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Original Article / Özgün Araştırma

Assessing Left Ventricular Dimensions in Patients During Coronary Artery Bypass Surgery by Transoesophageal Echocardiography

Koroner Arter Bypass Ameliyatı Boyunca Hastalarda Sol Ventrikül Boyutlarının Transözofagial Ekokardiyografi İle Değerlendirilmesi

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Abstract / Öz

Objective: Normative values for left ventricular (LV) end-diastolic area (EDA) and diameter (EDD) for intra-operative transoesophageal echocardiography (TOE) have not been established. We aimed to define the ranges of LV EDA and EDD for intra-operative TOE examinations in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods: A MEDLINE search for studies reporting LV EDA and EDD in patients undergoing CABG surgery was performed. Individual-level data set from 333 anaesthetised and ventilated patients with preserved LV function (study population) was obtained from eight studies. EDA and calculated EDD in the study population were compared with summary EDD values obtained using transthoracic echocardiography (TTE) in two studies of 500 awake patients with coronary artery disease (CAD). Further, the influence of pre-specified factors on EDD was evaluated in a multivariate regression model.

Results: The EDA and EDD values measured using TOE in the anaesthetised CABG patients were 16.7±4.7 cm² and 4.6±0.6 cm, respectively. TOE values of EDD in anaesthetised patients were 10%-13% less than those measured using TTE in two studies of awake patients (p<0.001). Body surface area, age and fractional area change, but not sex were factors that affected LV EDD.

Conclusion: The values for LV EDD measured through intra-operative TOE in anaesthetised ventilated CABG patients were 10%-13% less than the corresponding values measured using TTE in awake CAD patients. This finding indicates that independent normative values specific for intra-operative TE should be established for guiding intra-operative clinical decisions.

Keywords: Echocardiography, transthoracic echocardiography, transesophageal echocardiography, cross-sectional, coronary artery bypass surgery

Amaç: İntraoperatif transözofajiyal ekokardiyografi (TOE) için sol ventrikül (SV) diyastol sonu alanı (EDA) ve çapının (EDD) normal değerleri belirlenmemiştir. Bu çalışmanın amacı, koroner arter bypass greft (KABG) ameliyatı geçiren hastalarda yapılan intraoperatif TOE incelemeleri için SV EDA ve EDD aralıklarını tanımlamaktır.

Yöntemler: KABG ameliyatı geçiren hastalarda SV EDA ve EDD değerlerini rapor eden çalışmalar için bir MEDLINE araştırması yapıldı. Korunmuş SV fonksiyonu olan 333 anestezi ve ventilasyon uygulanmış hastanın (çalışma popülasyonu) bireysel verileri 8 çalışmadan elde edildi. Çalışma popülasyonundaki EDA ve hesaplanmış EDD değerleri, koroner arter hastalığı (KAH) olan 500 bilinçli hastayı içeren iki çalışmada transtorasik ekokardiyografi (TTE) kullanarak elde edilen özet EDD değerleri ile karşılaştırıldı. Ayrıca, önceden belirlenmiş faktörlerin EDD üzerindeki etkisi multivaryant regresyon modeli kullanılarak değerlendirildi.

Bulgular: Anestezi altındaki KABG hastalarında TOE kullanılarak ölçülen EDA ve EDD değerleri sırasıyla 16,7±4,7 cm² ve 4,6±0,6 cm olarak bulundu. Anestezi uygulanan hastalarda TOE ve EDD değerleri, bilinçli hastalar üzerinde yapılan iki çalışmada TTE kullanılarak ölçülen değerlere göre %10-%13 daha düşüktü (p<0,001). Vücut yüzey alanı, yaş ve fraksiyonel alan değişimi SV EDD'yi etkileyen faktörler olarak saptanırken, cinsiyetin etkilemediği görüldü.

Sonuç: Anestezi ve ventilasyon uygulanan KABG hastalarında intraoperatif TOE ile ölçülen SV EDD değerlerinin, bilinçli KAH hastalarında TTE ile ölçülen değerlere göre %10-%13 daha düşük olduğu izlendi. Bu sonuca göre, intraoperatif klinik kararlara rehberlik etmek için, intraoperatif TOE'ye özgü bağımsız normal değerler belirlenmelidir.

Anahtar sözcükler: Ekokardiyografi, transtorasik ekokardiyografi, transozofagial ekokardiyografi, kesitsel, koroner arter bypass ameliyatı

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Introduction

Transoesophageal echocardiography (TOE) has been recommended for all patients undergoing cardiac surgery and is accepted worldwide for the evaluation of unexplained haemodynamic instability in intra-operative management and decision-making (1, 2).

The left ventricular (LV) end-diastolic chamber dimensions, *i.e.* LV end-diastolic area and diameter (EDA and EDD), are regularly used to identify patients with low or normal LV volaemia and to guide intravenous administration of fluids (2-5). However, the clinical utility of EDA and EDD for intra-operative decisions and prognosis depends on the accuracy and reliability of normal values. In fact, the availability of normative reference values for cardiac chamber quantification is a prerequisite for accurate clinical application of echocardiography (6). Two large studies recently published normal values as assessed using transthoracic echocardiography (TTE) in young and healthy patients (6, 7). However, such values might not necessarily apply for patients with coronary heart disease. Further, even if normative values obtained using transoesophageal echocardiography (TOE) in awake subjects are applied (6, 7), anaesthetic drugs, positive pressure ventilation and patient positioning may have systematic effects on cardiac function and loading conditions causing small, but important differences in LV EDA and EDD measurements in the anaesthetised and ventilated patients (8-10). Finally, TTE values might be different from those for TOE as a consequence of small differences in the position of the echo probe and the slightly different standard echocardiographic cross-sectional views used in the two techniques (11). Nonetheless, reference values for LV EDA and EDD obtained from TTE studies performed in awake healthy patients are commonly applied as diagnostic criteria for the intra-operative TOE examination (12, 13).

The aim of this study was (1) to define the physiologic ranges of LV EDA and EDD in anaesthetised and mechanically ventilated patients undergoing coronary artery bypass graft (CABG) surgery as obtained using TOE immediately before surgery; (2) to compare the values obtained by intra-operative TOE with reference values obtained using TTE in awake, spontaneously breathing patients with coronary artery disease (CAD) and (3) to determine which patient factors affect LV EDA and EDD in patients undergoing CABG surgery. We hypothesised that the ranges for LV EDA and EDD measured using intra-operative TOE are different from those measured using TTE studies in awake patients.

Methods

This is individual-level data analysis including data from several published studies (3, 14-19). All patient data from studies included in this analysis were approved by the local institutional review boards, and written informed consent was obtained from all included patients.

Study population

We searched the MEDLINE database to identify studies reporting on EDA or indexed EDA (EDAI) values measured using transgastric TOE in the short-axis view at the transgastric mid-papillary level (TG mid SAX) in patients undergoing CABG surgery (20). The search included the period between January 1990 and May 2014. The following search terms were applied: 'transesophageal echocardiography cardiac surgery', 'transesophageal echocardiography CABG left ventricle', 'transesophageal echocardiography aorto-coronary bypass', 'transesophageal echocardiography CABG short-axis', 'transesophageal echocardiography CABG LVEDA', 'echocardiography cardiac surgery anaesthesia', 'CAD end-diastolic', 'CAD EDA', 'CAD LVEDA', 'CAD EDAI' and 'CAD LVEDAI'. We identified a total of 1131 citations. Eligibility criteria consisted of EDA values measured using TOE in the TG mid SAX view (20), including the papillary muscle (21). Further eligibility criteria were clinically stable haemodynamic conditions without the use of vasopressors or vasodilators during measurements and EDA measurements without the use of automatic border detection for the determination of EDA. Fifteen studies satisfied the eligibility criteria. The corresponding authors were contacted and requested to provide individual patient-level data. We obtained the original data from seven publications (3, 14-19). The authors of the eight other studies did not respond and were not able or willing to provide individual patient data. In addition, a co-author (JP) shared individual patient data from an unpublished TOE study that also satisfied the eligibility criteria. We thereby selected the study population including 333 patients who fulfilled the following additional pre-specified individual patient criteria: (1) preserved LV function defined as LV ejection fraction (EF) ≥45% or fractional area change (FAC) ≥40% (22); (2) isolated CABG surgery; (3) no previous cardiac surgery requiring sternotomy and (4) no relevant valvular heart diseases. The collected data of the study population included patient demographics, LV EDA and LV end-systolic area (ESA). In two studies (13, 16), the TOE data immediately before surgery but after anaesthesia induction and at the end of surgery were available for 78 patients. In both studies, 'before surgery' was defined as the time after induction of anaesthesia but before sternotomy, and 'after surgery' was defined as the time after sternal closure but before transfer to the intensive care unit.

Awake population

To compare EDD and EDA values in anaesthetised and awake patients, we searched MEDLINE for studies providing EDA values in awake CAD patients. Because the search retrieved no studies using the above-described MEDLINE search strategy, we expanded the search to include EDD using the following terms: 'CAD echocardiography', 'CAD end-diastolic diameter' and 'CAD LVEDD'. We identified a total of 876 citations. Eligibility criteria consisted of haemodynamically stable CAD patients with preserved LV function (EF ≥45% or FAC ≥40%) and the availability of TTE estimates of LV

EDD in the parasternal long-axis (LAX) view. Two studies including 139 and 361 patients fulfilled these criteria (23, 24). Because we were unable to obtain individual patient data from these two studies, we compared the TOE values from the study population with the summary estimates reported in the two TOE studies in the awake population.

Endpoints

The endpoints were LV EDA and EDD measured in the TG mid SAX view. EDD values were reported in only one TOE study. In contrast, the summary values in the awake population consisted exclusively of EDD measurements (23, 24). To compare EDD values, the TOE EDA values were mathematically converted into EDD values. Considering the circular symmetry of the LV cavity at the TG mid SAX view (20), we used the equation: $EDD=\sqrt{(4\times EDA/\pi)}$.

Factors influencing EDA/EDD values

Patient factors potentially influencing LV EDA and EDD values were tested using a linear regression model as described below. In addition, we tested if EDA values and calculated EDD values were different among male and female patients. Further, we analysed whether EDA values obtained immediately before surgery were different from those obtained immediately after surgery using data from two studies.

Statistical analysis

No formal sample size calculation was performed for this study. Data were presented as mean±standard deviation (SD) or number (percentage) as appropriate. Mean±SD (95% confidence interval [CI]) of the pooled data were compared using a two-sided *t* test for unpaired and paired measurements as appropriate. To evaluate factors influencing EDA and EDD, we inserted four pre-specified independent variables into the linear regression model. Sex was inserted as a dichotomous variable, whereas age (per year increase), LV FAC (per % increase) and body surface area (BSA; per m^2 increase) were entered as continuous variables into the model. A p value <0.05 was considered significant. Statistical analyses were performed using the IBM Statistical Package for Social Sciences software (version 21; IBM Corp., Armonk, NY, USA).

Results

Characteristics of the study population and the awake population

Individual data sets were obtained from 304 patients in seven published studies (3, 14-19) and from 85 patients in one unpublished study (Table 1). In all studies, LV EDA and ESA were measured using manual planimetry of the endocardial boarders at end-diastole and end-systole according to the guidelines provided by Lang et al. (21). The average LV EDA (mean±SD) obtained from each study is shown in Figure 1. Data from 56 patients were excluded due to impaired LV function (EF <45% or FAC <40%) providing a final sample size of 333 patients in the study population. Patient characteristics and the average LV dimensions from the study population are listed in Tables 2 and 3. The mean age in the study population was 64±9 years, and the proportion of male patients was 82%.

The two studies reporting EDD values measured in awake CAD patients enrolled 139 and 361 patients with preserved LV function, with 101 (73%) and 301 (83%) male patients (23, 24), respectively. The mean ages were 54±9 years and 58±10 years. Both TTE studies used M-mode imaging and LV EDD and end-systolic diameter were measured in the parasternal LAX view using the leading-edge-to-leading-edge technique at end-diastole and end-systole according to the guidelines provided by Lang et al. (21).

EDA and EDD values

The average LV EDA and calculated LV EDD values in the study population were 16.7±4.6 cm^2 and 4.6±0.6 cm, respectively. Excluding the patients from the unpublished study did not change these values. The average LV EDD values reported by Ghali et al. (23) and by Gruchala et al. (24) were 5.1±0.5

Table 1. Characteristics of studies providing individual data of 389 patients

First author, year	Patients	Male	Age (years)	Normal LV function*	Main anaesthetic
Cheung et al., 1994 (3)	31	N/A	N/A	25 (81)	Volatile
Seeberger et al., 1998 (18)	76	63 (83)	61±8	73 (97)	Volatile
Skarvan et al., 2003 (19)	42	35 (83)	64±10	33 (78)	Volatile
Poelaert et al., 2004 (16)	42	33 (79)	64±10	42 (100)	Propofol
Preismann et al., 2005 (17)	16	14 (88)	63±8	11 (69)	Volatile
Michaux et al., 2006 (15)	47	42 (84)	63±8	40 (85)	Volatile
Couture et al., 2007 (14)	50	38 (76)	68±8	44 (88)	Volatile
Poelaert, N/P	85	N/A	63±11	65 (76)	Propofol

Data are numbers (percent) or mean±standard deviation. All patients subsequently underwent coronary artery bypass graft (CABG) surgery. *Normal left ventricle (LV) function was defined as ejection fraction (EF) ≥45% or fractional area change (FAC) ≥40%.
N/A: not available; N/P: not published.

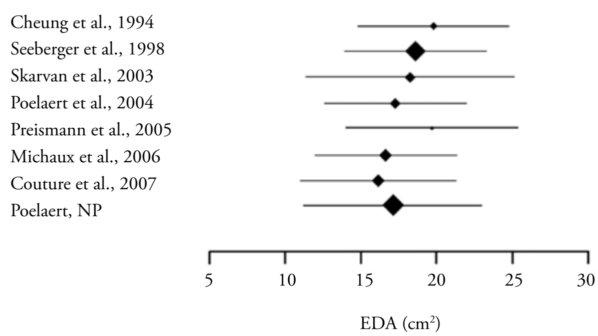

Figure 1. End-diastolic diameter area (EDA) in patients undergoing CABG surgery
Mean±standard deviation from the eight studies (3, 14-19) providing individual patient data are indicated. Studies performed during anaesthesia with isoflurane are indicated in black squares, and studies using propofol as main anaesthetic are indicated in white squares.
N/P: not published

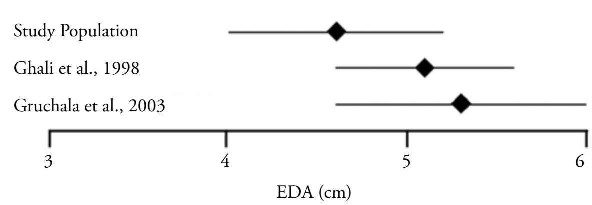

Figure 2. End-diastolic diameter (EDD) in the study population and in the awake population
Calculated EDD (mean±standard deviation) is lower in the anaesthetised study population with positive pressure ventilation than measured in the awake population constituted from two studies (23, 24)

cm and 5.3±0.7 cm, respectively (Figure 2). These TTE LV EDD values were 10%-13% greater than the calculated LV EDD values of 4.6±0.6 cm in the TOE study population (p<0.001 for both comparisons).

Factors influencing EDA and EDD values

The average TOE LV EDA values in females (15.3±4.6 cm^2; n=44) were less than those in males (17.2±4.7 cm^2; n=199; p=0.012). The average LV EDD values were also less in females compared to males (4.4±0.7 cm vs. 4.6±0.6 cm, p=0.008). When using indexed values corrected to BSA, LV EDAI and EDDI values were comparable among female and male patients.

In the multivariable linear regression model, BSA (0.83, 95% CI 0.40-1.26, p<0.001) and age (0.010, 95% CI: 0.002-0.018, p=0.020) were positively correlated with LV EDD, whereas FAC (–0.024, 95% CI: –0.030-0.019, p<0.001) was negatively correlated with LV EDD. Sex did not correlate with LV EDD (p=0.224). Similar correlations were obtained using LV EDA as the independent variable.

Table 2. Characteristics of the 333 patients of the study population

	Numbers of patients with data	Study population
Age (years)	310	64±9
Male	243	199 (82)
Height (cm)	333	170±8
Weight (kg)	333	80±13
Body surface area (m^2)	333	1.94±0.19
Body mass index (kg m^{-2})	333	27.4±3.8
Ejection fraction (%)	223	63±13
Fractional area change (%)	333	51±11

Data are mean±standard deviation or numbers (percentage)

Table 3. Echocardiographic parameters of the study population

	Study population (n=333)
End-systolic area (cm^2)	8.3±3.5
Indexed end-systolic area (cm^2 m^{-2})	4.3±1.8
End-diastolic area (cm^2)	16.7±4.6
Indexed end-diastolic area (cm^2 m^{-2})	8.7±2.3
End-diastolic diameter* (cm)	4.6±0.6
Indexed end-diastolic diameter* (cm m^{-2})	2.4±0.4

Data are mean±standard deviation. *End-diastolic diameter (EDD) was calculated as follows: $EDD=\sqrt{(4\times EDA/\pi)}$, where EDA is end-diastolic area

Among the 78 patients who had TOE measurements before and after surgery, postoperative TOE LV EDA values (16.2±6.3 cm^2) were significantly less than preoperative values (17.4±6.0 cm^2; p=0.006), whereas LV ESA did not change significantly. FAC also did not change significantly before and after surgery (50±15% vs. 49±16%; p=0.410).

Discussion

Based on individual-level data from 333 patients from eight clinical studies, LV EDA and EDD measured using intra-operative TOE in anaesthetised and mechanically ventilated CABG patients with preserved LV function during haemodynamically stable conditions prior to thoracotomy were 16.7±4.6 cm^2 and 4.6±0.6 cm, respectively. Intra-operative LV EDD values measured using TOE were 10%-13% less than published LV EDD values measured using TTE in awake CAD patients. This finding suggests that the common clinical practice of applying reference values obtained using TTE in awake patients as normative values for anaesthetised and ventilated patients assessed using TOE might be misleading and result in inappropriate intra-operative decisions regarding choice of therapy and prognosis. Further, this discrepancy between TTE and intra-operative TOE measurements highlights the need for studies designed to establish normative reference values specifically for intra-operative TOE studies in anaesthetised and ventilated patients. This conclusion is in agreement with two recently published studies (6, 7) which also claimed for reliable and accurate TTE reference values for chamber quantitation.

However, the normative values described by TTE in young and healthy individuals may not be representative for other populations to which they are applied (6, 7, 12, 13). Although some studies have reported nearly identical LV EDA and EDD values by both TTE and TOE in awake patients (25-27), the discrepancy between TOE and TTE measurements of LV EDA found in this study can be explained by several real, but subtle differences in the standard clinical imaging protocols used in TOE and TTE. Whereas the different echocardiographic approach, i.e. TTE vs. TOE, is unlikely to be causative factor (25-27), the standard cross-sectional imaging planes for measuring LV cavity dimensions in TTE and TOE are slightly but significantly different. Diameter measurements using the TTE parasternal LAX view are performed at the level of tips of the mitral valve leaflets (28). In contrast, LV cavity diameter in the study population was measured by using the TOE TG LV SAX view at mid-papillary level as recommended in the TOE guidelines published in 1999 (20) and valid until 2013. The normal anatomic shape of the LV has a smaller diameter at the mid-papillary level (closer to the LV apex) where the TOE measurements are performed compared to the diameter at the mitral valve leaflet tips (closer to the LV base) where the TTE measurements are performed. The recently updated TOE guidelines acknowledged this difference between TOE and TTE cross-sectional imaging planes for measuring LV cavity diameter and recommended to measure LV diameter using the TG LAX or the TG two-chamber views (2). Although this methodological difference between TTE and TOE is a convincing explanation for the differences found in the current study and may be minimised in the future with the updated TOE guidelines (2), reference ranges for LV EDA and EDD using this newly recommended approach have not been established. Clinicians are therefore likely to continue using the TG mid SAX view to measure LV EDA and EDD according to the first set of published guidelines (3, 20).

Interestingly, the normative value of LV EDD was determined as 4.43±0.48 cm using TTE in the NORRE study including young and healthy individuals (6). This value is comparable to the LV EDD value of 4.6±0.6 cm as determined in our TOE population but substantially lower in the studies by Ghali et al. (23) and Gruchala et al. (24), which report LV EDD values between 5.1 and 5.3 cm as assessed using TTE. It seems likely that the older age and cardiac comorbidities including CAD increase end-diastolic dimensions (29). However, the use of anaesthetic drugs and positive pressure ventilation as well as a relative intra-operative hypovolaemia might compensate for the 'dilative effect' of older age and cardiac disease on chamber dimensions.

Anaesthetic drugs and positive pressure ventilation may have relevantly influenced LV cavity dimensions in the TOE study population by affecting systemic vascular resistance, venous tone and venous return (30). The physiologic effects of general anaesthesia and positive pressure ventilation on LV cavity size were recently demonstrated in a magnetic resonance imaging study in healthy adults (10) and several echocardiographic studies in healthy subjects and in patients with cardiac disease (9, 31-33). All these studies reported that LV cavity dimensions were reduced during anaesthesia and positive pressure ventilation, most likely as a consequence of decreased venous return and LV preload.

The analysis of factors potentially affecting LV dimensions revealed that LV EDA and LV EDD were larger in males compared to females, but EDA and EDD values indexed for BSA became comparable. In agreement, there was no association of sex with EDDI and EDAI in the linear regression model after adjustment for BSA. Some weak positive associations between age and LV EDD were found, which is in agreement with normal changes that occur in the aging heart (29). Also, in agreement with earlier studies (3, 34), we found that LV EDA varied in response to differences in systolic function measured by FAC. Finally, LV EDA was significantly less immediately after surgery compared to its value immediately before sternotomy. Changes in heart rate, autonomic nervous system tone, decreased intravascular volume, or diastolic dysfunction as a consequence of reperfusion may all have contributed to the reduced LV EDA after surgery.

Study limitations

This retrospective study has several strengths and limitations: First, the study was based on pooled values from published studies that were identified by using detailed search strategies and predefined eligibility criteria; however, the literature search was limited to a single electronic database and did not comply formally with current standards for systematic reviews. However, the original objective of the study was to collect individual patient-level data from the previously published studies rather than comparing the summary data from different studies. Further, EDD was not included as a search term in the primary MEDLINE search, but a post-hoc search that included 'EDD' and 'end-diastolic diameter' as search terms did not reveal any additional TOE studies in anaesthetised patients, which could have been included in the analysis. Second, not all individual patient-level data sets were complete regarding patient characteristics and comorbidities. Third, the study relied on the investigators to adhere to the methodology described in their studies for performing the echocardiographic measurements. The studies were not standardised in terms of the precise cross-sectional imaging planes used, timing of measurements, haemodynamic conditions of the subjects, intravascular volume status, circulatory effects of any concurrent therapy, mechanical ventilator settings, or anaesthetic regimens administered. However, all the included TOE studies explicitly stated that measurements of LV cavity size were performed using the TG mid SAX view and that all measurements were performed during a period of stable haemodynamic conditions. Evidence to suggest that the methodology of the studies used in this analysis was uniform was that the patient-level measurements from each of the individual studies were not heterogeneous and yielded similar ranges for LV EDA (Figure 1). Fourth, due to the study design, measurements might not be completely comparable regarding preload. Fifth, although patient-level individual data were not obtainable from eight additional intra-operative TOE studies that fulfilled the eligibility criteria and were not available from the two TTE studies performed in awake patients, the consistency of the available data suggested that inclusion of additional patient-level individual data would unlikely change the results. Sixth, comparing LV cavity dimensions obtained using TOE and TTE required the conversion of LV EDA measurements in the study population to LV EDD assuming that the shape of the LV cavity in the TG SAX view was circular (20). This assumption seems to be limited by the fact that CAD is a regional disease but was generally valid because the eligibility criteria limited the study population to those with normal LV function. Further, published data support a nearly perfect correlation between EDD and EDA when measured independently (3), and the use of LV EDA measurements to generate LV EDD utilises a greater number of data points to generate the parameter and did not rely on a single linear measurement at two discrete points of the LV endocardium. Finally, the slightly older age of the study population is an unlikely confounder because the correlation between age and LV EDA and EDD in the multivariable linear regression was very weak.

Conclusion

Data from prior studies were used to determine the physiological ranges for LV EDA and EDD in anaesthetised and ventilated patients with preserved LV function measured through intra-operative TOE using the TG mid SAX view. The study found that values for LV EDD obtained using intra-operative TOE in the study population was 10%-13% less than corresponding TTE reference values obtained in a similar population of awake CAD patients. These findings question the common practice of applying normative values defined using TTE in awake patients for guiding intra-operative decisions and prognosis and indicate a need to establish specific normative reference values for intra-operative TOE measurements performed using the standard cross-sectional imaging planes.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Basel University.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.B., M.D.S.; Design - D.B., C.P., M.D.S.; Supervision - M.D.S., D.B.; Resources - A.T.C., P.C., I.M., J.P., S.P., M.D.S.; Materials - A.T.C., P.C., I.M., J.P., S.P., K.S., M.D.S.; Data Collection and/or Processing - C.P., D.B., G.L.B., A.T.C., P.C., I.M., J.P., S.P., K.S., M.D.S.; Analysis and/or Interpretation - D.B., C.P., G.L.B., A.T.C., P.C., I.M., J.P., S.P., K.S., M.D.S.; Literature Search - D.B., C.P., G.L.B., M.D.S.; Writing Manuscript - D.B., M.D.S.; Critical Review - D.B., C.P., G.L.B., A.T.C., P.C., I.M., J.P., S.P., K.S., M.D.S.

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