Transesophageal Echocardiography in Patients Undergoing Elective Coronary Artery Bypass Surgery

BY

INGRID PALMGREN
Transesophageal echocardiography (TEE) has become a useful tool in monitoring the heart in patients during open-heart surgery. This study was undertaken to evaluate whether it is feasible to use TEE to assess left ventricular myocardial viability in anesthetized patients scheduled for coronary artery bypass grafting (CABG).

A total of 84 patients were studied. To test myocardial viability, TEE and a low-dose dobutamine regimen were used. Echocardiographic data were analyzed off-line using a visual or semiautomatic analysis of segmental left ventricular wall motion (LVWM). Visual assessment was performed by readers blinded to the sequence of events. The agreement between readers in visual analysis of segmental LVWM in the transgastric short-axis view was 73% or higher. Segmental LVWM assessed by TEE was compared to hemodynamic data obtained by thermodilution pulmonary artery catheter (PAC) and coronary angiographic data. Also, using the same low-dose dobutamine stress regimen, TEE findings in the anesthetized patient perioperatively were compared with preoperative transthoracic echocardiography (TTE) findings in the awake patient.

TEE was found to be feasible and adequate for testing left segmental ventricular viability. A concomitant increase in stroke volume assessed by PAC and decrease in LVWM-score assessed by TEE was found with dobutamine stimulation. Abnormal segmental LVWM corresponded to angiographically stenosed supplying coronary artery vessels. During dobutamine stimulation, 69% of the corresponding segments responded which is a sign of viability. The LVWM response to preoperative TTE and perioperative TEE dobutamine stress was comparable except for a significant difference in the apical segments.

This study showed that perioperative TEE dobutamine stress could be used to test left ventricular viability and was also a valuable supplement to PAC, angiography and TTE. The acquired knowledge is important and suggest that further development of transesophageal ultrasound technology is warranted.

Key words: transesophageal echocardiography, low-dose dobutamine, viability, coronary artery bypass.
Till min förvåning
This dissertation is based on the following papers, which will be referred to by their Roman numerals:

I  Hultman J, Palmgren I, Landelius J, Andrén B

II Palmgren I, Hultman J, Houltz E

III Palmgren I, Hultman J

IV Palmgren I, Hultman J
   Perioperative transesophageal echocardiography with dobutamine as complement to preoperative coronary angiography. Submitted.

V Palmgren I, Andrén B, Ståhle E, Hultman J
   Transthoracic and transesophageal stress echocardiography in patients with left ventricular dysfunction. Submitted.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQ</td>
<td>acoustic quantification</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>DE</td>
<td>dobutamine stress echocardiography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EDA</td>
<td>end-diastolic area</td>
</tr>
<tr>
<td>ESA</td>
<td>end-systolic area</td>
</tr>
<tr>
<td>FDG</td>
<td>fluorodeoxyglucose</td>
</tr>
<tr>
<td>GAEF</td>
<td>global area ejection fraction</td>
</tr>
<tr>
<td>LAD</td>
<td>left descending artery</td>
</tr>
<tr>
<td>LCX</td>
<td>left circumflex artery</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVWM</td>
<td>left ventricular wall motion</td>
</tr>
<tr>
<td>PAC</td>
<td>pulmonary artery catheter</td>
</tr>
<tr>
<td>PCWP</td>
<td>pulmonary capillary wedge pressure</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>RCA</td>
<td>right coronary artery</td>
</tr>
<tr>
<td>SAEF</td>
<td>segmental area ejection fraction</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>TEE</td>
<td>transesophageal echocardiography</td>
</tr>
<tr>
<td>TTE</td>
<td>transthoracic echocardiography</td>
</tr>
</tbody>
</table>
Introduction

The introduction of transesophageal echocardiography (TEE) in the early 1980’s (1,2,3) gave physicians a semi-invasive tool for evaluation and monitoring of left ventricular function during open-heart-surgery. The transesophageal approach also allows the left ventricular contractility to be monitored without the interference of bone and air-filled structures of the thoracic cage and high quality images can be obtained in most patients (4). The transesophageal approach is considered safe and feasible. In a retrospective study of a single center series of 7200 adult cardiac surgical patients with intraoperative TEE, low incidences of TEE associated morbidity and mortality (0.2% and 0%, respectively) were observed (5). The most common TEE associated complications in this series were odynophagia (0.1%); dental injury, endotracheal malpositioning, upper gastrointestinal hemorrhage (0.03% each); and esophageal perforation (0.01%). Use of the transesophageal probe is contraindicated in patients with esophageal varices and esophageal diverticulum. Relative contraindications are gastric ulcer and/or gastrectomy, esophagitis, hiatal hernia (if severe) and cervical disk disease (6).

TEE has also become a valuable complement to the pulmonary artery catheter for detecting left ventricular dysfunction and for assessing hypovolemia and hypervolemia, both intraoperatively and postoperatively (7, 8). Perioperative episodes of myocardial ischemia as assessed by TEE and regional wall motion abnormalities are infrequently triggered by changes in hemodynamics (9). Echocardiography is more sensitive in detecting myocardial ischemia than electrocardiography (ECG). Although detection with echocardiography can occur earlier, the specificity is better with ECG (10).

Intraoperative monitoring of regional wall motion

TEE is often used intraoperatively in monitoring left ventricular regional wall motion. The normal ventricular wall thickens during systole and the endocardial surface moves inward toward the left ventricular cavity. Abnormal wall motion is described as hypokinesia when contraction is less vigorous than normal and generally slower than
normal and when wall thickening is diminished. Akinesia refers to the absence of wall motion (no thickening, no inward endocardial motion) and characterizes severe dysfunction. In dyskinesia there is a paradoxical motion as a result of myocardial infarction (11). The term tethering describes the dysfunction that occurs in normally perfused myocardium situated adjacent to the ischemic zone. Contraction abnormalities develop because there is an imbalance in myocardial oxygen supply and demand. In 1935 Tennant and Wiggers (12) described in detail how ligation of a coronary artery resulted in an almost immediate failure of contraction in the affected myocardium. The onset of visible wall motion abnormalities occurs within 10-15 seconds of coronary occlusion (13). Abnormal regional wall motion is regarded as a sensitive indicator of myocardial ischemia and is detected early by echocardiography (14). The transgastric short-axis view at the midpapillary muscle level is ideal in this respect because it includes segments of myocardium representing all three coronary arteries. This view is also easily identified and reproducible. Failure to obtain this view can occur in obese patients and patients with left ventricular dilatation in whom the heart lies transverse above the diaphragm.

**Pharmacological stress testing and TEE**

In patients with coronary artery disease (CAD) exercise testing is a widely used diagnostic stress test for detection, stratification and follow-up of CAD. However many patients are unable to exercise or unable to reach the required test level to provoke symptoms of ischemic CAD. Therefore an exercise independent strategy was developed for stress testing in patients with suspected CAD: pharmacological stress with dobutamine. The short half-life (2 minutes) of the drug makes it suitable for this purpose. Dobutamine is a synthetic catecholamine with a dextro form that binds to β₁- and β₂-receptors and a levo form that stimulates α-receptors. The affinity of dobutamine for cardiac muscle β₁- and α-receptors results in a positive inotropic, and to a lesser extent, a positive chronotropic effect. The peripheral arteries and the bronchial system react with dilatation to the β₂-stimulation. These various actions are dose dependent, with increased contractility at lower doses and progressive tachycardia developing at higher doses. The use of dobutamine to induce cardiac stress
started in the mid 1980’s, first in combination with thallium scintigraphy (15) and then with echocardiography for identifying multivessel CAD (16). Dobutamine stress was considered contraindicated in patients with acute myocardial infarction (within 10 days after an acute infarction), unstable angina, known relevant left main stem stenoses, manifest congestive failure, severe life threatening tachyarrhythmias, severe valvular stenosis, hypertrophic obstructive cardiomyopathy, acute peri-/myocarditis, endocarditis and aortic dissection (17).

There are two different ways of using dobutamine stress echocardiography. The viability test with low-dose dobutamine (5-10µg*kg⁻¹*min⁻¹) identifies hibernating myocardium and predicts recovery of segmental left ventricular function after revascularization (18). The ischemic test with high–dose dobutamine (doses up to 40µg*kg⁻¹) identifies ischemic wall motion abnormalities in the presence of coronary lesions due to an increasing myocardial demand (19).

The term hibernating myocardium, first used by Rahimtoola (20), describes left ventricular dysfunction resulting from chronic myocardial ischemia and demonstrating recovery of function after coronary revascularization. Another condition is stunning described as prolonged postischemic dysfunction without myocardial necrosis caused by periods of severe ischemia that are too brief to cause myocardial necrosis (21). In stunning contractile dysfunction can persist for prolonged periods hours to weeks after restoration of reperfusion. Viable myocardium retaining contractile reserve will demonstrate improved regional thickening during dobutamine stimulation. The down regulation of myocardial contractile function represents an adaptation of myocytes to balance oxygen demand and supply by decreasing oxygen consumption, thus preventing myocardial ischemic symptoms at rest and further myocardial damage. When coronary flow is restored, recovery of contractile function can take several days, weeks or even months. Several studies have shown that the ability to identify contractile reserve in patients with depressed left ventricular function has important prognostic value (18,22,23). Sensitivity is better in multi-vessel than in single-vessel disease and higher in 70% coronary stenosis than in 50% coronary stenosis (17). In a large series of 1118 patients who underwent high-dose dobutamine stress and transthoracic echocardiography dobutamine stress echocardiography was evaluated
and found to be safe by Mertes et al (24). Ciagorra et al (18) concluded that
dobutamine stress echocardiography provides a simple, cost-effective and widely
available method of identifying hibernating myocardium and predicting improvement
in regional left ventricular wall thickening.

**Dobutamine stress echocardiography compared with other methods for identification of viable myocardium.**

In patients with CAD and depressed left ventricular function, assessment of residual
viability is important for therapeutic management. Intact perfusion, preserved
metabolism and presence of contractile reserve are different aspects of cellular
viability. Positron emission tomography (PET) was the first non-invasive test shown to
predict functional recovery after revascularization and has been the reference
noninvasive method for assessing the presence of viable myocardium.
Fluorodeoxyglucose (FDG) has been used to assess glucose uptake and $^{13}$N-ammonia to
assess perfusion with PET. The combined evaluation of regional myocardial blood
flow and glucose metabolism allows identification of viable myocardium (25,26).
Increased glucose uptake in segments with reduced blood flow (metabolism-perfusion
mis-match) indicates the presence of viable myocardium, whereas a concordant
reduction in glucose utilization and blood flow indicates scar tissue and formation
necrosis. A segment was considered normal when the perfusion was normal.
Single photon emission computed tomography (SPECT) with thallium-201 (or
technetium-99m) has been used to study myocardial perfusion and preserved cell
membrane integrity and with FDG, to identify preserved metabolism.
Using low-dose dobutamine stress echocardiography (DE), with transthoracic
echocardiography (TTE) or TEE, dysfunctional segments are identified as viable if
they exhibit improvement in contractile function during inotropic stimulation, a
phenomena known as myocardial contractile reserve. It has been shown that
substantial numbers of segments with metabolic evidence of viability do not show
contractile reserve. Apparently DE underestimates viability compared with PET and
SPECT (27).
Bodenheimer et al (28) obtained punch biopsies during bypass surgery and showed that myocardial segments with contractile reserve had minimal fibrosis, whereas areas lacking contractile reserve had extensive fibrosis but also contained islands of viable myocytes. Thus, perfusion by thallium scintigraphy is probably more sensitive than contractile reserve by DE in identifying regions containing viable myocytes. However, contractile reserve by DE may prove to be more specific than perfusion techniques in predicting left ventricle (LV) functional recovery. Small amounts of viable tissue may be detected by PET but this tissue is unable to contribute to regional contraction after surgery. It may be that the areas are too small to augment in response to DE preoperatively and are unlikely to contribute to improved function after revascularization (29). The techniques also differ with respect to availability as PET is expensive and has limited availability compared to DE which is inexpensive, relatively simple to perform and widely available.
Aims of the study

The aims of the study were, in CABG patients:

1. to add automatic border detection, Acoustic Quantification (AQ), to the 2D image of the left ventricle and compare the intra- and inter-observer agreement in assessing segmental left ventricular wall motion with and without AQ. (Paper I)

2. to evaluate the feasibility of a low-dose dobutamine stress regimen and TEE for evaluation of left ventricular viability in anesthetized patients. (Paper II)

3. to study the relationship between TEE derived values of left ventricle (wall motion and dimensions) and hemodynamic data obtained by a pulmonary artery catheter (PAC) during low-dose dobutamine stress. (Paper III)

4. to investigate the importance of critical coronary artery stenosis for poststenotic left ventricular segmental function assessed by TEE during low-dose dobutamine stress. (Paper IV)

5. to compare the impact on segmental LVWM using low-dose dobutamine stress, preoperatively with (TTE) and perioperatively with (TEE). TTE was performed the preoperative day and with the patient fully awake and TEE perioperatively during anaesthesia. (Paper V).
Material and methods

Patients
The studies were approved by the Ethics Committee of Uppsala University. Informed consent was obtained from 84 patients scheduled for elective coronary artery bypass surgery who were included after assessing their eligibility. The age of the study population was 47-77 years. In all patients perioperative TEE was performed. In paper I-IV patients with a history of stable angina pectoris scheduled for elective CABG were included. The exclusion criteria were: myocardial infarction within 3 months, unstable angina, left main stenoses exceeding 50%, left ventricular aneurysm, arrhythmia, heart valve or esophageal disorders or left ventricular ejection fraction (LVEF) less than 30%. In paper V both the inclusion and exclusion criteria differed from paper I-IV. The inclusion criterion was a LVEF less than 30% as assessed by radionuclide ventriculography. Patients with impaired renal function (creatinine >130mmol/l), age>75 years and LVEF < 10% were excluded. In this study a transthoracic echocardiography examination was also performed in all patients the day before surgery. The same group of patients are presented in paper III and IV. In all papers medication with β-blockers was continued until the morning of surgery. Morphine-scopolamine was used as premedication. The TEE examination was performed before start of surgery but after induction of anesthesia and controlled ventilation.

Anesthesia and perioperative monitoring during TEE and dobutamine stimulation
In paper I anesthesia was induced with fentanyl (3-7µg*kg⁻¹) and pentothal (1-3mg*kg⁻¹). Repeated doses of fentanyl and inhalation of isoflurane maintained anesthesia.
In paper II-IV anesthesia was induced with fentanyl (30µg*kg⁻¹) and midazolam (50µg*kg⁻¹) and maintenance was achieved with a continuous infusion of fentanyl (0.16µg*kg⁻¹*min⁻¹) and midazolam (0.67µg*kg⁻¹*min⁻¹). In paper V anesthesia was
induced with alfentanil (23-39µg*kg\(^{-1}\)) and pentothal (1.7-2.9mg*kg\(^{-1}\)) and maintained with repeated doses of alfentanil/fentanyl and inhalation of isoflurane. In all studies pancuronium (0.1mg*kg\(^{-1}\)) was used for muscle relaxation. All patients were ventilated with 50% oxygen in air.

Continuous monitoring of ECG lead V\(_{5}\), arterial- and central venous pressures took place in all subjects. In paper III-V the pulmonary artery pressure was also monitored. Dobutamine was infused through a central venous line in the anesthetized patient (paper II-V) and through a peripheral cannula in the awake patient (paper V). In all patients the starting dose was 5µg*kg\(^{-1}\)*min\(^{-1}\) which was increased by 5µg*kg\(^{-1}\)*min\(^{-1}\) after 3-5 minutes. The endpoints examined were an improved or impaired LVWM, an increase in arterial pressure >40mmHg, a heart rate increase >20%, or ST-segment depression exceeding 0.2mm. These endpoints were chosen because they follow our normal clinical routine during CABG. All values were compared with baseline (no dobutamine).

**Perioperative TEE**

In paper I-IV a Hewlett Packard Sonos 1500 (HP, Andover, Mass., USA) ultrasound machine equipped with a 5MHz biplane transesophageal probe was used. In paper V a Sonos 2500 equipped with a 5MHz biplane transesophageal probe was used perioperatively. A Sonos 1500 equipped with a 2.5 MHz transthoracic transducer was used preoperatively. In paper II-IV only the transgastric short-axis view at the mid-papillary muscle level was chosen to assess LV segmental function. In paper I the 3-chamber esophageal long-axis view was added and in paper V transgastric long-axis, esophageal 2-chamber and 4-chamber views were added. TTE views were the parasternal long-and short-axis, apical 2-and 4-chamber views. Loops were saved as videorecordings or cine-loops.

**Different methods used in assessing regional LVWM**

Readers of echocardiography images

In paper II-V, the off-line assessment was made by one experienced reader, but in paper I there were two experienced readers. Readers were blinded to the sequence of
events except for the preoperative TTE investigation in study V. Apart from the off-line evaluation, the principal investigator made an on-line evaluation in the operating room during dobutamine stimulation in paper II-V. This evaluation was made to detect changes in segmental left ventricular function and also because the patients were anesthetized and incapable of reporting pain from myocardial ischemia.

**Visual assessment**

In all studies (I-V) a visual evaluation of LV regional wall motion was made from the regular 2-D image and in paper II-V only the standard 2D image was used to detect and assess the segmental left ventricular response to dobutamine stimulation. The transgastric short-axis image, at the mid-papillary muscle level of the left ventricle was chosen in all papers for the following reasons. Areas supplied by the three main coronary arteries are present in this view, which is usually easy to obtain. Moreover, the landmarks facilitate identification of an exact position for repetitive measurements. For evaluation the left ventricle in the transgastric short-axis view was divided into 4 segments (paper II) or into 6 segments (paper III, IV). In paper I the 3-chamber view was also added and the left ventricle was divided into 5 segments. In paper V the 2-chamber, 4-chamber and transgastric long-axis views were added (TEE) and the left ventricle was divided into 16 segments. These images were compared with TTE segments that were collected in the parasternal long-and short-axis and the apical 2- and 4-chamber views. The left ventricle segments were scored from 0=hyperkinesis/normal to 4=dyskinesis. In paper II segmental changes were assessed as improved, unchanged or dysfunctional.

**Acoustic Quantification (AQ)**

*Paper I.* Twenty-three patients were examined. Two independent observers made their assessments on two separate occasions with and without acoustic quantification (AQ) added to the 2-D image. AQ is a software algorithm based on the analysis of integrated backscatter. Accordingly, the steep increase in backscatter between cavity and tissue is detected and the endocardial border is outlined. This enables an on-line assessment of global left ventricular function, from changes in diastolic and systolic 2D area on a
beat to beat basis (30). However, in this study the primary aim was to compare the effect of AQ on intra- or inter-reader assessment of segmental LVWM.

**Computerized analysis**

*Paper II.* Twenty-two patients were included. A computerized system for real time acquisition was applied apart from the visual assessment of regional function (31,32). Images stored on the videotape were transferred to a computer system by means of a video digitizer at a rate of 25 images*sec^-1. Using a digitizing tablet the endocardial borders were outlined in systole and diastole. The fractional area change between diastole and systole was calculated and expressed as global area ejection fraction (GAEF). Ninety-six slices between the systolic and diastolic contours were calculated. These sliced areas were then added together to obtain 8 segments, and these 8 segments were added together to become 4 segments: anterior, lateral, inferior and septal. The segmental area ejection fraction (SAEF) was then normalized by calculating the SAEF/GAEF ratio, thereby obtaining a load-independent regional wall motion index.

**Perioperative TEE compared with hemodynamic measurements from PAC, coronary stenoses at the angiogram and preoperative TTE**

Hemodynamic measurements from PAC and echocardiographic data from TEE

*Paper III.* Twenty-four patients were included. Changes in TEE obtained data were compared with changes in hemodynamic data during dobutamine stimulation. Segmental LVWM was scored and changes in end-diastolic area (EDA), end-systolic area (ESA) and fractional area change (FAC=EDA-ESA/EDA) were calculated. Pulmonary wedge pressure was measured and thermodilution was used for cardiac output and calculation of stroke volume. This enabled the study of how changes in segmental LVWM in the transgastric short-axis view corresponded to changes in left ventricular stroke volume, and how EDA corresponded to PCWP.
Stenoses on the preoperative angiogram and segmental LVWM

**Paper IV.** The same patient population was used as in paper III. This study addressed how a severely stenosed coronary artery found on the coronary angiogram affects the poststenotic LV segmental function assessed with TEE in the transgastric short-axis view during low-dose dobutamine stimulation. It was assumed that the mid-anterior-septal (M-AS), mid-anterior (M-A), mid-septal (M-S) segments were supplied by the left descending artery (LAD), mid-posterior (M-P) and mid-lateral (M-L) were supplied by the left circumflex artery (LCX) and mid-inferior (M-I) by the right coronary artery (RCA).

Preoperative TTE in the awake patient and perioperative TEE in the anesthetized patient

**Paper V.** Fifteen patients were included. The same low-dose dobutamine protocol to test viability was used preoperatively in the awake patient with TTE and perioperatively with TEE in the anesthetized patient. There were two major objectives in this study to compare the TTE and TEE echocardiographic approach and to evaluate the effect of anesthesia on the response to low-dose dobutamine stimulation. The 16-segment model of the LV also made it possible to extend the comparison to the basal and apical myocardium of the LV.

**Statistical analysis**

All data (except for paper II) were collected and analyzed in a statistical program (Statistica 5.1 Stat Soft Inc., Tulsa, USA) and are presented as mean values ±SD. In all studies differences were considered significant at a level of p<0.05. In paper I analysis of variance (ANOVA) was used to compare differences between left ventricular segments and between the readers. Paired t-test was used to compare mean LVWM scores. To calculate the degree of agreement the formula \(1-(\text{difference in LVWM score}/\text{maximal possible difference in score})\times100=\text{agreement in %}\) was used (33). In paper II a type of variance analysis for repeated measurements, a hierarchical ANOVA (SuperAnova Abacus Concepts Inc., Berkley, Calif) was used to compare differences between baseline data and data obtained with the highest dobutamine dose for end-systolic area (ESA), end-diastolic area (EDA), segmental area ejection fraction.
(SAEF), global area ejection fraction (GAEF) and SAEF/GAEF. In paper III hemodynamic data and echocardiographic data were analyzed using a multivariate analysis of variance (MANOVA) for repeated measurements and Tukey’s HSD for unequal numbers (Spjotvoll/Stoline test) was used as post-hoc test. In paper IV, a t-test for dependent samples was used to test for significant differences.

Results

TTE and AQ in assessing regional LVWM

Paper 1. There was no intra-reader difference in assessment of regional LVWM in the short-axis view when AQ was added to the 2-D image. The inter-reader difference was highly significant both without and with AQ in this view. In the long-axis-view the intra-reader difference was significant whereas the inter-reader difference was non-significant. However, the overall intra-reader and inter-reader agreement was 73% or higher except for the intra-reader difference in the long-axis view. The results are presented in Table 1.
Table 1.
Intra-reader and inter-reader comparisons of LVWM assessment in the short- and long-axis view.

<table>
<thead>
<tr>
<th>Reader</th>
<th>Assessment</th>
<th>t-test</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SA</td>
<td>LA</td>
</tr>
<tr>
<td>Intra-reader</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>-AQ/+AQ</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Reader 2</td>
<td>-AQ/+AQ</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Inter-reader</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1-R2</td>
<td>-AQ</td>
<td>1</td>
<td>p=0.0001</td>
</tr>
<tr>
<td></td>
<td>+AQ</td>
<td>1</td>
<td>p=0.0001</td>
</tr>
<tr>
<td></td>
<td>-AQ</td>
<td>2</td>
<td>p=0.0001</td>
</tr>
<tr>
<td></td>
<td>+AQ</td>
<td>2</td>
<td>p=0.0001</td>
</tr>
</tbody>
</table>

The intra-reader comparison is between the 2D image without (-AQ) or with AQ (+AQ) on both assessment 1 and 2 (-AQ/+AQ). R.1 and R.2 = reader 1 and reader 2. SA = short-axis view, LA = long-axis view, ns = non significant.
Perioperative TEE with low-dose dobutamine stress for evaluation of myocardial viability: a feasible approach. Computerized and visual assessment of segmental LV function

Paper II. The semiautomatic off-line analysis identified no significant changes in regional or global LVWM with dobutamine. The ESA, EDA and GAEF are presented in Table 2. No changes in the SAEF/GAEF ratio were present with the dobutamine infusion compared with pre-infusion values.

Table 2.
The effect of dobutamine on endsystolic area (ESA) end-diastolic area (EDA) and global ejection fraction (GAEF).

<table>
<thead>
<tr>
<th></th>
<th>ESA (cm²)</th>
<th>EDA (cm²)</th>
<th>GAEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-dob</td>
<td>+dob</td>
<td>-dob</td>
</tr>
<tr>
<td>Mean</td>
<td>10.1</td>
<td>10.9</td>
<td>18.0</td>
</tr>
<tr>
<td>SD</td>
<td>6.0</td>
<td>6.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Range</td>
<td>2.7-25.1</td>
<td>1.8-24.1</td>
<td>7.9-32.6</td>
</tr>
</tbody>
</table>

No dobutamine (-dob) and dobutamine (+dob).

With visual assessment 36 segments were found dysfunctional at baseline. However, as shown in Table 3, of these 36 segments, 22 (61%) improved, 12 (33%) remained dysfunctional and 2 (6%) became more dysfunctional with dobutamine. Six segments with normal function at baseline became dysfunctional with dobutamine. All 8 segments that were dysfunctional with low-dose dobutamine were supplied by critically stenosed vessels.
Table 3.
The off-line visual assessment of the dysfunctional segments without dobutamine and with dobutamine. Numbers indicate segments.

<table>
<thead>
<tr>
<th>Segment</th>
<th>No dobutamine</th>
<th>Dobutamine 5 or 10µg<em>kg⁻¹</em>min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dysfunctional LVWM</td>
<td>Improved LVWM</td>
</tr>
<tr>
<td>Anterior</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Septal</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Inferior</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Lateral</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>22</td>
</tr>
</tbody>
</table>

Low-dose dobutamine stress and LVWM monitored with TEE versus hemodynamic data derived from PAC in patients scheduled for CABG

Paper III. Significant increases in SV and LVWM were observed, both signs of viability already at 5 µg*kg⁻¹*min⁻¹ of dobutamine (fig 1a, 1b) with further improvement at 10 µg*kg⁻¹*min⁻¹. In 2 patients stimulation was stopped at 5 µg*kg⁻¹*min⁻¹ because their systolic blood pressure had increased by > 40 mmHg. The remaining 22 patients were stimulated to 10 µg*kg⁻¹*min⁻¹ with further improvement in SV and LVWM. In figures 1a and 1b significant increase in SV, with a concomitant decrease in LVWM-score can be seen. Cardiac output, systolic artery pressure, mean artery pressure, diastolic artery pressure, pulmonary capillary wedge pressure and left ventricle stroke work increased significantly at 10 µg*kg⁻¹*min⁻¹, but heart rate and systemic vascular resistance did not change. Regarding the TEE data there was a significant decrease in LVWM-score and a significant increase in EDA.
Figure 1a.

A graphic presentation of the significant increase in SV (ml*beat⁻¹) with dobutamine. (On the x-axis the dose of dobutamine in µg*kg⁻¹*min⁻¹).

Figure 1b.

A graphic presentation of the significant decrease in LVWM-score with dobutamine. (On the x-axis the dose of dobutamine in µg*kg⁻¹*min⁻¹).
Perioperative TEE with dobutamine as complement to preoperative coronary angiography

*Paper IV.* With TEE there was a high number of abnormal segments in patients with three-vessel coronary disease. There were no major differences found in the number of stenotic LAD, LCX or RCA. Of the stenotic LAD, LCX and RCA supplied segments, 50/62 (81%), 25/38 (66%) and 9/18 (50%), respectively, displayed normal motion at baseline. With dobutamine stress another 22 segments of the 34 abnormal segments at baseline showed normal motion (Table 4). Consequently, only 12 segments were considered non-viable.

Table 4
Abnormal segments at baseline and their response to dobutamine.

<table>
<thead>
<tr>
<th>Number of stenotic vessels</th>
<th>No dobutamine</th>
<th>Dobutamine</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abnormal segments</td>
<td>Abnormal segments</td>
<td>Normal segments</td>
</tr>
<tr>
<td>LAD 21</td>
<td>12</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>LCX 19</td>
<td>13</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>RCA 18</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total number</td>
<td>34</td>
<td>12</td>
<td>22</td>
</tr>
</tbody>
</table>

Thus 60 (50+10) LAD segments, 30 (25+5) LCX segments and 16 (9+7) RCA segments were considered viable. Altogether these represented 69% of all segments. Four segments worsened with dobutamine, two hypokinetic segments became akinetic and two normal segments became hypokinetic. In these four segments a provoked ischemia could not be ruled out.

TTE and TEE stress in patients with severe LV dysfunction

*Paper V.* All 15 patients were assessed with both TTE and TEE. Two patients were not stimulated with dobutamine preoperatively because of severe chest pain and severe left
ventricular dysfunction, respectively. Another patient was considered too tachycardic for dobutamine stimulation at the time of TEE. Thus, 13 and 12 patients received dobutamine stimulation preoperatively and perioperatively, respectively. At baseline 240 segments were assessed with TTE preoperatively compared with 228 with TEE perioperatively. With TEE, at baseline, 5% of the segments were non-assessable and these were mostly the anteroseptal and/or posterior segments of the left ventricle. With dobutamine stimulation 208 segments and 192 segments were assessed with TTE and TEE, respectively. At baseline 57% (130/228) segments had the same motion score with TTE and TEE. Of the remaining segments, only 8% (19/228) differed by 2 steps in scored wall motion and the rest only by one step. Moreover, the number of improved segments with dobutamine stimulation was similar pre- and perioperatively. For further comparisons in LVWM score, segments were divided into basal, mid and apical. Response to dobutamine stimulation during TTE and TEE is shown in Table 5. The midsegments improved significantly as assessed by both techniques.

Table 5.
Segmental wall motion score with and without dobutamine. Values are mean±SD. Significant difference * = p<0.05.

<table>
<thead>
<tr>
<th>Segments</th>
<th>TTE baseline</th>
<th>TTE dobutamine</th>
<th>p</th>
<th>TEE baseline</th>
<th>TEE dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>1.83±0.42</td>
<td>1.72±0.45</td>
<td>0.216</td>
<td>1.82±0.52</td>
<td>1.72±0.59</td>
<td>0.053</td>
</tr>
<tr>
<td>Mid</td>
<td>2.35±0.27</td>
<td>1.99±0.38</td>
<td>0.003*</td>
<td>2.36±0.26</td>
<td>1.97±0.32</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Apical</td>
<td>2.60±0.36</td>
<td>2.31±0.49</td>
<td>0.014*</td>
<td>2.81±0.21</td>
<td>2.69±0.39</td>
<td>0.105</td>
</tr>
</tbody>
</table>

However in comparing TTE and TEE findings, only the apical segments differed significantly (Table 6).
Table 6.
Comparison of segmental wall motion score at baseline and with dobutamine stimulation obtained with TTE and TEE respectively. Values are mean ± SD. Significant difference *=p<0.05.

<table>
<thead>
<tr>
<th>Segments</th>
<th>TTE baseline</th>
<th>TEE baseline</th>
<th>p</th>
<th>TTE dobutamine</th>
<th>TEE dobutamine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>1.82±0.40</td>
<td>1.87±0.51</td>
<td>0.73</td>
<td>1.69±0.46</td>
<td>1.72±0.60</td>
<td>0.90</td>
</tr>
<tr>
<td>Mid</td>
<td>2.35±0.26</td>
<td>2.38±0.25</td>
<td>0.75</td>
<td>2.01±0.39</td>
<td>1.97±0.32</td>
<td>0.76</td>
</tr>
<tr>
<td>Apical</td>
<td>2.65±0.36</td>
<td>2.85±0.20</td>
<td>0.06</td>
<td>2.33±0.50</td>
<td>2.69±0.39</td>
<td>0.01*</td>
</tr>
<tr>
<td>All</td>
<td>2.28±0.48</td>
<td>2.37±0.53</td>
<td>0.17</td>
<td>2.01±0.51</td>
<td>2.13±0.60</td>
<td>0.22</td>
</tr>
</tbody>
</table>
**Discussion**

TEE intraoperatively is a useful tool during open-heart surgery. It provides a new window to monitor left ventricular function without interference from other structures in the thoracic cavity. TEE can be used as a sensitive and continuous monitoring tool of global and segmental left ventricular function and when used intraoperatively, TEE reveals the cause of acute hypotension and onset of left ventricular ischemia more rapidly and safely than PAC (7,9,34). TEE also detects ischemia as LVWM abnormalities minutes before ECG changes are observed (7). Beaupre et al (35) first reported the use of TEE for intraoperative detection of new segmental wall motion abnormalities. They found pronounced akinesia in previously normal segments but ECG immediately postoperatively did not indicate an infarct until 18 hours later. However not all new intraoperative LVWM abnormalities are followed by ECG changes indicative of infarction postoperatively (36). It has been concluded that intraoperative TEE is more sensitive in detecting myocardial ischemia than ECG but ECG is more specific. Most often the transgastric short-axis view is used both to assess LVWM and to monitor preload and LV global function (37). This view is easily identified by the papillary muscles and it is suitable for continuous monitoring of segmental LVWM as myocardium supplied by the three major coronaries is viewed in this cross-section. Another important issue in CABG surgery is to distinguish between viable and non-viable myocardium. The reason is that already scared tissue does not benefit from extra blood supply, i.e. this tissue does not show any contractile reserve on stimulation. In off-pump CABG surgery this may be important because the position maneuvers of the heart to gain access to the LCX and RCA areas increase the risk for myocardial ischemia (38). Therefore it seems reasonable to supplement the angiographic finding with an evaluation of segmental LVWM. We also found that all dysfunctional segments with low-dose dobutamine were supplied by critically stenosed coronary vessels. To separate viable from non-viable myocardium places an increased demand on LV function. For this purpose the pharmacological TTE using dobutamine is widely accepted (39,40,41).
In the literature two different dose regimens of dobutamine are described. The low-dose dobutamine regimen (5-10µg*kg⁻¹*min⁻¹) aims to separate viable and non-viable myocardium and the high-dose regimen (up to 40-50µg*kg⁻¹*min⁻¹) aims to provoke ischemic changes. It has been argued that a biphasic dobutamine stress test should be performed to test LV-segments for both ischemia and contractile reserve (39). However in our study we adopted the low-dose regimen with the aim to test viability only. Another reason was that our patients were anesthetized and unable to report pain from myocardial ischemia. Thus endpoints for the low-dose dobutamine stress were kept within narrow limits to ensure that ischemia was not provoked. With the decision already made to perform CABG for ischemic heart disease, it could be argued whether the use of an inotropic drug and the concomitant stress would further damage the myocardium. However, we found no adverse outcome using the low-dose dobutamine regimen in our study. Consequently we concluded that the method was feasible and safe in patients scheduled for elective CABG. Interestingly we found a comparable increase between LVWM with low-dose dobutamine and TTE with the same dose in awake patients. A weaker response in anesthetized patients on β-blockade might have been expected but our results did not confirm this. When comparing the evaluation of the 16 segments with TTE and TEE, the anterior-septal basal and posterior basal segments with TEE could not be easily assessed because of the difficulty in obtaining good images of the basal segments with TEE. Hoffman et al (42) also found it difficult to image these basal LV segments with TEE.

We also compared hemodynamic data derived from PAC with TEE data during low-dose dobutamine stress and found a concomitant increase in SV and decrease in LVWM-score indicating an improved LVWM. Furthermore, there was a significant increase in measured PCWP and outlined EDA, while there was no change in ESA or FAC. Hogue et al (43) concluded in their study that EDA and ESA were significantly greater while FAC was significantly lower in patients with myocardial ischemia but there were no significant differences in PCWP with and without ischemia. They found it plausible that monitoring of EDA, ESA and FAC could be complementary to the evaluation of LV regional function. In our study comparing PAC and TEE there was only a significant increase in EDA without changes in ESA and FAC. Still, we do not
think that the isolated increase in EDA was indicative of ischemia because the simultaneous significant increase in LVWM and SV during low-dose dobutamine stress indicated viability and contractile reserve. In addition there were no signs of ischemia on ECG in the V₃ lead.

TEE could also be a useful complement to PAC for estimating of loading conditions, as left ventricle compliance is often impaired in patients scheduled for CABG. PAC derived data and PCWP do not always correlate with left ventricle dimensions and volume especially not in patients with increased wall thickness (44,45). Changes in loading conditions are more evident and thereby easily detected in the trans-gastric short-axis view compared with the long-axis view of the LV.

TEE and dobutamine stress could also be useful in patients needing non-cardiac surgery when there is no time for preoperative cardiac investigation. By identifying those patients who have an increased risk for cardiac complications, a better guide for perioperative management and plan for more intensive postoperative care is achieved (46).

In clinical practice echocardiographic assessment of regional wall motion is based on a qualitative “eyeball” assessment of ventricular motion and thickening. This assessment is usually transferred to numbers. Currently there is some confusion about what these numbers represent as two scales exist and both are approved by ASE/SCA (the American Society of Echocardiography/Society of Cardiovascular Anesthesiologist). According to Shanewise one of the authors of the guidelines (47), assigning numbers to the qualitative descriptions should not be taken to mean that these data are on an interval scale. Regional wall motion score may not even belong on an ordinal scale. It may not be appropriate to compare numerical derivates of regional wall motion scores, in fact it may be preferable to use the descriptive terms when communicating about wall motion findings.

In our study the inter-reader (different readers) and the intra-reader (same reader at different occasions) agreements was good when evaluating the transgastric short-axis view with and without AQ. However, the agreement was less in the esophageal 3-chamber long-axis view. The explanation is that
it is more difficult to obtain a good image in the 3-chamber long-axis view and consequently it is more difficult to evaluate. We found the degree of agreement between intra- and inter-reader appropriate for practical clinical use in this setting may help to improve. With the aim to improve and make the assessment of regional LVWM more objective two novel echocardiographic techniques have been developed. Color kinesis is a modality based on the endocardial border detection and AQ. Tissue doppler imaging (TDI) is a technique that color codes myocardial motion and myocardial velocity. Both techniques are possible to use for on-line monitoring (48,49). Thus this provides new possibilities to decrease inter-observer variability and increase inter-institutional agreement.

We also used a semiautomatic computer assisted program to assess segmental LVWM. Interestingly, with this program no changes in wall motion were found during dobutamine stimulation but changes were seen on the visual assessment. This discrepancy can be explained: firstly the semiautomatic program used was dependent on a manual tracing of the EDA and ESA areas and only one heart cycle was used. Also, the program was unable to compensate for rotation and translation of the heart during contraction. However, in the visual analysis numerous heart cycles could be studied, which made it easier to compensate for rotation and translation of the heart.

Conclusions

We found that TEE low-dose dobutamine stress in assessing segmental LVWM was feasible and safe in patients scheduled for CABG surgery. No adverse effects of this stress were found on already ischemic myocardium nor in some patients with severely impaired left ventricle function.

As a monitoring tool for global LV function, TEE and improved LVWM in the transgastric short-axis view were concomitant with increased SV as measured by PAC. LVWM abnormalities corresponded to critically stenosed coronary vessels. In visual off-line analysis of LVWM both inter-reader and intra-reader the agreement were good especially in the transgastric short-axis view. The AQ technique did not change this finding.
The preoperative response to TTE low-dobutamine stress in the awake patient was similar to the response in the same patient who was anesthetized and examined with TEE.

The visual assessment of LV function in the transgastric short-axis view was found to be indicative of global LV function.

The findings are interesting and they imply that the use of TEE perioperatively could be extended beyond monitoring preload and segmental LVWM abnormalities to include detection of segmental LV viability. Consequently we think that perioperative TEE and low-dose dobutamine stress could be useful in identifying LV contractile reserve prior to start of coronary artery bypass surgery.
Acknowledgements

I wish to express my sincere gratitude to:

Jan Hultman, my tutor, for introducing me to the exciting world of echocardiographic images. For constant enthusiasm, support and guidance over the completion of this thesis.

Lars Wiklund and Ulf Sjöstrand, for generously providing me with the time that made writing this thesis possible.

Hans Tydén, for generously providing facilities for research and also for support and belief in the completion of this thesis.

Elisabet Ståhle, co-author, for encouragement, valuable advice and for introducing me to “the female way of reperfusion”.

Bertil Andrén, co-author, for skilful evaluation of echocardiographic images and for patiently answering thousands of questions about echocardiographic examination.

Göran Granath, for guidance in the statistical labyrinth.

Gina Eriksson and Leslie Shaps, for excellent linguistic revision.

Johan Landelius, co-author, for skilful evaluation of echocardiographic images.

Erik Houltz, co-author, for generously sharing extensive knowledge in the use of computerized analyses of echocardiographic images.

Inga-Lisa and Carl-Rudolf, my parents, for never-ending support. Gabriella, my sister and colleague, for always being encouraging and understanding.

My family, for love and support and:

Ida, my daughter, for believing in girl power,

Anders, my son, for making me realize what is really important in life...bandy and

Torbjörn, my husband, for always looking at the bright side of life.

My colleagues at the department of Cardiothoracic Anesthesiology and all the staff at the operating unit and 50 B for your patience and encouragement. Last but not least, many thanks to all the participating patients.
This study was supported by grants from
Erik, Karin och Gösta Selanders Stiftelse,
Josef och Linnea Carlssons Minnesfond,
Kungliga Vetenskapssamhället,
The Swedish Heart and Lung Foundation and
Uppsala County Association against Heart and Lung Diseases.
References


33. Öst LG. Reliabilitetsmätningar vid observationer och skattningar Scandinavien Journal of behavior therapy 1979;8:133-159.


Errata

On page 16, line 18 “……biplane transesophageal probe……”, should be “….multiplane transesophageal probe……”