Sunnybrook
HEALTH SCIENCES CENTRE

Title: Reassessing Normative Cardiac Chamber Measurements: A Comparative Study of TTE and TEE under General Anesthesia.

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Background

Transesophageal echocardiography (TEE) has become an indispensable tool in managing patients undergoing cardiac surgery or those with significant cardiac conditions, particularly given its utility in settings where transthoracic echocardiography (TTE) faces limitations, such as during resuscitation or in assessing shock [1, 2].

Despite the growing reliance on TEE, the lack of standardized normative values for chamber measurements under general anesthesia poses a challenge. Even though its integral role, normative values for TEE chamber measurements, essential for accurate diagnosis and monitoring, are based on benchmarks set over two decades ago [3]. Cohen et al. established normal values for adult TEE measurements, based on a review of studies using single-plane TEE. However, this foundational work did not formally compare TEE with TTE [3]. This gap in the research has not been adequately addressed in subsequent years. Previous studies have often focused on limited chamber assessments and did not account for the altered physiological conditions during surgery [4].

The reliance on these dated norms without a formal comparative analysis of TTE poses significant limitations, particularly as it does not reflect the advancements in imaging technology and the evolving understanding of cardiac physiology under various clinical conditions. Furthermore, the absence of a comprehensive evaluation across all cardiac chambers under conditions that mimic current clinical practices, such as during general anesthesia and positive pressure ventilation, highlights a critical knowledge gap. This limitation is compounded by the fact that general anesthesia and positive pressure ventilation can significantly alter cardiac function, affecting sympathetic tone, venous return, and cardiac output, thus potentially influencing measurement results [5, 6].

Given this context, our study seeks to critically reexamine and update the normative values for TEE by directly comparing them with TTE measurements in a contemporary cohort of patients undergoing cardiac surgery under general anesthesia. By addressing the limitations of prior studies and reflecting on current clinical practices, this project aims to establish a more relevant and robust foundation for the use of TEE in cardiac assessment and monitoring. Our primary objective is to assess the agreement between TTE and TEE measurements in terms of chamber dimensions, with a secondary focus on how these measurements correlate in patients subjected to the varying physiological conditions induced by general anesthesia.

Study Design

Prospective, single-center, observational, longitudinal cohort study evaluating the agreement between transthoracic echocardiography (TTE) and intraoperative transesophageal echocardiography (TEE) measurements in patients undergoing cardiac surgery.

Study Population

Patients will be recruited from the cardiac surgery patient pool at the Sunnybrook Health Sciences Centre, primarily through the anesthesia pre-assessment clinic. After obtaining approval from the ethics board, a total of 114 patients will be enrolled, with an anticipated recruitment rate of approximately 2-3 patients per week. With Sunnybrook Health Sciences Centre handling approximately 810 cardiac cases annually, of which approximately 80% are for coronary revascularization, this recruitment rate is feasible and will ensure a

diverse and representative sample of the cardiac surgery population.

Study Objectives and Hypothesis

Primary objective:

To assess the agreement between transthoracic echocardiography (TTE) and intraoperative transesophageal echocardiography (TEE) measurements of cardiac chamber dimensions in patients undergoing cardiac surgery.

Secondary objectives:

- **To investigate the correlation between TTE and TEE measurements under varying physiological conditions induced by general anesthesia and positive end-expiratory pressure (PEEP).** General anesthesia combined with positive pressure ventilation (PPV) can reduce systolic LV and RV function to levels indicative of dysfunction in a substantial proportion of patients without myocardial disease, affecting cardiac function through changes in lung volume, venous return, diastolic interactions between the ventricles, and intrathoracic pressure. This study will assess how these varying physiological conditions influence the agreement between TTE and TEE measurements.
- **To evaluate the impact of different cardiac conditions on the agreement between TTE and TEE measurements.** Patients with chronic obstructive pulmonary disease (COPD) and other cardiac conditions present unique challenges for echocardiographic assessment due to their distinct hemodynamic profiles. The effects of PEEP in these conditions include alterations in left ventricular preload, afterload, contractility, and ventricular compliance, which can unpredictably impact cardiac output. This objective will explore how COPD and various other cardiac conditions affect the correlation between TTE and TEE

measurements. The specific conditions to be evaluated include hypertension (HTN), diabetes mellitus (DM), smoking history, alcohol use, history of atrial fibrillation, history of stroke or transient ischemic attack, chronic kidney disease, liver disease, other comorbidities, and The New York Heart Association (NYHA) functional classification (I-IV). These insights will help determine the applicability of normative values across diverse patient populations.

Hypothesis:

We hypothesize that there will be a correlation level between fair and moderate agreement between TTE and TEE measurements of cardiac chamber dimensions in patients undergoing cardiac surgery. Additionally, we anticipate that the correlation between TTE and TEE measurements will vary due to different physiological conditions induced by general anesthesia. Finally, we expect that the agreement between TTE and TEE measurements may vary depending on the specific cardiac conditions present in the patient population.

Inclusion Criteria:

- Age ≥ 18, able to provide informed consent.
- Patients scheduled for coronary revascularization cardiac surgery under general anesthesia.
- With normal left ventricular (LV) systolic function, defined by an ejection fraction of 50% or more, and normal right ventricular (RV) systolic function.
- Requiring intraoperative echocardiographic assessment.

Exclusion Criteria:

- Patients with contraindications to either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE).
- History of poor-quality echocardiography data that preclude accurate assessment.
- Undergoing emergency cardiac surgery.

Methodology

Preoperative and postoperative TTE examinations will be performed routinely by registered sonographers in the cardiology echocardiography laboratory in awake patients within two weeks prior to scheduled surgery. The reported TTE findings will be used as a screening tool to include only patients with normal LV and RV function. The TTE images obtained will then be measured by two different examiners.

For both TTE and TEE, measurements will be taken over 3 to 5 consecutive beats. End-diastolic measurements will be defined as the R-wave on ECG. End-systolic measurements will be defined as the end of the T-wave on ECG. These measurements will be normalized to body surface area (BSA) using the Mostellar formula.

<u>Transthoracic Echocardiography Measurements:</u>

TTE measurements will follow the ASE chamber quantification guidelines 2015:[7]

Left Ventricle:

- The LV linear internal measurements, at end-diastole (LVIDd) and end-systole (LVIDs), will be measured in the parasternal long axis view (PLAX) perpendicular to the LV long axis at the level of mitral valve leaflet tips.
- Interventricular septum (IVS) and posterior wall thickness (PWT) will be measured in

the same view using M-mode approach.

- LV mass will be calculated using the linear method formula or 0.8 x (1.04 x [IVSd + LVIDd + PWTd)^3 - LVIDd^3]) + 0.6.
- LV volumes and ejection fraction will be measured from the apical four- and two-chamber views, based on biplane method of disks summation.
- LV area will be measured in the parasternal short axis view (PSAX) at the papillary muscle level by tracing the endocardium and excluding the papillary macules.
- LV fractional area change (FAC) will be calculated using the equation (end-diastolic area [EDA] – end-systolic area [ESA]/EDA) x 100.

Right Ventricle:

- The RV internal linear measurements will be measured in the RV-focused A4C view at end-diastole. Measurements will include basal linear dimension (RVD1), mid-cavity linear dimension (RVD2), and longitudinal dimension (RVD3).
- Proximal RV outflow diameter (RVOT prox) will be measured in the PLAX from the anterior RV wall to the IVS-aortic junction, or PSAX from the anterior RV wall to the aortic valve at end-diastole.
- Distal RV outflow (RVOT distal) will be measured in the PSAX, proximal to the pulmonary valve at end-diastole.
- RV wall thickness will be measured at end-diastole in the subcostal 4C view using M-mode.
- RV area measurements will be obtained from the RV-focused A4C by tracing of EV endocardial border.
- RV systolic function will be assessed using TAPSE and FAC. RV FAC was calculated based on the equation (EDA – ESA/EDA) x 100.

Left Atrium:

- LA measurements will include anteroposterior (AP) diameter measured at PSAX and PLAX at the aortic valve level at end-systole. Area will be measured in A4C and A2C views at end-systole.
- LA volume will be assessed using the LA Area and Length method in the A4C and A2C views, using the formula [0.85 x A4C Area (cm^2) x A2C Area (cm^2)]/LA Length (cm).

Right Atrium:

- RA internal linear dimensions will be measured in the A4C view. Major-axis will be measured from center of tricuspid annulus to the superior atrial wall. Minor-axis will be obtained perpendicular to major-axis by measuring lateral border of right atrium to interatrial septum. RA area will be measured in the same view at end-systole.
- RA volume will be assessed in the A4C view by the Area-Length method based on the formula [0.85 x RA Area (cm2) x RA Length (cm)]/10.

Aortic Valve:

- Left ventricular outflow tract (LVOT) will be measured in PLAX at mid-systole using inner edge to inner edge convention.
- Aortic annulus will be measured in PLAX at mid-systole using inner edge to inner edge convention.
- The Sinus of Valsalva, ST junction, and maximal diameter of the proximal ascending aorta will be measured in the same view at end-diastole using the leading edge to leading edge convention.

Transesophageal Echocardiography Measurements:

Intraoperative TEE studies will be performed as part of routine care by the National Board of Echocardiography-certified echocardiographers. Echocardiography images will be obtained using commercially available ultrasound machines.

Left Ventricle:

- LV internal dimensions will be measured at end-diastole (LVIDd) and end-systole (LVIDs) in the transgastric two-chamber (TG 2C) (90°) view perpendicular to the long axis of the LV, immediately below the mitral valve and at the mid-papillary muscle level.
- LV end-diastolic area and end-systolic area will be measured in the TG SAX (0°) midpapillary view by tracing the LV cavity and excluding the papillary muscles.
- The LV fractional area change will be calculated using the equation (EDA – ESA/EDA) x 100.
- LV end-diastolic and end-systolic volumes will be measured in the TG 2C view (90°) using Simpson's biplane method. LV ejection fraction will be calculated using the formula 100 x (end-diastolic volume – end-systolic volume/end-diastolic volume).
- IVS and PWT measurements will be acquired in the TG SAX (0°) view of LV immediately below the mitral valve leaflet at end-diastole using M-mode and leading edge to leading edge method.
- LV mass will be assessed using the linear method formula.

Right Ventricle:

- RV diameters will be measured in the midesophageal four-chamber (ME-4C) (0°) RV focused view. Measurements included RV EDA and RV ESA, obtained by tracing the endocardial RV at end-diastole and end-systole, and end-diastolic basal (RVD1), mid (RVD2), and long-axis (RVD3).
- RVOT will be measured in the ME RV inflow-outflow view (60-75°) at aortic valve and at pulmonary valve. RV wall thickness will be measured at end diastole – using M-mode in the ME 4C RV focused view.
- RV FAC will be calculated using the equation (EDA – ESA/EDA) x 100.
- Lateral tricuspid annulus anatomic M-mode (AMM TAPSE) will be measured in the ME-4C RV focused view by placing the cursor at the lateral tricuspid annulus and angling it towards the apex.
- RV function will be assessed using RV FAC and AMM-TAPSE as these measurements had good agreement with TTE based on previous literature [8].

Left Atrium:

- LA AP diameter will be measured from posterior LA wall to aortic annulus in the ME SAX (30-45°) and ME LAX (135°) views at level of aortic valve.
- LA minor axis will be measured in the ME 4C LV focused view at end-systole from the lateral wall to the interatrial septum. Major axis will be measured from distance from center of the valve of annulus to the center of the superior LA wall. LA area and volume will be obtained by the Area-Length method in the LV focused ME 4AC and ME 2AC at end-systole.

Right Atrium:

- RA minor axis will be measured in the ME 4C RV focused view at end-systole from

anterolateral wall to the interatrial septum. Major axis will be measured from distance from center of valve of annulus to center of superior RA wall. RA volume will be obtained by the Area-Length method in the RV-focused ME-4AC at end-systole.

Aortic Valve:

- LVOT and aortic annulus measured in the ME aortic valve LAX (135°) view at mid-systole using the inner edge to inner edge method at hinge points of aortic leaflets.
- Sinus of Valsalva, ST junction, and maximal diameter of proximal ascending aorta will be measured from the ME aortic valve LAX (135°) view at end-diastole, using the leading edge to leading edge method.

Data Collection

1. Demographic and clinical characteristics: age, gender, weight, height, BMI, COPD, HTN, DM, smoking history, alcohol use, history of atrial fibrillation, history of stroke or transient ischemic attack, chronic kidney disease, liver disease, peripheral artery disease, valvular heart disease, and NYHA functional classification (I-IV).
2. Cardiac procedure type: CABG, Valve, CABG + valve, redo procedures.
3. Preoperative and perioperative echocardiographic measurements by TTE following established guidelines and protocols. Measurements include cardiac chamber dimensions, ventricular function parameters, and valve assessments.
4. Limited-quality sonographic examinations.
5. Inter-observer repeatability and intra-observer reproducibility of ultrasound measurements (assessed by computing repeatability and reproducibility coefficients).

Statistical Analysis

Descriptive statistics will summarize demographic, clinical, and echocardiographic data. Continuous variables will be described using median and interquartile range, and dichotomous and polytomous variables were summarized using frequencies.

Sample size calculation was based on achieving a power of 80%, with an anticipated dropout rate of 10%. The correlation between TTE and TEE measurements in previous literature ranged between 0.76 and 0.93 [8-11]. Considering a conservative correlation value of 0.75, as suggested by prior studies, a sample size of 114 patients was determined to be necessary.

The primary outcome will be the agreement between TTE and TEE measurements of chamber dimensions. Secondary outcomes include correlations between measurements under varying physiological conditions induced by general anesthesia. Statistical analysis will include descriptive statistics, Bland-Altman analysis, and calculation of Lin's concordance correlation coefficient. Additionally, subgroup analyses will be conducted to assess the impact of different cardiac conditions on measurement agreement.

With the independent measurement by two examiners of fifteen randomized echocardiography data sets, blind to each other's measurements, the interobserver variability was calculated. The Bland-Altman (BA) method was applied to assess the agreement between observers, providing the level of agreement (LOA) between the two measurements and summarizing the agreement graphically [12]. The intraclass correlation coefficient (ICC) and its 95% confidence intervals (CIs) were calculated using agreement between ratings. The same examiner repeated the measurements in fifteen randomized echocardiography date sets measurements to estimate the intraobserver variability. No adjustments were made for multiple comparisons. All p-values and 95% confidence intervals were 2-sided, with an alpha level of 0.05.

All analyses were conducted using SAS software, Version 9.4 of the SAS System for Windows, and R version 3.4.1.

Knowledge Translation

Dissemination of Findings: The study results will be disseminated through various channels, including peer-reviewed publications in cardiology or anesthesia journals, conference presentations, and seminars at academic institutions.

Clinical Guidelines and Practice: The study findings can contribute to the development or

refinement of clinical guidelines for echocardiographic assessment in patients undergoing cardiac surgery. This may include recommendations for optimizing the agreement between transthoracic echocardiography (TTE) and intraoperative transesophageal echocardiography (TEE) measurements, as well as guidance on interpreting echocardiographic data under varying physiological conditions induced by anesthesia.

Educational Resources: Educational resources, such as online modules or workshops, can be developed for clinicians involved in cardiac surgery and echocardiography training programs. These resources can emphasize the importance of accurate echocardiographic assessment and provide guidance on best practices based on the study findings.

Quality Improvement Initiatives: Hospitals and healthcare institutions can use the study findings to implement quality improvement initiatives aimed at standardizing echocardiographic protocols and enhancing interobserver variability in echocardiographic measurements. This may involve training programs, protocol revisions, or the implementation of quality assurance measures.

Collaboration with Stakeholders: Collaboration with key stakeholders, including cardiac surgeons, anesthesiologists, echocardiographers, and patient advocacy groups, will facilitate the translation of study findings into clinical practice. Engaging stakeholders throughout the research process can ensure that the study addresses relevant clinical questions and that the findings are effectively disseminated and implemented.

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