that regular cardiac follow-up during and after chemotherapy treatment can prevent heart failure due to cardiotoxicity. The method of choice for monitoring these patients is echocardiography. The method is versatile and easily accessible, but suffers from limitations due to reduced acoustic windows in some patients. The objective of the present study is to explore the impact of postoperative changes in the tissue near the acoustic windows on image quality.

Literature framework: Theory on ultrasound physics and clinical echocardiography serve as the basis for this study. The ability of echocardiography in detecting chemotherapy-related heart failure is also addressed.

Method: This was an observational study of clinical practice, and included consecutive, unselected patients referred to baseline echocardiogram prior to starting adjuvant chemotherapy. 116 patients were included; data on surgery, smoking habits, age and body mass index were collected. Image quality was defined as the presence or absence of measurements of two-dimensional strain and/or three-dimensional ejection fraction, which are reported to be most sensitive in detecting subclinical signs of cardiotoxicity. Multivariate logistic regression was performed to assess the impact of relevant variables on image quality.

Results: 24 patients (21%) had reduced image quality. There were no significant difference between left-and right sided surgery, except for patients with left sided breast implant. Age and daily smoking were found to be associated with reduced image quality

Conclusion: Postoperative tissue changes were not found to reduce echocardiographic image quality, except for for patients with left-sided breast implants. Larger studies are needed to confirm these results.

Sammendrag

Formål: Det er vist at regelmessig kardiologisk oppfølging i løpet av og etter cellegiftbehandling kan forebygge hjertesvikt som følge av denne behandlingen. Den foretrukne metoden for oppfølging av disse pasientene er ekkokardiografi. Dette er en allsidig og lett tilgjengelig undersøkelse, men begrenses av redusert akustisk innsyn hos noen pasienter. Formålet med denne studien er å undersøke i hvilken grad postoperative forandringer etter brystkreftkirurgi påvirker den ekkokardiografiske bildekvaliteten

Teoretisk forankring: Ultralydfysikk og klinisk ekkokardiografi er basis for denne studien. Bruk av ekkokardiografi til å finne tegn til cellegiftrelatert hjertesvikt står også sentralt.

Metode: Dette var en observasjonell studie av klinisk praksis. Pasienter som ble henvist til kardio-onkologisk poliklinikk før oppstart av cellegiftbehandling, ble fortløpende inkludert. Uregelmessig hjerterytme var eneste eksklusjonskriterium. 116 pasienter ble inkludert. Data om kirurgi, røykevaner, alder og kroppsmasseindeks ble samlet inn. Bildekvalitet ble definert som tilstedeværelse eller fravær av todimensjonal strain og/eller tredimensjonal ejeksjonsfraksjon, som rapporteres å være mest sensitive når det gjelder å oppdage subkliniske tegn på cellegiftbetinget hjertesvikt. Multivariat logistisk regresjonsanalyse ble gjort for å utforske i hvilken grad relevante variabler påvirket den ekkokardiografiske bildekvaliteten.

Resultat: 24 pasienter (21%) hadde redusert bildekvalitet. Det var ingen signifikant forskjell mellom venstre- og høyresidig opererte, foruten de med venstresidig brystimplantat, Alder og daglig røyking var assosiert med redusert bildekvalitet

Konklusjon: Postoperative forandringer etter brystkreftkirurgi ble ikke funnet å redusere ekkokardiografisk bildekvalitet, foruten hos pasienter med venstresidig brystimplantat. Større studier er nødvendig for å bekrefte disse funnene.

Acknowledgements

From the day I learned my first ultrasound physics in Trondheim, I knew this was the right choice. Echocardiography is truly amazing, and it still feels great to see the first parasternal image occur on the screen every time I start examining a new patient.

I am thankful for the years I had together with the cool and skilled imaging group and the rest of the staff during the inclusion of 2500 participants in the ACE1950 study. This huge project really opened my eyes to research. Osman Pervez, Erika Nerdrum Aagaard, Brede Kvisvik and Thea Vigen, thank you for the good times!

With the internationally recognized PRADA-trial going on in the same corridors, I was introduced to the emerging field of cardio-oncology. Geeta Gulati, amazing work with that one! Thank you for that. And thanks for the opportunity to participate in establishing the first cardio-oncology outpatient clinic in Norway. It is great working with you.

Geeta has moved on with her career. For the cardio-oncology clinic, that is no problem, because Tone Nerdrum is now responsible. As an expert cardiologist and supervisor during my echotechnician education, I am grateful for all the great work and the interesting discussions we have every Friday – my favourite day of the week.

And to all the patients we meet at the cardio-oncology clinic: I wish you all the best, and promise we will do everything we can to take care of your heart while you run through this rollercoaster that cancer treatment truly is.

Kjetil Steine: Thank you so much for being my supervisor. Thank you for sharing your insights in research and writing, and for always having the door open. I am really grateful for your enthusiasm and great support through this process.

Kristian, my cool and VBA-skilled brother: Thank you for great discussions on Excel-stuff (which I pretend I understand) and for the amazing work with the macro. It really saved days, or even weeks, of work!

Dear Ragnhild, my super-girlfriend, super-wife, and super-mom: Thank you for letting me do this! I really look forward to spending the evenings and weekends with you and our great children, Oskar, Jonatan and Eira. Is daddy done with this master stuff? Yes, now I'm done!

Flateby, May 15, 2018

Eivind Bjørkan Orstad

Contents

Tables and figures

Abbreviations

2D	Two-dimensional
2DE	Two-dimensional echocardiography
3D	Three-dimensional
3DE	Three-dimensional echocardiography
BCT	Breast conserving therapy
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
GLS	Global Longitudinal Strain
HER-2	Human epidermal growth factor receptor 2
LVEF	Left ventricular ejection fraction
LV	Left ventricle/left ventricular
MD	Doctor of Medicine (lat *Medicinae Doctor*)
MUGA	Multigated radionuclide angiography
MRI	Magnetic resonance imaging

Introduction

Breast cancer is the most common form of cancer among women, with about 3500 new cases every year [1]. Survival rate increases, and along with that a growing concern with unfavorable side effects of the cancer treatment [2]. Cardiotoxicity is among these side effects. It has been known for several decades, and various strategies have been proposed to detect and prevent heart damage following cancer therapies [3].

Several methods for monitoring heart function during and after breast cancer therapy are available, ranging from cardiac biopsies and blood samples to different imaging modalities like magnetic resonance imaging (MRI), echocardiography and multigated radionuclide angiography (MUGA) [4]. Echocardiography has emerged as the method of choice, due to its widespread availability, versatility and ability to assess additional information about haemodynamic, cardiac structure and valvular function.

However, the relatively moderate reproducibility of echocardiography is an important limitation [4]. Inter-operator variability is well-recognized, and for breast cancer-patients, it is advised to leave the echocardiographic examinations at as few hands as possible [3]. Reduced image quality is another relevant issue that has an impact on reproducibility [5].

Smoking, body habitus and age are among the well-known predictors of reduced image quality [6]. In addition, previous surgery in the area of the acoustic windows may affect image quality [7]. This applies to the patients that undergo surgical treatment for left-sided breast cancer, as the surgery is performed nearby the important apical acoustic window. These patients constitute about 50% of this patient population, as breast cancer is about evenly distributed between left and right side, with left side being slightly more frequently affected [8].

Background

Cardiotoxic agents

Anthracyclines, a chemotherapic agent commonly used in treating breast cancer, is well known for its potential cardiotoxic side-effects. These agents are believed to cause an immediate toxic effect on cardiac myocytes, but it may take months or years before these damages become clinically apparent [9]. Anthracyclines lead to cell apoptosis; irreversible cell damage. Furthermore, anthracyclines seem to affect the heart in a dose-dependent way and its effects are influenced by coexisting conditions such as cardiovascular risk factors [3]. This category of left ventricular (LV) dysfunction is referred to as type I cancer therapeutic-related cardiac dysfunction [3].

Trastuzumab is a relatively new drug for treating breast cancer in Human epidermal growth factor receptor 2 (HER-2) positive patients (about 20 % of all breast cancer patients). It has impressive clinical benefits and significantly increased survival with a relatively low incidence of adverse effects [10]. The cardiotoxic mechanisms for this drug is not fully understood, but it seems to disturb the pathways that regulate cardiac contractility, function and structure [11]. The cardiotoxic effects of this drug do not seem to be dose-dependent and are, at least partially, reversible [3]. The nature of cardiotoxicity following trastuzumab administration seems to be unpredictable and with individual variations, making it even more complicated to monitor [12]. Furthermore, trastuzumab may exacerbate anthracycline-induced heart failure when given sequentially or concomitantly [3].

Ultrasound physics

Ultrasound is defined as sound waves with a frequency above 20 kHz. For imaging of cardiac structures, ultrasound frequencies are usually from 2 to 2,5 MHz [13]. Imaging of anatomical structures with ultrasound is based on reflection of short sound pulses sent from a transducer. When a pulse hits a tissue boundary (for example myocardium-blood) an echo is returned to the transducer. Based on the time the sound pulse needs to return to the transducer, the depth of the structure can be determined [14]. The same principle is used to measure the depth of the sea from a boat: A sound pulse is sent from the water surface. The speed of sound in water is fixed an known, and thus the depth at a given point can be measured by the time the sound pulse needs to meet the seabed and be reflected back to the surface [14].

Unlike water, the human body consists of various tissues with different speed of sound, and more important, different density [7]. The average speed of sound in blood, muscles, liver and other soft tissue is about 1540 m/s. Fat has a speed of sound that is lower; 1430 m/s. Bone has a much higher speed of sound; 3190-3406 m/s, and speed of sound through air is 333 m/s. When an ultrasound beam meets an interface, some of the beam is reflected, whereas the rest of the beam passes through. [14]. How much is reflected and how much propagates through the second medium, is determined by acoustic impedance (ζ), defined as the product of the density (ρ) and speed of sound (c) in the second medium ($\zeta = \rho c$) [7]. Ultrasound is energy that is applied to a medium, forming a wave that passes along towards a tissue interface. If this new tissue is very dense, like bone, problems will occur in transferring the energy from the original sound wave across the tissue interface, and hence most of the energy will be reflected. In short, it is the difference in acoustic impedance that determines the amount of reflection or propagation of a sound wave. If the difference is large, as between tissue and air, most of the energy will be reflected. But when the difference in acoustic impedance is low, as between tissue and blood, most of the energy from the ultrasound will pass through and produce new echoes from deeper inside the organ of interest [14].

Speed of sound and acoustic impedance are some basic features of medical ultrasound, and explain for example the problems with imaging a patient with air filled lungs due to chronic obstructive pulmonary disease (COPD). In addition, various types of imaging artifacts may occur due to irregularities in the tissue. Acoustic shadowing is caused by calcified areas in the near field blocking transmission of the ultrasound wave beyond that point [7]. Reverberations occur when an ultrasound beam encounters a reflector on its path back to the transducer. Some of the energy is reflected back to the first reflector, while some returns correctly to the transducer, and is correctly mapped by the machine software. When the beam that hit the second reflector eventually returns to the transducer, later than the original beam, the machine software will assume that the second reflected beam is from a reflector further away from the transducer. This phenomenon can repeat itself, causing a characteristic 'stepladder' shape in the echocardiographic image. [15] These stationary artifacts may interfere with imaging of the left ventricular myocardium and thus cause problems with certain echocardiographic analyses, like two-dimensional strain [16]. Reverberation artefacts was the leading cause for discarding segments in a two-dimensional strain feasibility study [16]. This analysis is explained below.

Echocardiographic modalities in follow-up of breast cancer patients

Echocardiography is the method of choice in cardiac follow-up of patients who are exposed to certain types of chemotherapy [3], and is an integrated part of the examination, which also includes ECG, blood pressure and a clinical examination. Blood samples of cardiac biomarkers can also be included [4].

There are various types of information available from an echocardiographic examination. Systolic (ejection phase), diastolic (filling phase) and valvular function are the most important [17, 18]. Valve assessment is particularly important in a radiation therapy setting. Valvular affection is included as one of the manifestations of so-called ‘radiation-induced’ heart disease, which also include pericarditis, rhythm problems, coronary artery affection and myocardial infarction [19]. Echocardiography is the method of choice for first-line imaging in follow-up after irradiation [19].

Diastolic function should be assessed as a part of the echocardiographic examination. The findings, however, are difficult to interpret in this patient group. Changes in diastolic parameters can be caused by fluctuations in LV filling patterns due to chemotherapeutic side effects as nausea and vomiting [3]. Diastolic dysfunction as a predictor of subsequent decline in systolic function is proposed, but these studies are small [20, 21].

Systolic function measured by echocardiography remains as the most robust method for detection of cardiotoxicity [3]. This condition is defined as a left ventricular ejection fraction (LVEF) decline by 10 percentage points to a value below 53%, which is the normal reference value [3]. In the following, the most important echocardiographic windows and methods for assessing LV systolic function are presented, with their strengths and limitations.

Echocardiographic acoustic windows

The heart can be observed from different acoustic windows. The most important windows for assessing left ventricle and the left-sided heart valves, are the parasternal and the apical windows [7].

Parasternal images are obtained through an intercostal space on the left side of the sternum (Figure 1) [7]. When the probe is properly angulated, a so-called long axis image of the heart appears, with right ventricle closer to the chest wall (top of the ultrasound image), and the left ventricle from the heart valves to the right and towards apex to the left. This view provides a clear view of the valvular function and the relative size and function of the heart chambers. Left ventricular (LV) function can be assessed by measuring the diameter and wall thickness through the heart cycle [17].

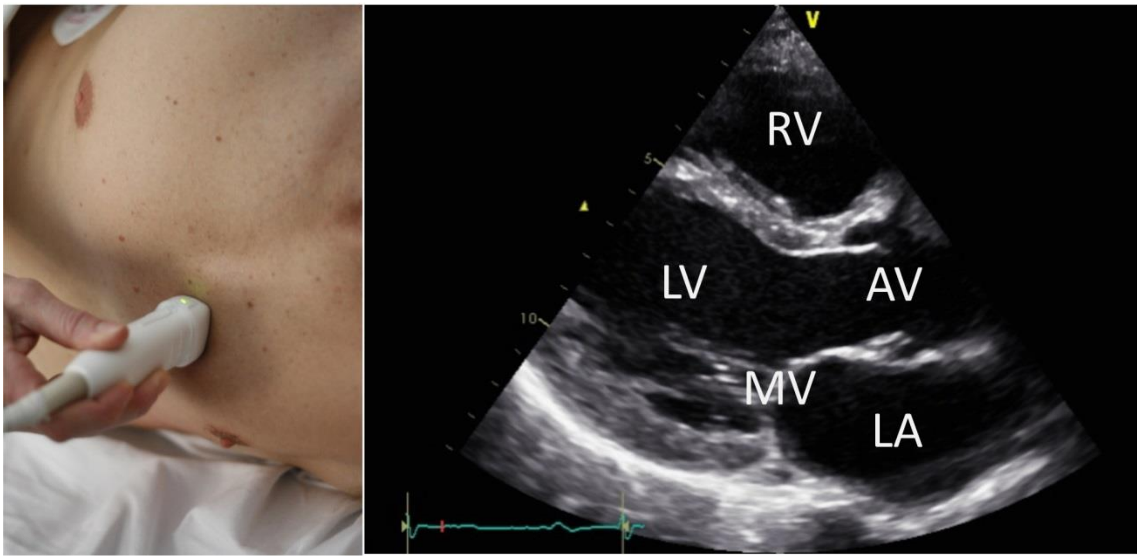

Figure 1. Parasternal long axis. RV: Right ventricle; LV: Left ventricle; AV: Aortic valve; MV: Mitral valve; LA: Left atrium

When moving the probe more lateral and one or two intercostal spaces below the parasternal window, an apical image can be obtained (Figure 2) [7]. From this view, all the four heart chambers are visible. When rotating the probe, different segments of the left ventricle can be assessed. Apical images of the left ventricle are the basis for various measurements. The most important of these methods are explained below.

The dotted line illustrates a typical scar after mastectomy. Note the proximity to the apical acoustic window (Figure 2).

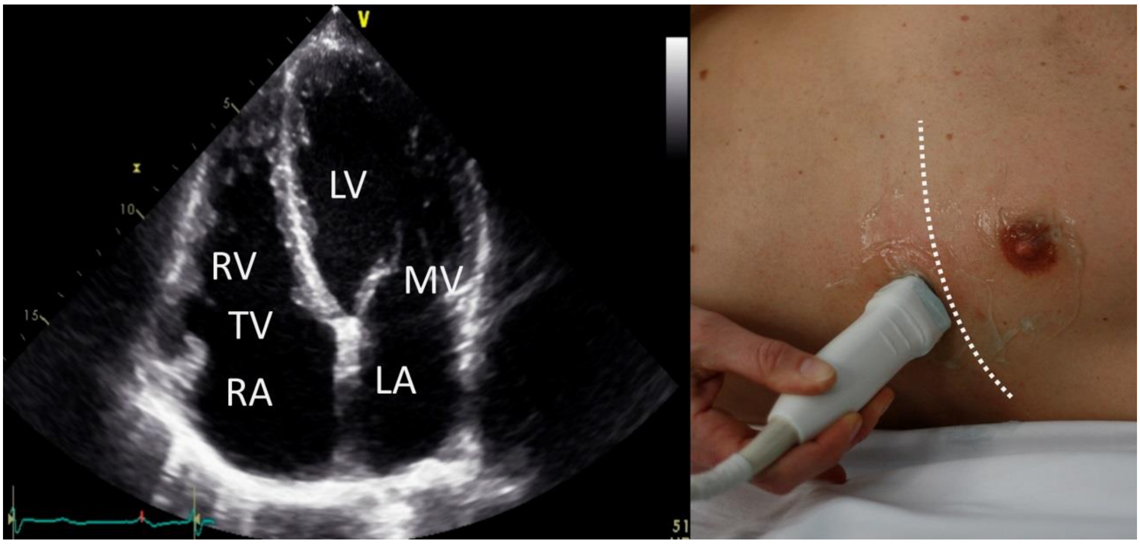

Figure 2. Apical 4-chamber view. RV: Right ventricle; LV: Left ventricle; TV: Tricuspid valve; MV: Mitral valve; RA: Right atrium; LA: Left atrium

Two-dimensional left ventricular ejection fraction

LVEF is expressed as the ratio between stroke volume and end-diastolic volume. There are several methods for calculating two-dimensional (2D) LVEF. The biplane summation of disks method (modified Simpson's rule) is based on a mathematical construction of a number of elliptic discs that are constructed based on tracing of the endocardial border in two apical images is the most recognized [22]. LVEF is a cornerstone in assessment of LV systolic function and plays a central role in many guidelines [3, 23, 24].

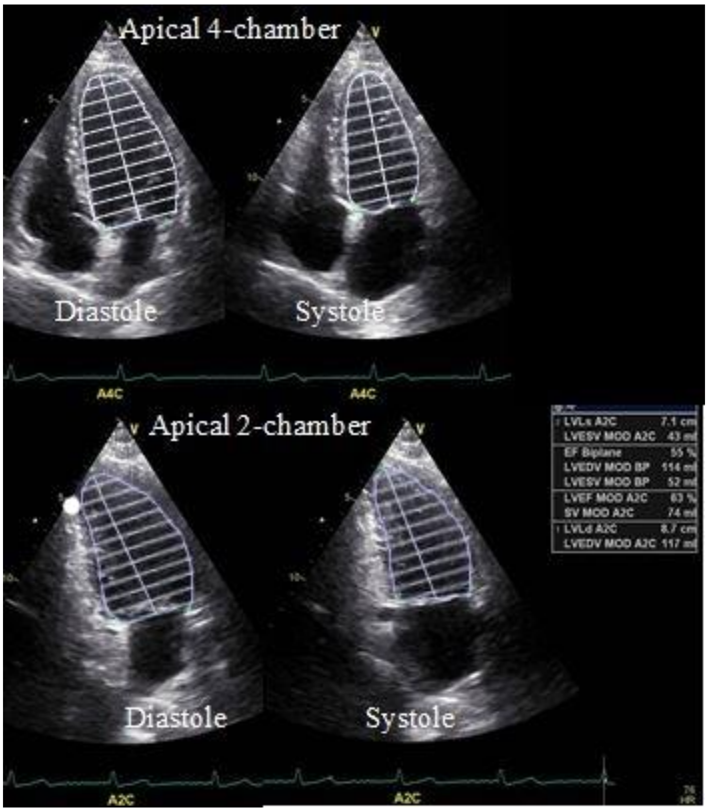

Figure 3. 2D LVEF by the biplane summation of disks. Endocardial border is traced in systole and diastole for both 4-chamber and 2-chamber view. A number of diameters (horizontal lines) are calculated and serve as basis for calculation of volumes for a number of elliptic shaped discs. The volumes of these disks are summarized and presented as LV volumes in systole and diastole. LV ejection fraction can then be calculated, as the ratio between stroke volume (end-diastolic volume – end-systolic volume) divided by end-diastolic volume

2D LVEF calculation has some important limitations. Firstly, volume calculations from 2D images are based on geometrical assumptions and may cause measuring errors. Secondly, LVEF is load dependent. Information about preload and afterload must be accounted for when interpreting ventricular function, including LVEF. Thirdly, LVEF is influenced by heart rate, with decrease at higher rates. Finally, arrhythmia as atrial fibrillation makes it difficult to measure correct LVEF as LV filling varies when the heart rhythm is irregular [22].

A correct measure of LVEF requires a well-defined tissue-blood interface of left ventricle [17]. Adequate images for measuring 2D LVEF are obtainable in most patients. However, a major limitation of 2D LVEF is the relatively moderate reproducibility, due to the possible changes in cut plane from one examination to another [4, 22]. In order to optimize reproducibility, the current recommendations for cardiac follow-up of breast cancer patients advise to let each patient be examined by the same operator using the same equipment [3, 4].

Myocardial deformation imaging by 2D speckle tracking echocardiography

Speckle tracking echocardiography is a technique that can identify acoustic markers, so called speckles, in the grayscale image. These speckles are identified and followed from frame to frame throughout the cardiac cycle. Displacement and velocity are calculated for each speckle, thus allowing calculation of segmental strains [25].

Different types of systolic deformation (strain) can be measured; longitudinal, radial and circumferential [26]. Global longitudinal strain (GLS) is most widely used, and is one of the recommended methods for assessing LV function [17]

GLS is calculated with automated or semi-automated software, depending on vendor. The repeatability is superior to manual tracing of LV volumes for EF calculation [22], which makes it a more suitable method for follow-up of patients where small temporal changes are important to detect [3].

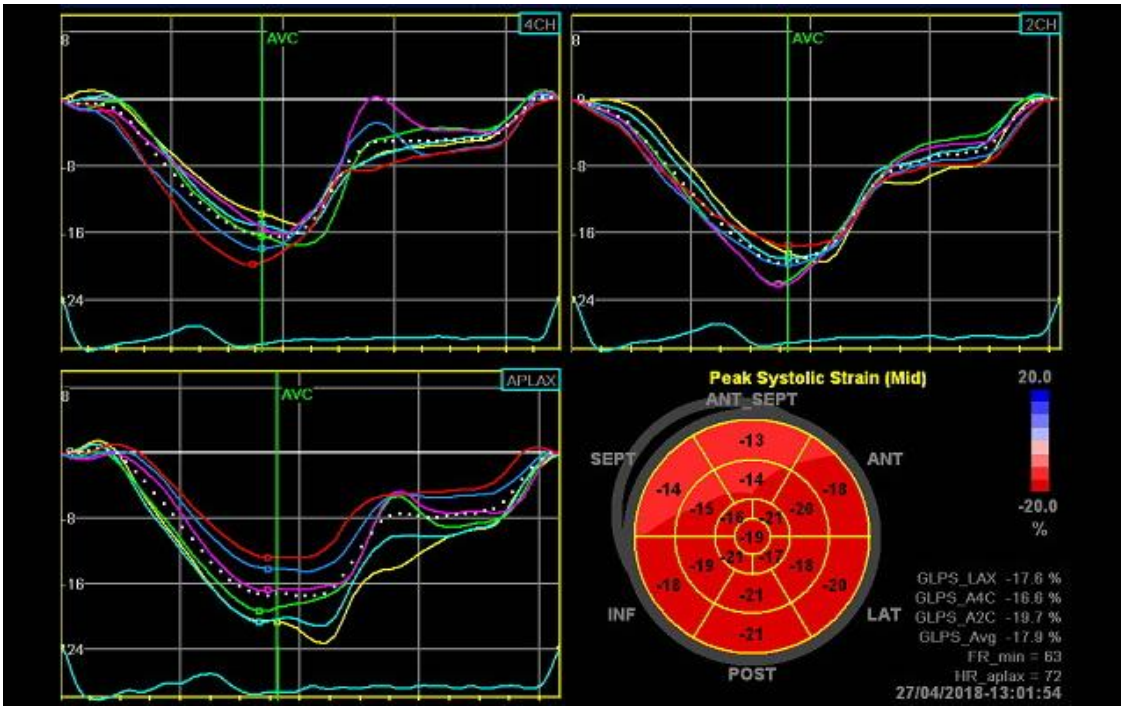

Figure 4. 2D strain by speckle tracking. The red circle in the lower right corner is a so-called Bulls-eye plot of the left ventricle. The outer ring represents the basal segments, the middle ring represents the midventricular segments and the centre represents the apical region. The numbers and colour codes correspond; dark red and high numbers indicate normal values. Lighter shades of red indicate reduced strain. The three curves represent strain curves for the three apical images. In normal hearts, these curves should follow the same pattern. Deviance from the typical pattern could be due to segmental abnormalities like ischemic heart disease, or tracking problems due to image artefacts.

Three-dimensional echocardiography

Since three-dimensional ehcocardiography (3DE) was piloted in the 1980s, the method and technology are refined, and 3DE is now available in standard echocardiographic equipment. The important theoretical advantage over standard 2D-echocardiography is the absence of geometrical assumptions. However, 3DE underestimates LV volumes compared to MRI. MRI is considered the gold standard for cardiac volume and EF measurements. With increasing investigator experience, 3DE measurements improve in agreement with MRI [27]. 3DE is, if available, the preferred modality for evaluating patients before, during and after cancer therapy, and should be used at centers that use 3DE in their daily routine [3].

The test-retest-variability is less in 3DE compared to 2D echocardiography, which make the method suitable for serial examinations [28]. A study that investigated the reproducibility of various echocardiographic modalities in follow-up of breast cancer patients, found that 3DE yielded the lowest temporal variability [29]

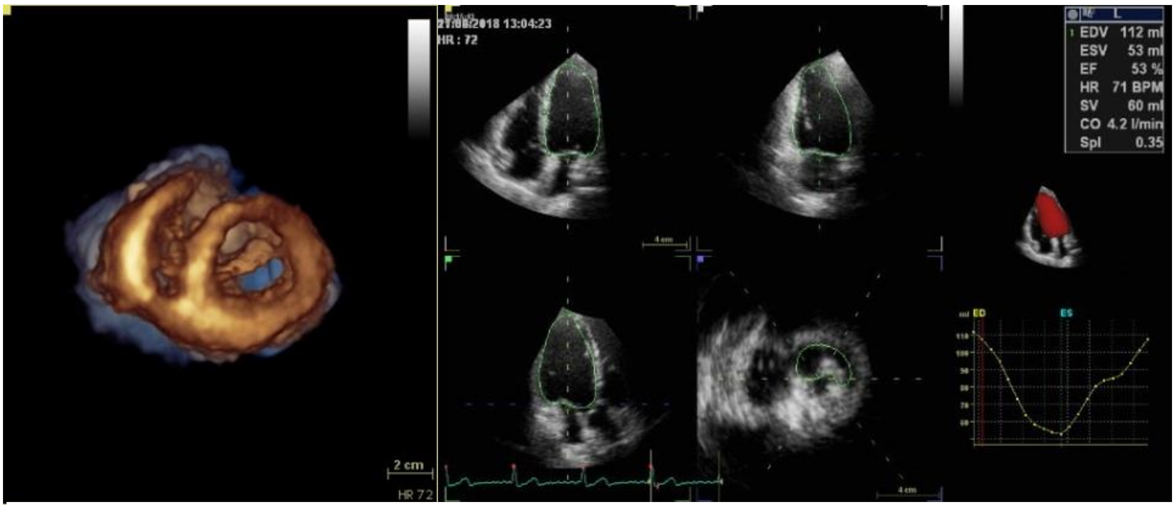

Figure 5. Two different presentations of the same 3D images of the left ventricle. To the left; the left ventricle is seen from the apex. The mitral valve is observed open in the middle of the circular structure. The bean-shaped structure to the left is the right ventricle. The tricuspid valve can be observed, at approximately the same depth as the mitral valve. The picture to the right shows LV volume measurement using a semi-automated procedure. The same 3D-dataset is presented in the three standard apical projections. The operator can adjust the suggested endocardial borders in end-systole and end-diastole. When accepted, the software calculate LV volumes and EF based on the 3D-dataset

Limitations and considerations of echocardiography in a breast cancer population

Studies suggest that novel echocardiographic methods, such as 2D strain and 3DE, are suitable for detecting early signs of LV dysfunction, which is essential in terms of adjusting chemotherapy or adding cardioprotective medication [3, 29]. However, these methods require decent image quality and thereby have some limitations in a clinical setting [30]. Furthermore, breast reconstruction surgery using silicone implants, reduces the acoustic windows and hence the chance of obtaining echocardiographic images of sufficient quality [31].

Besides the well-known factors for reduced image quality, as outlined above, the factor that separates these patients from other patients, is that about 50% of the patients have undergone surgery in the area of the echocardiographic acoustic windows. Radiology studies investigating postoperative breast imaging report the finding of fluid collection in the surgery area in 50% of the patients 4 weeks [32] after surgery, decreasing to 25% after 6 months. Additional changes in the breast tissue, such as calcification and scar formation are also reported as postoperative findings [33, 34]. Such changes may affect ultrasound propagation through the breast tissue in a similar way as the factors mentioned above, and hence reduce the echocardiographic image quality.

Objectives

The main aim of this study was to assess the possible impact of postoperative changes of tissue on echocardiographic image quality. The main objective of this study was as follows:

> *To what extent will left sided breast cancer surgery, compared to right sided, affect the echocardiographic image quality?*

From this objective, the following hypotheses were outlined

> *H0: Breast cancer surgery does not serve as an independent risk factor for reduced image quality in the present population*
> *H1: Breast cancer surgery does serve as an independent risk factor for reduced image quality in the present population*

Secondly, we aimed to assess the overall feasibility of echocardiography in cardiac follow-up of the present patient population, including the investigation of other possible predictors for reduced image quality, which may impact on the ability to perform advanced echocardiographic analyses.

Two clinical examples

As outlined above, echocardiographic image quality rely on a number of factors, including body habitus, lung status, postoperative changes, the quality of the echo machine and operator experience. To highlight some of the perspectives outlined above, two cases from the study population are presented.

Case 1 – middle-aged, non-smoking woman with normal BMI

The first patient was about 50 years old. She was diagnosed with left sided breast cancer, and underwent breast conserving therapy some weeks prior to baseline examination in our cardio-oncology clinic. She underwent an echocardiographic examination by an experienced sonographer. The parasternal images were of excellent quality, with a good overview of the aortic and mitral valve. From the apical window, however, the apex of the left ventricle, which is located to the left, near the chest wall, was partially obscured by a shadow (Figure 1). This artefact is called near-field clutter

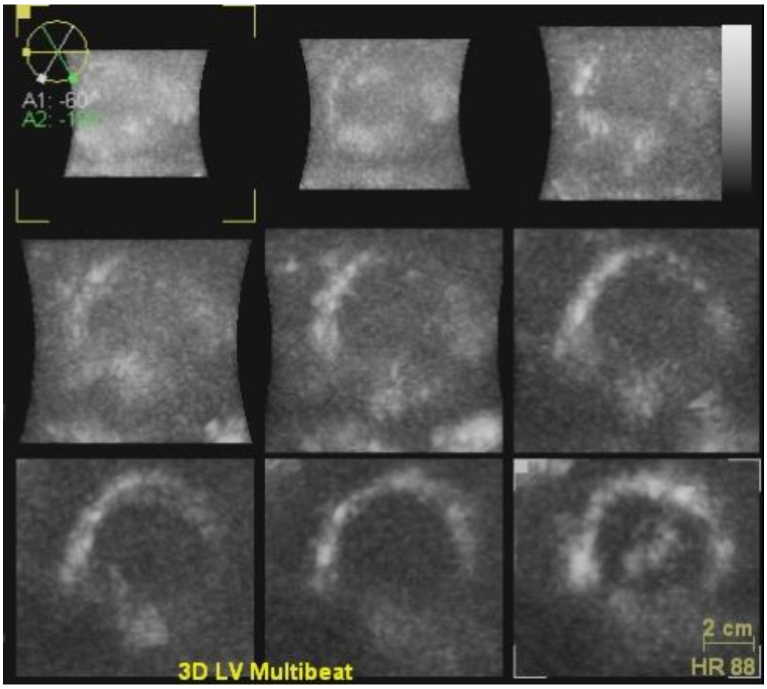

Figure 6. Three-dimensional image of the left ventricle, divided in 9 "slices" from the apex in the upper left corner, to the basis in the lower right corner (apical guiding images in the left column). The endocardial borders are visible in the basal segments of the image, while obscured by near field clutter in the apical segments

[15], and occurs due to strong reflectors in the near-field. 2D strain and 3DEF could not be measured due to this artefact.

When the patient returned after 3 months for a follow-up examination by the same operator, the 3D image from the apical position yielded sufficient-quality images with improved delineation of the endocardial border and the surrounding myocardium (Figure 5).

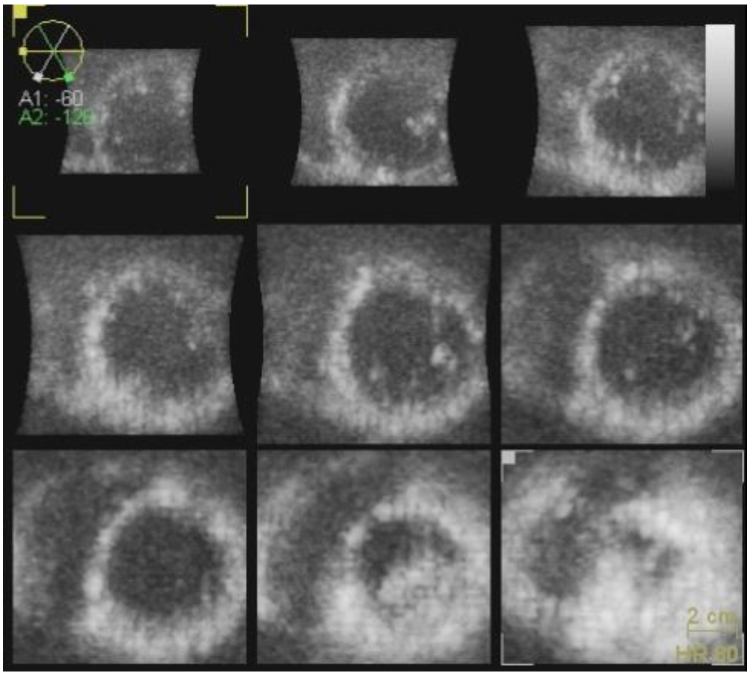

Figure 7. Same patient after 3 months. Improved image quality in the apical segments

Santoro and colleagues [35] suggest that image quality can be affected by breast cancer surgery, based on a study that included echocardiography before and after surgery. This case may support these findings, in addition to Mendelssohn's findings of fluid collections in the surgical area after breast conserving therapy in 50 % of the patients 4 weeks after surgery, gradually decreasing in the following months [34]

Case 2 – 70 years old woman with high BMI

This patient was attending our cardio-oncology follow-up program. The baseline echocardiogram following a left sided mastectomy was of poor quality, without the possibility of performing 2D strain or 3D analysis.

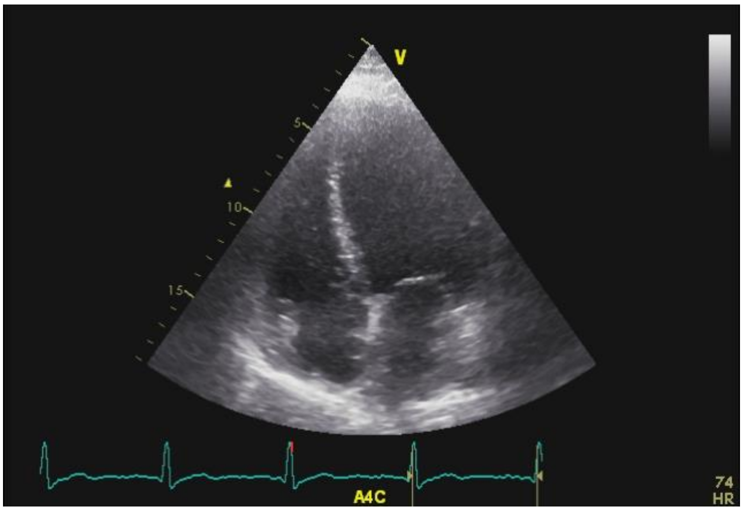

Figure 8. Apical 4 chamber some months after left sided mastectomy. The lateral LV wall (upper right part of the image) is not visible

A few months after her mastectomy, she was admitted to the hospital because of a medical condition. Echocardiography (Figure 6) was performed by an expert cardiologist. The reduced image quality was noted and explained by mastectomy and obesity.

When reviewing the digital image archive, it occurred that this patient had undergone an echocardiographic exam some years ago, before her cancer diagnosis and subsequent mastectomy. These images (Figure 7) were obtained by another expert cardiologist, and were of comparable, poor quality. If the second cardiologist had reviewed the patient's earlier examinations, this would have been revealed, and hence the poor image quality in the second examination would not have been explained by mastectomy. The overall image quality, however, was sufficient for obtaining a conclusive echocardiogram.

These two cases highlight some perspectives of what constitutes the objective of this study. The findings in the first case suggest that postoperative changes may affect image quality, especially the first weeks after surgery. The second case shows that

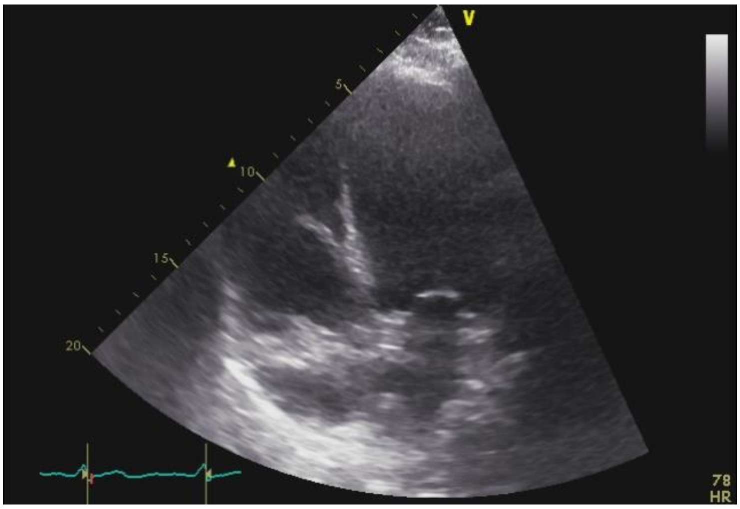

Figure 9. Apical 4 chamber some years before cancer diagnosis and mastectomy. The overall image quality is overall comparable with the image obtained after mastectomy

reduced image quality not necessarily is a result of postoperative changes in the tissue surrounding the acoustic windows. Inferences cannot be drawn from isolated cases like these, but an exploration of a larger sample of this patient group may provide further insight into the effect of postoperative changes on echocardiographic image quality.

Methods

A literature search was conducted in cooperation with a research librarian in the databases Embase and Medline. The Medical Subject Headings-terms Echocardiography and Breast Neoplasms were used, connectorwords OR and AND, in addition to truncations, were used as appropriate. Keywords ‘image quality’ and ‘artifact’/’artefact’ were used to limit the literature search. The search was limited to articles from 2010 until today, with a total number of 335 articles. The search result was reviewed, and relevant articles were included. In addition, important articles included expert consensuses and guidelines were included. Reference lists of articles were studied, and relevant articles from here were also included.

Echocardiography is an examination that heavily relies on several factors to provide reliable results. It is well recognized that inter-operator- and test-retest-variability are high for some of the measurements, especially calculation of LV volume and EF by 2D echocardiography [22]. This may influence reliability in individual follow-up. Preceding the establishment of the cardio-oncology clinic, these limitations were addressed, and effort was made to meet them. Most of the examinations, about 75%, were performed by one person (an experienced sonographer), while the analyses were performed by an experienced doctor or an expert cardiologist.

Reduced image quality in echocardiography is well recognized, and care should be taken in performing a standardized examination with optimized image quality to increase the quality of the interpretation [17]. Information on image quality is an integrated part of a clinical echo report and should always be added to explain the presence or absence of measurements [36, 37]. The grading of image quality is based on the cardiologist's experience and reflects to which degree the cardiac structures are visualized and hence whether different parameters can be measured.

An alternative to this subjective assessment of image quality is to define it as the absence or presence of specific measurements, as outlined in an article from the Tromsø study [6]. The purpose of this study was to identify determinants of echogenicity in a general population. The dependent variable was if a subject was measurable or unmeasurable, based on the presence or absence of defined key measurements.

This approach was chosen for the present study. The measurements of interest were GLS by 2D speckle tracking and 3D EF, as outlined above. During the speckle tracking (2D strain) analysis, the operator accepted, rejected or slightly modified the software's preliminary results, based on experience and visual assessment of the software tracking patterns. Images of sufficient quality were included in the analysis, and later, the echocardiographic report. Insufficient trackings were excluded from the report. Measuring 3D EF was performed in a similar way; the software's tracings of LV volume was accepted, modified or rejected before exporting the final report to the patient's journal. Hence, presence of these measurements was coded as adequate image quality, while absence of them equaled reduced image quality.

All cardio-oncology consultations are organized in a dedicated calendar within the hospital's journal system. These consultations were reviewed chronologically to ensure that no patients were missed. A total of 341 consultations were reviewed, from November 2016 to February 2018. Of these, 116 were eligible for inclusion in the present study.

The inclusion criteria included undergone breast cancer surgery and referral to baseline echocardiogram prior to chemotherapy. Atrial fibrillation or frequent ventricular extra systoles (n=2) were the only exclusion criteria, as these conditions do not allow echocardiographic assessment of 2D strain and 3D EF.

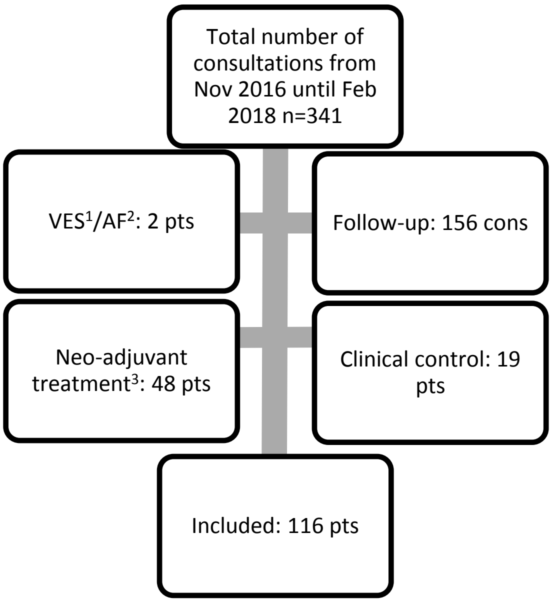

Figure 10. Inclusion of patients in the observational study. [1]ventricular extra systole; [2]atrial fibrillation; [3]chemotherapy prior to surgery

Patient data were collected from electronic patient records. Echocardiographic measurements were collected from the clinical picture archiving and communication system (ComPACS (Medimatic, Genova, Italy). An Excel spreadsheet was saved for each patient. Data were anonymized and saved at the hospital's research server according to Data protection officer approval. An Excel macro was used to extract the data from each spreadsheet into one common spreadsheet. The macro allowed specification of which values to extract from the patient-specific spreadsheets, thus making it a time-saving tool.

Analysis

The statistical analyses are outlined in the article. Below is an elaboration on the collected variables included in the analyses.

The main object of this study was to assess the impact of surgery on image quality. It is well recognized that echocardiographic image quality is affected by a number of factors, which were collected and included.

Surgery in the area of the acoustic windows may affect image quality, as outlined above. The variable “side of surgery” constituted the main object of this study. In addition, type of surgery and eventual presence of a breast implant was coded.

Smoking can lead to lung diseases with increased lung volumes. The speed of sound in air is very different from in soft tissue, causing ultrasound attenuation and reduced image quality [7]. For this reason, smoking history was included as one of the independent variables. Patients who reported current daily smoking or daily smoking until the date of surgery, which in all cases were < 8 weeks ago, were coded as smokers. Patients who reported occasional smoking or who had quitted more than half a year before the echocardiographic examination were coded as non-smokers.

A similar problem occurs in obese patients, with increased distance from the probe to the object of interest, and hence increased ultrasound attenuation, in addition to the ultrasound’s reduced ability to penetrate fatty tissue [7]. There are different ways to define obesity. Waist-hip ratio provided about the same odds ratio (OR) for nonmeasurability in the Tromsø study as BMI [6]. As opposed to waist-hip-ratio, data for calculating BMI were readily available in the current data set, as height and weight were registered when visiting the cardiologist. BMI is a well-recognized classification of weight status [38], thus making it a versatile measurement of obesity in the present study.

Age may affect image quality. In a clinical setting it seems easier to obtain high quality images in young patients than in elder. Age is also the most important predictor for nonmeasurability in a general population, and is by Schirmer and coworkers [6] explained as a sum of the different detrimental effects on tissue from longstanding obesity and emphysema in present- and ex-smokers. Age was included as a continuous variable, and was contrasted by constructing a dichotomous variable > 1 standard deviation (SD) above mean.

As outlined above, there are several variables that may influence on image quality. The impact of each of these should be considered, and thus a logistic regression approach was chosen. The main outcome of a logistic regression model is odds ratio (OR), where odds is the probability of belonging to a group, for example having a malignant disease, given the presence or absence of one or more predictors, like smoking or use of contraceptives [39]. OR is the relationship between odds in the two groups (malignant disease/not malignant disease) [40]. In the present study, OR is the relationship between odds for belonging to the adequate- or reduced image quality group given the presence of the different predictors (side of surgery, type of surgery, smoking, lung disease, age).

There are several methods for conducting a multivariate logistic regression analysis. For this study, a stepwise selection approach was chosen, as described by Altman [41] and Bowers [39]

Results

As outlined above, inter-observer-variability is a limitation of echocardiography. A chi square test of independence was performed to assess the differences between operators. Operator 1 had a total of 77 examinations, 21% of the examinations had reduced image quality. For operators 2 and 3 the numbers were 19 examinations, 16% with reduced image quality and 20 examinations, 25% with reduced image quality, respectively. In absolute numbers and percentages there were some differences, but, probably due to the low number of examinations by the two latter operators, the chi-square test for independence showed no significant differences between operators (χ^2 (N=116) 0.51, p=0,79, phi 0,07). The assumptions for performing a chi square test was violated, as 2 cells (33,3%) had expected count less than 5. SPSS cannot perform Fisher’s exact significance tests in 2x3 tables, an online resource was used to assess Fisher´s exact test for the current contingency table [42].

There are several methods for conducting a multivariate logistic regression analysis. For this study, a stepwise selection approach was chosen, as described by Altman [41] and Bowers [39] A univariate logistic regression analysis of all possibly relevant variables was performed. Variables with p-value <0,25 [39] was included in a multivariate logistic regression model.

The independent variables were tested for collinearity, by the method proposed by Pallant [43]. Collinearity diagnostics were performed separately for left and right side surgery, as these two groups naturally would be highly intercorrelated. No collinearities were found, tolerance values were >0,5.

Discussion

Echocardiographic acquisition and interpretation rely on a number of factors, among them the experience of the operator. Imaging artifacts are common and have to be recognized and adjusted for during the exam, by changing the machine settings or imaging position [15]. Assessment of intra-and inter-observer variability is common in clinical trials and feasibility studies [29].

The present study was an observation of clinical practice, and thus not designed as a regular trial with data on intra- and inter-observer variability. However, all examinations and analyses were performed by trained personnel. In addition, care was taken to include as few as possible in the examinations of this patient group. Due to the well-known limitiations related to inter-observer-variability in echocardiography, it is recommended that each patient, as far as possible, is examined by the same operator using the same equipment [3, 4].

Boyd and colleagues [21] suggested that mastectomy may impact on echocardiographic image quality, and they also found a clear association between left-sided breast implants and reduced image quality. These findings were in line with those in the present study. However, for mastectomy, only a subtle, non-significant increase in nonmeasurability was found compared to the BCT group. A relationship between mastectomy and image quality cannot be rejected. The absent relationship in the present dataset may be a false-negative result due to the low number, and hence a type II error.

The imaging problems related to breast implants, and possibly mastectomy, is expected to decrease over time, as the patients with these types of surgery will be reduced to a minimum. The European Society of Breast Cancer Specialists state that 85-90% of early stage breast cancer patients should receive BCT as their surgical treatment [44].

The purpose for cardiac follow-up of breast cancer patients is to detect and prevent the short- and long term effects of cardiotoxicity [4]. Echocardiography is a useful imaging modality for the majority of these patients, but has well-known general limitations and some that are specific for the breast cancer population [3]. Among the general limitations is the ability to obtain sufficient-quality images in elder and smoking patients, and hence a reduced feasibility in monitoring these patients [6]. These limitations are parallel to the risk factors for developing cardiotoxicity during adjuvant chemotherapy, which, among others, are age > 65 years old and smoking [4]. Ultrasound technology is continuously evolving [17], and some of the problems caused by artefacts in difficult patients may be overcome. It is important to address the feasibility issue, and find the best method for monitoring each patient [45].

The results of this study must be interpreted with care due to the limitations of the study design and the low number of participants. It provides an overview of the patient population and the clinical feasibility of echocardiography in this specific patient group. Future studies with a larger number of participants are needed to assess the impact of surgery on echocardiographic image quality.

Presentation of the article

The present study is carried out as an internal quality control of clinical practice, as outlined in the Approval from the hospital data protection officer. The results will be reported to the Head of the cardiology department at Akershus University Hospital. The approval states that results that may have clinical relevance and public interest can be published.

A decision on publishing has not been made. The following article is written using the instructions for authors and templates from Scandinavian Cardiovascular Journal. Instructions for authors are available online at https://tandfonline.com/action/authorSubmission?journalCode=icdv20&page=instructions

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Article:

Does it matter if it's left or right? Echocardiographic image quality in patients after breast cancer surgery

Eivind Bjørkan Orstad[1,2], Kjetil Steine[1,2]

[1]*Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway*

[2]*Faculty of Medicine, University of Oslo, Oslo, Norway*

Dr. Kjetil Steine MD

Department of Medicine, Akershus University Hospital

University of Oslo

NO-1478 Lørenskog (Norway)

E-Mail: kjetil.steine@medisin.uio.no

Word count : 2929

Does it matter if it’s left or right? Echocardiographic image quality in patients after breast cancer surgery

Objective

It has been shown that regular cardiac follow-up during and after chemotherapy treatment can prevent heart failure due to cardiotoxicity. The method of choice for monitoring these patients is echocardiography. The method is versatile and easily accessible, but suffers from limitations due to reduced acoustic windows in some patients. The objective of the present study thus is to explore the impact of postoperative changes on image quality.

Design

This present study included consecutive, unselected patients referred to baseline echocardiogram at the cardio oncology outpatient clinic at Akershus university clinic prior to start of-adjuvant chemotherapy. 116 patients were included; data on surgery, smoking habits, age and body mass index were collected. Image quality was defined as the presence or absence of measurements of two-dimensional strain and/or three-dimensional left ventricular ejection fraction, which both are reported to be the most sensitive methods in detecting subclinical signs of cardiotoxicity. Multivariate logistic regression was performed to assess the impact of relevant variables on image quality.

Results

24 patients (21%) had reduced image quality. Left sided breast implant (OR 5,77), age (OR 3,89) and daily smoking (OR 3,58) were found to be associated with reduced image quality. No other significant associations between surgery and reduced image quality were found.

Conclusion

Left sided breast cancer surgery was not found to reduce echocardiographic image quality, except for the presence of breast implants. Larger studies are needed to confirm these results.

Keywords: echocardiography, cardiotoxicity, breast cancer, image quality, speckle tracking, three-dimensional echocardiography

Introduction

Breast cancer treatment has improved over the last decades, and 5-year relative survival from breast cancer is now 89 % from 71 % in the mid-70s [1]. Along with increased life expectancy the cost of unintended side-effects such as reduction in left ventricular (LV) systolic function has become more apparent [2].

Cardiac dysfunction caused by chemotherapeutic drugs, so-called cardiotoxicity, has been recognized since the 1960s, and is defined by a reversible or irreversible decline in LV systolic function [3]. Cardiotoxicity is commonly classified by the mechanisms causing the dysfunction; type I and type II. Type I represents dysfunction caused by irreversible cell damage, type II affect the heart in a reversible manner. The two most important groups of chemotherapeutic agents treating breast cancer, anthracyclines and trastuzumab can affect the heart as type I and type II cardiotoxity, respectively. Treatment options include pausing or cessation of chemotherapy and introduction of cardioprotective medication [4].

Non-invasive imaging modalities have evolved through the last decades, providing reliable tools for monitoring LV function and detecting subclinical signs of heart failure. Current recommendations [3] state that a cardiac follow-up including cardiac imaging by echocardiography should be an integrated part of chemotherapeutic cancer treatment.

Transthoracic echocardiography (TTE) is the method of choice for monitoring LV function in cancer patients because of its widespread availability, repeatability and lack of radiation exposure. There are multiple parameters available for assessing LV systolic function by echocardiography. Traditionally, two-dimensional (2D) ejection fraction (EF) has been used to monitor changes in LV function for patients undergoing cancer therapy [3]. Three-dimensional (3D) assessment of LV volumes and EF and myocardial function by two-dimensional speckle tracking echocardiography (STE), however, are gaining more clinical importance in this group of patients. These markers are more sensitive than 2D EF and may register more subtle changes, but rely on adequate image quality [5].

It is well known that factors like body habitus and smoking history may influence image quality and hence validity, reliability and reproducibility of the echocardiographic examination [6]. Postoperative changes after breast cancer surgery may also reduce echocardiographic image quality [3, 6], however, studies addressing this issue are limited.

The aim of this study was to investigate the impact of postoperative changes on echocardiographic image quality in an unselected breast cancer population. We hypothesized that left-sided surgery was an independent predictor of reduced image quality.

Study population and participants

The PRADA trial [2] was conducted at Akershus university hospital from 2011 to 2014. This study was a randomized controlled study to assess the effect of cardioprotective medication in patients receiving potentially cardiotoxic adjuvant chemotherapeutic treatment for breast cancer. As a consequence of the findings in this study and a growing concern for this patient group, it was decided to establish a cardio-oncology outpatient clinic at the cardiology department, Akershus university hospital, for these patients. In cooperation with the oncology department, all breast cancer patients who were eligible for adjuvant chemotherapeutic treatment, were referred to the cardio-oncology outpatient clinic for baseline and follow-up clinical consultation, including blood pressure, electrocardiogram (ECG) and echocardiogram.

Patients referred to baseline echocardiogram after breast cancer surgery, were included in the present study. There were no exclusion criteria but irregular atrial fibrillation or other cardiac arrhythmias, which makes it difficult to perform certain echocardiographic analyses. The most common cardiac arrhythmia, atrial fibrillation, was an important exclusion criterion in a clinical feasibility study of 3D echocardiography for assessment of LV systolic function [7].

The study protocol was approved by the data protection officer at Akershus University Hospital November 2017.

Definition of reduced image quality

Global longitudinal strain (GLS), based on speckle tracking echovcardiography, and 3D LV EF stand out as sensitive markers of subclinical left ventricular dysfunction [5, 8]. The presence or absence of one or both of these parameters was defined to classify image quality as a dichotomous variable; sufficient or reduced. This approach has previously been chosen by Schirmer and coworkers in a population study on image quality [9].

All patients included in the present study were examined as patients at the cardio-oncology outpatient clinic. The echocardiographic analysis was performed on the same day as the consultation, as the majority of patients were starting their chemotherapy treatment short after. During the analysis, the physician accepted or rejected analysis of GLS and 3D EF based on visual assessment of the semi-automatic applications, and by reviewing the internal quality control of the applications. Images with insufficient tracking of LV myocardium for 2D strain or LV endocardial borders for 3D EF were excluded from the report, and thus echocardiograms with missing values for either of these measurements were classified as reduced image quality.

Echocardiographic examination and analysis

All examinations were performed by an experienced MD, an expert cardiologist and an experienced sonographer, using a Vivid E9 (GE, Horten, Norway) with a 2,5 MHz 2D transducer and a 3D matrix-array transducer. Standard parasternal and apical views recordings were performed with the patients in supine left lateral position. For each view, four consecutive cardiac cycles were recorded during breath-hold. Additional recordings were obtained in cases of valvular regurgitations or other clinically relevant pathologies. A customized protocol was used to ensure that all necessary images were recorded in order to optimize the consistency in the examinations [10].

GLS and 3D EF analyses were performed by a MD or a cardiologist on the same day as the recordings, using the analysis software installed on the machine (Echopac BT 13) or via a dedicated plug-in for offline analysis (EchoPac plugin software version 201). 2D strain was measured from the three apical views using a semi-automated analysis application, Automated Functional Imaging (AFI, GE). Minor adjustments were done when necessary. Values for the three segments and the average strain value were reported. 3D EF was measured using a semi-automated analysis application (4D Auto LVQ, GE). Minor adjustments were done to optimize tracking of the endocardial border. 3D EF, end-systolic- and end-diastolic volumes were reported. The remaining conventional echocardiographic measurements were performed using the hospital's clinical picture archiving and communication system (ComPACS (Medimatic, Genova, Italy).

Data collection was conducted following the approval of the study protocol by the data protection officer at Akershus University Hospital. Echocardiographic data were exported as xml-files from ComPACS, anonymized and saved in a dedicated research server as described in the Data protection officer approval. The data were organized in one Excel file together with other clinical variables, including information about surgery, lung disease and smoking status, and exported to SPSS for statistical analysis.

Statistical analysis

Data were presented as mean +/- standard deviation or as frequencies and percentages. Differences between groups were performed using Student's t-test after testing for normal distribution, chi square test and Fischer's exact test, where appropriate (SPSS 23.0; SPSS Inc., Chicago, IL, USA). Age and BMI was negatively skewed in the reduced image group. A Mann-Whitney U test was performed, confirming the result from the t-test.

Univariate logistic regression analyses were used to explore relationships between image quality and various clinical variables including surgical history. Variables with sufficiently low p-values were included in a multivariate logistic regression model. P-values <0,05 were considered statistically significant in the final model.

It is well recognized that inter-operator- and test-retest-variability are high for some of the measurements, especially calculation of LV volume and EF [11, 12]. In this study, due to its observational nature, inter-observer measurement variability was not assessed. However, a chi square test of independence was performed to explore variability between operators indicated no significant association between operator and reduced image quality. This variable was therefore excluded from the logistic regression model.

Results

During the period from November 2016 until February 2018, 116 patients were eligible for inclusion, all women. 24 patients (21 %) presented with images of insufficient quality for GLS and/or 3D EF analysis (Table 1). Patients with reduced image quality were older than those with sufficient image quality, but the difference was not statistically

significant (p=0, 25). When contrasting the age variable over and below 1 SD increase (+12,8 years), the association was stronger between age and reduced image quality, but still not significant (χ^2 (N=116) 3,6, p=0,07 (Fisher's exact test), phi 0,18). The same subtle differences was seen when comparing BMI in the two groups (p=0,29).

For lung diseases, a larger between-group difference was observed (5,4 % vs 12,5 % in the adequate/reduced image quality group, respectively). The numbers in this group was small, with only eight patients in total with confirmed lung disease. Smoking, theoretically affecting the lungs and disturbing the propagation of ultrasound, was more frequently observed in the reduced-image group (29,2% vs 14,1%).

The variables of interest in this study, side of surgery, were overall nearly equally distributed in the two groups. A slightly larger fraction of left sided surgery patients had reduced image quality (50% vs 39,1%) than patients who had undergone right sided surgery (50% vs 60,9%), but the differences were not statistically significant (p=0, 34). When dividing into subgroups, the differences between groups decreased for the left-sided BCT-group, with a nearly equal distribution between the two groups (27,2% vs 25,9 %). For mastectomy patients, there were a small, but nonsignificant difference, with 12,5% with reduced image quality and 8,7% with sufficient image quality. There were larger between-group differences in the left implant group. 12,5 %

of patients with reduced image quality had a left sided implant as opposed to 4,3 % in the adequate image quality group.

In a univariate logistic regression model, all relevant independent variables were tested to find predictors for reduced image quality. Variables with a p-value < 0,25 [13] were included in a multivariate logistic regression model, in a stepwise selection manner. In this model, age > 1 SD, daily smoking and left implant were found to be predictors of reduced image quality when controlled for the other variables in the model.

Conventional echo variables were obtained in almost all patients in both groups (Table 3). It is noted that 2D EF was measurable in 114 of 116 patients.

Discussion

In addition to left-sided implant, increased age and possible lung affection remain as predictors of reduced echocardiographic image quality. This is in line with other studies that have addressed such predictors [9, 14]. Previous smoking was considered to be included in the model, but rejected. It is well known that smoking affects the lungs in various ways, including COPD and interstitial lung abnormalities [15]. The effect of smoking cessation on these abnormalities and hence ultrasound penetration through the lung tissue, remains unclear, but the overall improvement of lung function and the reduced risk of developing tobacco-related lung diseases is well known [16]. A study investigating various predictors for reduced echocardiographic image quality, found that daily smoking was an independent predictor of unmeasurability [9].

In the multivariate logistic regression model, daily smoking was included, as a sufficiently low p-value (0,09) from the univariate logistic regression was present. The p-value decreased to 0,04 when controlling for the other variables in the multivariate model.

This observational study showed that feasibility of advanced echocardiography in our study population was in line with a comparable study [14]. No clear associoation between type and side of breast cancer surgery was shown, except the well-established limitation in echocardiographic image quality caused by breast implants [14, 17, 18].

The total number of patients that underwent mastectomy with or without primary reconstruction was 33. This gave a prevalence of 28% in the study population, which was lower than for the PRADA trial [2], which was conducted at the same hospital three to seven years earlier (38%). This decline of prevalence was in line with the annual report from the Norwegian breast cancer registry, where an increase in breast conserving surgery was seen over the last years [19]. Being a surgical procedure directly affecting the tissue near the apical acoustic window, a larger fraction of patients with reduced image quality would not have been surprising in this subgroup. The possible effect of mastectomy on image quality has been addressed by others [3, 18, 20], and a small difference in percentage of left side mastectomy patients with adequate or reduced image quality was observed in the present study (8,7 vs 12,5). The non-significance of this difference (p=0,70) may be due to low numbers, and hence a type II error cannot be ruled out.

Physiologically, right sided surgery was not expected to affect echocardiographic image quality. The theoretical influence of postoperative tissue abnormalities on ultrasound beam propagation does not apply when the surgical site is at the opposite site of the echocardiographic window. The object of this study was to explore eventual differences between patients with right sided breast cancer and left sided breast cancer in terms of echocardiographic image quality. When exploring the differences between groups with adequate and reduced image quality in patients who had right-sided surgery, there were no significant differences either overall or when dividing into subgroups based on type of surgery. These findings were in line with those who had undergone left-sided BCT or mastectomy. However, in the right implant group, only one of six (17%) patients presented with reduced image quality, in contrast to three of seven (43%) for left side.

In a clinical setting, advanced echocardiographic analyses, such as 2D strain and 3D EF, are preferred in monitoring subclinical decrease of LV systolic function [3]. It is widely accepted that these analyses cannot be obtained in all patients [3, 4]. The main reasons for this are suboptimal image quality and irregular heart rhythm. Atrial fibrillation and frequent extra systoles were exclusion criteria in this study, but only two patients were excluded due to irregular heart rhythm. The main objective, however, was to assess the impact of postoperative tissue changes on image quality, not to explore the overall feasibility of GLS and 3D EF.

Conventional echocardiographic measurements have been proposed to act as alternatives when advanced echocardiographic measurements cannot be performed [3]. The advantage of most of the conventional measurements is that they are obtainable in almost all patients, as seen in this study (Table 3). 2D EF is still a cornerstone in echocardiography, despite its well-known limitations [11]. Other conventional echocardiographic measurements of LV longitudinal systolic function, such as tissue doppler and mitral annular plane systolic excursion, are proposed as predictors of reduced EF in chemotherapy patients [21], and these measurements are recommended to be assessed especially in the cases where advanced measurements are not available [3]. In short, conventional echocardiographic measurements are easily obtainable and may predict decreased LV function. However, a deeper discussion of this topic is beyond the scope of the present study.

Strengths and limitations

The most important strength of this study is the absence of many exclusion criteria and thus investigation of feasibility of advanced echocardiographic modalities in a ‘real life’ setting. Inclusion- and exclusion criteria of feasibility studies may favour patients with adequate acoustic windows [7, 14, 18]. Furthermore, the stringent design of the imaging protocol and the clinical assessment of patients that were referred to the cardio-oncology outpatient clinic ensured that necessary data for performing relevant statistical analyses were present.

A limitation of this study is the low number of included patients. With a relatively low prevalence of reduced image quality, it was not possible to present results with sufficient statistic power. A larger number of patients could probably have revealed more significant between-group differences and thus more significant results and conclusions.

The present investigation was an observational study of clinical practice. However, no inter- or intra-operator variability has been assessed, which is of importance for the interpretation of the results. An experimental design with imaging pre- and postoperative imaging could have provided further insight in the impact of surgery on image quality.

Conclusion

In addition to the presence of left-sided implant, age and smoking habits were the most important predictors for reduced image quality after breast cancer surgery. Subtle, non-significant differences were observed in the left mastectomy group; however, the present study was underpowered to make any significant conclusions on these differences. Larger studies are needed to decide if left-sided mastectomy is important for reduction of image quality.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Table 1. Background characteristics of 116 breast cancer patients referred to the cardio-oncology outpatient clinic for baseline cardiac examination prior to adjuvant chemotherapy

Variable	**Adequate image quality (n=92 (79 %))**	**Reduced image quality (n=24 (21 %))**	**p-value**
Age (y)	55,7 (12,4)	59,1 (14,3)	0,25
BMI (kg/m^2)	26,2 (4,9)	27,5 (6,6)	0,29
Daily smokers, yes	13 (14,1%)	7 (29,2%)	0,13[2]
Lung disease, yes	5 (5,4%)	3 (12,5%)	0,36[2]
Left-sided surgery	36 (39,1%)	12 (50%)	0,34
BCT[3]	25 (27,2%)	6 (25,0%)	0,83
Mastectomy[4]	8 (8,7%)	3 (12,5%)	0,70
Implant[5]	4 (4,3%)	3 (12,5%)	0,15[2]
Right-sided surgery	56 (60,9%)	12 (50%)	0,34
BCT[3]	43 (46,7%)	9 (37,5%)	0,42
Mastectomy[4]	8 (8,7%)	2 (8,3%)	1,00[2]
Implant	5 (5,4%)	1 (4,2%)	1,00[2]

Data are given as mean (SD) or as numbers (%). [1]BMI: Body mass index;[2]Fisher's exact test; [3]BCT: Breast conserving therapy; [4]Surgical removal of the breast; [5] One patient had bilateral implant following right-sided mastectomy.

Table 2. Univariate and multivariate logistic regression analysis of possible predictors of reduced image quality in the study population

	Univariate			Multivariate[3,4]		
Variable	OR	p	CI (95%)	OR	p	CI (95%)
BMI[1]	1,05	0,29	0,96-1,13			
Age	1,02	0,25	0,99-1,06			
Age > 1 SD	2,75	0,06	0,94-8,00	3,89	0,02	1,23-12,27
Daily smokers, yes	2,50	0,09	0,87-7,21	3,57	0,03	1,14-11,18
Lung disease, yes	2,49	0,24	0,55-11,24			
Left sided surgery	1,56	0,34	0,63-3,84			
BCT[2]	0,89	0,83	0,32-2,51			
Mastectomy[3]	1,50	0,57	0,36-6,15			
Implant	3,14	0,15	0,65-15,12	5,77	0,04	1,10-30,18
Right sided surgery	0,64	0,34	0,26-1,59			
BCT[2]	0,68	0,42	0,27-1,72			
Mastectomy[3]	0,96	0,96	0,19-4,82			
Implant	0,76	0,80	0,08-6,80			

[1]BMI: Body mass index; [2]BCT: Breast conserving therapy; [3]Surgical removal of the breast;

[3]Variables with p<0,25 from univariate logistic regression; [4]Nagelkerke R square 14%

Table 3. Measurability of conventional echocardiographic measurements in 116 patients divided in two groups; with image quality sufficient or insufficient for advanced echocardiographic analyses

Variable	**Sufficient image quality (n=92 (79 %))**	**Insufficient image quality (n=24 (21 %))**	**p-value[1]**
MAPSE[6]	91 (98,9%)	22 (91,7%)	0,11
2D EF[7]	92 (100%)	22 (91,7%)	0,04
TDI Em[8]	90 (97,8%)	23 (95,8%)	0,51

Data are given as numbers (%) of performed measurements.[1]Fisher's exact test; [6] MAPSE: Mitral Annular Systolic Plane Excursion, linear measurement of left ventricular longitudinal function; [7]2D EF: Two-dimensional ejection fraction; [8]TDI Em: Tissue doppler measurement of left ventricular diastolic function. Corresponding measurement of systolic function can be obtained in the same image.