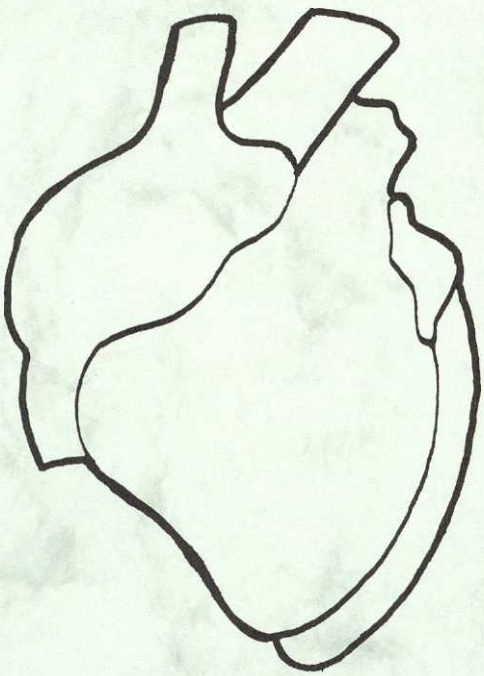
Left Ventricular Systolic and Diastolic Function During Cardiac Anesthesia.

Echocardiographic and Doppler Studies in Patients Undergoing Coronary Artery Bypass Surgery.

Erik Houltz



Göteborg 1995

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AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen, med vederbörligt tillstånd av medicinska fakulteten vid Göteborgs Universitet, offentligen försvaras i föreläsningssal S1, Sahlgrenska Sjukhuset, Göteborg fredagen den 2 juni 1995 kl 13.00.

av

Erik Houltz
leg. läk.

Avhandlingen baseras på följande delarbeten:

I. Houltz, E, Hellström Å, Ricksten S-E, Wikh R and Caidahl K
Early effects of coronary artery bypass surgery and cold cardioplegic ischemia on left ventricular diastolic function. Evaluation by computer assisted transesophageal echocardiography.
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Abstract

Patients with coronary artery disease (CAD) have disturbances in left ventricular (LV) contraction and relaxation. Symptoms of congestive heart failure in these patients may be caused both by decreases in the systolic and the diastolic function, and the development of concomitant ischemia that could decrease the left ventricular function even further. When patients with CAD is subjected to surgery for coronary artery bypass grafting (CABG), the heart is exposed to anesthetic drugs, surgical stress and a period of cardiac arrest during cardiopulmonary bypass (CPB). The effects of these interactions on LV function is incompletely understood. The aim of the present study was to investigate the effects of these factors on LV systolic and diastolic function in patients with a preoperative ejection fraction greater than 0.5, during CABG.

A total number of 127 patients, scheduled for CABG, were included in the studies. The hemodynamic values obtained during anesthesia were: radial arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressures, together with cardiac output measured by thermodilution. Using a transesophageal echoprobe, LV short axis images and mitral Doppler flow profiles were recorded and later analyzed by means of a computer based analysis system for the presence of systolic or diastolic dysfunction. The heart function was studied: 1. Before and after CPB. 2. Before and after the introduction of nitrous oxide (N_2O), that was investigated prior to CPB and also after CPB. 3. Before and after surgical stress. 4. Before and after the introduction of one of the inhalation anesthetics halothane, enflurane or isoflurane, and 5. At increasing doses of the endogenous vasodilator adenosine after cardiac surgery.

The findings in previous studies of a decrease in diastolic LV function after CPB could not be confirmed, and these previous findings are probably explained by an increase in heart rate (HR) rather than by a decrease in LV diastolic function. The introduction of N_2O did not decrease global or regional LV systolic or diastolic function prior to CPB, but caused regional systolic disturbances, together with a decrease in diastolic function after CPB, that might be explained by the development of myocardial ischemia caused by N_2O after CPB. Surgical stress caused by sternotomy during fentanyl-nitrous oxide anesthesia did not induce regional LV wall motion changes indicative of myocardial ischemia. Treatment of surgical hypertension by inhalation anesthetics confirmed previously described negative inotropic effects of halothane, while isoflurane induced regional wall motion abnormalities indicating the appearance of myocardial ischemia, possibly caused by the concomitant increase in HR. Evaluation of the effects on diastolic function of halothane and isoflurane, when used to prevent surgical hypertension, revealed a decrease in early diastolic relaxation caused by both anesthetics, while isoflurane also caused an increase in end-diastolic stiffness, that was not seen with halothane. In the dose-response study of adenosine ECG changes consistent with ischemia developed in two patients, confirming findings in previous studies. No echocardiographic or Doppler indications of myocardial ischemia were found.

Key words: Heart: ventricle, systole, diastole, Echocardiography, Doppler, wall motion, anesthetics: inhalation, halothane, enflurane, isoflurane, nitrous oxide, adenosine

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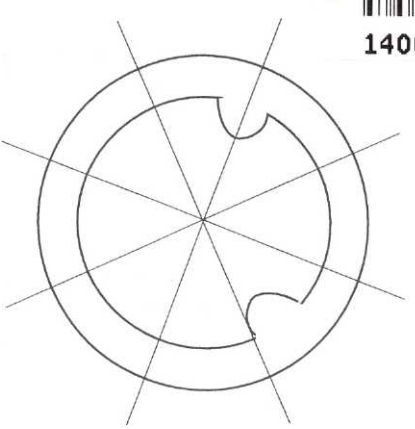

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To Birgitta and Martin

Original Studies

This thesis is based on the following studies, which will be referred to in the text by their roman numerals

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Contents

Abbreviations

The following abbreviations are used throughout this thesis:

2-D echo	two-dimensional echocardiography
AEF	area ejection fraction
A_{max}	maximal velocity of mitral flow during atrial systole
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	cardiac index
CO	cardiac output
CPB	cardio-pulmonary bypass
CVP	central venous pressure
E/A	E_{max}/A_{max}
ECG	electrocardiography, electrocardiogram
EDA	end-diastolic area
E_{max}	maximal velocity of mitral flow during early diastole
ESA	end-systolic area
GAEF	global area ejection fraction
HR	heart rate
LV	left ventricular
MAP	mean arterial pressure
MPAP	mean pulmonary artery pressure
N_2O	nitrous oxide
PCWP	pulmonary capillary wedge pressure
PVR	pulmonary vascular resistance
RWMA	Regional wall motion abnormalities
SAEF	segmental area ejection fraction
SV	stroke volume
SVR	systemic vascular resistance
VTI	velocity-time integral
$VTI_{0\text{-}33\%}/VTI_{Tot}$	fraction of velocity-time integral of mitral Doppler flow during the first third of diastole to total diastolic velocity-time integral
VTI_A	velocity-time integral of mitral Doppler flow during atrial systole
VTI_E	velocity-time integral of mitral Doppler flow during early diastole

1

Introduction

A central question in the practice of anesthesia is whether the choice of anesthetic technique or management of anesthesia affects the outcome of the patients. In two recent studies, evaluating patients undergoing anesthesia for cardiac surgery, it was clearly shown that the outcome of the patients was affected by which particular anesthetist who was performing the anesthesia, indicating the importance of the anesthetic management of these patients (1, 2). In order to study the effects of anesthetics and anesthetic management, it is important to evaluate patients in a clinical setting, i.e. to conduct the anesthesia in a manner that is as close as possible to what is considered a "normal anesthetic procedure", and to deviate from this procedure only in the variables studied.

As coronary artery surgery is performed in patients with compromised coronary circulation and myocardial function, it seems appropriate to evaluate effects of various anesthetics on the heart function because myocardial ischemia is always a potential risk in these patients. This thesis will consequently focus on the effects of myocardial revascularization, the most commonly used inhalation anesthetics, nitrous oxide (N_2O), halothane, enflurane and isoflurane,

and postoperative afterload reduction with the endogenous vasodilator adenosine, on left ventricular (LV) function, as evaluated by transesophageal two-dimensional and Doppler echocardiography.

Detection of myocardial ischemia by ECG and LV regional wall motion analysis

The presence of perioperative myocardial ischemia can be detected by ST-analysis on ECG (3) or by the development of regional wall motion abnormalities (RWMA) on two-dimensional echocardiographic (2-D echo) images of the left ventricle (4). Of these two methods, 2-D echo is the more sensitive (5), while the sensitivity and specificity of ST-segment analysis remains to be clearly evaluated (6). Regional wall motion analysis can be performed by visual observation of the echocardiographic LV short axis images, by one or more observers. Using a scoring system, each of four to sixteen segments are assigned a score from a four-graded scale, and a significant change in motion is usually defined as a decrease of two or more degrees of motion in one segment (7). This method, although widely used, is impaired by some

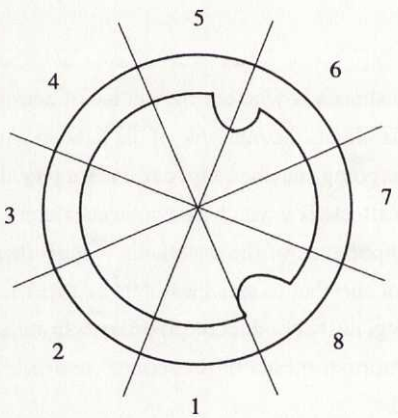

Fig. 1 *Schematic representation of the left ventricular short axis image. The eight segments used in the present studies are shown. All tracings were started at the anterior papillary muscle and followed the endocardium clockwise.*
The segments represent approximately: 1-2 anterior, 3-4 septal, 5-6 inferior and 7-8 lateral wall.

shortcomings. The scoring technique is a highly subjective method and very dependent on the experience of the observer, and the definition of RWMA is arbitrary and seems to be based more on consensus than on objective evaluation (7). In order to overcome these shortcomings of the visual observation method, a different approach to the analysis of RWMA was used. The wall motion in each of eight segments (fig 1) was quantitatively calculated, using computer assisted and statistical methods, to evaluate ischemia-induced changes in regional wall motion.

Analysis of LV diastolic function

The observation that decreased LV diastolic relaxation could be the limiting factor of physical capacity in the presence of normal systolic function was made already by Henderson in 1923 (8). LV diastolic function has been a focus of increased interest during the last 10 years, since it was shown that symptoms of congestive heart failure could develop in patients with normal LV systolic function (9), and that these patients had, together with normal ejection fraction, abnormal diastolic relaxation. It was shown that up to 40 % of patients with chronic ischemic heart disease, developing symptoms of heart failure, had apparently normal systolic LV function, but impaired diastolic filling mechanics (9-11). A further indication of the importance of the diastolic relaxation for the mechanical function of the heart was the finding that, in patients with restenosis after percutaneous angioplasty, only those patients that showed a diastolic dysfunction developed clinical signs of cardiac failure (12). Studies in patients undergoing coronary angioplasty (13-16) and in patients with Prinzmetal's angina (17), have shown that a decrease in diastolic relaxation is an early and sensitive sign of acute myocardial ischemia.

On the cellular level, LV diastolic relaxation is an energy consuming process, dependent on the uptake of calcium from the myocardial cytoplasm into the sarcoplasmic reticulum and on the pumping of calcium over the sarcolemma of the myocyte (18). Factors affecting this calcium flux will thus affect the active relaxation of the myocyte, and studies of human ventricular myocardium from failing hearts have shown abnormal intracellular calcium handling (19).

Diastole is usually divided into an active component which corresponds to the early active relaxation and a passive component, corresponding to resistance of the myocardium to passive stretch (20). The diastolic relaxation starts in late systole and when the pressure in the left ventricle falls below the aortic pressure, the aortic valve closes. The period of continued LV pressure decrease, until LV pressure is below atrial pressure and the mitral valve opens, is called isovolumic relaxation. After the opening of the mitral valve, the continued pressure drop causes an inflow of blood from the atrium into the left ventricle, and the rate of decline in LV pressure, dependent on the rate of relaxation, determines the atrio-ventricular pressure gradient and thereby the velocity of LV early diastolic inflow.

In order to evaluate early LV relaxation, a number of methods have been used. In animal studies, intracavitary pressure measured by tip-manometer pressure catheters, and LV volume calculated from sonomicrographic crystals sewn to the epicardium, is a widely used method (21). In humans, radionuclide and angiographic methods have been used, but the most common method at present is analysis of the Doppler flow profile through the mitral valve during diastole (22, 23), and this method has been shown to have a good correlation to both

radionuclide (24) and angiographic (25) methods. The mitral Doppler flow profile is also influenced by extracardiac factors affecting the early diastolic flow, however. Among these factors preload, afterload, and heart rate (HR) are the most important, and, in order to evaluate the LV diastolic function from the Doppler flow profile, these factors must be measured and their effects compensated for (22, 23, 26).

The passive end diastolic component of LV diastolic function can be evaluated by calculation of LV chamber stiffness, defined as the change in LV ventricular pressure relative to the change in volume (27). In order to calculate the stiffness, LV volume measurements must be performed at two or more LV pressures, as this entity depicts the change in chamber volume for a given change in pressure.

The effect of coronary artery bypass grafting and cold cardioplegic arrest on LV systolic and diastolic function

One of the main events during coronary artery bypass surgery is when the patient is placed on cardiopulmonary bypass (CPB) and the heart is arrested. The aortic cross-clamping leads to a depletion of high energy phosphates, an increase in intracellular calcium, increased resting tension and ultimately to cell damage. In order to reduce metabolic demand and myocardial damage to the heart during this period, the myocardium is perfused by a cardioplegic solution, that has a high potassium content and thereby stops contractions and a low temperature which slows the cardiac metabolism (28). It has been shown that coronary revascularization improves systolic and diastolic function in patients with coronary artery disease (CAD) when investigated days to months after surgery (29-31). The primary interest for the cardiovascular anesthetist is, however, the combined effects of the cardioplegic arrest, that could be expected to decrease heart function, and the revascularization, that would potentially improve function. Investigations of systolic function shortly after CPB have shown a decrease in systolic function, that seems to reach a nadir 2 to 4 hours after weaning from bypass (32-36). Diastolic function has also been investigated in patients early after CPB and coronary revascularization (37-39), but these studies are hampered by not taking into account the increase in HR, that is usually about 30-40 % in the period immediately after weaning from CPB. The interpretation of the previous studies, showing a decrease in diastolic function is thus dubious, especially as studies on the effect of HR on mitral Doppler indices of diastolic function shows a linear negative correlation between HR and the mitral Doppler indices (40-44).

Effects of nitrous oxide on LV systolic and diastolic function in patients with coronary artery disease

The effects of N_2O on heart function and central hemodynamics are complex. For many years after its introduction as an anesthetic, N_2O was believed to be without hemodynamic effects (45). It was then found that N_2O possesses a depressing action on systolic myocardial function (46-54), that is usually offset by an activation of the sympathetic nervous system (47, 55-63). Studies on coronary circulation during N_2O administration have shown N_2O to cause a constriction of the epicardial coronary arteries (64, 65). Evaluation of the incidence of perioperative ischemia after N_2O in patients undergoing coronary artery surgery has been performed prior to CPB, and has not shown N_2O to induce LV ischemic changes (66-68). On the other hand a study in patients with coronary disease undergoing non-cardiac surgery showed an increase in signs of myocardial ischemia evaluated from myocardial lactate, ECG and cardiokymography (69). Animal studies have shown N_2O to have deleterious effects on the heart after exposure to ischemia, that could be compared to the ischemic event of CPB (70). No studies simultaneously evaluating systolic and diastolic effects of N_2O in humans have been presented as yet. There is thus some controversy over the effects of N_2O in patients with CAD, and there could well be differences in the effects of N_2O on systolic and diastolic LV function after CPB as compared to before bypass.

Effects of surgical stress and volatile anesthetics on global and regional systolic function in patients with coronary artery disease

Sternotomy may cause signs of sympathetic nervous stimulation such as systemic vasoconstriction leading to hypertension, and tachycardia, when performed during opiate-N_2O anesthesia. This surgical stress reaction occurs in both low- and high-dose opioid anesthesia, and increases the myocardial oxygen demand (71-77). The myocardial oxygen extraction increases, indicating that an unfavorable oxygen supply-demand situation is induced by the surgical stress (74-77), and may ultimately lead to stress-induced myocardial ischemia, that develops independently of the opioid dose used (71, 72, 74, 75, 77, 78). An indication that this mechanism is of importance for the outcome of the patients is the results from the investigation by Slogoff and Keats, mentioned above, where a greater incidence of hypertension and tachycardia was found in the group of patients anesthetized by the anesthetist whose patients showed a poorer outcome (1).

A common clinical solution to the problem of treating surgical stress, caused by sternotomy, is to use one of the volatile anesthetics to increase the depth of anesthesia, and thus to decrease the myocardial oxygen demand. The central hemodynamic effects of the commonly used inhalation anesthetics halothane, enflurane and isoflurane have been investigated in a few studies in this clinical setting, but with conflicting results. In one study both halothane and enflurane were found to decrease pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) (79), while in another study halothane further increased PCWP without changes in SVR, in contrast to isoflurane which reduced afterload and PCWP, when these anesthetics were used to control increased systemic arterial pressure during surgical stress (73). The myocardial metabolism has also been investigated in addition to central hemodynamic parameters. In one study isoflurane caused no ECG or metabolic signs of myocardial ischemia (76), while in another study, using higher concentrations of isoflurane, HR increased and lactate production was induced in some patients, indicating the development of myocardial ischemia (77). Halothane has also been shown, in one study, to induce lactate production in some patients and to improve myocardial lactate metabolism in other patients (80). No studies on the cardiometabolic effects of enflurane, when used to treat intraoperative hypertension, have been presented.

Although the correlation between intraoperative hypertension and increased myocardial oxygen demand, and thus the risk of myocardial ischemia, seems clearly established, the potential risks and benefits of the common practice to treat this hypertension by the administration of one of the volatile anesthetics is thus not yet sufficiently evaluated.

Effects of halothane and isoflurane on diastolic function

The effects of these inhalation anesthetics on diastolic function have neither been investigated in healthy humans nor in patients with heart disease. Animal studies generally show early diastolic relaxation to be impaired by inhalation anesthetics (81-84), and, as was mentioned above, the proposed mechanism is a decrease in reuptake of calcium into the sarcoplasmic reticulum, a mechanism expected to prolong the early diastolic relaxation (85). Effects on LV chamber stiffness are varying (81, 84, 86-92), but isoflurane has not been shown to increase LV chamber stiffness (81, 84, 92), while halothane in some studies is shown to induce an increase in stiffness (89-91). The effects on animal preparations can, however, not immediately be translated to effects on human subjects with CAD.

Adenosine as a vasodilator after coronary artery surgery

Post CPB hypertension, usually caused by increased SVR (93, 94), is common after cardiac surgery. The increase in SVR leads to an increase in LV workload and a decrease in cardiac output (CO) (95). This well-recognized problem is usually treated by administration of arterial vasodilators, the most popular being nitroprusside and nitroglycerin. These agents have some shortcomings, however. Nitroprusside is a short acting nitrate that dilates both arterial resistance and venous capacitance vessels, and that is toxic at prolonged administration. Nitroglycerin also dilates arterial resistance vessels, but has its main effect on the venous capacitance vessels (96).

Adenosine is an endogenous purine that has been shown to exert its powerful vasodilating effects almost exclusively on the arterial resistance vessels and in the coronary vascular bed (97-100). It is extremely short acting with a half-life that is only a few seconds (101). Adenosine thus seems almost ideal as a vasodilator after cardiac surgery. As studies on the effects of adenosine on the coronary circulation have shown adenosine to be a powerful coronary vasodilator, this characteristic of adenosine has raised the question whether adenosine is capable of inducing myocardial redistribution of flow, and ischemia, after coronary artery surgery (102, 103). Infusion of adenosine has induced cardiac lactate production in some patients and ST-depression in some patients, although not all patients with lactate production developed ST-changes and vice versa (101, 104). Thus there is some evidence that adenosine might induce myocardial ischemia in susceptible patients after CABG, although the question is not fully resolved.

2

Aims of the studies

- To evaluate the early effects of coronary artery bypass surgery and cold cardioplegic arrest on LV systolic and diastolic function.
- To investigate whether nitrous oxide affects LV systolic and diastolic function in patients with coronary artery disease, and to explore if the response to nitrous oxide is different after, as compared to before, cardiopulmonary bypass and coronary revacularization.
- To compare the effects of the inhalation anesthetics halothane, enflurane and isoflurane on LV global and regional systolic function during surgical stress in patients with coronary artery disease.
- To compare the effects of the inhalation anesthetics halothane and isoflurane on early LV diastolic relaxation and end-diastolic stiffness in patients with coronary artery disease.
- To study the effects of the endogenous vasodilator adenosine on LV systolic and diastolic function in the post-cardiopulmonary bypass period, with special regard to its potential to cause myocardial ischemia.

3

Material and Methods

These studies were performed in patients with CAD of a severity sufficient to justify cardiac surgery for coronary revascularization. Although the inclusion criteria aimed at investigating a patient group that was kept as homogeneous as possible, the variation in the severity of the disease in individual patients guaranteed a large amount of variation among the variables measured. The present studies were thus designed to minimize the effects of this variation. In order to achieve this goal, a repeated measures design, i.e. a design were the patients served as their own controls, was used where possible.

Patients

All studies were performed in patients with two or three vessel coronary artery disease and a normal preoperative systolic LV function, defined as an ejection fraction greater than 0.5, determined on the preoperative cardioangiography. No patients with valve disorders were included. All patients were treated with beta-receptor blocking agents, that were continued until the morning of surgery. In study V, patients that were or had been on dipyridamole therapy were excluded. No other requirements regarding the patients medication had to be met for inclusion in the studies. The patients received their cardiac medication on the morning the day

of surgery, prior to the premedication. A total number of 127 patients were included. The majority of patients in study V were also included in study II.

Anesthesia

A standardized anesthetic procedure, that was modified to fit the experimental procedure of each individual study, was used in all patients. The premedication consisted of flunitrazepam (1 mg) and a combination of morphine (10 mg) and scopolamine (0.4 mg), that was administered 30 - 60 minutes prior to induction of anesthesia. Anesthesia was induced with thiopental (3 - 5 mg/kg) and fentanyl (5 - 10 μg/kg). Pancuronium (100 μg/kg) was used for muscle relaxation. After induction, the anesthesia was maintained with N_2O and incremental doses of fentanyl in study III and IV and by fentanyl alone in study I and II. Ventilation was controlled to keep pCO_2 between 35 and 40 mmHg and $pO_2 > 90$ mmHg. During sternotomy one of the inhalation anesthetics halothane, enflurane or isoflurane was used for pressure control, either according to a randomization procedure in study III and IV, or at the attending anesthetists discretion in studies I, II and V. During CPB, only fentanyl was used, and after weaning from CPB, anesthesia was maintained by fentanyl and N_2O in study V, or by fentanyl alone in study I and II until completion of the study protocol. In studies III and IV no investigations were carried out after CPB, and the management of anesthesia was left to the judgment of the attending anesthetist (fig 2).

Measurements of central hemodynamics and ECG monitoring

Prior to induction of anesthesia, in all patients, an arterial catheter (Viggo-Spectramed, 20 G, 1.0 mm x 45 mm), was inserted into the left radial artery. After anesthesia-induction, a central venous catheter was placed in the left subclavian vein and a Swan-Ganz thermodilution pulmonary artery catheter (USCI®; CR Bard Inc., Billerica, MA, USA) was inserted through the right jugular vein and, under fluoroscopy, guided into the pulmonary artery, for central hemodynamic measurements. The pressure receptors were calibrated against atmospheric pressure and maintained at the mid-axillary level throughout the investigations. A Siemens Sirecust® monitoring system (Siemens AG, Erlangen, Germany), was used to record ECG and central hemodynamic variables. PCWP recordings were obtained together with CO measurements, that were performed in triplicate, using thermodilution with iced saline. Calculation of CO was performed by the Sirecust® monitoring computer. Body core temperature was noted using the thermodilution catheter thermistor.

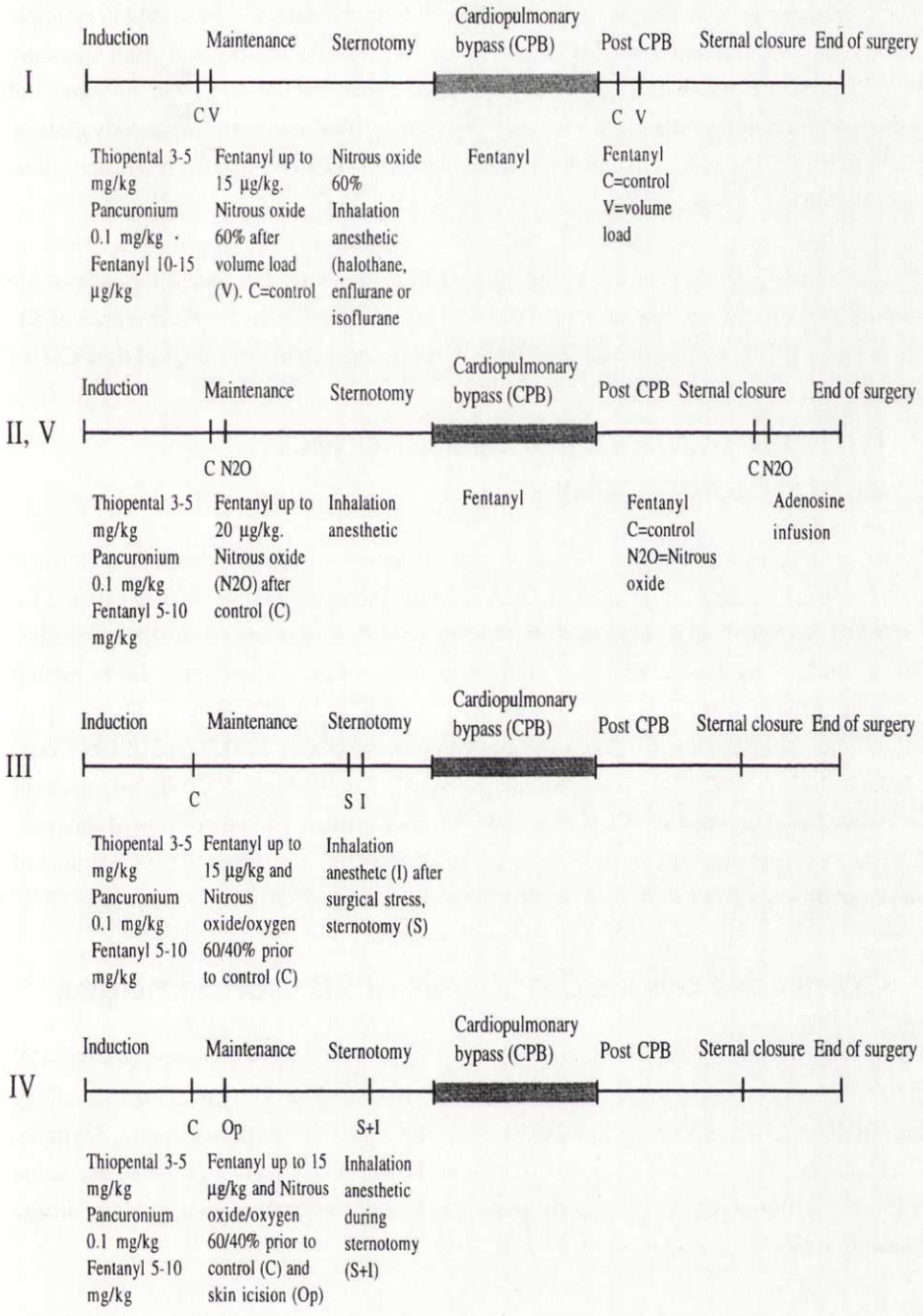

Fig 2. *Anesthetic procedures used in the five studies. The horizontal lines are decribing the order of interactions, but times are not proportional. Study II and V were performed in the same group of patients.*

The hemodynamic variables measured were HR, systolic, diastolic and mean (MAP) systemic and systolic, diastolic and mean (MPAP) pulmonary arterial pressures, central venous pressure (CVP), PCWP and CO. Using standard formulas, stroke volume (SV) and systemic and pulmonary vascular resistances (SVR and PVR), were calculated from the measured variables. In study III, cardiac index (CI), stroke volume index and systemic vascular resistance index, were calculated.

Two standard ECG-leads (leads II and V_5) were continuously monitored throughout the studies. The ST-segment was examined 60 or 80 ms after the J-point for the presence of ST-elevation or ST-depression in lead II and/or V_5, using paper strip recordings of the ECG:s.

Two-dimensional transesophageal echocardiography

When induction of anesthesia, intubation and placement of catheters were completed, a transesophageal echocardiographic ALOKA®, 5 MHz monoplane probe (studies I-III and V), or an ACUSON 3.5/5 MHz biplane probe (studies I and IV), was inserted into the esophagus. The position of the probe was adjusted to obtain a trans-gastric short axis view of the left ventricle, at the mid-papillary level. Using an ALOKA® SSD 870 (ALOKA Co, Tokyo, Japan) echocardiography system (studies I-III and V) or an ACUSON 128XP (ACUSON Corp., Mountain View, Calif., USA) echocardiography system (studies I and IV), real time images of the heart were recorded on VHS videotape for later off-line computer assisted analysis. Together with the echocardiographic images, an ECG-signal was recorded for the timing of end-diastole.

Computer assisted analysis of 2D-echo images

The computer system used for analysis of the LV short axis images consisted of a 486-DX personal computer equipped with a frame-grabber card (VisionPlus AT™, Imaging Technology Inc., Bedford, MA, USA) and a digitizer board (SummaSketch™, Summagraphics, Seymour, Conn., USA). The software used was written at the MEDNET computer laboratory at the Medical Faculty of the University of Gothenburg, and consisted of two parts; an image acquisition module and an analysis module (105).

The video images were transferred from video-tape to the frame-grabber at an acquisition rate of 25 images per second. The acquired images could then be viewed frame by frame, in slow motion or in real time, and by means of the digitizing board, the endocardium was outlined in diastole and systole, diastole defined as the frame at the R-wave on ECG and systole as the

frame with the smallest LV area. To confirm that a correct measurement was achieved, the outline was superimposed on the moving picture of the left ventricle, and adjusted if necessary to adhere as close as possible to the endocardium. The analysis module offered the choice of corrections for rotational and translational movements of the heart, and algorithms for radial or centerline segmental wall motion analysis. In order to use the rotational correction, the digitizing process had to start at a fixed reference point in the heart, and in the present studies the tracing of the endocardium was always started at the anterior papillary muscle (the reference point), and the systolic contour rotated until the reference points of the systolic and diastolic contours fell on the same radius. To correct for translational movements of the heart, the centroids of the areas enclosed by the systolic and diastolic contours were calculated (106, 107), and the systolic area was moved until the two centroids coincided. This correction, called a floating reference, was used in study V. In studies I-IV a fixed reference was used, i.e. no corrections for translational movements were made.

When the systolic and diastolic contours had been corrected for rotational and translational movements, a centerline was drawn midway between the contours and divided into 96 segments of equal length. Lines were then drawn through each of these segments, perpendicular to the centerline, between the systolic and diastolic contour, dividing the area between these contours into 96 "slices". These "slice areas" were then added together 12 by 12, clockwise, starting at the anterior papillary muscle, to obtain 8 segment areas, representing the LV-short axis area change from systole to diastole in these 8 segments, representing approximately the anterior wall (segment 1-2), the septal wall (segment 3-4), the inferior wall (segment 5-6) and the lateral wall (segment 7-8) (108).

The output from the two-dimensional computer analysis package used in these studies consisted of end-systolic area (ESA), end-diastolic area (EDA), global area ejection fraction (GAEF), and segmental area ejection fraction (SAEF) for each of the eight segments.

Doppler echocardiography

In order to obtain Doppler flow profiles for analysis of diastolic filling of the left ventricle, the transesophageal echo probe was withdrawn from the transgastric view and angled dorsally until a long axis view of the left ventricle was obtained. When a good view of the mitral valve had been ascertained, a pulsed Doppler line was placed through the mitral valve, as parallel as possible to the mitral flow, with the measuring caliper at the tips of the mitral leaflets. The flow profiles were then recorded on VHS videotape and also saved on paper strips. An ECG tracing was always saved together with the Doppler flow curves.

Computer assisted analysis of mitral Doppler flow profiles

The off-line analysis of the Doppler flow profiles was performed using the same computer system as was used to analyze the 2-D echo-images, i.e. a 486-DX personal computer equipped with a frame-grabber card and a digitizing tablet. The software used was written at the MEDNET computer laboratory.

The flow profiles were either transferred from the video-tapes to the computer by means of the frame-grabber as previously described, or digitized from the paper strips. In both cases, the outer contour of the flow profile was traced from the start of the mitral flow, using the digitizing tablet. The computer program used a semi-automatic algorithm, requiring the user to indicate the end of the early filling and the start of atrial filling together with the ECG R-waves before and after the mitral flow. Minor irregularities in the digitized mitral Doppler envelope was removed by the computer program, using a digital filter.

Of the mitral Doppler indices calculated by the computer program, the following were used in studies I, II, IV and V; the peak velocities of early and atrial diastolic filling (E_{max} and A_{max}), the ratio between E_{max} and A_{max} (E/A), the deceleration slope and time of the early diastolic filling (E_{dec}-slope and E_{dec}-time), the velocity-time integrals of the early and atrial diastolic filling (VTI_E and VTI_A), and the ratio between VTI_E and VTI_A (VTI_E/VTI_A), together with the ratio of the velocity-time integrals between the filling during the first third of the diastole and the total velocity-time integral of the diastole ($VTI_{0\text{-}33\%}/VTI_{Tot}$) (fig 3).

Coronary anatomy

In study III, the pre-operative cardioangiographic examinations of all patients were examined by an experienced cardiovascular radiologist for the presence of steal prone coronary anatomy, as defined by Buffington et al (109). This definition requires a total occlusion of at least one of the major epicardial coronary arteries, with collateral flow into the vascular bed distal to the occluded artery, and proximal stenosis (>50% reduction of the inner diameter of the vessel) of the artery supplying the collateral flow.

Calculation of end-diastolic stiffness

End-diastolic stiffness, the myocardial resistance to passive stretching, was calculated in two of the studies (study I and study IV).

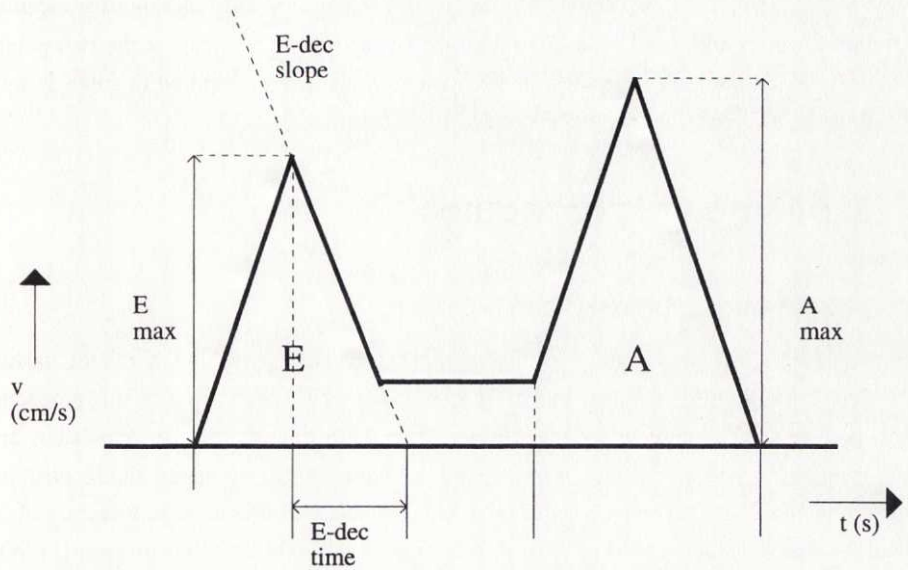

Fig. 3 *Schematic representation of the mitral Doppler flow profile. E is the early diastolic and A the atrial diastolic filling component, E max is the maximal blood flow velocity during early filling and A max the maximal blood flow velocity during atrial filling. E-dec time and E-dec slope denotes the deceleration time and rate of the early diastolic filling phase.*

The end-diastolic pressure-area relation is known to be curvilinear in shape, and in vitro and in vivo animal studies have shown that it, as long as the end-diastolic pressure remains greater than 3 mmHg, fits reasonably well to an exponential function (27). In the above mentioned studies the function:

$$PCWP = B * e^{S \cdot EDA},$$

has been used to describe the relation between end-diastolic pressure and end-diastolic area. In this function *PCWP* denotes the pulmonary capillary wedge pressure, *EDA* the end-diastolic area and *B* and *S* are two constants. By transforming this function to its logarithmic form:

$$\ln PCWP = \ln B + S * EDA,$$

that is a linear equation, the end-diastolic stiffness *(S)*, describing the slope of the line, can be solved from two points on the pressure-area curve using the formula:

$$S = \frac{\ln(PCWP_2) - \ln(PCWP_1)}{EDA_2 - EDA_1},$$

where $ln(PCWP_1)$ and $ln(PCWP_2)$ are the natural logarithms of the pulmonary capillary wedge pressures and EDA_1 and EDA_2 are the LV end-diastolic areas, at the two points, respectively. In the present studies the two points on the curve, required to solve S, were obtained by a volume loading procedure described below.

Experimental procedures

Volume loading (studies I and IV)

In order to evaluate the LV end-diastolic resistance to passive stretching, a volume loading procedure was performed in two studies. In studies I and IV a passive leg-raising procedure was performed after induction of anesthesia, when intubation, placement of catheters and transesophageal echo-transducer were completed. With the patients in the supine position, measurements of central hemodynamics and echo-Doppler variables were performed, and the patient's legs were then raised approximately 60 degrees while the LV filling pressure (PCWP) was monitored, to confirm that an increase in filling had occurred. Identical measurements were then performed after stabilization of the PCWP. In study I a volume loading procedure was repeated also after weaning from CPB. At this occasion, 5 minutes after weaning, the above mentioned measurements were performed with the patient in the supine position, before and after infusion of the remaining blood from the heart-lung machine.

Administration of N_2O (study II)

Measurements of central hemodynamic and echo-Doppler variables for analysis of the effects of N_2O, in study II, were performed after 10 minutes of inhalation of N_2O in oxygen (60% / 40%). This procedure was performed pre-CPB after induction of anesthesia and repeated post-CPB after sternal closure.

Surgical stress (study III)

Sternotomy, that was performed during fentanyl-N_2O anesthesia in study III, is known to cause a surgical stress response with intraoperative hypertension. Hemodynamic measurements, echocardiographic images and ECG recordings were obtained prior to skin incision and 1 minute after sternotomy.

Administration of inhalation anesthetics (studies III and IV)

In study III, the patients were randomized to receive one of the three inhalation anesthetics; halothane, enflurane or isoflurane. In study IV the patients were similarly randomized to receive either halothane or isoflurane.

In study III, the inhalation agent to be studied was thus administered in concentrations adequate to treat the increase in systemic arterial blood pressure, caused by the surgical stress, with the aim to reduce the MAP back to the same level as before sternotomy (the end-point). In study IV, the inhalation anesthetic was introduced during sternotomy to avoid intraoperative hypertension and thus to maintain MAP at the preincision level. End-tidal concentrations of the inhalation anesthetics were measured by a Siemens Servo Gas Analyzer (Siemens AG, Erlangen, Germany). Measurements of the effects of the inhalation anesthetics on central hemodynamics and echo-Doppler variables were performed when the MAP was brought back to preincision levels (study III), or 10 minutes after the introduction of the volatile anesthetic (study IV).

Adenosine infusion (study V)

Adenosine was infused after the end of the surgical procedure, with the patients still on the operating table, but with no ongoing surgery. Anesthesia was maintained by fentanyl and N_2O. The adenosine was infused in incremental doses (0, 30, 60 and 120 μglkglmin) through the central venous catheter into the superior caval vein. Measurements of central hemodynamics, ECG, Doppler and transesophageal echocardiographic variables were performed after 5 minutes of infusion at each infusion rate. Values obtained before the start of the adenosine infusion were considered as control values.

Statistics

The main statistical models used in these investigations were analysis of variance (ANOVA) procedures. Because repeated measures were performed on the same subjects, a within subjects (repeated measures) design was used. In order to evaluate differences between the measurements, single-degree of freedom comparisons (contrast analyses) were performed. This method of evaluation was chosen because the measurements in a within subjects model are not independent, thus rendering the common post-hoc tests invalid (110). Where only two measuring occasions were present, at a single level, a paired Student's t-test was used for comparison.

Where the material was divided into sub-groups, the groups receiving for example different inhalation anesthetics, a two-way (study III and IV) or three-way (study III), within-subjects ANOVA was used. Differences in treatment effects between the sub-groups over the measuring occasions were evaluated by the interactions generated by the ANOVA model.

When the experimental procedure was repeated on more than one occasion (study I and II), a one or two-way hierarchical ANOVA was used, with the repetition (i.e. pre- and post-CPB) as the higher level, and the experiment, as the lower level. The segmental wall motion evaluation performed in studies II, III and V was analyzed by a special case of the within subjects, hierarchical ANOVA procedure, called profile analysis (111), where the wall motion of the eight segments was used as the lower level (the profile), and the measuring occasions were used as the higher level(s).

A dose-response study was performed in study V, where adenosine was infused in increasing doses. To evaluate whether dose-dependent changes were caused by the adenosine infusion, an extension of the ANOVA procedure, analysis of linear trend, was performed on hemodynamic and mitral Doppler variables.

In study I, where it was known from previous studies that the Doppler indices studied had a linear relation to HR, and where the HR changed in a consistent manner between measurements, an analysis of covariance (ANCOVA), was performed, with HR as a covariate changing over time. This procedure analyzes whether a correlation between the variable measured and the covariate exists among the subjects studied at each measuring occasion, and if such a correlation is present, its effect is compensated for, before comparisons between the measuring occasions are performed.

Inter and intra-observer correlations between the two-dimensional and Doppler indices (study I, III and IV), were evaluated using the Pearson product-moment correlation (study I and III) and coefficient of variation (study IV).

The data are presented as means ± standard error of the mean (SEM) in studies I and III-V, and as means ± standard deviation (SD) in study II.

4

Results

The results obtained in the studies of this thesis are here described under five main headings. The following subjects are addressed below: 1) effects of coronary artery bypass surgery and cold cardioplegic arrest on LV diastolic function. 2) effects of N_2O on LV systolic and diastolic function, before and after CPB. 3) effects of stress-induced intraoperative hypertension on LV regional systolic function. 4) effects of halothane, enflurane and isoflurane on LV systolic and diastolic function when used to control intraoperative hypertension, and 5) effects of adenosine on LV systolic and diastolic function after CPB.

Effects of coronary artery bypass surgery and cold cardioplegic arrest on LV diastolic function

In this study (study I) measurements were performed both in the pre-CPB and the post-CPB period. In addition to central hemodynamic variables, early diastolic function was evaluated by mitral Doppler flow analysis, and end diastolic stiffness by a volume loading procedure.

Doppler indices before and after CPB

The mitral Doppler flow profile was also evaluated before and after CPB. The E_{dec}–slope and A_{max} increased. while the E_{dec}–time, E/A, VTI_E and $VTI_{0\text{-}33\%}/VTI_{Tot}$ decreased. E_{max} and VTI_A were unchanged (fig 4). These changes could be caused by an impaired diastolic relaxation, but could also reflect extracardiac changes, as changes in loading conditions and HR are known to affect the Doppler indices. As the increase in HR was over 30%, the effect of the HR increase was compensated for, using an ANCOVA procedure as previously described. After this compensation, only the increase in A_{max}, after CPB, remained significant. Volume loading increased E_{dec}–slope, E_{max}, A_{max}, and VTI_E, both before and after CPB.

The early diastolic relaxation was also studied by the E_{max}/PCWP relation. This index was studied before and after CPB, before and after the volume loading procedure. No changes in the slope of the E_{max}/PCWP line was found post-CPB, compared to pre-CPB (fig 5).

End-diastolic stiffness after CPB

In order to further evaluate the effects of CPB on LV end-diastolic properties, the myocardial stiffness was calculated before and after CPB. LV end-diastolic stiffness was unchanged by CPB, the corresponding values being 0.088 ± 0.015 and 0.097 ± 0.018 respectively (fig 6).

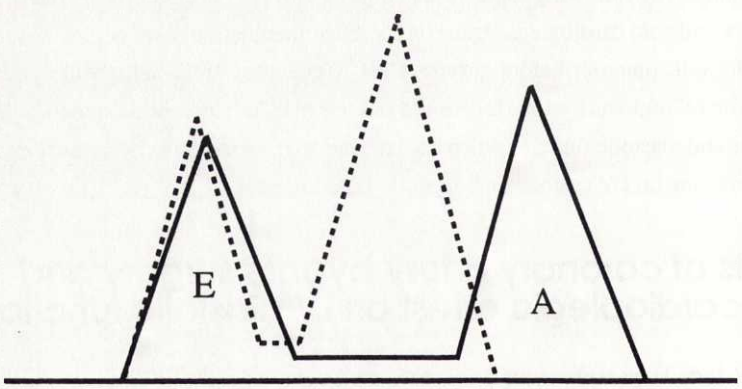

Fig. 4 *Schematic representation of the mitral Doppler flow profile before (solid line), and after cardiopulmonary bypass (dotted line).*

Central hemodynamic findings and 2-D echo variables before and after CPB

CO and HR increased after CPB, together with a decrease in MAP and SVR. No changes were found in PCWP, CVP, MPAP or SV post-CPB compared to pre-CPB.

Volume loading induced similar changes in the pre- and post-bypass situation with increases in systemic, pulmonary and filling pressures. No changes were found in HR or SVR after volume loading. The only difference found among the 2-D echo variables was an increase in EDA, while ESA and AEF remained unchanged between the pre- and post-CPB measurements. Volume loading increased both the EDA and the ESA to approximately the same extent, both pre- and post-CPB.

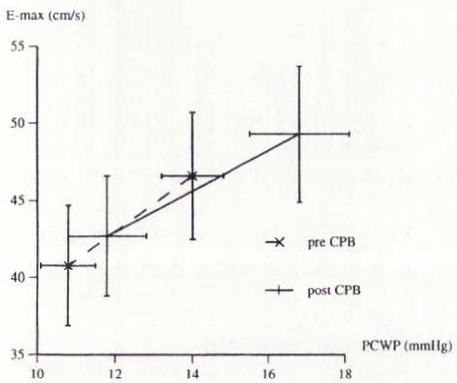

Fig. 5 *The effect of a preload increase on the early diastolic filling velocity (E_{max}) before and after cardiopulmonary bypass. No significant change in the response to the preload increase was found.*

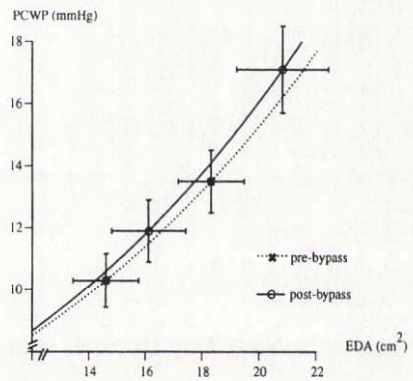

Fig. 6 *End-diastolic stiffness before and after CPB. The points are fitted to an exponential equation. The slope of the lines represents the end-diastolic stiffness.*

Effects of N_2O on LV systolic and diastolic function

The effects of N_2O on LV function were investigated in study II. Global and regional systolic performance together with diastolic function, evaluated from the mitral Doppler flow profiles, were examined before and after the introduction of N_2O, before and after CPB.

N_2O and central hemodynamics

Post-CPB control values of CO and HR were higher, SVR was lower, while SV was unchanged, compared to corresponding pre-bypass values. These data are in agreement with data from study I. N_2O caused decreases in MAP, CO, SV and HR, both before and after CPB. The

introduction of N_2O did not affect PCWP or PVR prior to CPB, but decreased PCWP and increased PVR after CPB.

Global and regional echocardiographic indices after N_2O

N_2O did not affect the ESA, EDA or the AEF, neither before nor after CPB. The LV regional wall motion was not affected by N_2O before CPB (fig 7), but after CPB the development of RWMA, affecting anterior and septal segments, were detected (fig 8).

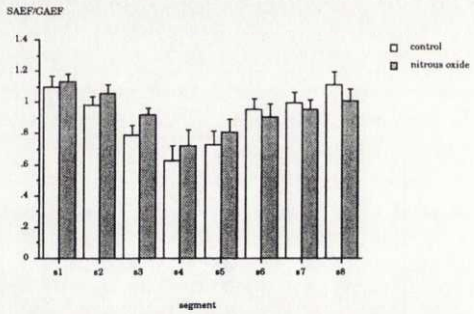

Fig. 7 *Regional wall motion after N_2O before cardiopulmonary bypass*

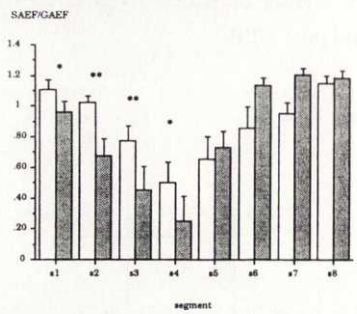

Fig.8 *Regional wall motion after N_2O post cardiopulmonary bypass*

The effects of N_2O on Doppler indices of diastolic function

A considerable difference was found in the mitral Doppler indices after introduction of N_2O in the pre-CPB period, compared to the effects of N_2O post-CPB. Pre-CPB, the A_{max} and the VTI_A decreased while the E/A and $VTI_{0\text{-}33\%}/VTI_{Tot}$ increased. No changes were found in E_{max}, VTI_E, E_{dec}–slope or E_{dec}–time (fig 9). After CPB, however, E/A was unchanged as were VTI_A and $VTI_{0\text{-}33\%}/VTI_{Tot}$, while the E_{dec}–slope increased (fig 10). These changes indicate that N_2O caused a shift of the diastolic inflow into the left ventricle towards early diastole in the pre-CPB period, but that this effect was not seen after the introduction of N_2O in the post-

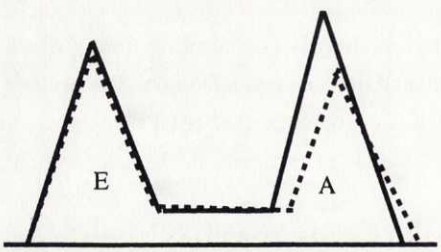

Fig. 9 *Schematic mitral Doppler flow profile before CPB. Solid line is control. Dotted line after introduction of N_2O.*

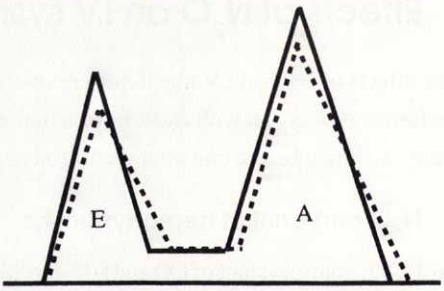

Fig. 10 *Schematic mitral Doppler flow profile after CPB. Solid line is control. Dotted line after introduction of N_2O.*

CPB period.

ECG analysis after N_2O

The ECG tracings of leads II and V_5 were examined for the presence of ST-segment changes indicative of myocardial ischemia. No such changes were found after the introduction of N_2O, however, neither before, nor after CPB.

Surgical stress, intraoperative hypertension and LV wall motion

In study III, the effects of sternotomy, during fentanyl – nitrous-oxide anesthesia, on central hemodynamics, LV global and regional wall motion, were investigated. The surgical stress caused increases in arterial and filling pressures, both in the systemic and the pulmonary circulation, while no changes were found in CI or SV. The SVR increased substantially (50%). The GAEF decreased but this decrease was symmetrically distributed, and no newly developed RWMA were found, when the changes in global wall motion were compensated for using the SAEF/GAEF ratio, a load independent index for regional wall motion.

Volatile inhalation anesthetics and surgical stress

The effects of the halogenated volatile anesthetics halothane, enflurane and isoflurane on global and regional LV wall motion and central hemodynamic variables, were investigated in study III. The effects of halothane and isoflurane on LV diastolic properties and central hemodynamics were further explored in study IV. Administered end–tidal concentrations were for halothane 0.61 ± 0.14 % and 0.80 ± 0.09 %, and for isoflurane 1.03 ± 0.10 % and 1.13 ± 0.09 %, in studies III and IV respectively. The end-tidal concentration of enflurane in study III was 0.86 ± 0.14 %.

Central hemodynamic effects of the volatile inhalation anesthetics

Due to the study design used in these studies, where the inhalation agents were used to treat (study III) or to prevent (study IV) an increase in MAP, caused by sternotomy, the effects on central hemodynamics are to be viewed as the combined effects of stress-induced sympathetic activation and the inhalation anesthetics. The main interest should thus be focused on differential effects between the anesthetics studied.

The end-point of inhalation anesthetic administration was reached in both study III and IV for all the volatile anesthetics studied, i.e. MAP during administration of the inhalation agent was not significantly different from pre-incision control measurements. The MAP, CVP and PCWP

were increased to approximately the same extent while SV and SVR remained unchanged by all the volatile anesthetics in both studies, compared to pre-incision control values. Differences between the volatile anesthetics were found in their effects on HR, that was increased by enflurane in study III, and by isoflurane in both study III and IV, while halothane did not affect HR in either study. CO was slightly increased by isoflurane in both studies, due to the HR increase, while no change was seen with halothane or enflurane. Although the increase in CO in the isoflurane groups did reach significance in study III only, the interaction between the effect of halothane and the effect of isoflurane on CO was significant in both study III and study IV.

Effects of volatile anesthetics on LV global and regional wall motion

The AEF was investigated in both studies III and IV. In both studies halothane decreased the GAEF, while isoflurane caused no change in GAEF. Enflurane, that was examined in study III induced no change in GAEF. The changes in EDA and ESA were evaluated for halothane and isoflurane in study IV, where both anesthetics were found to increase the EDA. Halothane also increased the ESA, while for isoflurane, although a small numerical increase was present, this increase did not reach significance.

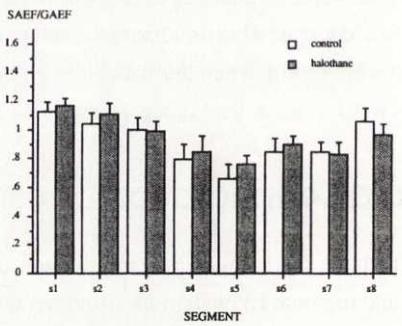

Fig. 11 *LV regional wall motion before and after halothane. No change in the LV profile was found.*

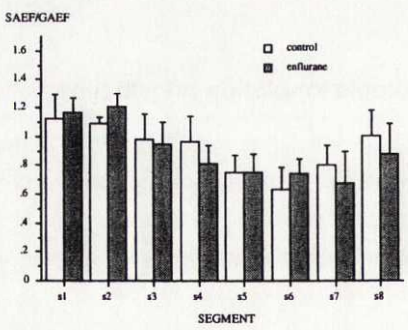

Fig. 12 *LV regional wall motion before and after enflurane. No change in the LV profile was found.*

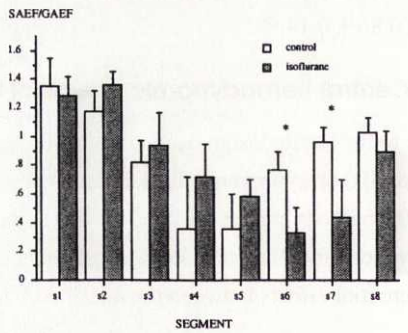

Fig. 13 *LV regional wall motion before and after isoflurane. A significant wall motion change was caused by isoflurane.*

Changes in regional wall motion , as assessed by the SAEF/GAEF ratio, were investigated after halothane, enflurane and isoflurane in study III (fig 11 -13). Halothane and enflurane were not found to cause any changes, but isoflurane induced newly developed RWMA, i.e. a decrease in the SAEF/GAEF ratio, that was most prominent in segment 6 and 7, corresponding to the inferio–lateral wall of the left ventricle.

Effects of the volatile anesthetics on diastolic function

The LV mitral Doppler filling profile, investigated in study IV, showed an increase of E/A and decreases of E_{dec}–time, A_{max}, VTI_E, and VTI_A for both halothane and isoflurane. E_{dec}–slope increased for halothane while no change was found for isoflurane. No changes were found in E_{max}, $VTI_{E/A}$ or $VTI_{0\text{-}33\%}/VTI_{Tot}$ for either anesthetic. To investigate end-diastolic stiffness, the end-diastolic pressure-area relation was evaluated after the introduction of the volatile anesthetics, and the result was compared to the pressure-area curve obtained by a volume loading procedure performed after the induction of anesthesia. The pressure-area relationship in the halothane group was found to lie almost exactly on the predicted pressure-area curve,

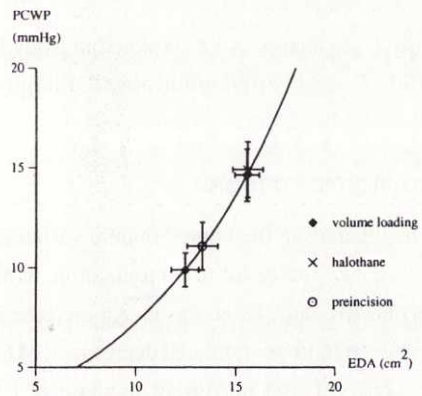

Fig. 14 *Effect of halothane on LV end-diastolic stiffness. The end-diastolic pressure-area relation does not deviate from the line after the introduction of halothane.*

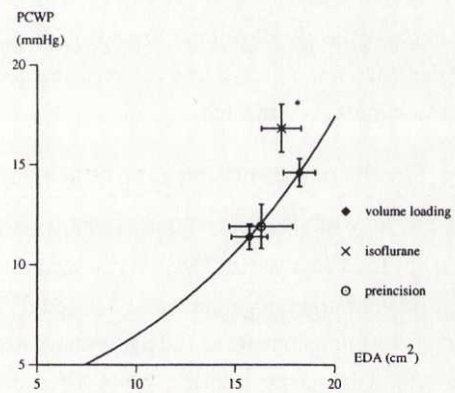

Fig. 15 *Effect of isoflurane on LV end-diastolic stiffness. The end-diastolic pressure-area relation moves to the left from the line after the introduction of isoflurane, indicating an increase in end-diastolic stiffness.*

while isoflurane caused an increase in stiffness that moved the pressure-area relationship to the left of the predicted curve fig (14-15).

Evaluation of the ST-segment after introduction of the volatile anesthetics

Neither in study III, where lead V_5 was examined, nor in study IV, where both leads II and V_5 were studied for the presence of ST-segment changes, did any of the inhalation anesthetics studied induce changes consistent with myocardial ischemia.

Interaction between coronary anatomy and regional wall motion

The patients in study III were divided into two groups according to whether steal prone coronary anatomy was present or not. The interaction between regional wall motion, inhalation anesthetic and coronary anatomy was then evaluated. No difference in the incidence of newly developed RWMA between patients with or without steal-prone anatomy was found in the halothane or enflurane groups, while in the isoflurane group RWMA seemed to be more common in the sub-group without steal-prone coronary anatomy.

Systolic and diastolic effects of adenosine on the left ventricle

This study (study V) was performed in the same group of patients as were studied in study II. Adenosine was administered in increasing doses: 30, 60 and 120 µg/kg/min after the surgical procedure was completed.

Effects of adenosine on central hemodynamic variables

A low dose of adenosine (30 µg/kg/min) caused no changes in the hemodynamic variables, except for a decrease in MAP. When the infusion rate was increased to 60 µglkglmin, MAP decreased further, together with SVR and PVR, while HR and CO increased. An increase in adenosine infusion rate to 120 µg/kg/min caused an even more pronounced decrease in MAP and the vascular resistances, while SV and CO increased, and no further increase in HR occurred. CVP, PCWP or MPAP were not affected by any dose of adenosine. A significant linear trend was found for MAP, HR, CO, SV, SVR and PVR during the adenosine infusion.

2-D echo variables after adenosine

Increasing doses of adenosine did not affect neither the AEF, nor the ESA or EDA. Analysis of regional wall motion showed no changes to be caused by the adenosine infusion at any dose.

Diastolic mitral Doppler flow during adenosine infusion

The mitral Doppler flow indices were not affected by an adenosine infusion rate of 30 µglkglmin. When the infusion rate was increased to 60 µglkglmin, the only effect on the Doppler indices was a shift of flow towards late diastole shown by a decrease in $VTI_{0\text{-}33\%}$/ VTI_{Tot}. At the highest adenosine dose, 120 µglkglmin, E_{dec}–slope and in E_{max} increased. No

further decrease in $VTI_{0\text{-}33\%}/VTI_{Tot}$ occurred when the adenosine infusion rate was increased from 60 µg/kg/min to 120 µg/kg/min. The linear trend analysis showed a significant linear trend for E_{dec}–slope, E_{max}, A_{max} and the $VTI_{0\text{-}33\%}/VTI_{Tot}$.

ST-segment analysis during adenosine infusion

ST-changes consistent with myocardial ischemia developed in two patients during adenosine infusion. A significant linear trend was also present for ST-depression at increasing doses of adenosine.

5

Discussion

Some aspects on the methods used in this thesis will first be discussed below. The discussion will then be divided in four parts covering the LV systolic and diastolic effects of, CPB and cold ischemic arrest, N_2O, when administered before and after CPB, Surgical stress caused by sternotomy and the treatment of this stress by volatile anesthetics, and adenosine infusion after completion of surgery.

Methodological considerations

Detection of myocardial ischemia

Impaired LV function, as detected by the methods used in this thesis, may be caused by myocardial ischemia. No "golden standard" for identification of the presence of myocardial ischemia is available, however, and although an increase of the lactate content in coronary sinus blood, indicating a myocardial net lactate production, is a strong indicator of myocardial ischemia (112), the possibility of concomitant regional lactate consumption and production renders the analysis of cardiac venous lactate a rather blunt method for the detection of LV myocardial ischemia. It has also been shown that myocardial lactate metabolism is heterogeneous

in patients with CAD and that a significant amount of lactate can be released by the myocardium at a time when a net myocardial lactate extraction is present (113). It is also well recognized that not all venous drainage goes via the coronary sinus, but also that some myocardial venous blood is drained directly into the right atrium and thus is unavailable for lactate analysis.

Another widely used method for detection of myocardial ischemia is analysis of the ST-segment on electrocardiography. ECG is known to be a relatively insensitive method to detect subendocardial ischemia (114), and the use of a limited number of leads, that is necessary in the intraoperative setting during cardiac surgery, makes it difficult to detect even significant transmural ischemia by ECG (115).

LV wall motion

It has long been known from animal studies that regional myocardial ischemia, caused by a decrease in blood supply to a segment of the left ventricle, is immediately followed by a decrease in the normal systolic motion of the affected LV segment (116). This RWMA appears within 15 seconds after coronary occlusion (117), simultaneously with the onset of myocardial lactate production (118), and before the appearance of changes on ECG (119). In its mildest form, the inward systolic wall motion during systole is just delayed in time, but with increasing ischemia, motion in the affected segment first decreases then disappears, and finally an inverse motion pattern appears (120, 121). Myocardial ischemia is, however, not the only cause of RWMA. The interaction between the right and left ventricle may cause regional motion disturbances, that appear especially in the septal segments of the left ventricle, when changes in pre- or afterload causes changes in the right-left ventricular interaction (122). The motion abnormalities caused by a left bundle branch block could also be mistakenly interpreted as RWMA (123), and finally the normal LV wall motion is unevenly distributed in the normal heart (124),

Analysis of regional wall motion

In the present studies transesophageal echocardiographic short axis images of the left ventricle were used for analysis of LV regional wall motion. As mentioned in the introduction, the common method of visual evaluation of LV wall motion from short axis images suffers from the limitations of being highly subjective and dependent on the experience of the observer and also on an arbitrary definition of myocardial ischemia (7).

Schnittger et al described a computerized method, that was adapted for the present studies, where regional wall motion is analyzed by calculating the fractional area change, i.e. the area between the systolic and the diastolic endocardial contours, for each of eight segments (125). This method allows the comparison of AEF in the same segment at several occasions, and the

development of RWMA would lead to a reduction in AEF for the affected segment. One problem with this method is, however, that changes in AEF also develops as a consequence of changes in loading conditions, i.e. a decrease in afterload will increase the segmental wall motion, thereby increasing the global AEF, and an increase in afterload will most likely show the opposite pattern. In order to overcome this limitation of our method the segmental AEF was normalized to global AEF for each segment, thereby forming a *load independent measure* of regional wall motion that was named the segmental vs. global AEF or the SAEF/GAEF ratio (III) (fig 16-17).

Correction for lateral LV motion: Another problem with LV short axis wall motion analysis is that the endocardium, apart from the motion between systole an diastole, also moves with the heart and thus shows a lateral motion and also a rotation. The lateral motion of the heart

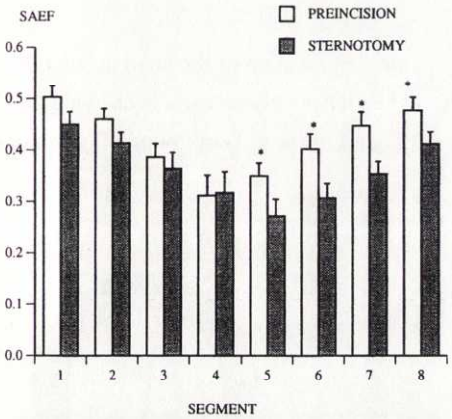

Fig. 16 *LV segmental wall motion before and after surgical stress. Changes in the wall motion profile indicates newly developed RWMA. *=p<0.05 for changes compared to control. Afterload increased between measurements (III).*

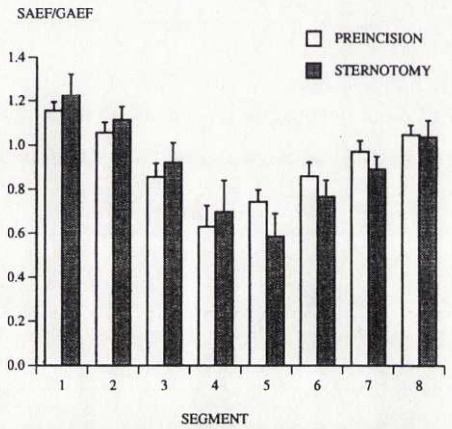

Fig. 17 *The same data as in the figure to the left. The segmental area ejection fraction has been normalized to global AEF. No signs of RWMA remains, showing the load independence of SAEF/GAEF.*

from systole to diastole can lead to a decrease in segmental wall motion in one part of the LV circumference, with a corresponding increase in the opposite part of the LV circumference (125). This effect can be removed by the use of a floating reference system where the LV short axis centroid, that can be thought of as the center of gravity of the area enclosed by the endocardial outline (106, 107), is calculated in systole and diastole and the systolic endocardial outline is then moved until its centroid falls over the diastolic centroid (126, 127). Although this correction removes the error caused by the lateral movement of the heart between systole and diastole, it also may remove any RWMA developing between measurements and thus decrease the sensitivity of the analysis (fig 18), and it has been shown that when analyzing the

short axis image of the left ventricle a fixed reference system gives more reproducible results than a floating reference (108). As lateral movement of the heart is small as long as the pericardium or sternum is closed, this floating reference concept was used only in study V, where comparisons were performed in the same group of patients and where the adenosine infusion was expected to cause a substantial decrease in afterload, which could possibly increase the lateral motion of the heart. Because the regional wall motion is unevenly distributed in the normal heart, with the septal segments showing a lower and the lateral segments a higher motion than the average for the whole left ventricle (128-131), the LV wall motion analysis using the fixed reference concept reflects this uneven distribution, whereas the correction imposed by the floating reference tends to even out the differences resulting in an altered representation of the normal pattern of LV wall motion. This difference is clearly visible in study V, where a floating reference system was used, compared to study III, where the regional wall motion was analyzed using a fixed reference system.

Correction for LV rotational motion: Although rotational movement of the heart around the long axis was described already by William Harvey (132), it has only recently been evaluated by Mirro et al in normal subjects and in patients with heart disease. They found only minor

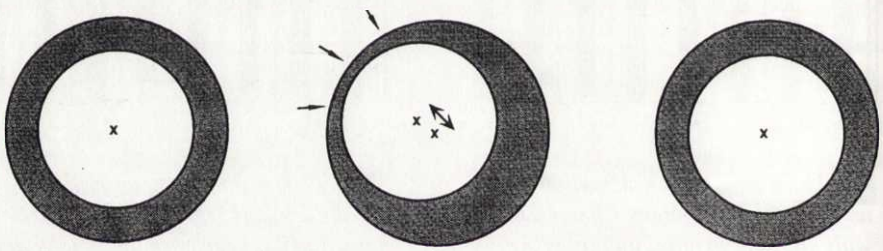

Fig. 18 *Correction for lateral LV motion. Normal motion in the left figure. When the heart moves between systole and diastole a decreased motion is simulated (arrows). Correction by moving the centroid (double arrow) leads to normalization of the motion picture. From this figure it can be concluded that a "real" decrease in motion can also be removed by moving the centroid in this fashion, thereby decreasing sensitivity of the analysis.*

rotational movement in normal subjects (3°, range 0 - 6°), and in patients with heart disease (3.2°, range 0 - 7°) (133). In the present studies, in order to correct for rotational movement of the heart, a similar method as described in the previous section was used. All endocardial traces were begun at the anterior papillary muscle and when both the systolic and diastolic traces were completed, the diastolic endocardial outline was rotated around the centroid until the starting points of both the systolic and the diastolic outlines fell on the "radius" from the centroid to

the starting point in the diastolic outline. As the drawbacks of decreased sensitivity, described above for correction of lateral heart movement, are not present for the correction of rotation around the LV long axis, this correction was used in all the studies.

Correction for angulation of the LV cross-section image: One cause for errors in the computerized analysis of LV wall motion, and also in the visual inspection method, is angulation of the LV cross-section image. A LV short axis image of the normal left ventricle is approximately circular in appearance when the 2-D echo-plane is perpendicular to the long axis of the left ventricle. If, however, the echo-image is obtained at any other angle to the LV long axis, the image will become elliptic and the "slices" cut by evenly spaced radii from the centroid will become uneven in size. A point on the systolic endocardial outline will then not follow the radius drawn from the centerline to the diastolic outline, but will move at an angle to the radius (fig 19).

In order to overcome this problem the *centerline method of analysis* was developed (108). After the above mentioned corrections for lateral and rotational movements have been applied if deemed necessary, a centerline is constructed midway between the systolic and diastolic

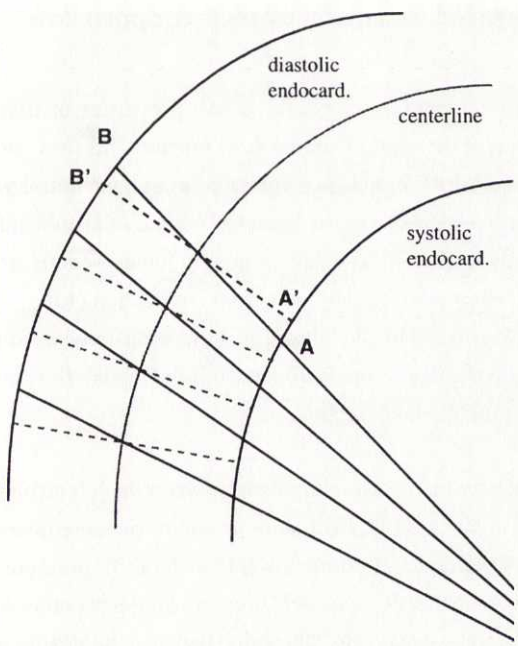

Fig. 19 *Centerline method for correction of elliptc shape of the LV short axis image. The radius from the centroid will follow the line from A to B, while a point on the endocardium will move from A' to B'. A line perpendicular to the centerline between the systolic and diastolic endocardial outlines will more closely represent the motion of the point from A' to B'.*

endocardial outlines. This centerline is then divided in evenly spaced intervals and lines drawn perpendicular to the centerline, dividing the area between the systolic and diastolic outlines into segments. The areas of these segments will be unaffected by the shape of the LV cross section image and a point on the systolic endocardial outline will more closely follow the line, perpendicular to the centerline, to its intercept with the diastolic outline (fig 19).

LV early diastolic relaxation

A decrease in the early LV diastolic relaxation is a sensitive indicator of myocardial ischemia that appears even earlier than LV systolic wall motion changes or ST-changes on ECG (13-17). Acute myocardial ischemia is not the only cause of disturbances in early diastolic relaxation, however. Up to 40% of patients with clinical signs of chronic congestive heart failure may have normal systolic LV function but decreased early diastolic relaxation (9, 10), and the reversible LV dysfunction seen after a brief period of LV ischemia, called "myocardial stunning", that has been ascribed to a decrease in contractility, may in fact have a component of diastolic dysfunction (134, 135). As the volatile inhalation anesthetics halothane, enflurane and isoflurane have been shown to impair the sarcoplasmic re-uptake of calcium during diastole (85), a decrease in diastolic relaxation after administration of these agents could be expected.

Measurement of LV early diastolic relaxation by mitral Doppler flow analysis

In the present studies the early diastolic relaxation, i.e. the active properties of diastolic relaxation, was analyzed by evaluation of the mitral Doppler flow profile. This flow profile, that is a graphic representation of the diastolic blood flow velocity through the mitral valve, consists of an early part, the E-wave, corresponding to the "passive" early LV diastolic inflow, a low-flow phase, diastasis, when only a small inflow due to the pulmonary venous flow is present, and finally a late part, the A-wave, corresponding to atrial contraction (136) (fig 3). A large number of indices, believed to reflect diastolic relaxation, have been derived from the mitral Doppler flow profile (137). The calculations made from the mitral Doppler flow profile in the present studies are described in the methods section.

The mitral Doppler flow is determined by the pressure gradient between the left atrium and ventricle. When LV relaxation starts in late systole, the LV intracavitary pressure decreases until the aortic valve closes, when the LV pressure becomes lower than the aortic pressure. The continued relaxation of the left ventricle further decreases LV pressure until it becomes lower than the LV atrial pressure, when the mitral valve opens. The period between the closure of the aortic valve and the opening of the mitral valve is called the isovolumic relaxation period. The rate of pressure decline during this period is believed to be a sensitive measure of the relaxation rate of the left ventricle during early diastole, as the "isolation" of the left ventricle from the

circulation when all valves are closed leaves the rate of relaxation as the only factor affecting the rate of pressure decrease (23). Measurement of the relaxation rate during the isovolumic relaxation period requires placement of LV intracavitary pressure transducers however, and is thus not easily available for human studies. When the LV intracavitary pressure decline continues after the opening of the mitral valve, a pressure gradient builds up between the left atrium and the left ventricle, causing the early diastolic inflow, the E-wave in the mitral Doppler flow profile.

When a disturbance of early diastolic relaxation occurs, the rate of LV relaxation decreases, and when the mitral valve opens, the decrease in LV pressure caused by the continuing relaxation becomes slower, leading to a lower pressure gradient between atrium and ventricle, reflected in a decreased maximal early inflow velocity, a decreased E_{max} (23, 26). The deceleration of the early diastolic inflow will also be decreased and prolonged leading to an increase in E_{dec}-time and a decrease in E_{dec}-slope (138). This decrease in E_{max} leads to a decrease in E/A, that is probably the most commonly used index of diastolic function. The area under the mitral Doppler flow profile, the velocity time integral, or stroke distance, is proportional to the volume flow, as long as the mitral orifice can be assumed to have a constant area. The volume flow is also affected by a decrease in early diastolic relaxation, when early diastolic filling decreases, a shift of flow towards late diastole occurs, resulting in decreases in the velocity time integral of early diastolic filling, the VTI_E, and the amount of filling during the first third of diastole the $VTI_{0\text{-}33\%}/VTI_{Tot}$. Consequently the late diastolic filling increases with an increase in VTI_A (fig 20). The reduced early LV filling observed with diminished myocardial relaxation may, however, be offset, in part, by an increase in left atrial pressure, that will again increase E_{max} and E_{dec}-slope, decrease E_{dec}-time, and if anything, increase E/A, a phenomenon called pseudonormalization (22).

Studies on the effects of various extracardiac factors on the flow profile have shown, that all mitral Doppler flow indices are affected. The most important factors influencing the flow profile are age, HR, preload and afterload.

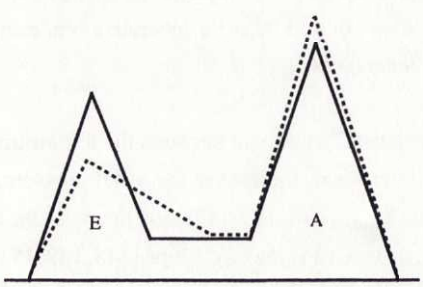

Fig.20 *Schematic representation of changes in the mitral Doppler flow profile caused by a decrease in early diastolic relaxation. The solid line represents normal filling and the dotted line decreased early diastolic relaxation.*

Studies in normal healthy subjects have shown the E/A to have a linear relation to age, with the E/A about 2 in children, decreasing to below 1 at the age of 65 (fig 21). This age related decrease in E/A seems to be caused both by decreases in the early filling component with a decrease in E_{max}, and an increase in the atrial filling component, increasing A_{max}. Age dependency affects the VTI indices in a similar fashion with a decrease in VTI_E and $VTI_{0\text{-}33\%}$/ VTI_{Tot} and an increase in VTI_A (44, 139-144).

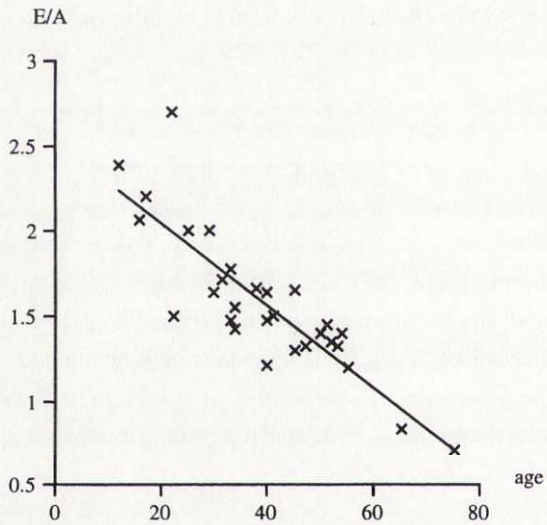

Fig 21. *The relation between E/A and age. Normal controls were extracted from 28 studies on diastolic function, from the literature, and the mean age for each group was plotted against the mean E/A. A total of 1063 allegedly normal subjects were studied in these investigations. (r=0.89)*

Several of the mitral Doppler indices are linearly correlated to HR (40-44). The early inflow component of the mitral Doppler flow profile decreases with increasing HR, thereby imitating a diastolic dysfunction. Increasing HR also moves the E-wave towards the A-wave until, at heart rates over 90-100 bpm, the E- and A-waves can no longer be separated, rendering the evaluation of the mitral Doppler flow profile impossible.

As the early mitral flow is dependent upon the pressure gradient between the left atrium and the left ventricle, it follows that an increase in preload, increasing the atrial pressure, will increase the pressure gradient and thus increase E_{max} (138, 145-147), and decrease the E_{dec}-time (147). A decrease in preload decreases E_{max} (145-154), the E_{dec}-slope (148, 149, 153) and increases E_{dec}-time (145, 151, 155). The effects of preload variation on atrial filling is varying between studies, with no effect on A_{max} in some investigations, leading to a decrease in E/A

with a decrease in preload (145, 148, 149, 152-154), while a concomitant rise in both E_{max} and A_{max} after a preload increase maintains the E/A unchanged in other studies (138, 145, 147). This discrepancy is probably due to concomitant effects of other variables that may affect the atrial contribution to LV diastolic filling, such as reflex changes in HR, and also to the fact that changes in A_{max} after a small preload change could be small enough to go undetected. When the LV filling pressure is plotted against E_{max}, at different filling pressures, a linear relation between the filling pressure and E_{max} is obtained. The slope of this line has been shown to decrease due to decreased early relaxation (138), and the slope of the preload-E_{max} relation also decreases when the left ventricle is subjected to ischemia (146). In the present studies preload was increased by a volume loading procedure in studies I and IV (table 1). The pattern found was similar in both studies with increases in the E_{dec}-slope and E_{max}. Increases in A_{max}, and VTI_E did reach significance in one study each. These results are in line with the effects of a preload increase on the mitral Doppler indices as discussed above.

Table 1. Effects of preload increases on mitral Doppler variables

	study I pre-bypass		study IV pre-bypas	
	control	volume load	control	volume load
E-dec slope	157.6 ± 17.8	195.8 ± 24.3**	180.7 ± 21.4	223.2 ± 27.7*
E-dec time	277.8 ± 14.1	275.5 ± 22.9	239.3±13.4	243.2 ± 19.7
E-max	40.8 ± 3.9	46.6 ± 4.1*	40.2 ± 4.1	47.5 ± 4.8**
A-max	50.3 ± 3.6	55.3 ± 3.8**	48.1 ± 3.4	53.2 ± 3.4
E/A	0.81 ± 0.05	0.86 ± 0.06	0.83 ± 0.06	0.89 ± 0.07
VTI-E	7.8 ± 0.8	8.7 ± 0.7*	7.4 ± 0.8	8.1 ± 0.8
VTI-A	6.2 ± 0.5	6.4 ± 0.6	5.0 ± 0.4	5.5 ± 0.4
VTI-E/ VTI-A	1.29 ± 0.11	1.46 ± 0.13	1.47 ± 0.10	1.47 ± 0.10
VTI 0-33%/ VTI TOT	0.37 ± 0.02	0.38 ± 0.02	0.37 ± 0.02	0.37 ± 0.02

E-dec slope, deceleration slope of early diastolic filling ($cm^{*}s^{-2}$), E-dec time, time from peak early diastolic flow to zero flow (ms), E-max, maximal velocity of mitral flow during early diastolic filling (cm/s), A-max, maximal velocity of mitral flow during atrial systole (cm/s), E/A, ratio between E-max and A-

The effects of changes in afterload are not as well investigated as the effects of changes in preload, but an increase in afterload causes a pattern opposite that of a decrease in preload (156, 157), with a decrease in early filling reflected in a decrease of E_{max}, although the early flow seems to be more affected by changes in early diastolic filling, while changes in afterload tends to have greater effects on the atrial component of the diastolic filling. No study investigating the effects of an isolated decrease in afterload, on mitral Doppler flow indices, has, to my knowledge, been presented.

Administration of increasing doses of adenosine in study V caused a decrease in SVR without affecting LV filling pressure, confirming previous findings of adenosine as an arterial resistance vessel dilator without major effects on venous capacitance vessels (158). Adenosine caused a small increase in HR, however, (9% at the highest adenosine dose), and the changes in the mitral Doppler indices found during adenosine infusion are most likely the combined effects of the increase in HR and the reduction in afterload. As the expected effects of an increase in HR on the mitral Doppler indices are known, some conclusions about the effects of the afterload reduction can be drawn. The changes found were increases in E_{dec}-slope, E_{max}, A_{max}, and a decrease in the $VTI_{0\%-33\%}$ / VTI_{Tot}. The HR increase could add to the increase in E_{dec}-slope, although this increase (30%), seems to be too large to be explained by the increase in HR alone. The HR increase would further be expected to decrease E_{max} and E/A, while an increase in E_{max} and no change in E/A were found, leading to the conclusion that the afterload reduction causes an increase in E_{max}, that is large enough to offset the decrease caused by the increase in HR.

LV end-diastolic stiffness

While the early diastolic relaxation is a complex process consisting of the combined effects of the active relaxation process, the LV myocardial dynamic properties (the LV viscoelastic characteristics) and the previously described extracardiac factors, the end-diastolic stiffness (or its reciprocal, the end-diastolic compliance) is a more easily grasped concept. When the diastolic inflow into the left ventricle is completed, before the beginning of systole, the left ventricle is in its most relaxed state during the cardiac cycle. The slope of the curve describing the intracavitary pressure-volume relationship at this point during the cardiac cycle reflects the intrinsic stiffness of the ventricle (27). Animal studies have shown this pressure-volume relation to be approximately exponential in shape (27). This means that an increase in LV-volume is accompanied by an increase in pressure following an exponential function. Whether this function can be approximated by a two-constant exponential function, within the physiological range of LV-filling pressures, or if a more complicated approach is necessary, remains controversial (159). More important is, however, that a measured end-diastolic pressure-volume relation does not describe the end-diastolic stiffness, but *at least* two volume measurements, at different pressures, are necessary to describe the end-diastolic stiffness, as an infinite number of curves can be drawn through any single point, while the two-constant exponential function is completely described by two points. In the present studies (I, IV), the two-constant exponential function concept was adopted, and the LV end-diastolic volume was substituted with end-diastolic short axis area, as it has been shown that this area closely reflects the LV volume (160, 161). Another reason for allowing this approximation of LV end-diastolic volume was that the present studies did not focus on absolute volume measurements, but rather on the relative changes in end-diastolic stiffness and thus in end-diastolic volume.

The influence of early diastolic relaxation on the end-diastolic stiffness is not a well explored area. In fact no previous studies have been presented where mitral Doppler flow analysis has been performed together with evaluation of end-diastolic stiffness or compliance, neither in healthy subjects, nor in patients with heart disease. It can be hypothesized from animal data (162), however, that a substantial decrease in early diastolic relaxation will ultimately lead to an increase in end-diastolic stiffness, and this notion is supported by the earlier described findings that decreased early diastolic relaxation in patients with heart disease is accompanied by clinical signs of increased LV filling pressures.

Effects of coronary artery bypass grafting and cardioplegic arrest on LV diastolic function

Previous studies in patients with CAD have shown that this disease is associated with a decrease in diastolic function (163, 164), and that coronary revascularization decreases the LV end-diastolic stiffness, and the impaired Doppler derived indices of early diastolic LV relaxation, when evaluated weeks to months after surgery (29-31). In the early period after coronary artery bypass grafting (CABG), however, the potential improvement in diastolic function, caused by revascularization, may be offset by an ischemia-induced, reversible diastolic dysfunction (134, 135). Only a few studies have been presented, investigating the effects of CABG on LV diastolic function in the early phase after coronary surgery, and there is no previous study in which both the active and the passive components of diastolic function have been evaluated both before and in the early phase after CABG.

When evaluating the mitral Doppler flow profiles after CABG and cardioplegic arrest, changes in almost all Doppler indices of diastolic function were found. E_{dec}-time, E/A, and VTI_E decreased, together with a shift of the diastolic flow towards late diastole, reflected in a decrease of the $VTI_{0\text{-}33\%}/VTI_{Tot}$, together with increases in E_{dec}-slope and A_{max}. Another finding, however, was an increase in HR of almost 30% after CPB compared to the pre-CPB value. This increase in HR is also present in previously published studies on the effects of CABG and cardioplegic arrest on diastolic function, and is even greater in these studies, reaching over 40% (37-39). As have been mentioned above, changes in HR greatly influences the Doppler indices, and a linear relationship between HR and these indices in the same direction as found after CPB has been described (41, 44). In order to compensate for this confounding factor an analysis of covariance (ANCOVA) was performed, using HR as a covariate changing over time. This analysis confirmed that a correlation exists between the Doppler indices and HR, and when the effect of the HR-increase was compensated for, only the increase in A_{max} remained significant (fig 22).

In the above mentioned studies on the effects of CABG and cardioplegic arrest on diastolic function (37-39), data similar to the present findings have been presented. In all three studies a similar increase in HR was found. In spite of this finding the authors of these studies have interpreted their results as indicative of a diastolic dysfunction induced by CABG and cardioplegic arrest.

In order to further evaluate the effects of CABG and cardioplegic arrest on LV diastolic function, our patients were also subjected to a volume loading procedure, to compare end-diastolic stiffness before and after CABG and cardioplegic arrest. End-diastolic pressure-area curves were constructed before and after CPB, as described above. Using a formula derived from the M-mode formula $V = d^3$:

$$V = \frac{8 * A}{\pi} * \sqrt{\frac{A}{\pi}},$$

where V is the volume, A is the short axis area, and d is the short axis diameter, approximations of the changes in LV end diastolic volume by volume loading pre- and post-CPB could be made. From these calculations the increase in end-diastolic volume induced by the volume loading was found to be approximately equal (35-40%) before and after CPB. If CPB and the cardioplegic arrest had induced an increase in LV stiffness, this volume increase would have been expected to cause a greater increase in PCWP, after, compared to before CPB. In study

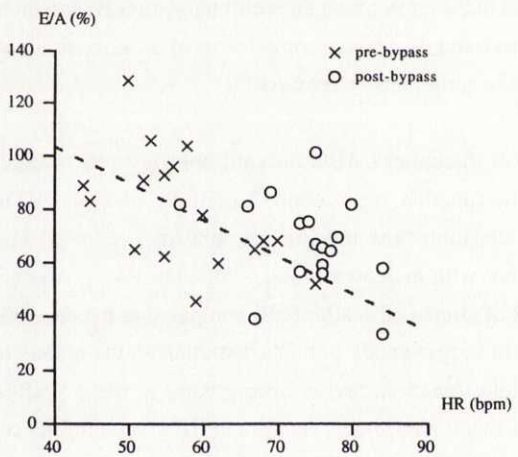

Fig. 22 *E/A plotted against HR. An illustration of the ANCOVA. A regression line is plotted, using the pre-bypass values. When the post-bypass values are compared to this line it can be seen that the increase in HR at the post-bypass measurement explains most of the decrease in E/A (I).*

I no such differences between the increases in PCWP, caused by volume loading, were found, however, and subsequently the conclusion of this study is that no increase in end-diastolic stiffness was caused by CPB and cold cardioplegic arrest. A similar investigation was recently performed by Wallace et al using a preload decrease to obtain the necessary points on the pressure-volume curve (165). These investigators found end-diastolic stiffness to be unchanged by CABG and cardioplegic arrest, results that were thus confirmed in study I.

Some limitations with study I needs to be mentioned. The increase in HR, the effects of which were compensated for by the ANCOVA procedure, might obscure a decrease in diastolic function too small to reach significance with the methods used here. In order to reach a definitive answer to the question whether CABG and cardioplegic arrest can affect early diastolic relaxation, it would have been appropriate to compare the various Doppler indices at individual levels of HR, before and after CPB. The end-diastolic stiffness curve has been shown to closely follow the function used in this study within the physiologic range of pressures and volumes (27). It has however recently been proposed that a better approximation of the end-diastolic stiffness curve is reached if a function using a greater number of constants, requiring a greater number of points on the curve for solution, is used (159).

Effects of nitrous oxide on systolic and diastolic LV function, and central hemodynamics, before and after coronary artery bypass grafting.

The effects of N_2O have been investigated in a number of studies. As N_2O has too weak anesthetic properties to be used as the single anesthetic agent for surgical procedures, fentanyl was used as the basic anesthetic agent and N_2O was then added to the fentanyl analgesia. It is well known that the choice of the basic anesthetic agent greatly influences the hemodynamic response to N_2O (166). Prior to CPB, N_2O induced decreases in HR, MAP, CO and SV. These findings are similar to the findings previously described after the addition of N_2O to opiates in humans during surgery (50, 66, 68, 167-174). The hemodynamic response to N_2O did not differ between the pre- and post-CPB measurements, except for PVR, that was unchanged by N_2O prior to CPB, but increased significantly after bypass, also confirming findings in previous studies (50, 171), and PCWP that also was unchanged by N_2O prior to CPB, but decreased after bypass. Our findings verify that N_2O, when added to an opiate analgesic, mainly exhibits cardiodepressant actions, and that the sympathetic stimulation usually seen when N_2O is added to an inhalation agent (175-177), is weaker when N_2O is added to an opiate, although the increase in PVR, that was also seen in our patients, has been ascribed to an alpha-adrenergic stimulating effect of N_2O (176).

The baseline values of CO, HR and the filling pressures were higher while SVR and PVR were lower after CPB. These differences in baseline values are most likely explained by the different situations in which these values were obtained; in the pre-CPB situation with no surgical stimulation, versus the post-CPB situation with ongoing surgery, with an increased level of circulating catecholamines and blood-volume as well as a decreased hematocrit. It is, however, of interest to note that, despite these profound hemodynamically different situations, N_2O exerted virtually the same effect on the hemodynamic variables.

The control GAEF increased post-CPB, a finding that could be attributed to an improved myocardial contractility or to the lower SVR in the post-CPB situation. N_2O, however, caused no changes in the GAEF, neither before nor after CPB. Previous studies on the effect of N_2O on pre-CPB global function have not shown any changes in GAEF after introduction of N_2O (67). The findings presented here confirms that this finding also holds true after CPB and myocardial revascularization. Studies of regional wall motion changes after the introduction of N_2O in patients with CAD, have so far only been presented for patients prior to CPB, and no wall motion changes indicative of the development of myocardial ischemia, have been reported (66-68, 178). This was also confirmed in study II. When N_2O was added to fentanyl anesthesia after CPB, however, a wall motion response that was quite different from the response seen when the heart was exposed to N_2O prior to CPB, was found. The segmental wall motion analysis showed a significant change in regional wall motion, indicative of development of myocardial ischemia.

Studies in dogs anesthetized with opiates or inhalation anesthetics have shown that N_2O can depress regional myocardial wall motion, indicative of myocardial ischemia, in the presence of a critical coronary artery stenosis (179-183). In a number of recent studies, however, it was shown that N_2O does not cause ischemia in animals with critical coronary stenosis if HR and coronary perfusion pressure were kept constant (53, 184, 185). N_2O may, however, theoretically cause regional hypoperfusion and ischemia in an area supplied by a stenotic coronary artery, as it has recently been shown that N_2O can constrict epicardial coronary arteries with no effect on the resistance vessels in the myocardium. Moffit et al demonstrated that N_2O, when added to fentanyl, halothane or enflurane, could induce myocardial lactate production in some patients with CAD (52). Recent studies on the effects of N_2O on regional wall motion could not, however, demonstrate that N_2O induces RWMA in patients with CAD, as was also confirmed in study II.

The effects of N_2O on the functional recovery of stunned myocardium were recently studied by Siker et al in a dog model (70). These authors showed that dogs exposed to N_2O, before and after a short period of coronary artery occlusion, had higher mortality, and prolonged functional recovery in survivors, compared to dogs not exposed to N_2O. They concluded that the decreased segmental function of the ischemic region could not be attributed to differences in oxygen demand or supply compared to control (70). These findings could well be compared to the situation after CPB, where the heart has been subjected to a period of ischemia during the aortic cross clamping, and where N_2O induced wall motion abnormalities as shown in study II. The cause of this N_2O-induced functional impairment after ischemia is not immediately obvious. One possible explanation could be the property of N_2O to form hydroxyl radicals that are cytotoxic in the hypoxic myocardium (186).

The development of RWMA could also be attributed to the introduction of air bubbles into the coronary circulation, either during the coronary surgery or as microbubbles that emanate from the heart-lung machine. As N_2O diffuses much more rapidly than nitrogen, an air bubble would tend to expand in the presence of N_2O because of a rapid diffusion of N_2O into the bubble, balanced by a much slower diffusion of nitrogen out of the bubble (187). The introduction of N_2O in a situation when air bubbles are present in the coronary arterial vascular bed, has previously been shown to cause ischemia in animals (188). Extreme care was taken in de-airing the coronary grafts before removing the graft clamps, however, and a period of at least 30 minutes elapsed from weaning from bypass until N_2O was introduced, allowing for absorption of any air bubbles present. These precautions could at least be expected to reduce the risk of ischemia caused by expansion of air bubbles.

When N_2O was added to fentanyl prior to CPB, the E/A-ratio increased together with an increase in the $VTI_{0\text{-}33\%}/VTI_{Tot}$, that would indicate an increase in early diastolic relaxation. The increase in the E/A could also, however, be influenced by the decreased HR caused by the addition of N_2O. After CPB, N_2O induced a different mitral Doppler flow pattern with a decrease in the E_{dec}-slope, a decrease in A_{max} and no change in E/A, in spite of the decrease in HR. No significant increase in the early diastolic inflow occurred when N_2O was introduced after CPB. As the SVR remained unchanged after the introduction of N_2O, both pre- and post-CPB, changes in LV outflow impedance do not seem to be the cause for the different patterns found. LV preload was, however, reduced by N_2O after CPB. This, numerically small, difference could explain the reduction in E_{dec}-slope but would, in the absence of other changes, be expected to lead to a decrease in $E\text{-}_{max}$ and E/A and an increase in E_{dec}-time. Therefore a more plausible explanation seems to be that N_2O causes an increase in early diastolic relaxation, that is present prior to CPB, as indicated by an increase in the E/A and redistribution of flow to the early part of diastole. This increase in E/A and the $VTI_{0\text{-}33\%}/VTI_{Tot}$ is, however, absent when N_2O is added after CPB. A possible explanation for this differential effect of N_2O on diastolic function before and after CPB, is that N_2O induces myocardial ischemia after, but not before CPB, causing both RWMA as well as diastolic dysfunction.

Effects of surgical stress and volatile anesthetics on systolic and diastolic function and central hemodynamics in patients with CAD

It should be noted that there is a difference in design between study III and IV. Study III was designed to separately investigate the effects of surgical stress and the volatile anesthetics by first investigating the effects of sternotomy under fentanyl-N_2O anesthesia, that has previously

been shown to cause a sympathetic stimulation and thus an increase in arterial blood-pressure (72, 74, 75, 78), and then, by the introduction of one of the volatile agents, explore the effects of treatment of the surgical stress by the inhalation anesthetic, aiming at a reduction of the arterial blood-pressure back to the pre-incision level. In contrast, in study IV, the increase in arterial blood pressure, caused by the sternotomy was immediately treated by introduction of the inhalation agent, with the aim to keep the blood pressure stable at the pre-sternotomy level. The results obtained in study IV thus are the added effects of surgical stress and the volatile anesthetic.

The hemodynamic effects of the commonly used inhalation anesthetics have previously been investigated in a great number of studies (90, 189-213). Isoflurane has generally been shown to cause the most pronounced reduction in SVR (198, 205, 206, 211, 213), and a greater increase in HR compared to halothane and enflurane (198, 205, 208, 211, 213). The hemodynamic findings in the present studies (III, IV) reflect these previous findings, but also the differences in design in the two studies. When the control values are compared to values obtained after the introduction of the inhalation anesthetics, the findings in the two studies are similar. HR increased for isoflurane and enflurane, but remained unchanged with halothane. When the results from study III are viewed from the two-step procedure performed in this study, it follows that the introduction of the inhalation anesthetics decreased the MAP back to the preincision values and that this reduction was due to a decrease in SVR. HR was increased by sternotomy in all three groups and the above mentioned differences appeared after the introduction of the inhalation agents, and the CO was unchanged by sternotomy and increased after introduction of isoflurane, decreased after halothane and remained unchanged after enflurane.

The effects of surgical stress on LV global and regional wall motion were investigated in study III. Previous investigations during sternotomy during fentanyl-N_2O anesthesia have shown a substantial increase in sympathetic activity, reflected by increases in arterial and pulmonary blood pressures, filling pressures and HR (77, 80). These findings were confirmed in the study III. The SAEF decreased in 4 of 8 segments during surgical stress, but the GAEF also decreased, and when the SAEF/GAEF ratio was evaluated, no significant regional changes could be detected, indicating that the changes observed in the SAEF were due to an increase in afterload caused by the sympathetic activation during the surgical stress, and that when this afterload increase was compensated for, by the use of the load independent index SAEF/GAEF, no segmental changes remained. These results indicate that despite a substantial increase in arterial blood pressure and a smaller increase in HR was caused by the surgical stress, no signs of ischemia developed. A plausible explanation for this finding is the protective effect of the beta-receptor blockade that was a requirement for inclusion in these studies.

The GAEF was decreased after the introduction of halothane in both study III and IV, while enflurane, in study III and isoflurane in both study III and IV, did not affect the GAEF. This finding could be due to a more pronounced negative inotropic effect of halothane, compared to enflurane and isoflurane. The regional wall motion analysis, performed in study III, showed isoflurane to cause the development of RWMA, while halothane and enflurane did not induce any changes in regional wall motion when used to control the intraoperative hypertension caused by the sternotomy.

Isoflurane has previously been shown to cause ECG changes and net lactate production, that has been interpreted as the development of myocardial ischemia. Reiz et al, showing isoflurane to be a more potent coronary vasodilator than halothane or enflurane, suggested that the development of ST-changes with isoflurane, could, in some patients, be attributed to a redistribution of myocardial blood flow from an area supplied by a stenosed epicardial coronary artery, to an area supplied by a coronary artery without stenosis, thereby causing ischemia in the area supplied by the stenosed coronary artery, a so called "coronary steal " phenomenon (214). A further conclusion from this study may be that isoflurane-induced signs of regional myocardial ischemia can have different causes, such as an increase in HR and a decrease in coronary perfusion pressure. Further studies have shown ECG and metabolic signs (lactate production) of development of myocardial ischemia in patients after induction of anesthesia with isoflurane (215-217), and recently a study in patients undergoing CABG, combining ECG, lactate and echocardiographic methods for analysis of the incidence of myocardial ischemia, confirmed a greater incidence of myocardial ischemia after isoflurane, compared to enflurane (6). Despite a large amount of work, the question whether isoflurane causes regional myocardial ischemia, and if so, whether coronary steal is one of the responsible mechanisms, is still under debate. In one study, using the same protocol as in study III, Sahlman and coworkers did not find the lactate production detected after isoflurane to be caused by myocardial redistribution of blood flow, but attributed their findings to an increase in HR caused by isoflurane (77).

In study III the development of RWMA after control of intraoperative hypertension with isoflurane, but not after halothane or enflurane, supports the previously described findings that isoflurane can cause regional myocardial ischemia. The patients included in study III were also divided into two groups, according to the presence of steal-prone coronary anatomy as described by Buffington et al (109). No indication of a decrease in regional wall motion was found in the group with steal-prone coronary anatomy, but rather a tendency of improved motion, when compared to the group without steal-prone coronary anatomy. The groups were fairly small however, and this result should be interpreted with some caution.

The effects of halothane and isoflurane, on LV diastolic function, were investigated in study IV. The active component of diastolic relaxation was evaluated from the mitral Doppler flow profiles. Extracardiac factors that could obscure the findings were as previously described SVR, that was unchanged, PCWP, that increased to approximately the same extent with both anesthetics, and HR that increased with isoflurane and was unchanged with halothane. Both anesthetics were found to decrease the E_{dec}-time, increase E_{dec}-slope and leave E_{max} unchanged. A_{max} decreased leading to an increase in E/A. In view of the 40% increase in PCWP, a quite different pattern would have been expected if extracardiac factors were the only cause of changes in the mitral Doppler profile. In the studies I and IV, where a volume loading procedure was performed after induction of anesthesia, that increased PCWP approximately to the same extent as with the inhalation anesthetics, a completely different pattern was found, with increases in E_{max}, A_{max}, VTI_E and VTI_A, while no changes were found in the E/A or E_{dec}-time, as discussed above. These findings are the expected pattern after an increase in preload with an increased early diastolic atrial-ventricular pressure gradient, while the findings in study IV indicate that halothane and isoflurane induced a pronounced decrease in early diastolic relaxation with a "pseudonormalized" mitral Doppler flow pattern. Previous in vivo studies have shown a prolonged isovolumic relaxation after halothane, while the effects of isoflurane are more varying with some studies showing no effect of isoflurane on early diastolic relaxation, and one study showing a prolongation of relaxation of equal magnitude to that of halothane. The present findings indicate a decreased early diastolic relaxation after both halothane and isoflurane. The findings were approximately equal after both halothane and isoflurane, but isoflurane also caused a 13% increase in HR, that was not seen after halothane. The previously described relation between HR and the mitral Doppler indices, with decreases in E_{max} and E/A, and an increase in A_{max} with increasing HR suggests that the decrease in LV early diastolic relaxation after isoflurane was even more pronounced than after halothane.

The impairment of early myocardial relaxation induced by halothane was not of sufficient magnitude to interfere with overall LV end-diastolic chamber stiffness. The increase in PCWP, seen when halothane anesthesia is used to control stress-induced intraoperative hypertension thus reflects a decrease in systolic function, that was also reflected by a decrease in AEF. In other words, halothane anesthesia does not alter the LV pressure-area relationship in patients with CAD. These findings are in line with most of the previous animal studies where it has been shown that halothane does not increase LV end-diastolic stiffness (81, 84, 86-88, 92). There are, however, some studies describing an increase in myocardial stiffness with halothane (89-91). In contrast, control of intraoperative hypertension with isoflurane was associated with a significant leftward shift of the LV end-diastolic pressure-area relationship, indicating an increase in LV end-diastolic stiffness. In previous animal studies on the effects of isoflurane on LV end-diastolic mechanical properties, it was shown that isoflurane did not affect the LV end-diastolic pressure-volume relationship (81, 84, 92). The finding of an increase in LV end-

diastolic stiffness during isoflurane anesthesia in patients with CAD would therefore imply that measurements of PCWP will not only reflect LV end-diastolic dimension but would also reflect changes in LV end-diastolic stiffness. One conceivable explanation for this finding could be that isoflurane induces myocardial ischemia (218), as it has recently been shown that regional myocardial ischemia is associated with a decrease in myocardial distensibility (219).

Effects of adenosine on LV systolic and diastolic function

The effects of adenosine infusion in humans have previously been investigated in a number of studies (97-99, 101, 102, 104, 158, 220). It has been shown that adenosine is a powerful vasodilator, acting almost exclusively on the resistance vessels in the systemic and pulmonary circulation and has no effect on the capacitance vessels, leading to a decrease in SVR and PVR without affecting the filling pressures (102, 221-223). The effects of adenosine are thus different from the effects of the commonly used vasodilator sodium nitroprusside (SNP), that also is a powerful vasodilator, but with effects both on arterial resistance vessels and venous capacitance vessels (96). These effects of adenosine were confirmed in study V, where adenosine caused dose dependent decreases in MAP, SVR and PVR without effects on PCWP or CVP. CO an SV increased together with HR. The elimination of adenosine is extremely rapid, with a half life of less than 10 seconds (222, 224), but can be prolonged after treatment with dipyridamole (102, 220). Patients on dipyridamole were subsequently not included in study V.

Adenosine is also a coronary vasodilator, and the effect of adenosine on the coronary circulation is more pronounced than for SNP (101). Previous investigations on the effects of adenosine infusion on myocardial blood flow and metabolism after CABG have shown that adenosine may induce a pronounced coronary vasodilation and myocardial net lactate production in some patients, indicating the development of myocardial ischemia in these patients, ST-segment depressions also developed in this patient group, but lactate production and ST-segment changes did not always present in the same patients (104). In a study by Ogilby et al, regional wall motion and myocardial perfusion were analyzed using radionuclide angiography in a group of CAD patients receiving a high dose of adenosine, 140 µg/kg/min (225). These authors found perfusion defects in 41% of the studied segments, while motion abnormalities were present in 4% of the segments only. Öwall et al studied the regional wall motion by echocardiography after infusion of a low dose of adenosine, 30 µg/kg/min, in patients after coronary artery bypass surgery and did not find an increased incidence of RWMA in their patient group (226). Study V, confirmed the previously described findings. No increased incidence of RWMA were induced by adenosine after CABG. ECG analysis

revealed a small linear ST-depression trend, however, and when individual ECG's were evaluated, it was found that two patients met the criteria for myocardial ischemia at the highest adenosine dose. These findings are in line with data from Zäll et al (104). Thus, there is some evidence that adenosine induces myocardial ischemia detected with one method, but that this result could not be confirmed with another method that is regarded as more sensitive for detection of ischemia.

Ogilby et al suggested that a diastolic dysfunction might be induced by adenosine (225), as they demonstrated an increase in PCWP with adenosine, but no change in end-diastolic volumes. In order to further explore this hypothesis, the mitral Doppler flow profile was evaluated at increasing doses of adenosine. Increases in E_{max} and A_{max} were found, together with a decrease in $VTI_{0\text{-}33\%}/VTI_{Tot}$. No change in E/A was induced by adenosine. This combination of changes in the mitral Doppler flow profile can well be explained by the concomitant decrease in afterload and increase in HR, and does not indicate that the adenosine infusion decreased early diastolic relaxation, as suggested by Ogilby.

In conclusion there is some ECG-evidence that myocardial ischemia may be caused by adenosine, without being able to confirm these findings by two-dimensional and Doppler echocardiographic evaluation of LV regional and early diastolic function. A possible explanation of these findings is that the profound afterload reduction caused by adenosine obscures 2-D echo detection of any changes in wall motion that might develop by the adenosine infusion.

6

Conclusions

- Coronary artery bypass grafting (CABG) and cold cardioplegic arrest do not affect early diastolic relaxation or end-diastolic stiffness. Previously described changes in Doppler flow indices of early diastolic relaxation after CABG are explained by a heart rate increase.
- Nitrous oxide improves LV early diastolic relaxation, without signs of ischemia, prior to CABG, but causes diastolic dysfunction and regional wall motion abnormalities, indicative of ischemia, after CABG.
- When used to treat intraoperative hypertension, halothane decreases systolic function to a greater extent than enflurane or isoflurane, but isoflurane induces regional wall motion abnormalities, that are not seen with halothane or enflurane.
- Isoflurane, and to a lesser extent halothane, induces decreases in early diastolic function, that is more pronounced for isoflurane. Isoflurane also increases end-diastolic stiffness.
- Adenosine infusion after coronary artery bypass causes ECG-signs indicative of myocardial ischemia in some patients, but no changes in echocardiographic regional systolic, or mitral Doppler diastolic, indices suggestive of ischemia.

7

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8

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För en fullständig lista av ingående delarbeten, se avhandlingens början.

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