LUNG EMPHYSEMA

&

CARDIAC FUNCTION

KIRSTEN JÖRGENSEN

The Sahlgrenska Academy
AT GÖTEBORG UNIVERSITY

2008
LUNG EMPHYSEMA & CARDIAC FUNCTION

Kirsten Jörgensen
Department of Anaesthesiology and Intensive Care Medicine
Institute of Clinical Sciences, The Sahlgrenska Academy,
Göteborg University, Sweden


jorgensen.kirsten@gmail.com

Papers I to IV are reprinted with permission of the publishers
Front cover: Australian Colours
Printed by Intellecta Docusys AB
Göteborg, Sweden 2008
To Søren, Anna and Niels
ABSTRACT

Patients with severe lung emphysema have poor quality of life because of impaired lung function and reduced exercise tolerance. Concomitant heart disease in severe emphysema is well recognised. The prevailing view is that mainly the right side of the heart is involved, while the issue of left ventricular (LV) involvement is less studied. The aim of this thesis was to evaluate cardiac performance and dimensions in patients with severe emphysema, using pulmonary artery thermodilution technique, transoesophageal echocardiography and magnetic resonance imaging.

The main findings were that patients with severe emphysema have impaired cardiac performance as reflected in subnormal values of stroke volume and cardiac output compared with patients/volunteers with normal lung function. This impaired cardiac performance is caused by inadequate diastolic filling (decreased preload) of the right and left ventricle. Myocardial contractility is not affected, but the left ventricle is hypovolemic and operates on a steeper portion of the LV function curve.

One possible explanation for the decreased biventricular preload is a low intrathoracic blood volume caused by the hyperinflated lungs. In patients with severe emphysema, lung volume reduction surgery improves LV end-diastolic dimensions and filling and thereby performance, which at least partly could explain the improved exercise tolerance seen after the operation.

Levosimendan has combined inotropic and vasodilatory effects and is used in the treatment of severe heart failure. The effect on diastolic function in humans is not entirely understood. Therefore, the aim was to evaluate whether levosimendan has lusitropic effect in patients with diastolic dysfunction, using pulmonary artery thermodilution technique and transoesophageal echocardiography. The main finding was that levosimendan shortens isovolumic relaxation time and improves LV early filling.

In conclusion, patients with severe emphysema have compromised cardiac performance as reflected in impaired LV filling and low stroke volume. The decreased ventricular preload is explained by a low intrathoracic blood volume most likely caused by the hyperinflated lungs. Lung volume reduction surgery, improves LV function. Levosimendan exerts a direct positive lusitropic effect in patients with diastolic dysfunction.

Key words: Emphysema; hemodynamics; ventricular end-diastolic volumes; lung volume reduction; ventricular function; transoesophageal echocardiography; magnetic resonance imaging; diastole; simendan; hypertrophy.
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


CONTENTS

LIST OF PAPERS
CONTENTS
ABBREVIATIONS
INTRODUCTION
BACKGROUND
Chronic obstructive pulmonary disease
Intrinsic positive end-expiratory pressure in severe emphysema
Cardiopulmonary interactions in healthy subjects and in COPD patients
Lung volume reduction surgery in severe lung emphysema
Assessing systolic and diastolic function
Pharmacological aspects on diastolic function
AIMS OF THE INDIVIDUAL STUDIES
MATERIALS AND METHODS
Patients
Anaesthesia and surgery
Hemodynamic measurements
Two-dimensional echocardiography
Doppler echocardiography
Magnetic resonance imaging
Experimental protocols
Statistics
RESULTS
Systemic hemodynamics and left ventricular dimensions and filling in patients with severe emphysema before and after lung volume reduction surgery (I)
Left ventricular performance in patients with severe emphysema (II)
Intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema (III)
Effects of levosimendan on systolic and diastolic function in patients with left ventricular hypertrophy and normal ejection fraction (IV)
DISCUSSION
Methodological considerations
Assessment of cardiac preload
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEF</td>
<td>area ejection fraction</td>
</tr>
<tr>
<td>A-max</td>
<td>peak early diastolic filling velocity, cm/s</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>AO</td>
<td>ascending aorta</td>
</tr>
<tr>
<td>AS</td>
<td>aortic stenosis</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>AVR</td>
<td>aortic valve replacement</td>
</tr>
<tr>
<td>bpm</td>
<td>beat per minute, min⁻¹</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area, m²</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CI</td>
<td>cardiac index, L/min/m²</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output, L/min</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure, mm Hg</td>
</tr>
<tr>
<td>CW</td>
<td>continuous wave (Doppler)</td>
</tr>
<tr>
<td>DAP</td>
<td>diastolic artery pressure, mm Hg</td>
</tr>
<tr>
<td>DPAP</td>
<td>diastolic pulmonary artery pressure, mm Hg</td>
</tr>
<tr>
<td>E/A</td>
<td>proportion of E-max versus A-max</td>
</tr>
<tr>
<td>EDA</td>
<td>end-diastolic area, cm²</td>
</tr>
<tr>
<td>EDAI</td>
<td>end-diastolic area index, cm²/m²</td>
</tr>
<tr>
<td>EDV</td>
<td>end-diastolic volume, mL</td>
</tr>
<tr>
<td>E-dec slope</td>
<td>deceleration slope of early diastolic filling, cm/s²</td>
</tr>
<tr>
<td>E-dec time</td>
<td>time from peak early diastolic flow to zero flow, ms</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction, %</td>
</tr>
<tr>
<td>E-max</td>
<td>peak early diastolic filling velocity, cm/s</td>
</tr>
<tr>
<td>ESA</td>
<td>end-systolic area, cm²</td>
</tr>
<tr>
<td>ESAI</td>
<td>end-systolic area index, cm²/m²</td>
</tr>
<tr>
<td>ESV</td>
<td>end-systolic volume, mL</td>
</tr>
<tr>
<td>ESPVR</td>
<td>end-systolic pressure-volume relationship, elastance</td>
</tr>
<tr>
<td>ET</td>
<td>ejection time, ms</td>
</tr>
<tr>
<td>FAC</td>
<td>fractional area change</td>
</tr>
<tr>
<td>FEV₁</td>
<td>forced expiratory volume in first second, L</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>FEV₁ percent of predicted, %</td>
</tr>
<tr>
<td>FFE</td>
<td>fast field echo</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity, L</td>
</tr>
<tr>
<td>FRC%</td>
<td>functional residual capacity, percent of predicted, %</td>
</tr>
</tbody>
</table>
FVC = forced vital capacity, L
h = wall thickness, mm
HR = heart rate, min⁻¹
I:E = the proportion of inspiratory time to expiratory time
IPPV = intermittent positive pressure ventilation
ITBV = intrathoracic blood volume, L
ITBVI = intrathoracic blood volume index, L/m²
ITP = intrathoracic pressure, cm H₂O
IVCT = isovolumic contraction time, ms
IVRT = isovolumic relaxation time, ms
LA = left atrial
LV = left ventricular
LVEDA = left ventricular end-diastolic area, cm²
LVEDAI = left ventricular end-diastolic area index, cm²/m²
LVEDS = left ventricular end-diastolic stiffness, mm Hg/cm²/m²
LVEDV = left ventricular end-diastolic volume, mL
LVEDVI = left ventricular end-diastolic volume index, mL/m²
LVEF = left ventricular ejection fraction
LVESA = left ventricular end-systolic area, cm²
LVESAI = left ventricular end-systolic area index, cm²/m²
LVESV = left ventricular end-systolic volume, mL
LVESVI = left ventricular stroke volume index, mL/m²
LVOT = left ventricular outflow tract, mm
LVRS = lung volume reduction surgery
MAP = mean artery pressure, mm Hg
MPAP = mean pulmonary artery pressure, mm Hg
MRI = magnetic resonance imaging
MTT = mean transit time, s
NM = non-linear mixed effect modelling, NONMEM
P = pressure, mm Hg or cm H₂O
PA = pulmonary artery
P_aCO₂ = arterial tension of carbon dioxide, kPa or mm Hg
P_aO₂ = arterial oxygen tension, kPa or mm Hg
PCWP = pulmonary capillary wedge pressure, mm Hg
PDE = phosphodiesterase
PEEP = positive end-expiratory pressure, cm H₂O
PEEPᵰ = intrinsic positive end expiratory pressure, cm H₂O
PRSWI = preload recruitable stroke work index, g/cm²*10⁻²
PTT = peak transit time, s
PVR = pulmonary vascular resistance, dynes*s/cm⁵
PVRI = pulmonary vascular resistance index, dynes* s/cm²/m²
PW = pulse wave (Doppler)
qf = quantification of aortic flow
r = radius, mm
ResV = residual volume, L
ResV% = residual volume, percent of predicted, %
ROI = region of interest
RR = respiratory rate, min⁻¹
RV = right ventricular
RVEDV = right ventricular end-diastolic volume, mL
RVEDVI = right ventricular end-diastolic volume index, mL/m²
RVEF = right ventricular ejection fraction
RVESV = right ventricular end-systolic volume, mL
RVESVI = right ventricular end-systolic volume index, mL/m²
RVSVI = right ventricular stroke volume index, mL/m²
SAP = systolic artery pressure, mm Hg
SD = standard deviation
SEM = standard error of the mean
SPAP = systolic pulmonary artery pressure, mm Hg
SPV = spontaneous ventilation
SV = stroke volume, mL
SVI = stroke volume index, mL/m²
SVR = systemic vascular resistance, dynes*s/cm⁵
SVRI = systemic vascular resistance index, dynes* s/cm⁵/m²
SW = stroke work, g*m
SWI = stroke work index, g*m/m²
TEE = transoesophageal echocardiography
TLC = total lung capacity, L
TLC% = total lung capacity, percent of predicted, %
V = velocity, cm/s
WM = wall mass, g
σ = sigma, wall stress, mm Hg
τ = tau, time constant, s
INTRODUCTION

Patients with severe lung emphysema have poor quality of life because of impaired lung function and reduced exercise tolerance. The functional features consist of severe expiratory airflow obstruction and considerable hyperinflation due to destruction of lung parenchyma and loss of lung elasticity. Intrathoracic (intrapleural) pressure is increased (less negative) due to generation of a high intrinsic positive end-expiratory pressure.

To understand the hemodynamic consequences of these features, it is important to realize that the respiratory and the cardiovascular systems are not separate but tightly integrated. Ventilation can profoundly interact with cardiovascular function due to complex, sometimes conflicting, sometimes coordinated processes. These interactions depend on whether ventilation is spontaneous (SPV) or mechanically assisted (intermittent positive pressure ventilation, IPPV) and may be further complicated by co-existing heart or lung disease.

Heart function in emphysema

Concomitant heart disease during the course of chronic obstructive pulmonary disease (COPD) is well recognized. The prevailing view is that mainly the right side of the heart is involved, while the issue of left ventricular (LV) involvement is controversial and less studied. The few existing studies on LV function in patients with severe emphysema have exposed contradictory results. Two studies showed normal LV function, whereas one study demonstrated abnormal LV function curves in the majority of patients with COPD. Others have suggested that LV systolic dysfunction, assessed by LV area ejection fraction, is unusual in patients with COPD without pulmonary hypertension. In patients with emphysema and pulmonary hypertension, however, LV area ejection fraction may be decreased due to ventricular interaction.

The present thesis is therefore focused on LV performance in patients with severe emphysema. LV systolic and diastolic functions were evaluated in these patients using transoesophageal echocardiography (TEE), magnetic resonance imaging (MRI) and the pulmonary artery thermodilution technique. Patients were examined under general anaesthesia before and after lung volume reduction surgery (LVRS) to assess LV diastolic filling pattern and dimensions. A volume loading procedure was performed preoperatively to assess LV preload responsiveness and load independent indices of systolic function. In awake and
spontaneously breathing patients with severe emphysema, eligible for single lung transplantation, right ventricular (RV) and LV dimensions, wall mass and performance, as well as intrathoracic blood volume (ITBV) were estimated. The clinical implications of the results of these studies may provide a better understanding of heart-lung interaction present in patients with COPD, contributing to an improved hemodynamic management of these patients with respect to intravenous fluid therapy and to the hemodynamic response to positive pressure ventilation in the perioperative setting.
BACKGROUND

Chronic obstructive pulmonary disease
COPD is a major cause of morbidity and mortality. The defining characteristics of COPD are the presence of expiratory airflow limitation that progresses slowly over a period of years and the progressive and permanent destruction of airspace distal to the terminal bronchioli. COPD encompasses chronic obstructive bronchitis with varying amounts of obstruction of small airways and hypersecretion as well as emphysema with permanent enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity and closure of small airways. This leads to hyperinflation and impaired gas exchange by mechanisms explained below.

Aetiology
Cigarette smoking is the most common cause of emphysema. Longitudinal monitoring of lung function reveals that substantial airflow obstruction due to an accelerated decline in lung function (two to five times the normal annual decline of 15 to 30 mL in forced expiratory volume in first second, (FEV₁)) occurs in only a minority (10-20%) of cigarette smokers. This strongly suggests that genetic factors may determine whether airflow limitation will develop. In patients with α₁-antitrypsin deficiency, emphysema develops that is exacerbated by smoking, indicating a clear genetic predisposition to COPD. However, less than one percent of patients with COPD have α₁-antitrypsin deficiency.

Cigarette smoke is thought to activate macrophages and airway epithelial cells in the respiratory tract, which release neutrophil chemotactic factors, including interleukin-8 and leukotriene B₄. Neutrophils and macrophages then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucus hypersecretion. Proteases are normally counteracted by protease inhibitors, including α₁-antitrypsin, but in smokers in whom COPD develops, there seems to be an imbalance between proteases – antiproteases. In patients with more advanced COPD, changes occur in the pulmonary circulation (pulmonary hypertension) and in the right heart (right ventricular dilatation and/or hypertrophy). Although the definition of emphysema is anatomic, biopsy material is rarely available to confirm the diagnosis. The presence of emphysema is inferred from a combination of history, pulmonary function data, and radiography.
Symptoms

Patients with emphysema present themselves with dyspnea, weakness and weight loss. Dyspnea is caused by hypoxia due to hyperinflation of the alveoli and impaired gas exchange.

Clinical findings

Pulmonary function studies may show airflow obstruction (a decrease in FEV1, but forced vital capacity (FVC) within normal range), a decrease in carbon monoxide diffusing capacity, and an increase in total lung capacity (TLC), functional residual capacity (FRC), and residual volume (ResV). The FEV1 has been found to be a good predictor of mortality for COPD. In severe COPD, with FEV1< 1L, 5 year survival is approximately 50%.

Lung auscultation reveals a sparsity of breath sounds. The lung destruction and air trapping, results in breathing pattern with small tidal volumes. The expiratory phase of respiration is noticeably prolonged, i.e. I:E ratio is increased. Exercise testing like shuttlewalk or 6 minutes walk can assess exercise performance. The radiographic features of emphysema are hyperinflation represented as depression and flattening of the diaphragm on the anteroposterior film and retrosternal air space on the lateral chest radiograph. Computed tomography (CT) provides a means of measuring tissue density. Emphysema reduces lung density, visualized as low attenuation areas on the CT scan. Lung perfusion scanning gives information on ventilation/perfusion ratio. At all stages of COPD, ventilation/perfusion inequality is the major mechanism impairing gas exchange leading to arterial hypoxemia.
Treatment

Smoking cessation is the only measure that will slow the progression of COPD and reduce the rapid decline in FEV<sub>1</sub>.<sup>7</sup> Medications used to improve breathing include bronchodilators (salbutamolphosphate), anticholinergics (ipratropium), methylxanthines (theophylline), corticosteroids and low-flow oxygen. Low-flow oxygen is the only treatment known to improve the prognosis of COPD.<sup>1,2</sup> probably due to its elimination of hypoxic vasoconstriction and diminution of pulmonary hypertension.<sup>113</sup> Pulmonary rehabilitation can improve exercise tolerance and quality of life in the short-term.<sup>4,134,141</sup>

Intrinsic positive end-expiratory pressure in severe emphysema

During spontaneous ventilation the inspiration of a tidal volume will “load” the elastic “springs” of lung and chest wall, whereas the energy expenditure in overcoming airway resistance will dissipate into heat. During expiration the emptying of the lungs is a passive process dependent on the elastic and resistive properties of the airway. The emptying can be shown to follow an exponential course according to:

\[ V(t) = V_0 \times e^{-\frac{t}{\tau}} \]

expressing that the decay in volume over time is an exponential curve dependent on a time constant, \( \tau \), equaling the elastic times the resistive properties of the lung, in other words:

\[ \tau = \text{compliance} \times \text{resistance} = \text{mL/cm H}_2\text{O} \times \text{cm H}_2\text{O}/\text{mL/s} = \text{s} \]

Thus, \( \tau \) has the unit of time. A general characteristic of exponential decay is that 63% of the initial volume (\( V_0 \)) is delivered within 1 \( \tau \), 86% within 2 \( \tau \), and 95% within 3 \( \tau \). Evidently, the time constant may be prolonged if compliance is high, resistance is high or both. With a long time constant the expiratory time may not allow for the exhalation of the tidal volume and part of this volume remains in the lungs when the next inspiration starts. This remaining volume causes hyperinflation and exerts a positive pressure at the end of expiration, which is termed intrinsic positive end expiratory pressure, PEEP<sub>i</sub>, or auto-PEEP.

In spontaneous ventilation, auto-PEEP will increase if respiratory rate, expiratory resistance (bronchoconstriction) is increased or abdominal musculature is recruited during expiration. PEEP<sub>i</sub> may result from expiratory flow limitation as a result of dynamic compression. In intermittent positive pressure ventilation, IPPV, auto-PEEP emerges from high respiratory rate, shortened expiratory time interval (as in inversed I:E ratio), and
increased resistance. In terms of respiratory work this is not of importance during IPPV (as the ventilator is the work horse), but auto-PEEP has implications for respiratory work in SPV and for hemodynamics in both SPV and IPPV. In SPV the patient will have to generate a negative pressure during inspiration overcoming the auto-PEEP before any volume is entering the lungs. This is clinically observed as the flattening of the diaphragm on chest X-ray and the use of auxiliary muscles during breathing in COPD patients.

Intrinsic PEEP is found in patients with COPD as a result of a defining characteristic of the disease: expiratory airflow limitation and emphysema. These two constitutive features may coexist in varying degrees. The airway flow limitation and the lung tissue destruction entail a sequence of pathophysiological events: PEEPi, expiratory flow limitation, pulmonary vascular hypertension, right heart hypertrophy, and cardiac decompensation. The vascular and cardiac manifestations are late events in the natural history of COPD.

**Cardiopulmonary interactions in healthy subjects and in COPD patients**

**Transmural, transpulmonary and intrathoracic pressures**

Transmural pressure, i.e. the difference between the intravascular and extravascular pressures, determines ventricular pre- and afterload. The vascular pressure recorded bedside is the intravascular pressure; i.e. the pressure in the vessel lumen relative to atmospheric (zero) pressure. The transpulmonary pressure is the pressure difference between alveolar pressure and intrathoracic/pleural pressure (alveolar minus pleural pressure) 78.

In the thorax, the extravascular pressure (intrathoracic or pleural pressure) normally is close to zero at the end of expiration and hence the intravascular pressure is equivalent to the transmural pressure in healthy people. Likewise, the transpulmonary pressure is close to zero at end-expiration. Changes in intrathoracic, transpulmonary and transmural pressures during spontaneous tidal ventilation have hemodynamic implications for both the RV and the LV. These implications differ for in- and expiration. This is summarised in figure 2 showing changes in airway pressure as mediated by pleural pressure during spontaneous breathing in a healthy person.
Cardiopulmonary interactions during spontaneous ventilation

Focusing on the LV, the hemodynamic implications during spontaneous ventilation, LV end-diastolic volume (LV preload) can be altered by ventilation in four ways.

First, since the RV and LV outputs are in series, changes in RV preload (RV end-diastolic volume) must eventually alter LV preload in the same direction. During inspiration, increasing lung volume above FRC, decreased (negative) intrathoracic pressure (increased transmural pressure) increases RV preload. Transpulmonary pressure decreases, thus lowering RV afterload. This leads to an increase in RV stroke volume (SV) and eventually to an increase in LV preload and LV SV \(^{100,101}\). This can be termed \textit{sequential interventricular interdependency}.

Second, the transient increase in RV end-diastolic volume during inspiration shifts the interventricular septum into the LV by interventricular interdependence, reducing LV end-diastolic volume, decreasing LV diastolic compliance and LV SV \(^{100,101,123}\). This can be termed \textit{simultaneous interventricular interdependency}.

Differences in RV and LV pressures during systole and diastole thus manifest themselves in displacement of the septum dependent on the septal tension (stress, \(\sigma\)): rightward displacement.
if LV wall stress exceeds RV wall stress, and leftward displacement if RV wall stress exceeds LV wall stress (for a description of this relationship, please see 21). Sequential and simultaneous interventricular interdependence are major factors in determining LV output during spontaneous ventilation when RV end-diastolic volumes may vary widely from expiration (small) to inspiration (large) 100.

Third, it has been hypothesized that increasing lung volume, whether by tidal volume or PEEP, restricts absolute cardiac volume by direct compression of the heart in the cardiac fossa 20. As the lungs expand the heart is compressed in the cardiac fossa and absolute biventricular volume is limited in a fashion analogous to cardiac tamponade 100, 101. Furthermore, it has been hypothesized that LV diastolic compliance is decreased 100, 101. Fluid resuscitation, however, returns end-diastolic volume to normal, and so cardiac output (CO) is returned to original levels 34, 57, 59, even in face of continued application of PEEP 16. Another explanation to the reduced biventricular volume during lung inflation is that lung expansion by PEEP reduces ITBV and thereby cardiac preload.

In patients with COPD and intrinsic PEEP (5-7.5 cm H2O = 3.7-5.5 mm Hg) inspiration demands negative pressures in excess of PEEPi before lung volume increases. Inspiration, however, will increase venous return and RV preload as the pressure gradient between the systemic venous system and right atrium increases. RV afterload is increased because of decreased area of capillary bed (compression due to hyperinflation and destruction due to emphysema) resulting in a decrease in RV SV in spite of increased preload. At end-expiration, the intrinsic PEEP and consequently the reduced transmural pressure results in a decrease in RV preload and eventually in LV preload because of the sequential interventricular interdependency 33. Translated into cardiac function, hyperinflation and PEEPi increases intrathoracic pressure and opposes venous return during diastole resulting in a reduction of the RV end-diastolic dimensions. Furthermore, increased transpulmonary pressure inhibits RV outflow during systole. The end result is a decrease in cardiac performance with low SV.

A fourth type of interaction is manifested in the late natural history of COPD where the pulmonary vascular hypertension emerges as a result of hypoxic vasoconstriction, progressive destruction of the pulmonary vascular bed as alveoli and alveolar septa are destroyed and external compression of the pulmonary vessels due to auto-PEEP. In this setting of pulmonary hypertension, the RV is ejecting its volume into a constricted vascular bed and afterload is increased. This results in bowing of the interventricular septum because of pressure excess of the RV relative to the LV during the diastolic phase. This has been
demonstrated by Roeleveld \textsuperscript{106} who used MRI to evaluate septal bowing in patients with pulmonary hypertension and is of relevance to III.

Gan et al \textsuperscript{40} likewise found that the substantial RV dilation and hypertrophy seen in patients with pulmonary hypertension, distorted the interventricular septum, compressed the LV and impaired LV filling through direct interventricular interaction. The resulting underfilling of the LV resulted in diminished SV.

**Cardiopulmonary interactions during intermittent positive pressure ventilation**

The hemodynamic implications during mechanical ventilation can be summarized as follows \textsuperscript{78, 101} (figure 3):

![Diagram](image)

*Figure 3. The hemodynamic implications during positive pressure ventilation (IPPV plus PEEP). Intrathoracic (pleural) pressure affects RV preload and LV afterload. Lung inflation (increasing transpulmonary pressure) affects RV preload and afterload as well as LV preload and afterload.*

Positive pressure ventilation increases intrathoracic pressure (ITP). Increase in ITP (pleural pressure) decreases LV afterload and augments LV ejection. The diaphragmatic descent increases intra-abdominal pressure, but the pressure gradient between the systemic venous system and right atrium remains low, diminishing venous return and hence RV preload. The LV SV is at a maximum at the end of the inspiratory period and at a minimum two to three
heart beats later (i.e. during the expiratory period). The cyclic changes in LV SV are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in RV filling and output.

Lung inflation alters pulmonary vascular resistance (PVR) independently of ITP as a progressive increase in transpulmonary pressure results in an increase in RV afterload. High levels of transpulmonary pressure induce pulmonary vascular collapse as transpulmonary pressure approaches pulmonary artery pressure.

**Intermittent positive pressure ventilation in COPD patients**

During IPPV, the basic rule is to avoid application of excessive pressure (at peak or plateau) during the respiratory cycle, though exact limits are disputed and may vary individually. Dynamic hyperinflation, or air trapping, occurs in COPD patients due to incomplete lung emptying (expiratory flow limitation) during expiration. This leads to a degree of hyperinflation of the lungs balancing the flow limitation (PEEP). The risk of hyperinflation can be reduced by applying a ventilatory pattern that allows deliberate hypoventilation and permissive hypercarbia i.e. small tidal volumes (6-7 mL/kg), low respiratory rate (RR 10-12 /min) and prolonged I:E ratio 1:4 ⁶. The application of PEEP in patients with PEEPi due to flow limitation does not cause an increase in lung volume, alveolar and intrathoracic pressure until a critical value of PEEP (Pcrit) exceeding the intrinsic PEEP is reached. Above this critical limit further hyperinflation is observed ¹⁰⁴ and the risk of hemodynamic and barotraumatic complications becomes imminent ²⁶.

**Lung volume reduction surgery in severe lung emphysema**

Lung volume reduction surgery for the treatment of severe emphysema was described in the late fifties by Brantigan et al ¹⁸. These investigators suggested that reducing the volume of hyperinflated, functionless parts of a diseased lung allows improved function of more normal parts of the lung. Because of high perioperative mortality, LVRS was later abandoned; it was reintroduced in 1994 by Cooper and co-workers ²⁸.

In LVRS the most emphysematous parts of the lung, targeted by chest CT-scanning and ventilation/perfusion scan are excised by use of mechanical staplers via median sternotomy. The excised amount of lung constitutes approximately 20-30% of the lung volume. To minimize air leaks, the staple lines are reinforced with bovine pericardial tissue ²⁷. In randomized, controlled, prospective studies ²⁹, ⁴², ¹⁰², ¹⁴², it has been demonstrated that
LVRS improves dyspnea, lung function, exercise tolerance, and quality of life in patients with severe emphysema. This improvement seems to reach a maximum after 36 months, thereafter declining as the disease progresses 38.

Although the effects of LVRS have been attributed to several possible mechanisms, enhanced pulmonary elastic recoil, correction of ventilation/perfusion mismatch and improved efficiency of respiratory musculature, the physiologic basis of reported improvements is not fully understood 37, 74. It has also been difficult to link the improvement in lung function tests to decreased dyspnea or increased quality of life after LVRS 69. Patients with localized upper lobe emphysema appear to benefit most from LVRS. In 2001, The National Emphysema Treatment Trial Research Group established that LVRS in patients who have a low FEV1 (<20% of predicted value) and either homogeneous emphysema or a very low carbon monoxide diffusing capacity (< 20% of predicted value), are at high risk for death after surgery and also are unlikely to benefit from the surgery 3. These guidelines have resulted in a complete cessation of referrals for LVRS from pulmonologists to the Department of Cardiothoracic Surgery at Sahlgrenska University Hospital.

### Changes in ventilatory mechanics after LVRS

Tschernko et al. 129-132 have described the effects of LVRS on emphysema lung mechanics in a number of studies. Their findings before and after surgery may be summarised as follows: preoperatively all patients had increased PEEPi, mean airway resistance (cm H2O/L/s), work of breathing (j/L) and decreased dynamic compliance (mL/cm H2O) and these deviations were accentuated by bicycle exercise. The minimal PEEPi levels were in the range of 5-7.5 cm H2O at rest and increased up to on average 12 cm H2O during exercise. Preoperative PEEPi was present in all patients, averaging 8.4 cm H2O (6.2 mm Hg) and decreased significantly to 1.1 cm H2O (0.8 mm Hg) 10-18 hours after surgery. Preoperative PEEPi correlated well with the increase in FEV1 after surgery. LVRS tended to normalise (improve) values of lung mechanic parameters and PEEPi remained so at least up to three months after operation.

Sciurba et al. 111 used oesophageal pressure at end-expiration as an index of pleural pressure. They found that oesophageal pressure as well as TLC and ResV decreased after LVRS whereas FEV1 increased. They ascribed the improvement in lung mechanics to increased elastic recoil.
Changes in pulmonary and systemic hemodynamics after LVRS

Data on the effects of LVRS on late pulmonary and systemic hemodynamics are scarce and the results of studies are controversial. Kubo et al. and Mineo et al. showed that cardiac index (CI) is increased six months after LVRS both at rest and during exercise. Kubo et al. suggested that the increase in CI after LVRS was caused by capillary recruitment of the previously compressed lung zones. Mineo et al. demonstrated that RV end-diastolic volume increased after LVRS and ascribed the increase in CI after LVRS to improved RV filling in turn caused by a decrease in intrathoracic pressure. These findings have not been corroborated by other investigators. Sciurba et al. showed that LVRS increased RV area ejection fraction, an indicator of systolic function. Although the authors did not measure RV outflow impedance, this finding was interpreted as an indication of an LVRS-induced reduction in pulmonary vascular resistance.

Indeed, improved cardiac function may contribute to the increased exercise capacity seen after LVRS, but the potential effects of LVRS on LV performance have not been discussed in detail. From the left ventricular point of view, diastolic LV function would be affected if the emphysematous lungs were considered as “intrathoracic space occupying processes”. Thus, if LV diastolic filling were abnormal in patients with severe emphysema, the effect of LVRS could be expected to relieve this “pulmonary tamponade”. It is, however, difficult to appreciate how a highly compliant structure can exert any kind of pressure on the heart.

Assessing systolic and diastolic function

Systolic function

Left ventricular systole is defined as the period between mitral and aortic valve closure. At the mechanical level, systole can be divided into two phases: 1. Isovolumic contraction and 2. Ejection (figure 4). In the isovolumic contraction phase, all four valves are closed, i.e. the volume of blood in the ventricles remains constant, but pressure rises rapidly. The maximal rate of pressure rise (dP/dt) during isovolumic contraction can be measured by positioning a micromanometer catheter in the LV. Left ventricular dP/dt is a well established index of systolic performance, and may be less load dependent compared with other indices of systolic function. It is, however, an invasive measurement and as such not applicable in the routine clinical setting.

Isovolumic contraction time (IVCT) and ejection time (ET) can be measured at the level of the mitral valve (mid oesophageal four-chamber view) and aortic valve (mid-
oesophageal aortic valve short axis view) respectively by continuous wave (CW) Doppler transoesophageal echocardiography. IVCT is defined as the time period between mitral valve closure, corresponding to the end of atrial contraction, and the beginning of LV ejection, corresponding to the aortic valve opening click or commencement of aortic flow. The ET is the time period between the opening and closing clicks of the aortic valve. Alternatively, in the deep transgastric long axis view, a CW Doppler signal can be positioned so that the aortic systolic and mitral diastolic waveforms are visualized simultaneously. This gives a more accurate value of IVCT. It is, however, frequently difficult to obtain a clear signal of both flow patterns at the same time.

When the pressure in the left ventricle exceeds that in the aorta, the aortic valve opens. This marks the beginning of the ejection phase, during which the pressure in the left ventricle and the aorta briefly rises to a maximum of about 120 mm Hg. The ejection phase ends with the closure of the aortic valve.

Figure 4. Left ventricular pressure-volume loop illustrating the changes in ventricular pressure with respect to volume in a counter clockwise fashion over time.

Determinants of systolic function
Systolic performance of the heart is dependent on preload, afterload and contractility. Cardiac preload is defined as the ventricular fibre length at the end of diastole, described clinically as the LV end-diastolic volume (LVEDV). A number of surrogate measures are used to estimate preload: pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP),
intrathoracic blood volume (ITBV) and end-diastolic area (EDA). ITBV is the sum of the end-diastolic volumes of the right atrium, the right ventricle, the left atrium, the left ventricle and the pulmonary blood volume. 

*Afterload* is defined as the wall tension that the LV or RV has to generate in order to eject blood out of the chamber. LV pressure may be elevated due to outflow obstruction, as in aortic stenosis (AS), or increased peripheral resistance, as in arterial hypertension and RV pressure may be elevated due to pulmonary valve stenosis or pulmonary hypertension. Using Laplace’s law, ventricular wall stress can be quantified. The law of Laplace states that wall stress ($\sigma$) is the product of pressure ($P$) and radius ($r$) divided by the wall thickness ($h$)

$$\sigma = \frac{P \times r}{2h}$$

In cardiac hypertrophy the increased wall thickness balances the increased pressure and wall stress remain unchanged. Preload and afterload can be considered as the wall stress present at the end of diastole and during LV ejection, respectively. In general, factors that increase wall stress increase oxygen demand.

*Contractility* is the intrinsic ability of a cardiac muscle fibre to contract at any given fibre length and afterload. If preload, afterload and heart rate (HR) are constant, changes in myocardial performance are attributed to change in contractility. The ejection fraction (EF) is the most commonly used non-invasive index of LV contractile function. It is assessed by echocardiography, angiography, MRI or radio-nucleotide ventriculography and calculated according to:

$$EF = \frac{(LVEDV - LVESV)}{LVEDV},$$

where LVESV = end-systolic volume. The EF, however, is sensitive to changes in preload, afterload, HR as well as synchronicity of contraction. Therefore it measures much more than contractility.

The LV end-systolic pressure-volume relationship (ESPVR, elastance) and the preload recruitable stroke work (PRSW) are two load-independent indices of LV contractile function. To estimate elastance, multiple end-systolic pressures and volumes must be measured during rapid and pronounced alterations in LV preload. On a pressure-volume diagram (figure 5), points defined by the end-systolic pressures and volumes from several myocardial contractions will be positioned on a single line (linear). The slope of this line is relatively independent of loading conditions and proportional to contractility (the steeper the slope, the greater the contractility). LV end-systolic pressure and volume can be measured
invasively, using micromanometer catheters during cardiac surgery. It is, however, possible to estimate end-systolic pressure using the dicrotic notch on the radial artery tracing.  

**Figure 5.** End-systolic elastance is the line connecting the end-systolic point of multiple pressure-volume loops obtained at varying preloads. An increased slope (steeper) represents increased contractility. ESPVR, end-systolic pressure-volume relationship.

PRSW, on the other hand, is a linear Frank-Starling analogue, describing the relation between LV stroke work (SW) and LVEDV:

$$PRSW = \frac{\Delta SW}{\Delta EDV}.$$ 

SW is defined as the area under the LV pressure-volume loop (figure 6). SW can be estimated from

$$SW = (EDV-ESV) \times (SAP-PCWP),$$

where SAP = systolic artery pressure. To generate the PRSW, preload needs to be varied by volume changes and accordingly, consecutive pressure-end-diastolic volume loops can be constructed (figure 7). In the figure, the shaded area corresponds to the LV stroke work (SW). Hence, SW can be plotted against end-diastolic volume for each loop (large black dots). The relationship between SW and EDV is linear and thus, the slope of the curve describes PRSW, an index of contractility which is considered to be independent of preload or afterload. PRSW can be assessed clinically at the bedside using thermodilution technique (PCWP) and echocardiography (EDA and ESA).
Figure 6. Stroke work is defined as the area under the pressure-volume curve. Stroke work is approximated as the product of stroke volume (EDV-ESV) and pressure (SAP-PCWP) developed during ejection of the stroke volume. End-diastolic pressure is approximated to PCWP and systolic pressure to SAP.

Figure 7. Preload recruitable stroke work (PRSW) is the relation between EDV and SW. The large black dots are EDV. The steeper the slope the higher the contractility.

Evaluation of LV function by two-dimensional transoesophageal echocardiography
The transgastric midpapillary short axis view can be used for assessing LV systolic function as well as preload \(^{24,25,122}\) and LV wall thickness \(^{96}\). The fractional area change (FAC) (or area
ejection fraction, AEF) is an index of systolic performance. FAC is the proportional change in the area of the LV short axis during systole and is given by the formula:

$$FAC = \frac{\text{EDA} - \text{ESA}}{\text{EDA}} \times 100$$

where EDA = end-diastolic area and ESA = end-systolic area. With the use of freeze frame images, the largest (EDA) and smallest (ESA) frame of a representative cardiac cycle is identified. The endocardial surfaces are then traced and the areas recorded. The papillary muscles are excluded from the tracing. Normal values for FAC are between 50 and 75%.

Preload can be assessed using EDA as a surrogate measure of LVEDV. Clements et al. have shown close agreement between EDA, assessed by TEE and EDV assessed by radionuclide angiography.

Ventricular wall thickness is assessed at end-diastole. Pressure overload (from AS or hypertension) produces concentric hypertrophy (wall thickness increased out of proportion to chamber size) and is associated with impaired relaxation (prolonged isovolumic relaxation time and reduced early filling) and reduced chamber compliance. Concentric LV hypertrophy can be assessed measuring infero-septal or antero-lateral wall thickness. A LV wall thickness > 11 mm indicates LV hypertrophy.

Diastolic function
Diastole is the period from aortic to mitral valve closure. At the mechanical level, diastole can be divided into four phases: 1. isovolumic relaxation; 2. rapid early filling; 3. diastasis; and 4. atrial contraction.

Isovolumic relaxation is the phase beginning with aortic valve closure (simultaneous with the dicrotic notch on the aortic pressure wave) and extending to the opening of the mitral valve. Ventricular volume remains unchanged and there is a rapid fall in intracavitary pressure due to active relaxation. Isovolumic relaxation can be quantified by measurements of LV pressure with a micromanometer catheter and thus the relaxation time constant tau (τ) can be assessed. Active relaxation is characterized by constant fractional decrease in pressure over time, \(\Delta P(t)/\delta t\), the fraction being τ times the pressure at the start of the relaxation (P₀):

$$-\frac{\Delta P(t)}{\delta t} = \tau \times P_0$$

This may be differentiated into the exponential decay equation

$$P(t) = P_0 \times e^{-\tau t}$$
With $\tau$ termed time constant. When isovolumic relaxation is slowed, $\tau$ is prolonged. The time constant, $\tau$, may be derived as the inverse slope to the natural logarithm of LV diastolic relaxation pressure plotted versus time. The normal range is 40 to 60 ms (figure 8).

![Figure 8. Two LV pressure waveforms show a normal contour and a waveform with delayed relaxation producing a prolonged time constant, $\tau$.](image)

The isovolumic relaxation time (IVRT) is a commonly used non-invasive parameter of ventricular relaxation. It is regarded as a reflective of $\tau$ \cite{84}. Thus, a direct correlation between IVRT and $\tau$ has been described \cite{82,84,145}. IVRT, however, is affected by both aortic \cite{68} and left atrial pressures \cite{82}. IVRT is prolonged in conditions that impair active relaxation and relates directly with $\tau$ and aortic closing pressure; it is shortened by a raised left atrial (LA) pressure, because this causes earlier opening of the mitral valve \cite{82,126}. An analytic expression relating IVRT to $\tau$, and to aortic and LA pressure is IVRT:

$$p_{La} = p_0 e^{IVRT/\tau},$$

where $p_0$ is ventricular pressure at the time of aortic closure at which time point $t$ is 0, and $p_{La}$ the left atrial pressure at the time when ventricular pressure equals the left atrial pressure.

Viewed on a logarithmic plot, LV pressure decreases with a slope equal to $-1/\tau$. Thus taking the logarithm of equation above yields

$$log(p_{La}) = log(p_0) - IVRT/\tau,$$

and hence

$$IVRT = \tau(log(p_0) - log(p_{La}))$$
This equation demonstrates that IVRT varies predictably with $\tau$, LA pressure and aortic closing pressure $^{95,126,147}$.

*Early diastolic filling* begins with opening of the mitral valve. The LV pressure will continue to fall even after the opening of the mitral valve. In fact, the LV pressure falls below the LA pressure as a result of elastic recoil, creating a suction effect. Rapid filling of the LV occurs during this phase. Normally, LV relaxation ends in the first third of rapid filling so that the rest of the LV filling is dependent on LV compliance, ventricular interaction, and pericardial constraint. Although the rapid filling phase comprises only 30% of diastole, it accounts for up to 75% of LV volume.

Ventricular filling slows during mid-diastole as the transmitral pressure gradient declines. This phase is known as *diastasis*. During this phase, LA and LV pressures are nearly equal. The filling comes from the *pulmonary veins* and contributes about 5% to the LV volume. *Atrial systole* increases the transmitral pressure gradient and accounts for the remaining 20% of ventricular filling. The contribution of atrial systole to ventricular filling increases substantially in conditions that impair myocardial relaxation, such as severe LV hypertrophy $^{44,116}$.

**Pathophysiology of diastolic dysfunction**

Diastolic dysfunction is defined as a condition in which a higher than normal LV filling pressure is needed for optimal stretch of the myocardial fibres $^{46,147}$. Focusing on *the four determinants* of diastolic function:

- **Myocardial relaxation** (early diastole) is an energy-dependent process influencing the isovolumic relaxation phase and part of the early filling phase. *Intracellular Ca$^{2+}$ overload*, as seen in ischemia, can prolong myocardial relaxation so that the early filling phase is affected. A proposed metabolic explanation is that generation of energy (adenosine triphosphate, ATP) is impaired, leading to a slow rate of Ca$^{2+}$ reuptake into the sarcoplasmatic reticulum.

- **Ventricular compliance** (mid-diastole) is a passive process that affects all three filling phases of diastole. The intrinsic factors entail increased myocardial stiffness resulting from fibrosis, muscular hypertrophy or a deposition of amyloid. The extrinsic factors that reduce ventricular compliance include the structures that surround the heart: pericardium, RV and lungs.

- *The pulmonary veins and left atrium* are the source for LV filling, and influence all three filling phases. An increase in the LA-LV pressure gradient (increase in preload)
enhances early diastolic filling whereas a decrease in preload (Valsalva manoeuvre or reverse Trendelenburg) attenuates early LV filling.

*Heart rate* influences myocardial relaxation and all three filling phases. In bradycardia most of the LV filling occurs before atrial contraction. In tachycardia early filling is shortened, there is no diastasis, and LV filling depends mostly on atrial contraction. The natural history of diastolic dysfunction is that, with time as the disease advances, abnormal relaxation progresses to reduced chamber compliance.

**Evaluation of diastolic function**

The evaluation of diastolic function is made using TEE. In conjunction with the anatomic and functional information provided by *two-dimensional echocardiography* (systolic function, preload and wall thickness) and *colour-flow Doppler imaging* (valvular regurgitation), diastolic function can be assessed using *CW Doppler imaging of mitral and aortic flow* (measurements of IVRT) and *pulsed Doppler (PW) imaging of mitral flow* (LV filling pattern) 44.

*Pulsed Doppler imaging of mitral flow*: The mitral Doppler flow profile reflects the transmitral pressure gradient and depends on the rate of LV relaxation, LV compliance and LA pressure. Following isovolumic relaxation and mitral valve opening, diastolic filling commences. The normal transmitral velocity profile consists of two peaks; a larger E wave due to early diastolic filling and a smaller A wave due to atrial contraction. A number of variables can be measured from the Doppler tracings. These include peak early diastolic and peak late diastolic filling velocities (E-max and A-max), deceleration rate (E-dec slope) and deceleration time (E-dec time) of early diastolic filling, and the ratio E-max/A-max (E/A) (figure 9). The deceleration time is the interval between time E-max and time at the linear extrapolation of E-dec slope to baseline. This interval reflects the mean LA pressure and LV compliance. A short E-dec time is seen in patients with reduced compliance whereas a long E-dec time is seen in patients with poor relaxation 95. IVRT generally parallels E-dec time, both becoming prolonged with abnormal relaxation, and becoming shorter with rapid relaxation and increasing filling pressures 85.

In young adults, LV relaxation is rapid resulting in nearly 95% filling during the early diastolic filling phase (E/A>2). By middle age, LV relaxation is slowed, early filling decreases and the contribution of atrial contraction increases to about 30% (E/A>1). In elderly people, further impairment of relaxation has occurred and about 50% of flow may occur during atrial systole (E/A=1) 110,116.
Three patterns of abnormal transmitral flow are recognized: impaired relaxation, pseudo-normalization and restrictive filling. Please refer to table 1.

**Impaired relaxation:** Impaired relaxation occurs in myocardial ischemia, LV hypertrophy and ageing. The Doppler transmitral flow velocity profile is characterized by a prolonged IVRT and a decreased initial transmitral pressure gradient. This results in a decrease in early filling and an increase in filling during atrial systole. Consequently, the E-max decreases relative to the A-max and the E/A ratio<1. In addition, the duration of LV relaxation is prolonged and results in prolonged E-dec time because the LA-LV pressure gradient takes longer to equilibrate. A subsequent compensatory increase in flow during atrial contraction accounts for the increase in A-max because of the relatively high atrial preload. Alterations in loading conditions (reduced preload or increased afterload) can also change a normal filling pattern into an abnormal one (E/A<1).

**Pseudo-normalization:** Typically diastolic dysfunction progresses from impaired relaxation to restrictive filling, but during this transition the Doppler transmitral flow velocity profile may assume a pseudo-normal pattern, that resembles normal filling. The pseudo-normalized filling pattern represents a moderate stage of diastolic dysfunction consisting of impaired myocardial relaxation as well as elevated LV filling pressure. At this stage, most
patients have an enlarged left atrium and the LA pressure tends to rise. As the LA pressure rises, the mitral valve opens earlier, shortening the IVRT. The gradient for early filling is greater, which will increase E-max. This in turn leads to a large rise in mid-diastolic LV pressure, which shortens the E-dec time and reduces A-max. Reducing the preload with head-up tilt or a Valsalva manoeuvre will decrease the LA pressure, and reveal an underlying impaired LV relaxation in patients with pseudo-normalized transmitral flow.

Restrictive filling: This transmitral filling pattern is seen in patients with reduced chamber compliance in association with an elevated LA pressure. The E-max is increased, consistent with very rapid filling during early diastole. The IVRT is shortened because the mitral valve opens prematurely as a consequence of the elevated LA pressure. The E-dec time is also shortened because early transmitral flow into the poorly compliant LV results in rapid equilibration of the LA and LV pressures. The A-max is decreased due to poor atrial contractility and the rapid increase in LV pressure, which can terminate late mitral inflow. E/A > 2.

Table 1. Stages of diastolic dysfunction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal adult &gt;40 years</th>
<th>Delayed relaxation</th>
<th>Pseudo-normal filling</th>
<th>Restrictive filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT (ms)</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
<td>60-100</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>E-dec time (ms)</td>
<td>&lt; 220</td>
<td>&gt; 220</td>
<td>150-200</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>E/A</td>
<td>&gt; 1</td>
<td>&lt; 1</td>
<td>1-2</td>
<td>&gt; 2</td>
</tr>
</tbody>
</table>

IVRT, isovolumic relaxation time; E-dec time, deceleration time of early diastolic filling; E/A, the ratio E-max/A-max. According to Oh et al. and Garcia et al. 41, 85.

Physiologic variables affect LV Doppler flow profiles. An increase in preload will result in an increase in E-max, a decrease in A-max, an increase in E/A ratio, a shorter IVRT and a shorter E-dec. time (similar to the restrictive pattern). Correspondingly, a decrease in preload reduces E-max and the E/A ratio, whereas E-dec time and IVRT increase. An increase in afterload exhibit a transmitral pattern similar to impaired relaxation, i.e. IVRT increases, E-max decreases, E-dec. time is prolonged and A-max increases.

In tachycardia, E-max decreases relative to A-max resulting in a reduced E/A ratio. E-dec time decreases and IVRT is shortened. A HR over 100 /min causes fusion of E- and A-
wave velocities. In atrial fibrillation there is a loss of A-wave. Bradycardia increases the E/A ratio.

The location of the PW Doppler sample volume, the respiratory pattern, arrhythmia and pacing as well as mitral and aortic regurgitation, can affect the transmitral blood flow velocity profile and make interpretation of the profiles difficult.  

**Left ventricular end-diastolic stiffness**

LV end-diastolic stiffness (LVEDS) is defined as the myocardial resistance to passive stretching, i.e. change in pressure per volume change (dP/dV). Thus, LVEDS is reciprocal to compliance (dV/dP). In other words, increased myocardial stiffness impedes myocardial lengthening.

LVEDS is calculated using the end-diastolic pressure-area relation: The end-diastolic pressure-area relation is known to be curvilinear in shape, and in vitro and in vivo animal studies have shown that as long as the end-diastolic pressure remains greater than 3 mm Hg, it fits reasonably well to an exponential function. In other words, an increase in LV volume is accompanied by an increase in pressure following an exponential function.

It can be described by the equation:

$$PCWP = B \times e^{S \times EDA}$$

PCWP denotes the pulmonary capillary wedge pressure, EDA the end-diastolic area and B and S are constants. By transforming this equation to its logarithmic form:

$$\ln(PCWP) = \ln(B) + S \times EDA,$$

a linear relation is obtained. LVEDS is defined as the slope of the end-diastolic pressure-area curve. This can be derived by solving the equation below with two connected values of PCWP and EDAI; one set obtained with the patient in supine position and one with the legs elevated (volume loading):

$$LVEDS = (\ln(PCWP_2) - \ln(PCWP_1)) / (EDA_I_2-EDA_I_1),$$

where $\ln(PCWP_1)$ and $\ln(PCWP_2)$ are the natural logarithms of the pulmonary capillary wedge pressures, and $EDA_I_1$ and $EDA_I_2$ are the indexed LV end-diastolic areas, before and after volume loading, respectively.
Pharmacological aspects on diastolic function

Cellular events
Both myocardial contraction and relaxation are energy consuming processes. During systole, when cytosolic Ca\(^{2+}\) is high, Ca\(^{2+}\) binds to troponin-C allowing formation of cross bridges between actin and myosin filaments and contraction starts. As long as Ca\(^{2+}\) is bound to troponin-C this energy-dependent process is repeatedly performed (cross bridge cycling). During diastole, when cytosolic Ca\(^{2+}\) is low, Ca\(^{2+}\) is removed from troponin-C and pumped back into the sarcoplasmatic reticulum, allowing dissociation of the actin-myosin cross bridges. The myofibrils relax and return to their original end-diastolic length.

Inotropic drugs
Patients with LV hypertrophy have limited coronary vasodilator reserve. Perfusion and tissue viability balances on a swords edge. Many inotropic agents accentuate ischemia by increasing myocardial oxygen demand. Positive inotropic drugs such as digoxin, β-adrenergic agonists, catecholamines and phosphodiesterase (PDE) III inhibitors rarely have a place in the treatment of diastolic dysfunction even though β-adrenergic agonists and PDE III inhibitors have lusitropic effect (enhanced sarcoplasmatic reuptake of Ca\(^{2+}\) and decreased Ca\(^{2+}\) affinity to troponin-C) [39, 148]. Their predominant effect, though, is an increase in intracellular cAMP and Ca\(^{2+}\) concentration in the myocytes, thus improving cardiac contractility. Oxygen consumption, however, increases and likewise the risk of Ca\(^{2+}\) overload, leading to tachycardia and ischemia, most pronounced in the groups of β-adrenergic agonists and catecholamines [39, 45, 89]. PDE III inhibitors do not seem to increase myocardial oxygen demand to a great extent, which is probably explained by its substantial vasodilating capacity [45].

Levosimendan belongs to a class of drugs known as Ca\(^{2+}\) sensitizers. This drug enhances myocardial contractility through myofilament Ca\(^{2+}\) sensitization by binding to troponin-C in a Ca\(^{2+}\) concentration-dependent manner and induces peripheral and coronary vasodilation by opening ATP-sensitive potassium channels without increasing oxygen consumption [66, 70, 76]. Additionally, with higher concentrations, levosimendan acts as a PDE III inhibitor [53].

LV systolic dysfunction is often accompanied by impaired LV relaxation and increased sensitivity to Ca\(^{2+}\) during diastole would further impede relaxation of the heart and worsen diastolic dysfunction. The effects of Ca\(^{2+}\) sensitizers on myocardial relaxation and diastolic function in man, however, are incompletely understood. In vitro studies have shown that Ca\(^{2+}\) sensitizers (EMD 57033, ORG 30029) may impair myocardial relaxation and elevate diastolic tension in failing human myocardium [50], whereas levosimendan, on the other hand, has
been shown to improve both systolic and diastolic function of cardiac muscle preparations from end-stage failing human hearts 58.

Recent clinical studies on levosimendan, using Doppler echocardiographic variables of LV diastolic function 31, 32, 92, have supported the experimental studies regarding lusitropy, but should, however, be interpreted with caution because these Doppler echocardiographic indices are preload-, afterload- and heart rate-dependent. Levosimendan has well known positive chronotropic and vasodilatory effects 119 and thus affects the Doppler echocardiographic indices used to evaluate early LV relaxation to a great extent. Therefore, clinical studies on the potential lusitropic effect of levosimendan are warranted.
AIMS OF THE INDIVIDUAL STUDIES

Paper I
To compare LV filling and dimensions in patients with severe emphysema with non-emphysematous patients, and to evaluate the effect of lung volume reduction surgery on left ventricular diastolic filling and dimensions.

Paper II
To compare LV systolic performance in patients with severe emphysema with non-emphysematous patients.

Paper III
To investigate whether hyperinflated lungs in patients with severe emphysema cause low intrathoracic blood volume (central hypovolemia) and hence small right and left ventricular end-diastolic volumes resulting in compromised left ventricular performance.

Paper IV
To investigate whether levosimendan in addition to its positive inotropic effect have positive lusitropic effect in patients with diastolic dysfunction.
MATERIALS AND METHODS

Patients

Paper I to III

In I, II and III, inclusion criteria for all patients in the study group (termed emphysema group) were a diagnosis of emphysema based on pulmonary function tests; FEV\textsubscript{1} between 20 and 35% of expected value, Res\textsubscript{V} over 200%, TLC over 120% of expected value and age less than 75 years. Furthermore, patients should have a normal echocardiographic examination (LV EF > 50% and systolic pulmonary artery pressure (SPAP) < 55 mmHg) and no history of cardiac disease. All patients had a smoking history and received optimal medical treatment with inhaled steroids and bronchodilators. The patients in I and II (5 women and 5 men) were scheduled for LVRS, while the patients in III (8 women and 5 men) were enrolled in the study when admitted for evaluation for single lung transplantation at Sahlgrenska University Hospital. The control group in I and II (6 women and 4 men) had a diagnosis of malignancy based on lung biopsy and a tumour location suitable for lobectomy. These patients were included to exclude the surgical procedure per se as the source of potential effect on measured variables. The control group in III consisted of healthy volunteers (6 women and 5 men). They were matched for age, gender, and body size and had no complicating cardiac or systemic disease. A total number of 44 patients were included. The majority of patients in I were also included in II.

Paper IV

In IV, 23 consecutive symptomatic patients with severe aortic stenosis, scheduled for aortic valve replacement (AVR) or AVR plus coronary artery bypass grafting were studied. Inclusion criteria were: 1) aortic valve area <1 cm\textsuperscript{2}, an aortic valve pressure gradient >50 mm Hg; 2) preoperative ejection fraction of more than 50% ; 3) LV wall thickness > 11 mm; 4) less than moderate aortic insufficiency; 5) coronary artery disease as a secondary finding on routine cardiac catheterization; 6) sinus rhythm before and after cardiopulmonary bypass (CPB); 7) uncomplicated weaning from CPB with no need for inotropic support. Patients with previously documented coexisting valve disease such as moderate mitral or mild tricuspid insufficiency or aortic subvalvular LV outflow tract obstruction were excluded from the study. Inclusion and exclusion criteria were confirmed by initial intraoperative TEE evaluation.
Anaesthesia and surgery

Paper I and II

The patients were premedicated with flunitrazepam (1 mg) and the patients in the emphysema group also received morphine (5-10 mg) and scopolamine (0.2-0.4 mg). A thoracic epidural catheter was inserted prior to induction of anaesthesia. After an epidural bolus injection with sufentanil (10-25 μg) and bupivacaine (15-20 mg) a continuous infusion of sufentanil (1 μg/mL) and bupivacaine (1 mg/mL) was initiated at a rate of 3-4 mL/h. Anaesthesia was induced with thiopental (3-5 mg/kg), fentanyl (1-2 μg/kg), and pancuronium (0.1 mg/kg). The patients were intubated with a left-angled double-lumen tube. Anaesthesia was maintained with enflurane in oxygen/air with a F\textsubscript{1}O\textsubscript{2} necessary to keep P\textsubscript{a}O\textsubscript{2} > 20 kPa. Ventilation was volume-controlled (6-7 mL/kg tidal volume) at a frequency of 15/min and an I:E ratio of 1:3, to maintain P\textsubscript{a}CO\textsubscript{2} between 5.0 and 7.0 kPa. PEEP was not applied. The patients were actively warmed by the use of warm-air blankets. The patients did not receive intravenous fluids during the induction or maintenance of anaesthesia. Bilateral LVRS was performed by median sternotomy as described by Cooper and Patterson \cite{27}.

Paper IV

The patients were premedicated with flunitrazepam (0.5-1 mg) orally and morphine (5-10 mg) and scopolamine (0.2-0.4 mg) subcutaneously. \(\beta\)-adrenergic blockers were continued during the perioperative period, including the morning of surgery, whereas angiotensin converting enzyme inhibitors, Ca\textsuperscript{2+} - channel blockers, and other cardiovascular medications were omitted on the day of surgery. Anaesthesia was induced with thiopental (1-3 mg/kg) and fentanyl (5-10 μg/kg). Tracheal intubation was facilitated with pancuronium (0.1 mg/kg). Before and after CPB, anaesthesia was maintained with sevoflurane in oxygen/air with a F\textsubscript{1}O\textsubscript{2} necessary to keep P\textsubscript{a}O\textsubscript{2} > 20 kPa. During CPB a continuous infusion of propofol was administered. Ventilation was volume-controlled to maintain P\textsubscript{a}CO\textsubscript{2} between 4.0 and 5.0 kPa during surgery. Intraoperative hypotension was treated with fluids, phenylephrine infusion, or both, and hypertension was treated with sodium nitroprusside infusion. Target mean artery pressure (MAP) during CPB was 50-90 mm Hg. AVR was performed according to the Department’s standard procedure. No inotropic drugs were administered during weaning from the CPB. The type of prosthetic valve placed (biological or mechanical) was decided by the surgeon and the patient preoperatively. The size of the valve was determined by the surgeon perioperatively.
Hemodynamic measurements

Paper I, II and IV

A cannula was placed in the left radial artery (I and II) or right femoral artery (IV). A pulmonary artery thermodilution catheter (131HF7, TD Baxter Healthcare Corporation, Irvine, CA, 92614-5686, USA) was inserted through the right internal jugular vein into the pulmonary artery. Continuous recordings of HR, SAP, diastolic artery pressure (DAP) and MAP together with SPAP, diastolic pulmonary artery pressure (DPAP) and mean pulmonary artery pressure (MPAP), and CVP were performed. The pressure transducers were zeroed against atmospheric pressure and maintained at the mid-axillary level throughout the experimental procedure. Thermodilution cardiac output in triplicate, and PCWP measurements were performed at each measuring point. SV, SW, systemic vascular resistance (SVR) and PVR were calculated and indexed to the patient’s body surface area (BSA) (SVI, SWI, SVRI and PVRI respectively).

Two-dimensional echocardiography

Paper I, II and IV

A multiplane transoesophageal echocardiographic transducer (ACUSON™, ACUSON Corp., Mountain View, Calif., USA) was used together with an ACUSON 128XP echocardiography system in I and II and a Sequoia echocardiography system (Sequoia c256, ACUSON Corp., Mountain View, Calif., USA) in IV. Using the transgastric mid-papillary short axis image of the left ventricle, the LV endocardial border was outlined in end-systole and end-diastole and LV ESA and EDA were calculated together with AEF. ESA and EDA were indexed to the patient’s BSA (ESAI and EDAI, respectively). In I and II, images were stored on Super-VHS videotape and later transferred to a computer system by means of a video frame grabber (VISIONplus-AT™, Imaging Technology Inc., Bedford, MA, USA). In IV, images were stored on magneto-optical discs and later transferred to a computer system (EchoPac PC Dimension version 4.0.x. GE Medical Systems. P.O. Box 414, Milwaukee, Wisconsin 53201 USA) for off-line analysis.

The indexed end-diastolic LV short axis area and the PCWP obtained in the supine position with and without passive leg elevation were used to calculate LVEDS

\[ \text{LVEDS} = (\ln PCWP_2) - \ln(\text{PCWP}_1) / (\text{EDAI}_2 - \text{EDAI}_1) \]

in I, and preload-recruitable stroke work \( (\text{PRSW} = \Delta SW / \Delta EDV) \) in II. Furthermore, the increase in SVI to a certain increase in preload, assessed by the change in PCWP or change in
EDAI, was estimated as: \(\Delta SVI / \Delta PCWP\) (mL/mmHg) and \(\Delta SVI / \Delta EDAI\) (mL/cm²*m²), respectively. LV EDAI was used as a surrogate variable for LV EDV.

**Doppler echocardiography**

**Paper I and IV**

In I and IV mitral Doppler profiles were recorded. After completion of the LV short-axis measurements, the transducer was withdrawn until a long-axis image was obtained in the midesophageal four-chamber view. A PW Doppler line was positioned with the measuring caliper at the tips of the open mitral leaflets and adjusted to be as parallel as possible to the mitral flow. Optimal sweep speed was set at 50 to 100 mm/s \(^9\). In I, the Doppler flow profiles were recorded on Super-VHS video tape and in IV on magneto-optical disc. The flow profiles were later transferred to a computer and evaluated with a digitizing tablet by means of a PC-based analysis system, as previously described by Houltz \(^56\) (I) or to a computer work station (EchoPac PC Dimension (IV). Three consecutive beats were digitized and their mean values were used for analysis. The following variables were derived from the mitral Doppler tracings: E-max and A-max, E-dec slope and E-dec time. The ratio of E-max to A-max (E/A) was calculated.

In IV, IVRT was measured by first positioning the CW Doppler sample volume at the tips of the mitral leaflets (mid-oesophageal four chamber view) (figure 10). The mitral flow profile was recorded, and the time from the R-wave in the ECG to the beginning of the E-wave was measured, \(t^E\). Thereafter, the Doppler sample volume was positioned at the aortic valve (midesophageal aortic valve short axis view). The aortic closing click was recorded and the time from the R-wave to the appearance of the aortic closing click was measured, \(t^A\). Optimal sweep speed was 100 mm/s. IVRT was calculated according to the formula

\[
IVRT = t^E - t^A.
\]

IVCT was measured as the time distance from the R wave to the aortic valve opening.
Figure 10. CW Doppler recording for calculation of IVRT. R-MO, time distance from R-wave in the ECG to mitral valve opening; R-AC, time distance from R-wave to aortic valve closure. IVRT was defined as the difference between R-MO and R-AC.

**Magnetic resonance imaging**

**Paper III**

The formation of a cardiac MR image requires a number of measurements. To compensate for cardiac motion, every measurement is performed at a fixed time delay after a trigger signal from the R wave on the ECG. An image (slice) can thus be reconstructed after acquiring data during several consecutive cardiac cycles. With retrospective gating, measurements are being made continuously, with simultaneous registration of the ECG signal. After acquisition, the data are attributed to the corresponding time frame and a complete cine loop is reconstructed displaying the full cardiac cycle. 

*Imaging protocol.* Each subject underwent a single MR examination performed on a 1.5-T MR system (Philips Intera, R9.3, Philips Medical Systems, Best, The Netherlands). Heart rate was continuously recorded and systolic and diastolic arterial blood pressures (sphygmomanometer) were recorded before start of imaging. Subjects in the emphysema group were allowed to breathe oxygen-enriched air during the entire examination.

*Cardiac volumes and function by cine MRI:* were obtained once in all participants. During the examination, multiple slices through the heart were acquired to encompass completely the ventricle in multiple phases within the cardiac cycle by using ECG triggering.
The images were acquired during breath hold in expiration with approximately 12 sections through the left ventricle in short axis view. In the short-axis, the contours describing the endocardial and epicardial border of the myocardium were delineated and the following parameters for LV and RV were evaluated using commercially available software (Easy Vision 5.1; Philips, Best, The Netherlands): EF (%), end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (cine-SV). Endocardial contours were traced on the diastolic and systolic images and the ventricular volume (diastolic or systolic) equals the sum of all the endocardial areas (of the diastolic or systolic images, respectively) multiplied by the slice thickness (figure 11 and 12). The LV wall mass (WM) was calculated by tracing the epicardial borders in diastole to obtain an epicardial volume. The volume of the myocardium was defined as the epicardial volume minus LVEDV. Multiplication of this value by the specific gravity for muscle (1.05 g/mL) yields the myocardial mass \(^{93,103}\). Papillary muscles were included in the volume and excluded in the mass determination \(^{117}\). EDV, ESV, and cine-SV were indexed to BSA (EDVI, ESVI and cine-SVI respectively).

Figure 11. Cine MRI showing the RV and LV in short axis view. Multiple slices through the heart are acquired to encompass completely the ventricle in multiple phases within the cardiac cycle by ECG triggering. The inner circle describes the endocardial border and the outer circle describes the epicardial border of the myocardium.
Figure 12. The cardiac cycle is divided into multiple phases. Each phase consists of 9 to 12 slices. The phases corresponding to end-diastole (phase 1) and end-systole (phase 7) are shown. The entire LV volume can be analysed, but this is very time consuming.

The septal curvature was measured in the short-axis image plane at the most basal level that showed the full myocardial walls around both ventricles and no outflow tracts or valves. Within this level, the cine image with the most evident deformation of the septum was used for quantification. Septal bowing was quantified by the curvature (defined as 1 divided by the radius of curvature in centimetres), as calculated by entering midwall septal image coordinates into an analytic fitting routine. The sign of the curvature was dependent on the convexity of the septum. A rightward (physiologic) curvature was denoted as a positive value, and a leftward curvature as a negative value.

Quantification of aortic flow using MR phase velocity mapping (qf) was performed once during breath-holding using a phase-contrast ECG-triggered 2D fast field echo (FFE) sequence at the level of the pulmonary artery, perpendicularly to the ascending aorta. Stroke volume was evaluated using the Easy Vision 5.1. (See above). Circular regions of interest (ROI) were placed over the ascending aorta. The contours of the ROI were delineated around the internal border of the vessel of interest on all images by automated contour detection. SV (qf-SV) was computed by integrating the flow over a complete cardiac cycle. Qf-SV was indexed to BSA, qf-SVI.

In quantification of aortic flow using MR phase velocity mapping, the signal intensity of the pixels is directly proportional to linear velocity (m/s). As the diameter of the
vessel (aorta) is measured, linear velocity (m/s) is converted to volume flow (L/s) by multiplication of vessel area; \( q_f \), thus, is a measurement of flow. Using retrospective triggering/gating the RR-interval can be filled with measuring points of the flow profile for the entire cardiac cycle \(^{128,152}\) (figure 13).

![Image of MR angiography](image)

**Figure 13.** The signal intensity of the pixels is directly proportional to linear velocity (m/s) in quantification of aortic flow using MR phase velocity mapping. As the diameter of the vessel (ascending aorta) is measured, linear flow (m/s) is converted to volume flow (L/s) by multiplication of vessel area.

Quantification of aortic flow using MR phase velocity mapping has been validated in vivo and in vitro and displays excellent accuracy and repeatability \(^{22,62}\).

*Contrast-enhanced, time-resolved, two-dimensional MR angiography of the heart and lungs for calculation of the peak transit time (PTT):* was performed twice in each patient for evaluation of repeatability. A 2D T1-weighted, flow-compensated FFE sequence was applied at the level of the pulmonary trunk and ascending aorta during intravenous gadolinium bolus injection (2 mL bolus of gadopentetate dimeglumine, Magnevist; Berlex Laboratories, Wayne, NJ), followed by 20 mL of saline, injected at a rate of 5 mL/s by using an automated power injector (Spectris Solaris Medrad, Indianola, Pa). Two-dimensional data sets were acquired at 0.559-1.1 second intervals (approximately 2 Hz) for 25-30 seconds after contrast material injection. Subjects were requested to hold their breath in expiration during the MR angiographic examination for at least 30 seconds or as long as was tolerable. Using the tracer (gadolinium), the transit of an intravascular marker across the lung can be calculated. The tracer was injected into the antecubital vein and contrast intensity as a function of time (ms) was recorded.
time was measured in the pulmonary artery and in the aorta. Time-intensity curves were generated for bolus transit through the ROI (Intera R 9.3, Philips Medical Systems, NL): the outflow part of the pulmonary artery (PA) and the ascending aorta (AO). The PA and AO curves were fitted to functions describing peak/pulse curves (PA) and multi-compartment impulse response exponential decay curves (AO) using the Origin software (Origin Version 7. Origin Lab Corporation. One Roundhouse Plaza. Northampton, MA 01060 USA). The PA–to–AO PTT was calculated by subtracting the time of peak signal intensity of the PA curve from that of the AO curve. PTT was used as an approximate of mean transit time (MTT) \(^{120}\) (figure 14).

![Graph showing peak transit time (PTT) calculation](image)

**Figure 14.** Typical recording of contrast intensity vs. time for the calculation of peak transit time (PTT). Full line square symbols indicate original values from pulmonary artery (PA) (left) and aorta (AO) (right). Superimposed with full line/circles are fitted curves according to pharmacokinetic models. PTT is calculated as the temporal distance between maximum values of intensity in the PA and AO fitted curves.

Cardiac output was measured using quantification of aortic flow by phase velocity mapping (qf-CO). The transit of the tracer through the lungs was used to estimate intrathoracic blood volume according to Zierler \(^{146}\):

\[
\text{ITBVI} = \frac{\text{MTT} \times \text{CO}}{60 \times \text{BSA}}.
\]

Furthermore, ITBVI was estimated from the contrast intensity versus time curves using a non-linear mixed effect modeling (NONMEM) approach. This uses the NONMEM program (version V, level 1.1, GloboMax LLC, Hanover MD, USA) with the first-order conditional
estimation and interaction analysis procedure. The structural model of the lung used, was a "tank in series" model. This type of model is suitable for describing intravascular peaks that are delayed and right skewed, and has been used previously to describe the lung kinetics of the intravascular marker indocyanine green in man. SVRI was calculated as MAP/qf-CI. All hemodynamic data and data on cardiac dimensions were normalized to BSA.

**Experimental protocols**

**Paper I and Paper II**

In these prospective, open, controlled studies, patients scheduled for LVRS and patients scheduled for lung lobectomy because of carcinoma were included. After induction of anaesthesia, systemic and pulmonary hemodynamics (pulmonary artery thermodilution catheter) and echocardiographic measurements (transoesophageal two-dimensional Doppler echocardiography) were performed before and immediately after end of surgery with the patient in the supine position (I) and with passive leg elevation (60-90 degrees) to increase ventricular preload (II).

**Paper III**

In this prospective, open, controlled study, patients with severe emphysema and healthy control subjects were included. Each patient/subject underwent a single MR examination, consisting of three parts: 1. Evaluation of RV and LV dimensions and function and interventricular septum curvature using cine MRI, 2. Quantification of aortic flow using MR phase velocity mapping and 3. Calculation of the cardiopulmonary PTT from the pulmonary artery to the ascending aorta, using contrast-enhanced, time-resolved, two-dimensional MR angiography.

**Paper IV**

In this blinded, placebo controlled study, the experimental procedure was performed in the operating room after completion of surgery. The patient was positioned in the supine position and sedated with sevoflurane at an end-tidal concentration of 1%. All patients had sinus rhythm and were subjected to atrial pacing by external pacemaker wires to establish a constant heart rate, 5-10 % over baseline, during the entire experimental procedure. Two baseline measurements of hemodynamic and echocardiographic data were obtained and immediately
followed by infusion of placebo or levosimendan (0.05 mg/mL) at two infusion rates: 0.1 μg/kg/min (Dose 1) and 0.2 μg/kg/min (Dose 2) after initial loading doses of 12 μg/kg. The loading doses of levosimendan were given over 10 minutes, followed by a continuous intravenous infusion for 20 minutes. The placebo group received equivalent volumes of isotonic saline as initial loading doses followed by a continuous infusion of isotonic saline at rates equal to that of the study group. A nurse prepared the study drugs and the investigators were blinded to the treatment (levosimendan/placebo) the patient was to receive. MAP was kept constant by infusion of a vasopressor (phenylephrine) and CVP was kept constant by infusion of hetastarch (Voluven, Fresenius Kabi, Bad Homburg, Germany). Measurements were performed at the end of each 30-minute treatment period during brief periods of apnea. One investigator obtained echocardiographic data while another performed hemodynamic measurements from the pulmonary artery catheter.

Statistics

The statistical methods used were analysis of variance for repeated measures (ANOVA), Student’s t-test, Fisher’s exact test, Bland & Altman and linear regression analysis.

In I the differential effects of surgery between the two groups were evaluated by a two-way ANOVA for repeated measurements. The effects of surgery within groups and differences between groups at baseline (before surgery) were analyzed by an analysis of interactions generated by a two-way hierarchical ANOVA followed by contrast analyses. In II, the differential effects of passive leg elevation between the two groups were evaluated by an analysis of interactions generated by a two-way ANOVA for repeated measurements. In IV the differential effects of the study drugs between the two groups were evaluated by a two-way ANOVA for repeated measurements.

An unpaired twotailed Student’s t-test was used to compare groups in II-IV. In IV, the Fisher’s exact test was used to compare groups, when appropriate.

In III and IV, Bland & Altman analysis was used to compare two methods with regard to repeatability and agreement. In III the repeatability of PTT measurements and the agreement between the two methods for estimation of ITBVI were assessed. In IV, the repeatability of the echocardiographic measurements (baseline 1 and baseline 2) was determined.

In III linear regression analysis was performed to relate LVEDVI and cine-SVI to qf-ITBVI. Furthermore cine-SVI was related to LVEDVI, LVSVI to RVSVI, LVEDVI to RVEDVI and RVSVI to RVEDVI. A p <0.05 was considered statistically significant. The data
are presented as mean ± standard deviation (SD) in III and mean ± standard error of the mean (SEM) in I, II and IV.
RESULTS

Systemic hemodynamics and left ventricular dimensions and filling in patients with severe emphysema before and after lung volume reduction surgery (I)

At baseline (before surgery) there were no differences between the LVRS group and the controls regarding MAP, MPAP, CVP or PCWP. However, CI, SVI, and SWI were significantly lower, whereas HR was significantly higher in the LVRS group compared with controls. See table 2. Both PVRI as well as SVRI were significantly higher in the LVRS group compared with controls at baseline. In the control group undergoing lobectomy, the surgical procedure did not affect hemodynamic variables, whereas LVRS significantly improved CI, SVI and SWI in the emphysema patients. Both PVRI and SVRI were significantly lower, whereas HR was unchanged after LVRS.

Baseline EDAI and ESAI were significantly lower in the LVRS group compared with controls, whereas the groups did not differ with respect to AEF. See table 3. Pulmonary lobectomy did not affect LV dimensions or AEF in the control group, whereas LVRS significantly increased EDAI in the emphysema patients. At baseline, the two groups did not differ with regards to LV end-diastolic stiffness. Surgery did not affect LV end-diastolic stiffness in either group (figure 15).

At baseline, the E-dec slope was significantly less pronounced and the E-dec time was significantly longer in the LVRS group compared with the controls. E-max and the E/A ratio were significantly lower in the LVRS group whereas the groups did not differ with respect to A-max at baseline. Pulmonary lobectomy affected none of these variables in the control group. LVRS significantly improved the E-dec slope and shortened the E-dec time, and increased significantly transmitral flow velocities as well as the E/A ratio (figure 16).
Table 2. Effects of LVRS or Lobectomy on Central Hemodynamic Variables.

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th></th>
<th>LVRS</th>
<th></th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop</td>
<td>Preop</td>
<td>Postop</td>
<td>p-value</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>68.3 ± 3.9</td>
<td>72.7 ± 2.9</td>
<td>71.4 ± 5.7</td>
<td>71.0 ± 3.9</td>
<td>0.47</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>22.6 ± 2.1</td>
<td>24.0 ± 1.2</td>
<td>26.0 ± 1.6</td>
<td>27.3 ± 1.6</td>
<td>0.97</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>12.0 ± 1.3</td>
<td>13.8 ± 0.6</td>
<td>14.1 ± 1.7</td>
<td>14.7 ± 2.1</td>
<td>0.56</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>11.3 ± 1.4</td>
<td>13.1 ± 0.7</td>
<td>12.2 ± 1.4</td>
<td>11.2 ± 0.9</td>
<td>0.16</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.36 ± 0.17</td>
<td>2.34 ± 0.17</td>
<td>1.86 ± 0.16</td>
<td>2.60 ± 0.18</td>
<td>0.002</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71.5 ± 4.6</td>
<td>73.3 ± 3.5</td>
<td>82.6 ± 3.9</td>
<td>86.1 ± 2.7</td>
<td>0.67</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>33.1 ± 1.34</td>
<td>31.9 ± 1.60</td>
<td>23.0 ± 2.14</td>
<td>30.8 ± 2.72</td>
<td>0.006</td>
</tr>
<tr>
<td>SWI (g*m/m²)</td>
<td>25.0 ± 2.05</td>
<td>25.8 ± 118</td>
<td>18.5 ± 2.34</td>
<td>29.2 ± 3.33</td>
<td>0.026</td>
</tr>
<tr>
<td>SVRI (dyn*s/cm²/m²)</td>
<td>1993 ± 152</td>
<td>2149 ± 211</td>
<td>2684 ± 286</td>
<td>1887 ± 153</td>
<td>0.010</td>
</tr>
<tr>
<td>PVRI (dyn*s/cm²/m²)</td>
<td>358 ± 47.5</td>
<td>347 ± 45.7</td>
<td>530 ± 39.5</td>
<td>400 ± 62.9</td>
<td>0.095</td>
</tr>
</tbody>
</table>

* = indicates p-values comparing differential effects of surgery between the two groups.
× = p<0.001 between group comparisons at baseline (Preop).
✓ = p<0.001, effects of surgery within groups. Values are presented as mean ± SEM.
Table 3. Effects of LVRS and Lobectomy on LV Dimensions and Stiffness

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th>LVRS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Postop</td>
<td>Preop</td>
</tr>
<tr>
<td>EDAI (cm²/m²)</td>
<td>6.57 ± 0.33</td>
<td>6.56 ± 0.27</td>
<td>5.62 ± 0.55</td>
</tr>
<tr>
<td>ESAI (cm²/m²)</td>
<td>3.04 ± 0.27</td>
<td>2.94 ± 0.19</td>
<td>2.77 ± 0.38</td>
</tr>
<tr>
<td>AEF</td>
<td>0.54 ± 0.03</td>
<td>0.55 ± 0.02</td>
<td>0.51 ± 0.03</td>
</tr>
<tr>
<td>LVEDS (mm Hg/cm²/m²)</td>
<td>0.56 ± 0.18</td>
<td>0.39 ± 0.18</td>
<td>0.30 ± 0.06</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SEM. *= indicates p-values comparing differential effects of surgery between the two groups. ‡ = p<0.001 between group comparisons at baseline (Preop). § = p<0.05 between group comparisons at baseline (Preop). ✓ = p<0.001, effects of surgery within groups.

Figure 15. PCWP as a function of EDA (= LV end-diastolic pressure-area curve) before and after LVRS. Preoperative: grey, postoperative: black. PCWP and EDA are measured in the supine position with and without passive leg elevation. The stiffness at any point along a given pressure-volume curve is equal to the slope of the tangent drawn to the curve at that point. Surgery did not affect end-diastolic stiffness in the emphysema group.
Figure 16. Schematic mitral Doppler flow profile before (grey) and after (black) LVRS. Preoperative E-max < A-max indicating impaired diastolic early filling. This phenomenon is partly normalized by LVRS. $V = \text{velocity, cm/s.}$

**Left ventricular performance in patients with severe emphysema (II)**

The patients participating in I were also included in II. After induction of anaesthesia, pulmonary and systemic hemodynamic and echocardiographic measurements were performed before and after volume loading (leg elevation). Volume loading was used to assess LV preload responsiveness, as the increase in SVI to a certain increase in preload ($\Delta$PCWP or $\Delta$EDAI) was calculated. Likewise, preload recruitable stroke work was calculated to obtain a load-independent index of systolic function.

Passive leg elevation induced a more pronounced increase in SVI in the emphysema group and a decrease in SVRI when compared with the control group. See table 4. The $\Delta$SVI/$\Delta$PCWP and the $\Delta$SVI/$\Delta$EDAI relationships were significantly higher in the emphysema group compared with controls. Preload-recruitable stroke work ($\Delta$SWI / $\Delta$EDAI) did not differ between the two groups (figure 17).

Baseline EDAI and ESAI were significantly lower in the emphysema group compared with controls, whereas the groups did not differ with respect to LV AEF. Passive leg elevation caused an increase in LV AEF in the emphysema group, which was not seen in the control group. EDAI increased to a similar extent in the two groups, while ESAI increased to lesser extent in the emphysema group, during passive leg elevation.
None of the patients in the emphysema group had obvious signs of RV hypertrophy and/or dilatation and in none of the patients a permanent bowing of the septum towards the LV was noted.

### Table 4. Effects of Passive Leg Elevation on Central Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Emphysema</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Leg elevation</td>
<td>Baseline</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>70.6 ± 4.0</td>
<td>81.1 ± 3.8</td>
<td>71.4 ± 5.7</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>21.7 ± 2.3</td>
<td>25.3 ± 2.1</td>
<td>26.0 ± 1.6</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>11.8 ± 1.3</td>
<td>15.4 ± 1.4</td>
<td>14.1 ± 1.7</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>9.7 ± 1.6</td>
<td>12.1 ± 1.7</td>
<td>12.2 ± 1.4</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.5 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>1.9 ± 0.12</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73.1 ± 4.6</td>
<td>73.3 ± 4.5</td>
<td>82.6 ± 3.9</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>34.0 ± 1.0</td>
<td>36.6±1.3</td>
<td>23.0 ± 2.1</td>
</tr>
<tr>
<td>SWI (g*m/m²)</td>
<td>27.1 ± 1.95</td>
<td>32.5 ± 1.89</td>
<td>17.8 ± 2.2</td>
</tr>
<tr>
<td>SVRI (dyn*s/cm³/m²)</td>
<td>2013 ± 155</td>
<td>2128 ± 161</td>
<td>2684 ± 286</td>
</tr>
<tr>
<td>PVRI (dyn*s/cm³/m²)</td>
<td>325 ± 45</td>
<td>295 ± 43</td>
<td>530 ± 40</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SEM. * indicates p-values comparing differential effects of leg elevation between groups.  † =p < 0.001 between group comparisons at baseline.
Figure 17. Preload recruitable stroke work ($\Delta \text{SWI} / \Delta \text{EDAI}$), which is supposed to be a relatively load-independent variable sensitive to changes in alterations in inotropic state, was not significantly different between the two groups, indicating no significant differences in contractile state between the two groups.

**Intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema (III)**

The finding in the previous studies that LV function is compromised in patients with severe emphysema due to small end-diastolic dimensions spurred the third study in which intrathoracic blood volume and cardiac dimensions were measured using MRI.

$L\text{VEDVI}$, $L\text{SVSI}$, $R\text{VEDVI}$, $R\text{SVSI}$, $L\text{VEF}$ and $R\text{VEF}$ were significantly lower in the emphysema group. In contrast, $L\text{VESVI}$, $R\text{VESVI}$ (table 5), LV wall mass index did not differ between the two groups. RV wall thickness was $<3$ mm in all patients. $qf$-$\text{ITBVI}$ and NONMEM-$\text{ITBVI}$ were both significantly lower in patients with emphysema compared with healthy volunteers (figure 18). The relationships between LVEDVI and cine-SVI (figure 19) and between RVEDVI and RVSVI were highly correlated. Both LVEDVI and cine-SVI correlated closely to $qf$-$\text{ITBVI}$ (figure 20). There was a close correlation between RVSVI and LSVSI and between RVEDVI and LVEDVI (figure 21). Septal curvature did not differ between the two groups.

SVI and CI were significantly lower in the emphysema group. HR and SVRI were significantly higher in the emphysema group.
There was no difference in mean PTT between the two groups. There was a good repeatability for estimation of PTT. The NONMEM calculated ITBVI (NONMEM-ITBVI) showed good agreement with qf-ITBVI.

Table 5. Cardiac Function with Cine Image Acquisition.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Emphysema</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (mL/m²)</td>
<td>66 ±12</td>
<td>84 ± 15</td>
<td>0.0022</td>
</tr>
<tr>
<td>ESVI (mL/m²)</td>
<td>34 ± 9</td>
<td>34 ± 11</td>
<td>0.9550</td>
</tr>
<tr>
<td>EF (%)</td>
<td>48 ± 7</td>
<td>60 ± 8</td>
<td>0.0006</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>31 ± 6</td>
<td>50 ± 7</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI (mL/m²)</td>
<td>73 ±12</td>
<td>91 ± 15</td>
<td>0.0042</td>
</tr>
<tr>
<td>ESVI (mL/m²)</td>
<td>41 ± 11</td>
<td>42 ± 11</td>
<td>0.7463</td>
</tr>
<tr>
<td>EF (%)</td>
<td>44 ± 9</td>
<td>54 ± 7</td>
<td>0.0067</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>32 ± 7</td>
<td>48 ± 8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Septal curvature (cm⁻¹)</td>
<td>0.33 ± 0.05</td>
<td>0.37 ± 0.06</td>
<td>0.177</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD*
Figure 18. Individual data on calculated intrathoracic blood volume index (ITBVI) by MR phase velocity mapping for quantitative aortic flow (qf) measurements (qf-ITBVI) in the control and emphysema groups. Statistical bars show mean value (diamond), SD and SEM. Filled circles represent emphysema patients and open circles represent controls.

Figure 19. Linear regression showing the close correlation between LVEDVI and LVSVI (cine-SVI). Filled circles represent emphysema patients and open circles represent controls.
Figure 20. Linear regression showing the close correlation between qf-ITBVI and LVEDVI. Filled circles represent emphysema patients and open circles represent controls.

Figure 21. There was a close correlation between RVEDVI and LVEDVI. Filled circles represent emphysema patients, and open circles represent control subjects.
Effects of levosimendan on systolic and diastolic function in patients with left ventricular hypertrophy and normal ejection fraction (IV)

To establish whether levosimendan exhibits lusitropic effects, patients with diastolic dysfunction were examined with central hemodynamics (pulmonary artery thermodilution catheter) and transoesophageal two-dimensional Doppler echocardiography, during controlled and maintained preload, afterload and heart rate conditions.

The patients in the levosimendan group consisted of 4 females and 8 males, whereas 6 females and 5 males were included in the placebo group. There were no differences between the groups regarding demographic variables (gender, age, height, weight and BSA), preoperative echocardiographic variables (aortic valve area, aortic valve gradient and LV ejection fraction) clinical presentation, preoperative medications, surgical variables (valve type, valve size, concomitant coronary artery bypass grafting), duration of CPB time or aortic cross clamp time. After separation from CPB, TEE revealed normal prosthetic valve function and no evidence of abnormal flow velocities or LV outflow obstruction for all patients, with or without the administration of levosimendan.

Baseline hemodynamic data were similar for both groups. In the levosimendan group, a dose-dependent significant increase in MPAP, CI, SVI and SWI and a dose-dependent significant decrease in SVRI were observed compared with placebo, whereas there were no significant differences in SAP, DAP, PCWP, CVP, or PVRI between the two groups (figure 22).

Baseline EDAI, ESAI and AEF were similar for both groups. There was a trend for an increase in AEF in the levosimendan group compared with placebo (p = 0.058), whereas there were no differences in EDAI or ESAI between the two groups.

At baseline, E-dec slope, E-dec time, E-max, A-max, E/A ratio, IVRT and IVCT were similar for both groups. In the levosimendan group, dose-dependent increases in E-max, A-max and E-dec slope were noted, whereas there was a trend for a decrease in E-dec time (p = 0.06) compared with placebo. There was no difference in E/A between groups (figure 23). IVRT decreased dose dependently with levosimendan compared with placebo (figure 24). There was a trend (p = 0.015) for a decrease in IVCT with levosimendan.

The infusion rates of phenylephrine at baseline and at the two infusion rates were 0.052 ± 0.021, 0.26 ± 0.081 and 0.26 ± 0.076 μg/kg/min respectively for the levosimendan group. Corresponding infusion rates for the placebo group were 0.017 ± 0.012, 0.101 ± 0.082 and 0.112 ± 0.091 μg/kg/min, respectively.
There was good reproducibility for repeated estimation of EDAI, ESAI, AEF, E-dec slope, E-dec time, E-max, A-max, E/A and IVRT.

![SVI Graph](image1)

**Figure 22.** The effect of levosimendan versus placebo on SVI. Filled circles represent levosimendan group and open circles represent placebo group. Data are represented as mean ± SEM.

![Flow Profile Graph](image2)

**Figure 23.** Schematic mitral Doppler flow profile before (grey) and after (black) levosimendan. V = velocity, cm/s.
Figure 24. The effect of levosimendan versus placebo on IVRT. Filled circles represent levosimendan group and open circles represent placebo group. Data are represented as mean ± SEM.
DISCUSSION

Methodological considerations

Assessment of cardiac preload

LV preload is routinely assessed by the CVP or the PCWP. However, it is increasingly evident that CVP and PCWP are poor predictors of LV preload particularly in patients ventilated with high intrathoracic pressures \(^{23, 35, 72}\). This also seems to be likely for patients with severe emphysema with high intrinsic PEEP, because CVP and PCWP in patients with emphysema do not differ from that seen in patients undergoing lobectomy, as shown in I and II and by Haniuda et al. \(^{51}\), despite the lower LV end-diastolic dimension in the former group.

Reviewing the literature regarding preload surrogates, Cheatham et al. \(^{23}\) found that CVP and PCWP were not reliable predictors of preload status in patients in treatment of acute respiratory failure requiring PEEP. The application of PEEP at any level >5 cm H\(_2\)O increased CVP and PCWP by an amount that was completely unpredictable. Luecke et al. \(^{72}\) assessed the impact of high intrathoracic pressures on LV volume and function in sheep using computed tomography. They also tested the hypothesis that RVEDV and ITBV represent cardiac preload and are superior to CVP and PCWP. The validity of these parameters was tested by means of correlation with LVEDV, the “true cardiac preload” \(^{72}\). The authors concluded that unlike cardiac filling pressures, RVEDV and ITBV provide valid estimates of cardiac preload even at high intrathoracic pressures. Wiesenack et al. \(^{140}\) measured ITBV using PiCCO (Photonic integrated Circuits using Crystal Optics), which estimate ITBV from intermittent CO assessment by transpulmonary thermodilution and global end-diastolic volume (GEDV) by transpulmonary single indicator dilution. They found that increased cardiac preload was more reliably reflected in ITBV than in CVP or PCWP.

LVEDA assessed by TEE as a predictor of preload has been studied by Cheung et al. \(^{24}\). They found that TEE was highly sensitive for detecting changes in LV function and preload following controlled decreases in the blood volume. The changes in LVEDA accurately reflected the decrement in conventional hemodynamic determinants of LV preload (PCWP) and PA pressures \(^{97}\). Swenson et al. \(^{122}\) used LVEDA and FAC to guide optimal LV filling in patients with well preserved LV function with and without LV hypertrophy. In patients with normal wall thickness, LVEDA and FAC corresponded to a range of filling pressures (PCWP 13–19 mm Hg) conventionally targeted to maximize LV performance. In patients with LV hypertrophy, PCWP ranged from 20 to 25 mm Hg at the stage in volume
resuscitation when LVEDA and FAC showed appropriate preload for optimal ventricular performance. These patients were managed correctly with supranormal PCWP but the identification of hypertrophy would still have to be made by TEE.

End-diastolic area versus end-diastolic volume: In I, II and IV, LVEDA was used as a substitute for LVEDV. Clements et al.²⁵ have shown that EDA closely reflects EDV, employing TEE and radionuclide angiography respectively. Furthermore, in the present studies focus was not on absolute volume measurements, but rather on the relative change in LV end-diastolic dimension.

Assessment of transmural filling pressure: One limitation of I and II was that the intrathoracic pressure was not assessed and therefore true LV transmural filling pressures could not be established. To overcome this problem, LV preload was assessed by LVEDA. Because of the low elastic recoil of the lungs in pulmonary emphysema, and less negative intrathoracic pressure¹²⁹,¹³⁰,¹³⁵, transmural LV pressures were probably lower in the emphysema group compared with controls.

Magnetic resonance imaging

Peak transit time versus mean transit time: In III, PTT was measured by subtracting the times of peak AO and PA signal intensities¹¹², rather than by subtracting the first moment of the curves to achieve mean transit time, which, by definition, is used for calculation of ITBV¹⁴⁶. However, it has been shown that PTT is an excellent approximate of mean transit time, PTT being less than 4% higher than mean transit time¹²⁰. The utility of the PTT approach for estimation of ITBV is supported by the NONMEM modeling analysis, which gave identical results.

Motion artifacts in magnetic resonance imaging: An impediment to MRI of the chest is artifacts caused by respiratory motion. To compensate for this, breath-holding was implemented. Many patients, however, have difficulty sustaining adequate breath-hold, and furthermore, a sustained breath-hold may cause a cranial diaphragmatic drift, (which can be substantial ~ 1 cm) resulting in registration errors¹²⁸. Thus, in III, patients in the emphysema group were less likely to hold their breath during expiration for 25-30 seconds. In spite of this, contrast-enhanced time-resolved two-dimensional MR angiography provided PTT measurements with a high repeatability. In addition, in our control group, PTT was 7.5 ± 1.6 seconds, which is comparable to 7.2 ± 1.2 seconds as shown by Shors et al. in their control subjects¹¹².

Papillary muscles and the calculation of ventricular volumes: The issue whether trabeculation and papillary muscles should be included in the calculation of ventricular volume or mass has been a matter of controversy³⁶,¹⁰⁷,¹⁰⁸. The ventricular trabeculation and the papillary
muscles were included in the volume analysis in III, because this technique is less time consuming.

**Magnetic resonance imaging versus echocardiography:** Cine MRI is well validated for quantifying the volumes and mass of the ventricles and it has become the clinical gold standard against which other techniques are assessed, because of its three-dimensional nature, which is not reliant on geometric assumptions. Accuracy and reproducibility is excellent, which has lead to a significant reduction in sample sizes for drug trials with heart failure. The accuracy of cine MRI for measurement of global LV volume has been achieved by comparing LV stroke volume with the stroke volume of the right ventricle or with aortic flow measured using velocity mapping, and showing their equivalence in normal human subjects.

Transthoracic echocardiography, on the other hand, is the most frequently used technique for assessment of LV function. It is readily available and non-invasive. LV volumes and mass can be measured using two-dimensional or M-mode echocardiography but reproducibility is lower than that for cine MRI. Furthermore echocardiography relies on geometrical assumptions and in patients with COPD, it can be difficult to obtain an adequate acoustic window because of the hyperinflated lungs, resulting in poor image quality.

**Levosimendan and cardiac function**

*Two-dimensional versus three-dimensional measure of LV AEF:* Levosimendan exerted a positive inotropic effect as reflected by the 25% increase in SVI. There was a trend for an increase in LV AEF in the levosimendan group compared with placebo by 12% (p = 0.0575). If we had used a volumetric method to measure LV EF, the increase in LV EF with levosimendan would probably have been more obvious.

*Estimation of isovolumic contraction time:* IVCT is defined as the time period between mitral valve closure and the aortic valve opening click. In IV, the time interval between the R wave and the aortic valve opening was used as a surrogate for IVCT, because this time period is more readily obtained by TEE.

*Phenylephrine and myocardial relaxation:* Levosimendan has vasodilatory effects and not surprisingly the study group required a higher dose of the pure α-agonist phenylephrine than the placebo group. To our knowledge, there are no data suggesting that phenylephrine has β-adrenergic properties, which could improve myocardial relaxation, or that myocardial α-receptor stimulation may improve myocardial relaxation. Therefore, we consider it unlikely, that the improved LV relaxation and diastolic filling seen in the levosimendan group was caused by the higher dose of phenylephrine.
Reduced ventricular end-diastolic dimensions in severe emphysema

In patients with severe emphysema it was shown that end-diastolic dimensions of both RV and LV are reduced compared with those of control patients, indicating that emphysema patients have a problem with cardiac filling (preload). Thus, LVEDAI was decreased in these patients subjected to anaesthesia and positive pressure ventilation, as assessed by TEE. The mitral Doppler findings from these patients, the decreased E-max, E/A ratio and E-dec slope and the increase in E-dec time were also suggestive of a low preload in emphysema patients.

Furthermore, MRI investigations revealed low LV and RV end-diastolic volumes in spontaneously breathing patients with severe emphysema compared with healthy controls. The lower EDAI in emphysema patients was associated with apparently normal PCWP compared with controls. However, PCWP estimates intracavitary left atrial pressure and LV end-diastolic pressure whereas the true LV transmural pressures were not assessed.

Impaired left ventricular performance in severe emphysema

Cardiac performance was compromised in patients with severe pulmonary emphysema, as demonstrated by a lower SVI, SWI and CI when compared with controls matched for gender, age and BSA. LV systolic function, as judged by the LV AEF did not appear to be different from the control group and impaired contractility probably does not cause the lower SVI and SWI in the LVRS group. Patients with normal contractility are not particularly sensitive to changes in LV outflow impedance and therefore the higher SVRI in the emphysema patients (33%) is probably not the main mechanism behind the lower SVI and SWI in these patients. A lower EDAI in combination with an apparently normal PCWP would suggest an increased LVEDS in the emphysema patients, in turn caused by external compression (pulmonary tamponade) from the hyperinflated lungs. However, LVEDS did not differ significantly between the two groups.

The finding in II that a certain increase in LV preload (PCWP or EDAI) caused a more pronounced increase in SVI and LV AEF is indirect evidence that the LV of emphysema patients seems to be hypovolemic in diastole. This indicates that the LV operates on a steeper portion of the (normal) Frank-Starling relationship in these patients and thus has a less than optimal diastolic stretch of the myocardial sarcomeres at baseline (figure 25). Furthermore, because the ejection fraction is preload dependent, the lower LV and RV EF in the emphysema patients in III, could probably be attributed to low end-diastolic volumes.
Figure 25. The relationship between EDV and SV. Patient with emphysema (A) operates on a steeper portion of the normal Frank-Starling relationship compared with a healthy subject (B).

Alternatively, the vigorous hemodynamic response to this standardised increase in preload in emphysema patients could be a sign of higher inotropic state of their LV, operating on leftward-shifted and steeper LV function curves. However, the relationship between stroke work (SWI) and LV end-diastolic dimensions (EDAI), the so-called preload recruitable stroke work, which is a relatively load-independent variable, sensitive to changes in alterations in inotropic state\(^{43}\), was not significantly different between the two groups, indicating no significant differences in LV contractile state between the two groups. This is further supported by the fact that baseline LV AEF did not differ significantly between the two groups in I. If anything, the two indices of LV systolic performance (PRSW and LV AEF) were slightly lower in the emphysema group. As a formal power analysis was not performed prior to the study, we cannot rule out the possibility that LV systolic function is slightly depressed in patients with emphysema. If so, one would have expected that the LV of the emphysema patients operates on a more flat LV function during a volume challenge and not a steeper one, as suggested by the data from II.
Why are the ventricular end-diastolic dimensions decreased in emphysema?

The lower RV and LV end-diastolic dimensions in patients with emphysema could be caused by external compression (pulmonary tamponade) from the hyperinflated lungs increasing end-diastolic stiffness. In I, however, it was shown that the LV end-diastolic pressure-area relationship is not different from that seen in non-emphysematous patients, indicating that the hyperinflated lungs do not increase LV end-diastolic stiffness in patients with severe emphysema (I).

Another mechanism for the impaired filling of the LV in patients with emphysema could be LV diastolic dysfunction caused by LV hypertrophy. However, LV wall mass is not increased in these patients with emphysema, as shown previously 136, 137 and in III. A third explanation for the low LVEDV in these patients could be a leftward shift of the interventricular septum, causing an underfilling of the LV, as has been shown in patients with primary pulmonary hypertension 40 and also in some patients with emphysema 137. This mechanism is less likely since the configuration of the interventricular septum did not differ between the groups (III). Furthermore, none of the patients in the present studies had severe pulmonary hypertension (SPAP > 55 mmHg), as evaluated by Doppler-echocardiography and none had RV hypertrophy.

In III a close relationship between ITBVI and LVEDVI and between LVEDVI and SVI was demonstrated, which strongly suggests that a low preload, caused by intrathoracic hypovolemia, contributed to the impaired LV performance seen in patients with severe emphysema. Data from III confirm the results from I: The anesthetized patients with severe emphysema demonstrated a lower LVEDAI and mitral Doppler flow indices of impaired LV filling when compared with anesthetized non-emphysematous patients. To our knowledge, a decreased ITBV compromising cardiac performance has not previously been demonstrated in patients with severe emphysema.

Why is intrathoracic blood volume decreased in severe emphysema?

Intrathoracic hypovolemia in patients with severe emphysema could be explained by the well-known dynamic hyperinflation and hence the generation of PEEP, seen in these patients 74, 129-131. Tschernko et al. have shown that minimal PEEP, levels range between 5-7.5 cm H2O in patients with severe emphysema 129, 130. In the present studies we did not measure PEEP, or intrathoracic pressure, which is a major limitation of the studies. However, ‘our patients’
characteristics and lung function data were identical to those described by Tschernko et al. Therefore, it would seem reasonable that PEEPi levels were high also in the present studies.

In patients with normal lung function, positive pressure-respiration with PEEP depletes the intrathoracic vascular bed and the heart, decreasing both pulmonary vascular and RV and LV end-diastolic volumes. Furthermore, PEEP induces changes in the mitral-Doppler derived indices indicative of impaired LV filling. One could speculate that the PEEPi-induced decrease in ITBV is caused by a decreased capacitance of the pulmonary vascular bed in emphysema due to the hyperinflated lungs, which may redistribute blood to the periphery.

**Lung volume reduction surgery improves cardiac preload in severe emphysema**

The suggestion that high PEEPi levels are of importance to explain the decreased intrathoracic blood volume in severe emphysema is supported by our findings that lung volume reduction surgery improves LV performance in emphysematous patients. This improvement was accompanied by an increase in LV end-diastolic area index and mitral Doppler flow indices of improved LV filling. Lung volume reduction surgery is associated with a diminution of PEEPi, which thus could normalize a low ITBV, as well as low RV and LV end-diastolic blood volumes in these patients.

Likewise the improvement in LV diastolic filling pattern, seen after LVRS, does not match a decrease in LV outflow impedance even though both PVRI and SVRI decrease after LVRS. Houltz et al. have previously shown that a selective dilation of systemic and pulmonary resistance vessels, unloading RV and LV, usually increases both E-max as well as A-max with no change in the E/A ratio, and no change in E-dec time. In I, however, particularly E-max and E/A ratio increased and E-dec time decreased. There was a comparably less pronounced increase in A-max. These LVRS-induced changes of the mitral Doppler flow pattern are expected when LV preload is increased.

A reduction in ITBV in severe emphysema could also be explained by a diminution of the pulmonary vascular bed and a decreased pulmonary blood volume, as a consequence of the disease, since all patients had severe emphysema. On the other hand, lung volume reduction surgery, which causes a further pruning of the pulmonary vascular tree, improved LV performance in emphysematous patients. This improvement was accompanied by an increase in LVEDAI and mitral Doppler flow indices of improved LV filling.
Cardiopulmonary transit time in severe emphysema

The cardiopulmonary transit time of an indicator is proportional to its volume of distribution (ITBV) and inversely proportional to flow (CO), according to fundamental principles of tracer kinetics. In III, PTT was measured by time-resolved MR angiography. It has previously been shown that PTT is significantly higher in patients with LV systolic dysfunction compared with healthy controls. In heart failure, PTT correlated positively with LV end-diastolic volumes. In patients with severe emphysema, PTT was not significantly different from controls, because the low CO, which would have increased PTT, was accompanied by a decreased ITBV, which will decrease PTT. In other words, the time required for oxygen uptake is maintained in emphysema patients, despite the low CO, because of the low ITBV.

Increased sympathetic activity in severe emphysema

In patients with severe emphysema, the high SVR and HR, might be the adaptive cardiovascular sympathetic reflex response to low LVEDV:s and stroke volumes as shown in the present thesis and by Vonk Noordegraaf et al. Lower stroke volume and LVEDV would unload arterial baroreceptors and cardiopulmonary volume receptors, respectively, inducing a reflex increase in sympathetic nerve activity, which would explain the increase in plasma catecholamines, SVR and HR seen in these patients.

The effects of levosimendan on left ventricular relaxation and early filling in diastolic dysfunction

In IV, the effects of incremental infusion rates of levosimendan on LV relaxation and systolic performance were studied immediately after aortic valve replacement for aortic stenosis during controlled and maintained preload, afterload and heart rate conditions. The main findings were that the beneficial effect of levosimendan on systolic performance was accompanied by an improvement in LV relaxation; that is, levosimendan has a positive lusitropic effect in patients with LV hypertrophy.

In light of the impaired relaxation seen in patients with LV hypertrophy, one would have expected that an enhanced Ca$^{2+}$ sensitivity might have negative effects because increased sensitivity to Ca$^{2+}$ would further hinder relaxation of the heart, worsening diastolic dysfunction. Indeed, it has been shown that Ca$^{2+}$ sensitizers prolong relaxation time and impair diastolic function. Levosimendan, on the other hand, does not prolong relaxation time. Unlike other
Ca\textsuperscript{2+} sensitizers, levosimendan acts through direct binding with troponin-C, selectively increasing the affinity of troponin-C for Ca\textsuperscript{2+} in a concentration-dependent manner\textsuperscript{48}. It thus binds to troponin-C at high systolic intracellular Ca\textsuperscript{2+} concentration and detaches from it at low diastolic concentration. An absence of Ca\textsuperscript{2+} sensitization under low prevailing Ca\textsuperscript{2+} concentrations during diastole would be of critical importance to prevent a worsening of heart failure. The mechanism responsible for the improvement of diastolic function, previously described in experimental in vitro studies\textsuperscript{50,58}, and demonstrated in the present study, is less understood. It has been shown that levosimendan also exerts a selective inhibition of PDE-III activity, particularly in human myocytes\textsuperscript{5,149}, which could explain the positive lusitropic effect, especially at higher concentrations\textsuperscript{53}.

**Increased contractility and intraventricular restoring forces**

One could argue that the improved LV early filling seen with levosimendan could be caused by the generation of LV intraventricular restoring forces resulting from the levosimendan-induced increase in inotropy. It has been shown in animals with structurally normal hearts, that when the LV contracts, the chamber may be compressed, generating restoring forces during systole, which allows filling to occur at lower than normal pressures\textsuperscript{67}. Their magnitude is inversely related to the end-systolic volume and occurs at low LV end-diastolic pressures (≈5 mm Hg)\textsuperscript{67}. We cannot completely rule out the possibility that the levosimendan-induced increase in LV filling is caused by the generation of restoring forces, particularly because stroke volume and LV AEF increased with levosimendan. However, we consider this mechanism less likely because LV filling pressures (PCWP) were within the range of 12-15 mm Hg in both groups in the present study and because neither PCWP nor ESAI differed significantly between groups.

**Determinants of left ventricular relaxation**

LV relaxation, an important element of diastolic function, is an energy-dependent process, involving the removal of Ca\textsuperscript{2+} from troponin-C, followed by the dissociation of actin and myosin cross bridges, thus allowing the myofibrils to relax and to return to their original end-diastolic length\textsuperscript{90}. LV relaxation is classically evaluated by the exponential time constant of isovolumic relaxation, tau, requiring cardiac catheterisation to measure LV pressure. IVRT, a commonly used non-invasive variable of LV relaxation\textsuperscript{68} is regarded as a reflection of tau. Thus, a direct correlation between IVRT and tau has been described\textsuperscript{82,84,145}. IVRT, however,
is affected by both aortic \(^{68}\) and left atrial pressures \(^{82}\). In an experimental study, Thomas et al. found that IVRT has a predictable quantitative relationship to \(\tau\) and to left atrial and aortic pressures \(^{126}\). IVRT was directly related to \(\tau\) and aortic pressure and inversely related to left atrial pressure.

In the present study, our aim was to study the potential direct effects of levosimendan on LV early relaxation, assessed by changes in IVRT. Therefore aortic and left atrial pressures were maintained at a constant level during the experimental procedure by colloid and vasopressor infusions. The evolution of arterial pressure and left atrial pressure was not significantly different between the two groups, suggesting that the 23% reduction in IVRT by the highest dose of levosimendan was caused by a more rapid isovolumic relaxation. Thus, in addition to the positive inotropic effect, levosimendan exerts a positive lusitropic effect in patients with LV hypertrophy and maintained systolic function.

IVRT is defined as the time interval between aortic valve closure (end-systole) and mitral valve opening. One limitation of the present study was that aortic/LV end-systolic pressure was not measured. Instead, mean aortic pressure was used as a surrogate for LV end-systolic pressure and controlled by phenylephrine infusion. We therefore cannot completely exclude the possibility that LV end-systolic pressure might have been decreased by levosimendan, which to some extent could have contributed to the fall in IVRT.

Aortic stenosis and diastolic dysfunction

Diastolic dysfunction with impaired LV relaxation and decreased LV chamber compliance is commonly seen in patients with severe aortic stenosis \(^{116}\). In addition, the ischemia-reperfusion injury after cardiac surgery and CPB might have further impaired diastolic function in the present study. Postoperatively and before drug administration, the transmitral blood flow velocity profile, showed a ‘pseudo-normalized pattern’, with a E/A ratio > 1, normal to moderately elevated E-dec time and IVRT \(^{41,85}\). This combined with higher-than-normal filling pressures and LV concentric hypertrophy with reduced LV end-diastolic dimensions \(^{65,118}\), indicates that a moderate stage of LV diastolic dysfunction with a decreased LV chamber compliance was present in our patients.

Levosimendan, in contrast to placebo, shortened IVRT, decreased E-dec time and E-dec slope (steeper), most likely through a more rapid and pronounced LV relaxation, causing a shorter time for equilibration of left atrial and LV pressures and improved early filling of the LV. Filling of the LV in late diastole caused by atrial contraction (A-max) was also increased, which could be explained by a levosimendan-induced improved contractility of
the left atrium. Despite the improved LV relaxation caused by levosimendan with improved LV filling, this positive lusitropic effect was not translated into an improvement in the LV end-diastolic pressure-area relationship. The LV end-diastolic area index was not increased with levosimendan compared with placebo at maintained LV filling pressures.

**Inotropic agents and diastolic dysfunction in aortic stenosis**

In a recent randomized controlled trial, Maslow et al. assessed the effects of epinephrine and milrinone on biventricular systolic and diastolic function after AVR for AS. According to their Doppler findings, both epinephrine and milrinone improved right and left ventricular systolic function whereas neither of the inotropic agents differed from placebo with respect to IVRT or early filling of the LV. The interpretation of their findings could be that milrinone and epinephrine have less obvious lusitropic effects in this situation, in contrast to the effects of levosimendan described in IV, or that the potential beneficial effects of the epinephrine or milrinone on Doppler echocardiographic variables of LV diastolic function were obscured by the fact that no measures were taken to control heart rate or loading conditions in their study.

The use of inotropes or vasodilators to treat patients with AS after AVR is controversial, because it may induce LV outflow (LVOT) obstruction. With septal hypertrophy, a reduction in the diameter of the LVOT leads to an increased velocity of blood and turbulent flow during systole. This creates a Venturi effect, which may entrain the anterior mitral leaflet. The end result is a LVOT obstruction and a mitral coaptation defect.

Maslow et al. evaluated the risk of LV outflow obstruction caused by epinephrine and milrinone stimulation and found no evidence of abnormal flow velocity profiles or LV outflow obstruction in any of the patients. Their findings were confirmed by data from the present study showing no signs of levosimendan-induced LV outflow obstruction.
CONCLUSIONS

In patients with severe emphysema, cardiac performance is impaired as reflected in subnormal values of stroke volume and cardiac output.

This impaired cardiac performance is caused by inadequate diastolic filling (decreased preload) of the right and left ventricle. Thus, the left ventricle is hypovolemic and operates on a steeper portion of the normal left ventricular function curve.

The decreased biventricular preload is explained by a low intrathoracic blood volume most likely caused by the hyperinflated lungs (high intrinsic PEEP).

In patients with severe emphysema, lung volume reduction surgery, a procedure known to alleviate intrinsic PEEP, improves left ventricular end-diastolic dimensions and filling, which at least partly could explain the improved exercise tolerance.

Levosimendan, in addition to its inotropic effects, exerts a direct positive lusitropic effect in patients with left ventricular hypertrophy and diastolic dysfunction as it shortens isovolumic relaxation time and improves early left ventricular filling.
ACKNOWLEDGEMENT

Numerous people from across the world have contributed with their knowledge and friendship in the completion of this thesis. It has been a great experience to work with people from different walks of academic life, and I appreciate the open-mindedness with which they have embraced my project.

With great didactic skills, my tutor Professor Sven-Erik Ricksten introduced me to the research process and transformed theoretical cardiac physiology into a practical experience.

Professors Björn Biber and Hengo Haljamäe, Heads of Department of Anaesthesiology and Intensive Care Medicine, The Sahlgrenska Academy provided me the opportunity to perform the studies.

Klaus Kirnø, MD, PhD. Former Head of Department of Cardiothoracic Anaesthesia and Intensive Care, Sahlgrenska University Hospital for his support and positive attitude towards research in the clinical arena.

Erik Houltz, MD, PhD. For teaching me transoesophageal echocardiography and helping me find my way in the statistics.

Markus Müller, MD, PhD. For sharing his extensive knowledge of cardiac MRI and adding a Swiss twist to the analysis of the MRI data.

Jacqueline Nel, Queen of the MRI tribe, for performing all the MRI examinations with professionalism and a great sense of humour, and for extending her friendship beyond the dark rooms of MRI to the colourful, vibrant and wine-flowing country of her native South Africa.

Richard Upton, B Sc, PhD, for introducing me to a mathematical approach to pharmacokinetic modelling and reducing my dread for equations.

Odd Bech-Hanssen, MD, PhD, for sharing his extensive knowledge in echocardiography, and for his great enthusiasm “in getting it right”.

Anders Thylén, MD, PhD and Katarina Karlsson, Transplantation Coordinator, for generously identifying and recruiting patients for the MRI study.

Professor Guy Ludbrook, for inviting me to work at The Royal Adelaide Hospital, for introducing us to “the Australian lifestyle” and for valuable advice on pharmacokinetic models.

Colleagues and staff at the Departments of Cardiothoracic Anaesthesia and Intensive Care and Cardiothoracic Surgery, for assistance and support during the clinical experiments.

All the volunteers who kindly participated in the MRI study.
Staff at the Departments of Radiology, and Clinical Physiology.

Inge and Ole Eshjerg Jørgensen, my parents, and Mette, my sister, for love and support during all times. Bent Sørensen, my brother in law, for enthusiastically helping me design the front cover.

Søren Søndergaard, MD, PhD. My husband and best friend. For love and support during times of joy as well as times of trouble. For generously and ardently discussing all matters between heaven and earth, and for sharing his extensive knowledge in science, computers, mathematics and linguistics with me. For his readiness to embark on new adventures to satisfy his family’s endless curiosity about the world outside home.

Anna and Niels, our wonderful children, the joy of my life.

These studies were supported by the LUA/ALF-project at Göteborg University, the Swedish Research Council, and the Göteborg Medical Society.
REFERENCES


65. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, and Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440-1463, 2005.


Ochi H, Ikuma I, Toda H, Shimada T, Morioka S, and Moriyama K. Isovolumic relaxation period as an index of left ventricular relaxation under different afterload conditions--comparison with the time constant of left ventricular pressure decay in the dog. *Jpn Circ J* 53: 1521-1529, 1989.


91. **Pagel PS, Kampine JP, Schmeling WT, and Wartlter DC.** Comparison of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized, chronically instrumented dog. *Anesthesiology* 73: 278-290, 1990.


71


