Ventriculography Modality in Detection and Evaluation of Cardiotoxicity in Breast Cancer Patients Receiving Chemotherapy: A Literature Review

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INTRODUCTION

Breast cancer is the most common cancer among women worldwide. According to Globocan 2020, there are 11.7% of new breast cancer cases [1,2]. In Indonesia, the number reaches 16.6% [3]. Recently, the breast cancer survival rate has increased due to advanced treatment in cancer. Despite the high survival rate and reduction of disease recurrence and all-cause mortality, the risk of cardiotoxicity produced by the treatment significantly contributes to mortality and morbidity in cancer survivors [4–12]. Cardiotoxicity is a functional or structural heart injury related to cancer treatment. Anthracycline and Trastuzumab, the most common drugs of choice in breast cancer patients, have a relatively high cardiotoxicity incidence, warranting serial cardiac monitoring [9,13–17]. In recent studies, diastolic parameters are considered a method for cardiotoxicity risk assessment [18,19]. Although assessment of left ventricular ejection fraction (LVEF) has been and continues to be the most widely used method for cardiotoxicity risk assessment before, during, and after administration of potentially cardiotoxic cancer drugs [20].

Several modalities for risk assessment of cardiotoxicity have been widely used, such as Ventriculography, cardiac magnetic resonance, and echocardiography. Ventriculography or Multigated Acquisition Scanning (MUGA) has been the gold standard for baseline and serial assessment of Left Ventricular Ejection Fraction (LVEF) for cardiotoxicity since 1970. However, several modalities have been proposed to substitute Ventriculography. This study aimed to find out whether Ventriculography can still be considered the gold standard to monitor and detect cardiotoxicity before, during, and after administration of the chemotherapy and compare Ventriculography with Cardiac Magnetic Resonance (CMR) and Echocardiography (Echo).

ABSTRACT

Background: Ventriculography or Multigated Acquisition Scanning (MUGA) has been the gold standard for baseline and serial assessment of Left Ventricular Ejection Fraction (LVEF) for cardiotoxicity since 1970. However, several modalities have been proposed to substitute Ventriculography. This study aimed to find out whether Ventriculography can still be considered the gold standard to monitor and detect cardiotoxicity before, during, and after administration of the chemotherapy and compare Ventriculography with Cardiac Magnetic Resonance (CMR) and Echocardiography (Echo).

Methods: A literature review was done by searching original literature with keyword combinations on PubMed, Cochrane, and ClinicalKey in the past five years (2016–2021) with language restrictions only in English. Of 1,381 pieces of literature, five pieces are included to review in this study.

Results: Ventriculography has high sensitivity and specificity in monitoring and detecting cardiotoxicity. Other modalities are CMR and Echo. CMR is more accurate although it is costly whilst Echo has high interobserver variability. Ventriculography and CMR have not shown interchangeable results. The literature also shows that Ventriculography could evaluate cardiotoxicity by assessing diastolic function.

Conclusions: Ventriculography can still be used as the gold standard for monitoring cardiac function and detecting cardiotoxicity at an affordable price and with acceptable side effects. It recommends choosing only one modality for serial monitoring due to not interchangeable results among modalities.
serial assessment of LVEF for cardiotoxicity since 1970 [21]. The high reproducibility and accuracy of regionally assessing cardiac wall motion, as well as its ability to quantitatively measure left ventricular function, make ventriculography a reliable diagnostic modality. In addition, the examination procedure is cost-effective [25] and not time-consuming, which only requires one to two hours of examination. The previous study has reported its usefulness in assessing perioperative cardiac risk and mortality [26]. Although it also has disadvantages, the most concerning disadvantage is exposure to ionizing radiation. Therefore, several diagnostic modalities have been proposed and studied to overcome this obstacle. Cardiac Magnetic Resonance (CMR) and Echocardiography (Echo) are frequently chosen as alternative modalities. CMR is a diagnostic modality that evaluates heart structure and function; hence, it could be considered an alternative. Moreover, CMR can quantify volume, biventricular function, and left ventricular mass [27,28]. Despite these benefits, CMR has low availability and high cost, making it more difficult to implement [22,29]. Echo is the most widely used modality for baseline and serial assessment of LVEF for cardiotoxicity, but the image quality of echocardiography is highly dependent on the acoustic window/imaging [29]. Additionally, echocardiography has high interobserver and intervendor variability. Two Dimensions (2D) echocardiography also requires significant myocardial damage to hinder the early detection of cardiac damage [27].

This study aimed to know whether Ventriculography can still be considered the gold standard to monitor and detect cardiotoxicity before, during, and after chemotherapy and to compare Ventriculography with CMR and Echo.

METHODS

Study Design

This study reviews the literature to know how Ventriculography monitors and detects cardiotoxicity before, during, and after administration of the treatment by its diagnostic values, as well as compares Ventriculography with CMR and Echo. A literature review synthesizes, analyzes, reviews, and studies various references to form a coherent argument or writing.

Literature Search

This study was screened manually by the author. Literature was searched by the search engine, including PubMed, ClinicalKey, and Cochrane. Keywords used were “ventriculography,” “MUGA scan,” “echocardiography,” “cardiac magnetic resonance,” “cardiotoxicity,” “breast cancer patients,” and “chemotherapy.” The keywords were combined with “AND” to look for literature with both keywords and “OR” to look for literature that has one of the keywords. Other than the search engine, the relevant literature was screened from literature references.

Data Extraction

Selected literature was extracted using Microsoft Excel. The extracted data included the author, published year, journal sources, purpose, methods, and findings according to the aim of this study.

RESULT

The process of collecting literature began by entering a keyword combination into the search engine. From the initial search, 1,381 pieces of literature were obtained (PubMed n = 774; ClinicalKey n = 330; Cochrane n = 275; and other sources n = 2). The other source of literature was a bibliography search from other literature. From a total of 1,381 pieces of literature, the initial search results were then selected based on the title, research repetition, and research continuation, which would be excluded and included by the most recent publication date. The 141 articles were further selected based on the title, abstract, and research inclusion criteria to be processed further, and 136 would not be further processed. Literature that is not processed further has titles and abstracts that are not following the research objectives and incomplete original literature. From this, 5 pieces of literature obtained were further processed. The researcher selected 5 collected pieces of literature after reading the full literature text and conducting a critical appraisal according to the literature research method selected.

Furthermore, summarizing the relevant pieces of literature, Table 2 depicts the comparison of Echo, Ventriculography, and CMR.

Huang et al. [33] demonstrate the comparison of LVEF performance in Ventriculography and CMR depicted in Table 3. They used CMR as a standard and verified that Ventriculography had high sensitivity, negative predictive value, and accuracy. Thus, Ventriculography was eligible as a modality to monitor and detect cardiotoxicity before, during, and after the administration of chemotherapy.

DISCUSSION

To assess cardiotoxicity, mainly the systolic function, the LVEF value is used. Ventriculography is a gold standard modality to assess LVEF to determine cardiac function before, during, and after chemotherapy. However, Ventriculography has ionizing radiation exposure, which is a concerning disadvantage; hence, several studies consider other modalities an alternative. From Huang et al. [33], Ventriculography clinical LVEF, which the clinician achieves, is modestly accurate
Figure 1. Literature searching strategy

Figure 2. Literature map

MUGA
- Huang, P. Nijjar, J. Misialek et al. (2017)
- V.Dhir, A. Yan, R. Nisenbaum et al. (2019)
- E.Reuvelkamp, B.Buiten, A.Nieuwenhuis et al. (2016)

Echo
- T.Tak, C. Jackel, S. Gharacholou et al. (2020)

CMR
- Huang, P. Nijjar, J. Misialek et al. (2017)
- V.Dhir, A. Yan, R. Nisenbaum et al. (2019)
- T.Tak, C. Jackel, S. Gharacholou et al. (2020)
<table>
<thead>
<tr>
<th>No.</th>
<th>Author (year)</th>
<th>Journal sources</th>
<th>Purpose</th>
<th>Study method</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tak et al. (2020) [30]</td>
<td>International Journal of Angiology</td>
<td>To compare CMR versus Echo to detect a reduction in left ventricular ejection function, suggestive of doxorubicin cardiotoxicity.</td>
<td>Retrospective study</td>
<td>It appears that CMR is superior to Echo for detecting doxorubicin-induced reductions in cardiac systolic function. However, Echo is less expensive and more convenient for patients because of its non-invasive character and bedside practicality.</td>
</tr>
<tr>
<td>2</td>
<td>Dhir et al. (2019) [31]</td>
<td>International Journal of Cardiovascular Imaging</td>
<td>To compare CMR and MUGA for LVEF assessment and examine the association between changes in brain NT-BNP and troponin-I and changes in CMR LV function and volume.</td>
<td>Prospective longitudinal two-centre cohort study</td>
<td>Both CMR and MUGA demonstrated significant LVEF decline at 6 and 12 months from baseline. CMR and MUGA LVEF are not interchangeable, warranting the selection and utility of one modality for serial monitoring. CMR is beneficial due to less radiation exposure and the accuracy of LV volume measurements. Changes in NT-BNP correlated with changes in LV volumes.</td>
</tr>
<tr>
<td>3</td>
<td>Klein et al. (2019) [35]</td>
<td>Nuclear Medicine Communications</td>
<td>To elucidate whether DD precedes LVEF decrease in trastuzumab-treated patients being monitored with radionuclide multigated acquisition for TIC</td>
<td>Retrospective study</td>
<td>Patients receiving trastuzumab ± anthracycline adjuvant therapy may develop DD before SD, therefore offering an opportunity for early referral to cardiologists.</td>
</tr>
<tr>
<td>4</td>
<td>Huang et al. (2017) [34]</td>
<td>Journal of Cardiovascular Magnetic Resonance</td>
<td>To compare the accuracy of LVEF obtained by contemporary clinical MUGA with reference LVEFs from CMR in consecutive patients</td>
<td>Cross sectional study</td>
<td>MUGA clinical LVEFs are only modestly accurate when compared with CMR reference LVEFs.</td>
</tr>
<tr>
<td>5</td>
<td>Reuvekamp et al. (2016) [32]</td>
<td>Journal of Nuclear Cardiology</td>
<td>To evaluate MUGA-derived diastolic and systolic function parameters in breast cancer patients treated with Trastuzumab to determine whether diastolic function parameters can be used as early detectors of TIC.</td>
<td>Retrospective study</td>
<td>MUGA can detect Trastuzumab-induced SD and DD. An impairment of MUGA-derived diastolic parameters does not occur prior to SD and, therefore, cannot be used as earlier predictors of TIC.</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fractions; MUGA, multiple gated acquisition scans; CMR, cardiovascular magnetic resonance; NT-BNP, natriuretic peptide; LV, left ventricle; DD, diastolic dysfunction; SD, systolic dysfunction; TIC, trastuzumab-induced cardiotoxicity; CMR, cardiac magnetic resonance; Echo, echocardiography
Table 2. Advantages and disadvantages of cardiac function imaging techniques

<table>
<thead>
<tr>
<th>No.</th>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</table>
| 1   | Echo     | • Wide availability, portable, inexpensive  
      • Relatively fast and safe exam  
      • Simultaneous assessment of chambers, function, valve, pericardium  
      • Highest temporal resolution  
      • No ionizing radiation  
      • Tissue velocity imaging and strain imaging can detect early cardiac dysfunction that is still in the subclinical stage | • Operator-dependent with high interobserver, intraobserver, and interscan variability  
      • Poor acoustic windows /imaging in patients with obesity or COPD  
      • Interpretation is highly dependent on the quality of the image generated. The image quality itself can be affected by body habitus  
      • Standard echocardiographic parameters have a poor cellular correlation  
      • Low sensitivity in assessing ejection fraction for early diagnosis GLS: inter-vendor variability, technical requirements |
| 2   | CMR      | • Highly accurate and reproducible  
      • High spatial and temporal resolution (multiplanar)  
      • High contrast between blood pool and myocardium  
      • Tissue characterization (i.e., detection of diffuse myocardial fibrosis based on acceptance of T2 and T1 mapping and extracellular volume fraction quantification)  
      • Simultaneous assessment of chambers, function, valve, pericardium, perfusion, and viability (morphological, functional, and extra-cardiac information)  
      • True 3D heart coverage  
      • No ionizing radiation | • Less available and not portable  
      • Longer exam time, requiring the patient to perform multiple breath-holds  
      • Expensive examination and time-consuming post-processing  
      • Artifacts  
      • Contrast reaction (rare)  
      • Renal impairment due to infrequent risk (likely <0.07%) of nephrogenic systemic fibrosis with gadolinium  
      • It cannot be used in patients with implantable devices that are not MRI-compatible (such as some pacemakers or implantable cardioverter-defibrillators)  
      • It cannot be performed on patient with claustrophobia  
      • Gadolinium accumulation potential in the brain  
      • Information on the role of this modality in early detection is still low |
| 3   | Ventriculography (MUGA) | • Reproducibility  
      • Availability  
      • High sensitivity and specificity in assessing ejection fraction  
      • There is no inter-and intra-observer variability | • Radiation exposure  
      • Limited morphological and functional information  
      • Low sensitivity in assessing ejection fraction for early diagnosis |

Echo, echocardiography; COPD, chronic obstructive pulmonary disease; GLS, global longitudinal strain; CMR, cardiovascular magnetic resonance; MUGA, multiple gated acquisition scans

Table 3. Performance of Ventriculography LVEFs compared with CMR LVEFs at thresholds of 50 and 55%

<table>
<thead>
<tr>
<th>No.</th>
<th>LVEFs threshold of 50%</th>
<th>LVEFs threshold of 55%</th>
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<tbody>
<tr>
<td>1</td>
<td>Sensitivity</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>Specificity</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>False-negative rate</td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>False-positive rate</td>
<td>49%</td>
</tr>
<tr>
<td>5</td>
<td>Positive Predictive Value</td>
<td>60%</td>
</tr>
<tr>
<td>6</td>
<td>Negative Predictive Value</td>
<td>74%</td>
</tr>
<tr>
<td>7</td>
<td>Accuracy</td>
<td>65%</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; CMR, cardiovascular magnetic resonance
compared to CMR. The study demonstrates a comparison between Ventriculography LVEFs performance and CMR LVEFs at 50 and 55% thresholds, which is measured by sensitivity, specificity, false-negative rate, false-positive rate, positive predictive value, negative predictive value, and accuracy. As depicted in Table 3 with an LVEFs threshold of 55%, Ventriculography demonstrates high sensitivity, negative predictive value, and accuracy. Nevertheless, it needs to know that, based on Dhir et al. [31] study, Ventriculography, and CMR monitoring are not interchangeable due to the wide Bland–Altman limits of agreement and weak concordance correlation coefficients at all time points between them. The comparison of Ventriculography and CMR from those two studies demonstrates a wide LVEF agreement [31,33]. Thus, consistency in using one modality for serial monitoring must still be carried out. The consideration of choosing CMR or Ventriculography depends on several things regarding the advantages and disadvantages of each modality. Even though CMR is more beneficial due to excellent intra-observer, inter-observer, and inter-study variability; it is essential to note that CMR is impossible to be chosen as serial monitoring modality due to its limited availability, scheduling, and high costs. At the same time, Ventriculography is more available, cost-effective, and not time-consuming [23,25].

In addition, other than Ventriculography, there is another low-cost and available modality, echocardiography (Echo) [35,36]. According to Tak et al. [30], it represents CMR is superior to Echo. Nonetheless, the population in this study is small, warranting further studies. Ventriculography and Echo are more available, inexpensive, and convenient than CMR. However, it is essential to note that high intervendor, interobserver, and intraobserver variabilities have been mentioned previously with Echo [35,36]. Moreover, the feasibility of 3-dimensional echocardiography-derived myocardial strain in selected populations can be as low as 85% [37]. To the best author’s knowledge, there has been no direct comparison of Ventriculography and Echo diagnostic value until writing this literature. However, Yang et al. [33] have shown a low correlation between Ventriculography LVEF and Echo LVEF. Furthermore, the study presented the high correlation between Echo LVEF and estimated LVEF using Mutual Information (MI) in Ventriculography. With this result, Ventriculography MI becomes a potential bridge to transfer the LVEF from Ventriculography to Echo [34]. Relevant literature is summarized to find out the advantages and disadvantages of these three modalities, listed in Table 2 [27,39,40].

Furthermore, as ionization radiation exposure might concern Ventriculography usage, several studies stated that Ventriculography requires minimal cumulative effective radiation dose. Thus, it is acceptable and safe [41,42].

Most of the monitoring only evaluates the systolic function, especially LVEF, even though, according to Klein et al. [35], diastolic dysfunction (DD) may precede systolic dysfunction (SD), especially for the patients who receive Trastuzumab and Anthracycline. Besides being able to detect SD through LVEF value, Ventriculography can detect DD through LV peak filling rate (PFR) and time to peak LV filling rates (TPFR). It is strengthened in Reuvekamp et al. [32] study illustrating Ventriculography’s ability to detect SD and DD induced by Trastuzumab and stated that the nuclear ventriculography test optimally assessed the LV dysfunction compared to other modalities. Its scanning involves taking multiple pictures of the heart at various angles. It becomes superior for the accuracy of left ventricle EF as it does not require geometric conformation and estimation of EF from certain areas of the ventricles [43]. Klein et al. [35], it is explained that LVEF is decreased in patients who received Anthracycline and Trastuzumab. However, during the four-month follow-up until the final follow-up, the LVEF value remains stable. For patients who received Anthracycline and Trastuzumab with normal diastolic function at baseline, the PFR value falls, implying DD precedes SD with interval dysfunction of 73 days. The PFR and TPR of the patients who had an abnormal diastolic function at baseline remained unchanged during therapy. From both studies regarding DD, we know that DD could precede SD in patients who received Anthracycline and Trastuzumab with normal diastolic function at baseline, but not in patients who receive Trastuzumab only [32,35]; hence, it is recommended to assess diastolic and systolic functions simultaneously.

CONCLUSIONS

Ventriculography as one modality for monitoring cardiac function and detecting cardiotoxicity in breast cancer patients receiving chemotherapy can still be used as the gold standard with affordable prices and acceptable side effects due to the minimum radiation exposure. Its usage is also applicable in Indonesia and might help patients who are not eligible for echocardiography. Nevertheless, it is recommended to choose only one modality for serial monitoring due to uninterchangeable results among modalities. Other than Ventriculography, CMR has better diagnostic values than Ventriculography in detecting cardiotoxicity but at a higher cost. In comparison with Echo, Ventriculography does not have any variability.

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DEclarations

Competing of Interest
The authors declare no competing interest in this study.

Acknowledgment

References


