PET in Heart Failure - Methods and Applications

BY

JENS SÖRENSEN
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Abstract

Positron Emission Tomography (PET) permits regional myocardial perfusion, fibrosis and oxidative metabolism to be non-invasively quantified with radioactive tracers such as [¹³O]-water and [¹¹C]-acetate. PET is an established research tool in congestive heart failure (CHF), a major cause of morbidity and mortality. However, as CHF is a syndrome that eventually affects all aspects of cardiac and systemic hemodynamic function, more clinically relevant information from a single PET scan is desirable. The aim of this thesis therefore was to develop and implement some new concepts in cardiac PET.

A new method for the measurement of cardiac output with any tracer was validated in animal experiments and CHF patients. The early pulmonary retention of [¹¹C]-acetate was inversely related to left ventricular (LV) function in animals and was directly proportional to lung water content and severity of LV diastolic dysfunction in patients.

Eight patients with acute myocardial infarction were followed with serial PET from 3 hours to 3 weeks after thrombolytic treatment. PET revealed that myocardial perfusion and the extraction and utilization of fuel substrates all decreased closer to the infarct centre. The rate of oxygen utilization within the infarct at 3 h predicted degree of myocardial fibrosis, pulmonary oedema and tissue viability at 3 weeks.

Seventeen patients with CHF due to chronic ischemic cardiomyopathy and severely reduced LV function were evaluated with [¹¹C]-acetate PET before and after coronary artery bypass surgery. There was a dramatic improvement in physical performance and symptoms, which was not correlated to the standard LV ejection indices. PET revealed that functional improvement was associated with improved LV loading conditions, reversed remodeling and homogenization of oxidative metabolism rather than increased output.

Keywords: congestive heart failure, myocardial ischemia, positron emission tomography, left ventricular dysfunction, tracer kinetic models

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urn:nbn:se:uu:diva-4654 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-4654)
In memory of my father Christian Sørensen, who died from a heart attack when I was fifteen.

I would probably not have been so eager to contribute in this field without you.
List of Papers

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


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### Abbreviations

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<th>Definition</th>
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<tr>
<td>AC-PET</td>
<td>[1-11C]-acetate PET</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery Bypass Grafting</td>
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<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
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<tr>
<td>CO</td>
<td>Cardiac Output</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>18F-Fluorodeoxyglucose PET</td>
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<tr>
<td>Lung&lt;sub&gt;AC-SUV&lt;/sub&gt;</td>
<td>Early regional pulmonary retention of [1-11C]-acetate</td>
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<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVEDV</td>
<td>Left Ventricular End-Diastolic Volume</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection fraction</td>
</tr>
<tr>
<td>LVESV</td>
<td>Left Ventricular End-Systolic Volume</td>
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<tr>
<td>MBF</td>
<td>Myocardial Blood Flow</td>
</tr>
<tr>
<td>MMRO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Myocardial Metabolic Rate of Oxygen</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>PCWP</td>
<td>Pulmonary Capillary Wedge Pressure</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PTF</td>
<td>Perfusable Tissue Fraction</td>
</tr>
<tr>
<td>rLW</td>
<td>Regional Lung Water content</td>
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<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle</td>
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<tr>
<td>SV</td>
<td>Stroke Volume</td>
</tr>
<tr>
<td>WAT-PET</td>
<td>[15O]-H&lt;sub&gt;2&lt;/sub&gt;O PET</td>
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<tr>
<td>WMI</td>
<td>Work-Metabolic Index</td>
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Introduction

This thesis deals with the development of some novel concepts in positron emission tomography (PET) and their use in the study of patients with failing hearts. The methodology of PET and the diseases of the failing heart are both complex matters and the following review does not have the ambition of covering more than a few salient aspects of either.

The syndrome of heart failure

The syndrome of congestive heart failure (CHF) is a leading cause of morbidity and mortality in the industrialized world. The majority of cases occur in patients with ischemic heart disease or hypertension (75%), but the heart may also weaken when the cardiac valves are dysfunctional, in myocardial inflammation or infection and toxic degeneration of the cardiac tissue.

The prevalence of CHF in the western world is 1-2%, increasing to 10% in the elderly population. The incidence of CHF is increasing despite a reduction in deaths resulting from coronary artery disease (CAD). It is believed that the rising incidence of CHF results from better interventions in acute myocardial infarction and improved care of CHF patients and more patients are therefore alive.

In spite of improved pharmacological treatment the prognosis of CHF is still poor and five-year survival resembles that of several major malignancies.

Patients presenting with symptoms of CHF generally suffer from exertional dyspnoea and circulatory congestion. Such symptoms might occur in both cardiac and renal insufficiency and might be discrete initially, so the demonstration of a cardiac dysfunction, structural or functional, is needed to establish a diagnosis of CHF.

Heart failure has been defined as a syndrome originating from the inability of the heart to pump sufficient amounts of blood to the tissues or failure to do so without an elevation of the cardiac filling pressures. There is no non-invasive gold standard test in the diagnosis of CHF and because of the
inherent complexity of a disease that affects the entire circulatory system (and thus potentially all organs) a variety of parameters are evaluated in each case. Some of the investigations performed to obtain these parameters are listed in Table 1.

**Table 1.** Some diagnostic investigations in suspected or manifest heart failure

<table>
<thead>
<tr>
<th>Investigation</th>
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<tbody>
<tr>
<td>History</td>
</tr>
<tr>
<td>Clinical examination</td>
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<tr>
<td>Electrocardiogram</td>
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<tr>
<td>Blood sampling</td>
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<tr>
<td>Exercise tests</td>
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<tr>
<td>Chest x-ray</td>
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<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>Radionuclide angiography</td>
</tr>
<tr>
<td>Myocardial perfusion scintigraphy</td>
</tr>
<tr>
<td>Right- and left heart catheterisation</td>
</tr>
<tr>
<td>Coronary artery catheterisation</td>
</tr>
<tr>
<td>Cine computed tomography</td>
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<tr>
<td>Cine magnetic resonance imaging</td>
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</tbody>
</table>

The diagnosis of heart failure is based on history, clinical examination, physiological tests, electrocardiography, biochemical assays and imaging studies. In acute or severe chronic cases the history and clinical examination often suffice to institute adequate symptomatic treatment, but the objective diagnosis requires the use of one or more imaging studies. The trusted diagnostic test is invasive catheterization of both right and left cardiac chamber in combination with x-ray ventriculography to directly measure cardiac output and left ventricular pressure-volume curves. However, catheterization is mainly used in advanced cases due to the morbidity associated with the invasiveness and the costs.

In a majority of cases, the cardiac pump dysfunction is primarily related to a failure of the left ventricle (LV). The duality of pump function (emptying and filling has to be balanced) has resulted in a number of terms, with which LV function is further characterised.

**Table 2.** Terms used to classify the dualism of cardiac function in heart failure.

<table>
<thead>
<tr>
<th>Dualism</th>
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<tr>
<td>Forward/Backward failure</td>
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<tr>
<td>Increased Preload/Afterload</td>
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<tr>
<td>Systolic/Diastolic dysfunction</td>
</tr>
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</table>

With more recent terminology this dualism is characterized by systolic dysfunction (a reduced emptying capacity) and/or diastolic dysfunction (a reduced filling capacity). Reduced emptying leads to a lowered stroke volume
(SV) and, as a compensatory mechanism, the LV filling pressures and end-
diastolic volume (LVEDV) increases. The term systolic failure is therefore
associated with the inability of the LV to expel enough blood to the systemic
circulation and is routinely diagnosed by the finding of a lowered SV, an
increased LVEDV or a lowered LV ejection fraction (LVEF = SV/LVEDV).
Reduced filling capacity of the LV occurs in prolonged relaxation or in-
creased stiffness within the myocardial wall. Relaxation is an active energy-
consuming process and might be prolonged as a consequence of any myo-
cyte dysfunction, while stiffness generally increases in proportion to non-
myocytal debris within the wall (i.e. fibrosis). Reduced distensibility of the
LV increases the pooling of blood in the lung vessels and propagates an ele-
vated left heart filling pressure backward, eventually leading to formation of
excess pulmonary water. Diastolic dysfunction is commonly evaluated by
echocardiographic indices of LV filling rates. The pulmonary effects of a
diastolic LV dysfunction might be seen on plain chest x-ray as distended
lung vessels and as increased parenchymal radiopacity.

A useful diagnostic entity should therefore assess relevant aspects of both
systolic and diastolic function simultaneously.

The index event in heart failure
The development of heart failure may begin with acute injury and abrupt
loss of myocytes, as in myocardial infarction or inflammatory myocarditis.
In other cases, there may be a more slowly progressing pathology, as in hy-
pertension or diabetes. In all cases, the underlying etiological cause func-
tions as an index event that diminishes cardiac function and triggers a multi-
tude of secondary adaptive mechanisms.

Heart failure due to coronary artery disease
In the case of myocardial infarction the regional loss of myocytes results in a
reduced stroke volume, which is compensated by several immediate mecha-
nisms. The systemic response to a reduced cardiac output includes neurohu-
moral activation to maintain peripheral perfusion pressure of vital organs by
arterial vasoconstriction. The venous return is increased by venous vasocon-
striction and salt-water retention, elevating the LV preload and hence the
stroke volume by the Frank-Starling mechanism. In addition, the heart rate is
elevated and the contractility of the remaining myocard is enhanced by direct
hormonal actions. This series of compensatory mechanisms is life-saving in
the acute phase of myocardial infarction but, when chronically sustained,
may have a deleterious effect on the non-infarcted myocard. Chronically
increased workload and hormonal stimulation induces hypertrophic growth on the cellular level to reduce the myocardial wall stress. Hypertrophy in itself increases the work load and wall stress of the myocard in a vicious circle leading to increased metabolic demands, myocyte death through apoptosis or frank necrosis and subsequent fibrosis. Eventually, the structural architecture of the cardiac chambers is adversely and often irreversibly remodeled. This process is schematically described in Figure 1.

**Figure 1.** The vicious circles of heart failure.

The challenge to diagnostic procedures in heart failure

Obviously, current diagnosis and treatment in heart failure has to address multiple aims: identification and reversal of the index event, unfavorable hemodynamic loading conditions and adverse cardiac tissue remodeling. The new armamentarium of laboratory medicine rapidly unravels the molecular foundations of cardiac disease and provides a fundament for new treatments paradigms such as gene therapy, stem cell therapy and modifica-
tion of receptor function. On the other hand, the human application of new
treatment modalities might be slowed because the current diagnostic oppor-
tunities generally probe the disease status in terms of morphology and func-
tion on the level of the entire organ. This lack of diagnostic technology has
lead to the formation of a concept called molecular imaging, in which Posi-
tron Emission Tomography (PET) plays an important role.

Positron Emission Tomography

PET is an advanced nuclear medicine technique used for non-invasive and
quantitative measurements of radioactivity concentration within living tis-
sues. The principle is based on the physical properties of certain isotopes
that, when decaying, emit a positron. The positron is a particle with a mass
equal to an electron, but with a positive charge. The positron almost imme-
diately collides with an electron and both are annihilated. In this process,
two high-energy photons are created and leave the site of annihilation in
opposite directions. The PET scanner is equipped with a large number of
scintillation detectors arranged in a ring surrounding the object of interest.
When two photons with equal energies are detected in coincidence (Fig. 2),
the event is stored in a dedicated data array called a sinogram. Typically,
many millions of coincidences are stored during a PET scan. Coincidences
are collected for a finite amount of time, called a time-frame. With modern
PET scanners, a time-frame can range from a few seconds up to several
minutes. Dynamic PET is a term used when several time-frames are col-
lected from the same area of the body to track the changes of radioactivity
concentration over time.

The completed sinogram is then converted into a three dimensional data
array in a process called image reconstruction. Each data entry in this new
data array contains the actual radioactivity concentration of a certain portion
of the body within the specified time-frame. The three-dimensional image
array can be viewed as a stack of tomographic slices on a computer display
with colour codes for the actual radioactivity concentration.
When kinetic information is wanted the dynamic PET data is processed further with dedicated computer software. Regions of Interest (ROI) are placed at will within the tissue and data resembling the changes of concentration over time is extracted. In advanced kinetic analysis, the time-activity curves of both the blood and the tissue of interest are needed. Some kinetic solutions allow a time-activity curve from a ROI within the right or left ventricular cavity of the heart to substitute the true blood curve. In other cases, direct blood sampling is needed. Advanced kinetic analysis typically involves the use of computer-aided mathematical modeling.

The exclusiveness of PET lies in fact that positron emitting isotopes such as $^{11}$C-carbon, $^{13}$N-nitrogen and $^{15}$O-oxygen are available. These atoms are the building blocks of all living matter and substitution of a stable isotope with the positron emitting counterpart enables us to track the distribution and metabolism of most endogenous compounds as well as most biologically active synthetic compounds. Hydrogen does not have a positron emitting isotope, but $^{18}$F-fluorine might in some cases function as a substitute.

The applications of PET in cardiology generally involve quantification of regional myocardial blood flow, energy metabolism and innervation, for which it is regarded the non-invasive gold standard. This information has been utilised in the diagnosis of myocardial ischemia $^{4}$ and prediction of outcome after coronary revascularisation $^{5}$.

**Figure 2.** The principle of PET
Myocardial blood flow

Blood Flow is defined as the volume of blood that passes a certain point per time unit (e.g. mL/min as in cardiac output). Perfusion is blood flow divided by tissue weight (e.g. mL/min/g). In the literature, myocardial blood flow (MBF) is generally synonymous to myocardial perfusion.

Measuring myocardial blood flow with PET

Several tracers have been introduced for the PET assessment of MBF in absolute terms. Of these, radiolabeled water $[^{15}\text{O}]-\text{H}_2\text{O}$ and ammonium $[^{13}\text{N}]-\text{NH}_3$ are the best validated. There are distinctive differences in the mathematical models underlying MBF calculations with these tracers. With $[^{15}\text{O}]-\text{H}_2\text{O}$, the MBF is determined from the washout rate of tracer by the Kety-Schmidt principle in a single compartment model. With $[^{13}\text{N}]-\text{NH}_3$, MBF is determined from the rate of tracer transport from blood into myocard in a model consisting of three compartments. Ammonium extraction in myocardial tissue is high but not 100% complete during the first pass through tissue and is inversely related to MBF, which is accounted for by the model. Water is freely diffusible and 100% is extracted during the first pass through the tissue, even at high MBF, and corrections for partial extraction are not needed. In both cases a correction for partial recovery of radioactivity within the region of interest is performed within the model. This correction is needed because, due to wall motion, a fraction of the region containing the myocardial wall consists of arterial blood within the cavity and vessels. With the $[^{13}\text{N}]-\text{NH}_3$ model, the non-blood fraction is set equal to the tissue fraction. The $[^{15}\text{O}]-\text{H}_2\text{O}$ model permits an additional fractional correction for non-perfused tissue such as scar, fibrosis and fat. Evaluation of this parameter, termed the Perfusable Tissue Fraction (PTF), is useful in differentiation of viable and non-viable myocard. In spite of these differences both tracers give comparable results in normal myocard, both at resting and hyperemic blood flows, but the differences in the way the models treat the partial tissue volumes introduce a discrepancy in fibrotic myocard.

A kinetic model with appropriate corrections for absolute measurements of MBF with the tracer $[1-^{11}\text{C}]-\text{acetate}$ was recently introduced in many ways, the corrections performed by the $[1-^{11}\text{C}]-\text{acetate}$ model are similar to those used in the $[^{13}\text{N}]-\text{NH}_3$ model.

Normal myocardial blood flow

Normal resting MBF in humans is repeatedly reported to be in the range of 0.8 – 1.0 mL/min/g tissue. Under maximal pharmacological vasodilation by
intravenously infused substances such as adenosine and dipyridamol MBF increases by a factor of 3 to 5, depending on the resting MBF.

Abnormal myocardial blood flow

Even in advanced cardiac disease global MBF at rest generally is not different from the normal values. Scarring and fibrosis might reduce regional MBF substantially, but is compensated for by remote myocard. Regional MBF in the infarct area might remain severely depressed even after thrombolytic treatment in acute myocardial infarction with re-established epicardial vessel blood flow\textsuperscript{14}, known as the “no-reflow” phenomenon\textsuperscript{15}.

The Coronary Flow Reserve (CFR), calculated as the ratio of maximal and resting MBF, has been found to be a sensitive marker of endothelial dysfunction even in early and asymptomatic phases of metabolic syndromes predisposing myocardial disease\textsuperscript{16-19}. The CFR is reportedly lowered in most cardiomyopathies and often in proportion to disease severity\textsuperscript{6}. In the case of epicardial vessel stenosis, resting MBF is maintained at normal levels until stenosis severity exceeds 80-90\%, but reduced CFR is detectable with PET already at 30\% stenosis and is abolished at 80\% stenosis\textsuperscript{20}. The basal MBF in the fully unloaded human heart is approximately 0.2 mL/min/g (20-25\% of normal resting MBF), as was recently determined in patients with implanted LV assist devices studied with 13NH3-PET\textsuperscript{21}.

Because perfusion under normal physiological conditions is tightly regulated by local tissue metabolic needs, a close correlation of MBF towards myocardial oxygen consumption is expected. Uncoupling of MBF and oxygen consumption is typically seen during pharmacologically induced vasodilation, but is also known to occur transiently under experimental conditions with reperfusion directly after prolonged ischemia\textsuperscript{22}.

Myocardial energy metabolism

Measuring myocardial energy metabolism with PET

The most studied aspect of myocardial metabolism in PET relates to glucose uptake and phosphorylation. The tracer 18F-fluorodeoxyglucose (FDG) is a synthetic analogue of native glucose that enters the myocyte by membrane-bound glucose transporters and is phosphorylised by hexokinase. FDG is not metabolized further and diffusion out of the cell is slow, so the phosphorylation step traps the molecule intracellularly.
While glucose combustion can not be read directly from kinetic FDG data, the overall glucose utilization is typically assessed by Gjedde-Patlak graphical analysis. This maneuver requires dynamic PET with simultaneous blood sampling. The ratio of tissue/plasma concentrations is plotted against normalized time and the slope of this relation is the clearance of FDG into myocard with a unit of $\text{min}^{-1}$. Multiplication of FDG clearance with true plasma glucose concentration ($\mu\text{mol/mL}$) yields glucose utilization in units of $\mu\text{mol/min/mL}$ myocardial tissue. The myocardial glucose transporter affinity of FDG is approximately two thirds compared to native glucose, so a lumped constant of 0.67 is introduced as a final step.

Recently, a model for the estimation of true glucose utilization with [1-$^{11}$C]-glucose and dynamic PET was validated. For quantitative purposes, this approach might be superior to FDG-PET.

A validated model for the quantification of fatty acid utilization and oxidation with PET is available.

The myocardial oxygen utilization ($\text{MMRO}_2$) is quantified with PET by two different approaches. The tracer [1-$^{11}$C]-acetate has been studied more extensively in this context. The myocardial uptake rate of acetate in tracer amounts is proportional to MBF, but once extracted, [1-$^{11}$C]-acetate is trapped as $^{11}$C-acetyl-COA within the mitochondria. The primary route out of the cell is via the tricarboxylic acid cycle and the radiolabel is cleared as $^{11}$C-CO$_2$. The rate of clearance of $^{11}$C from myocard thus reflects the flux through the tricarboxylic cycle and, hence, the rate of oxidative metabolism. As recently reviewed by Klein et al., this relation has been repeatedly confirmed under experimental conditions and in humans in a wide range of hemodynamic conditions.

The other approach for the regional quantification of MMRO$_2$ available with PET is by the direct use of [$^{15}$O]-O$_2$ delivered to the patient as gas for inhalation under steady state conditions. To calculate MMRO$_2$ with this technique, additional PET studies with [$^{15}$O]-H$_2$O and [$^{15}$O]-CO are needed to account for the regional MBF and blood volume, respectively. A comparison of the [1-$^{11}$C]-acetate and [$^{15}$O]-O$_2$ methods in patients with chronic ischemic heart disease has shown congruent results.

Myocardial efficiency

Measurements of MMRO$_2$ by PET studies with either [1-$^{11}$C]-acetate PET (AC-PET) or the [$^{15}$O]-O$_2$ technique permits the non-invasive assessment of the LV efficiency of external work, calculated as the product of stroke volume, arterial pressure and heart rate. This opens an exiting means of studying alterations of myocardial energetics even in the early phases of heart failure development and to evaluate the effect of oxygen-sparing treat-
ments\textsuperscript{32}. Stroke volume is typically assessed by Doppler echocardiography or MRI.

Normal myocardial energy metabolism

The myocardium has a very high turnover rate of energy-rich phosphorylated adenosine compounds, but these are produced on demand and intracellular storage of ATP is minimal\textsuperscript{33}. Contraction stops in seconds after discontinued oxygen supply. Myocardial oxygen consumption (MMRO\textsubscript{2}) at rest is approximately 5 µmol/min per gram myocardial tissue, which converts into 15-20 L of oxygen gas per day in the adult heart.

According to Braunwald\textsuperscript{34}, the major determinants of MMRO\textsubscript{2} are those related to work: tension development, contractile state and heart rate. In comparison other ATP-dependent processes, such as electrical conductance and basal costs, are believed to be relatively unimportant.

The basal MMRO\textsubscript{2} in the human heart is not known, but experiments in dogs indicate a drop from 8-15 mL O\textsubscript{2}/min/100 g in the contracting heart to only 2 mL/min/100 g when the heart is stopped by potassium infusion\textsuperscript{35}.

The carbon used for combustion in myocardial oxidative metabolism is derived from a variety of sources: free fatty acids, carbohydrate and to a lesser extent ketone bodies and amino acids. Substrate preference is highly related to plasma concentrations in the normal myocardium. At rest, free fatty acids constitute two thirds of the metabolic substrate for oxidative metabolism, while carbohydrates account for most of the remaining one third. During strenuous exercise, the plasma level of lactate rises in proportion to glycolytic activity in skeletal muscles and lactate is the preferred substrate for myocardial energy production in this situation.

Aging is associated with lowered myocardial fatty acid utilization and oxidation and glucose utilization is relatively increased at rest\textsuperscript{36}.

Abnormal energy metabolism in remodeled myocard

Altered myocardial metabolism appears to be an early feature of most conditions predisposing heart failure. In one study by the Turku group, the MMRO\textsubscript{2} and cardiac efficiency was assessed by the [\textsuperscript{15}O]-O\textsubscript{2} method and echocardiography in hypertensive subjects with and without LV hypertrophy (LVH) as well as in normotensive controls\textsuperscript{31}. Oxygen consumption was increased in hypertensive subjects without LVH compared to the other groups, but efficiency was reduced in subjects with LVH. In another study, myocardial fatty acid oxidation was inversely related to LVH\textsuperscript{37}.

Compared to normal volunteers, patients with idiopathic dilated cardiomyopathy have elevated myocardial glucose utilization, lowered fatty acid utilization and oxidation at comparable cardiac work, MBF and MMRO\textsubscript{2} \textsuperscript{38}. Not surprisingly, cardiac efficiency is reduced\textsuperscript{39}.
Abnormal energy metabolism in ischemic myocard

Several different patterns of myocardial dysfunction and metabolic alterations might occur in relation to ischemic heart disease. These patterns can be divided into those that occur in acute ischemia and those that are chronic consequences of prolonged ischemia. Acute ischemia enhances lactate formation by anaerobic glucose breakdown in the glycolytic pathway. Following a single ischemic event, glucose consumption seems to remain globally depressed for several days while MMRO₂ returns to normal values earlier, indicating a switch from glucose to fatty acids as oxidative substrate.

Chronic patterns of structural and function changes related to ischemia are sometimes structured in terms of repetitive stunning, hibernation, scarring and the indirect pattern of adverse remodeling in remote myocard. These patterns are believed to coexist in most patients suffering from chronic ischemic cardiomyopathy. Stunning is suspected in temporarily hypcontracting but structurally undamaged myocard with normal perfusion at rest and is believed to be a consequence of a previous ischemic episode. Repeated ischemia might introduce a state of prolonged contractile dysfunction with a high likelihood of recovery at revascularization. Using models of repetitive ischemia in dogs, myocardial perfusion recovers earlier than oxidative metabolism and contractile function. Hibernation is a term used by some investigators to describe a pattern of regionally hypoperfused and non-contracting myocard with preserved glucose metabolism. Others use hibernation to encompass all patterns of viable non-contracting myocard. The common denominator of repetitive stunning and either definition of hibernation is reduced coronary flow reserve and recovery of contractile function after revascularization.

Enhancing the use of PET in heart failure evaluation

Ideally, a single PET scan should simultaneously provide quantitative data on regional and global myocardial blood flow, microvascular function and energy metabolism, but also enable detection of abnormalities in both systolic and diastolic LV function as well as the systemic and pulmonary circulation in a quantitative and reproducible manner. A non-invasive method with these properties could provide new and important insights into the mode of action and efficacy of therapy and might be valuable in clinical decision making.

Radiolabeled water and acetate appears to be particularly well suited for further development. Both provide quantitative measurements of MBF. In addition, [¹⁵O]H₂O provides a quantitative assessment of regional fibrosis,
while [1-11C]-acetate is the tracer of choice for studies of oxidative metabolism.

Regulation of cardiac output is the bottom line in the development of heart failure and the ability to measure cardiac output directly from the PET data seems useful. Theoretically, cardiac output could be calculated from the time-activity curve obtained from the first pass of a tracer through an intraventricular region of interest (ROI) during dynamic PET in combination with standard indicator dilution techniques. The evaluation of this possibility preferably requires comparison with invasive standard methods under experimental conditions and such a study was undertaken in this project (Paper I).

There is currently no PET method for the detection of diastolic dysfunction. However, because increased lung water content is the symptomatic consequence of a pathologically elevated LV filling pressure, the pulmonary retention of diffusible PET tracers might be evaluated instead. The usefulness and accuracy of WAT-PET in this context was previously reported, but never as an integrated part of a cardiac PET scan. The usefulness of AC-PET in evaluation of pulmonary congestion is not known and this was an additional objective of the experimental study, as described in Paper I.

To test the feasibility of hemodynamic measurements in humans with PET, a study in symptomatic patients with a diagnosis of congestive heart failure due to ischemic cardiomyopathy was undertaken (Paper II). Because reduced cardiac output is mandatory in congestive heart failure, a strong relation between stroke volume and grade of heart failure was postulated. It was assumed that the pulmonary retention of the partially extractable tracer [1-11C]-acetate would be elevated in heart failure in proportion to the regional lung water content and that both AC-PET and WAT-PET could be used to detect changes in subclinical pulmonary oedema formation.

Of special interest is the opportunity to evaluate the response to treatment of acute myocardial infarction (AMI) as complete recovery of regional tissue function could prevent the development of heart failure. The primary goal of current treatment in AMI is early and complete restoration of epicardial blood flow by thrombolysis. Evidence of successfully applied thrombolysis is the finding of blood flow in the infarct-related artery on subsequent coronary angiography. Restoration of arterial blood supply is of course crucial for recovery of cellular function. Still, the reperfusion itself appears to cause tissue damage and symptoms of heart failure develop in a subset of patients in spite of arterial patency. The reasons for this have not been entirely clarified in humans, partly related to a lack of adequate non-invasive technology. Serially applied PET studies might be one way to fill in this gap,
preferably by investigating temporal alterations in microcirculatory and metabolic function within the acutely infarcted myocardium in humans in relation to global hemodynamic outcome (Paper III).

There is evidence that coronary artery bypass grafting (CABG) might reduce mortality in patients with chronic ischemic cardiomyopathy and left ventricular (LV) dysfunction\textsuperscript{47,48}. The beneficial effects have been attributed to the presence of hibernating myocardium\textsuperscript{49,50}, defined as ischemically compromised, but viable myocardium with reversal of reduced wall motion after revascularization. Several non-invasive techniques have been developed to outline the presence of this phenomenon on the individual level\textsuperscript{51}.

In the absence of a prospective, randomized clinical trial focused on mortality, the clinical decision on CABG in this patient category is based on the prospect of functional outcome in terms of symptom reduction and increased physical capacity. However, prediction of functional improvement after revascularization in prolonged chronic ischemic cardiomyopathy has been variable. LVEF is prognostically important\textsuperscript{2} and is generally used as a surrogate marker in cardiac viability studies, but clinically significant increases are rarely reported\textsuperscript{52}. Some recent reports showed significantly increased exercise capacity and NYHA class improvement after CABG at unchanged or even reduced LVEF\textsuperscript{53,54}. The underlying cardiac and global hemodynamic changes are not known. These changes might become apparent by integrating the capability of AC-PET to assess regional and global myocardial perfusion and oxidative metabolism simultaneous to measurements of systemic and pulmonary hemodynamics (Paper IV).
Aims

The **overall aim** of this project was to develop and validate an extended cardiac PET methodology to obtain a more complete and simultaneous assessment of cardiac functions from a single study.

**Specific aims** were to:

Establish a method for cardiac output measurements with PET independent of the chosen tracer molecule and evaluate stroke volume index as an indicator of LV systolic function.

Establish methods for the evaluation of pulmonary adaptations in heart failure with tracers of myocardial blood flow.

Investigate the potential of PET in evaluation of treatment in acute myocardial infarction and chronic ischemic cardiomyopathy with severely reduced LV function.
Methods

Animals (Paper I)
In the animal study, 24 steady-state experiments were performed in 5 domestic pigs. Pulmonary capillary wedge pressure (PCWP) and CO by thermodilution (COthermo) were recorded invasively simultaneous to AC-PET at baseline (n=9), dobutamine infusion (n=6), high dose metoprolol and morphine (n=6) and angiotensinamide infusion (n=3). 1-[11C]-acetate was injected as a rapid manual bolus. ROIs were placed in the right (RV) and left (LV) ventricular cavities. Time-activity curves were constructed and the area under the curve (AUC) was integrated from scan start to the time of visually determined recirculation by simple arithmetics. CO by PET (COPET) was calculated as injected dose / AUC. Image handling and curve analysis were repeated by a blinded observer. Total pulmonary extravascular retention of 1-[11C]-acetate, expressed as a percentage of the injected dose, was measured using a combination of transmission-, 15O-carbonmonoxide- and AC-PET scans.

PET in congestive heart failure (Paper II)
The ability of PET-derived hemodynamic data to evaluate patients with different severity of heart failure was investigated in Paper II. In this study, PET was compared to radionuclide angiography and echocardiography in patients with ischemic cardiomyopathy with NYHA class II (n=10) or III (n=18) congestive heart failure. Elderly male volunteers without history or signs of heart disease (n=11) underwent AC-PET as controls. First-pass AC-PET and WAT-PET data was used with indicator dilution techniques to measure cardiac output and hence stroke volume (SVI). The replicability of SVI measurements was evaluated by linear regression analysis. Early lung uptake of [1-11C]-acetate was converted to Standard Uptake Values (LungAC-
SUV) by the formula \( \text{Lung}_{\text{AC-SUV}} = \frac{[^{11}\text{C}]}{\text{in lung ROI from 2-4 min after injection divided by total injected dose divided by body weight in grams. Regional lung water content (rLW) was computed from the WAT-PET scan at near-equilibrium as rLW (g/mL) = 0.84 \times \frac{[^{15}\text{O} \text{in lung}]}{[^{15}\text{O} \text{in blood}]}, assuming a water mass of 0.84 g/mL in solid tissues. SVI, Lung_{AC-SUV} and rLW were compared to standard measurements of LV function by regression analysis. Differences between subject groups were assessed by analysis of variance.

PET in acute myocardial infarction (Paper III)

In the AMI study, eight patients were included. All were diagnosed with acute myocardial infarction, according to clinical and ECG criteria and all were treated with thrombolysis. Coronary angiography was performed 24h after start of fibrinolytic treatment and the percentage of residual stenosis in the infarct-related artery was measured.

A 12-lead ECG registration, 90-120 minutes after fibrinolysis was compared with the baseline ECG. A reduction of ST-elevation >70 % was judged as a sign of reperfusion.

An echocardiogram was performed before coronary angiography 24 h after inclusion and after 3 weeks. LV-function was visually estimated with wall motion score for each of 16 standard segments by one physiologist without prior knowledge of the patients. To evaluate the presence of residual stunning at the segmental level, low-dose dobutamine (up to 10 microgram/kg/min) echocardiography was performed at 3 weeks. Each segment was given a score in the range of 1 to 4, using 1 = normal wall motion, 2 = slight-moderate hypokinetic wall motion, 3 = severe and 4 = paradoxical wall motion (dyskinesia). Segmental wall motion scores were summed and averaged to form an index of global systolic dysfunction, which was used as an end-point.

PET was applied serially at three occasions: WAT-PET was performed at 3 h, 24 h and 3 weeks after the start of fibrinolytic treatment. AC-PET was performed at 3h only and FDG-PET was performed at 24h and 3w. ROIs were interactively defined in the AC-PET data and included the blood pool of the right and left ventricle and a large region in the lower left lobe of the lung. Additionally, the entire left ventricular wall was sectioned into four regions describing the infarct zone, remote zone and two intermediary zones. The stroke volume and regional lung water content (rLW) was evaluated from the WAT-PET data at each time-point. The absolute MBF and water-
Perfusable Tissue Fraction (PTF) in myocardial ROIs was measured from the WAT-PET data also at each time-point. AC-PET was applied only at 3h after trombolysis and regional MBF and oxidative metabolic rates of the myocardial regions was evaluated. Myocardial metabolic rate of glucose at 24h and 3w was evaluated with FDG-PET by the use of graphical Patlak analysis23.

PET in chronic ischemic cardiomyopathy (Paper IV)

Patients
The study population in this paper was defined as patients with severe coronary artery disease (2- or 3 vessel disease on coronary angiography) associated with severe LV dysfunction on the basis of LV angiography or echocardiography. Exclusion criteria were significant valve disease other than mild mitral valve insufficiency, LV aneurysm suitable for resection, chronic atrial fibrillation and decreased renal function (S-creatinine ≥ 130 mmol/L). Patients eligible and who approved participation were submitted to a radionuclide angiography. Twenty patients (19 male) with LVEF < 30% were consecutively recruited. During the course of the study one patient died and two were lost to follow-up. The actual study population therefore consisted of 17 patients (16 males).

Mean age was 69.9 years, range 49-76. Previous myocardial infarction had been documented in all but two patients (mean 1.7 ± 1.2, range 0-4). Mean duration of ischemic heart disease was 5.6 ± 6.3 years. Five patients had diabetic disease and eight had a history of hypertension. Ten patients had predominant symptoms of heart failure and seven patients had predominant symptoms of angina. Medical therapy for heart failure was given as ACE inhibitors (n = 15), beta-receptor blocking agents (n = 7), diuretics (n = 13) and digoxine (n = 4). Antianginal treatment included nitrates (n = 17) and calcium channel blockers (n = 3). All received antithrombotic medication. Except for antianginal agents and diuretics, all medical treatment was maintained throughout the study period.

Evaluation of outcome parameters
Functional evaluations were performed preoperatively and 7.2 ± 6.2 months (range 3-32) after surgery. Equilibrium-gated radionuclide angiography was used to document LVEF. A trained cardiologist performed a detailed ques-
tionnaire with grading of heart failure symptoms according to the New York Heart Association (NYHA) classification and grading of anginal symptoms according to the Canadian Cardiac Society classification.

2D-echocardiography was used to evaluate segmental LV wall motion by a standard 16-segment model. Wall motion in each segment was scored as 1: normal, 2: mildly- to moderately hypokinetic or 3: akinetic. Dysfunctional but viable tissue was defined as a segment with improved wall motion score after surgery.

During the course of the study, contractile function in a large fraction of segments deteriorated. Based on this finding, an alternative grouping was introduced: a viable segment was defined as stable normal, stable hypokinetic or improved wall motion. A non-viable segment was defined as stable akinetic or deteriorating wall motion.

Peak exercise capacity in Watt was determined by upright symptom-limited bicycle stress test with a standard protocol starting at 30 Watt workload with increments of 10 Watt per minute. Criteria for termination were maximal tolerable fatigue, dyspnoea or chest pain, significant ventricular arrhythmia or decrease in systolic blood pressure > 15 mmHg. Peak capacity at each investigation was normalized to the median of a large group of healthy volunteers with the same sex, age and weight and is presented as a percentage of expected peak capacity.

PET-related parameters

A one-compartment model was used to calculate the rates of segmental myocardial acetate uptake (K1) and washout (k2). The monoexponential washout rate (k_{mono}) of $^{11}$C from tissue was also calculated. K1 was converted to values of myocardial blood flow (MBF)\textsuperscript{12,13} in units of mL/min/g. Based on previously established algorithms\textsuperscript{55} and the correlation between k2 and k_{mono} in this study (k2 = 1.064 * k_{mono} + 0.013, r = 0.98), the k2 was converted to values of myocardial O\textsubscript{2} metabolic rate (MMRO\textsubscript{2}) as MMRO\textsubscript{2} = 70 * k2 -1.8 (µmol/min/g). Relative MBF and relative MMRO\textsubscript{2} (hereafter termed MBF\% and MMRO\textsubscript{2}\%) were calculated for all segments by indexing to the segment with the highest perfusion in each study. Absolute values of global MBF and MMRO\textsubscript{2} were averaged from all segments, weighted by segment size. Similarly, the relative values were used to calculate global heterogeneity indices of MBF and MMRO\textsubscript{2} to indicate the overall size and severity of microcirculatory and metabolic abnormalities. In this view, a 50% reduction of MBF in 20% of the myocard would constitute a global MBF\% of 90%. The global balance of microcirculatory and metabolic heterogeneity was calculated as MBF\%− MMRO\textsubscript{2}\%.

Cardiac output was measured by the indicator dilution principle as described in Paper I and II, using the right ventricular cavity time-activity
curve, and indexed to body surface area. Systemic Vascular Resistance (SVR) was estimated as mean arterial blood pressure / cardiac index. Stroke volume Index (SVI) was calculated as cardiac index / heart rate. LV end-diastolic volume Index (LVEDVI) in mL/m² was estimated as SVI / LVEF. LV end-systolic volume index (LVESVI) in mL/m² was estimated as LVEDVI – SVI.

LV myocardial efficiency was assessed as a Work-Metabolic index by dividing LV minute work (SVI * heart rate * systolic blood pressure) by k2 as previously described.

The early pulmonary retention of [1-11C]-acetate was measured at described in Paper II as an indicator of pulmonary congestion.

PET protocols

PET was performed with a GE 4096 scanner (GE Medical Systems, Uppsala, Sweden) or a Siemens/CTI HR+ scanner (CTI, Knoxville, TE). After positioning of the heart within the field of view, a 10 minute transmission scan was performed for attenuation correction.

Tracers were injected intravenously as rapid boluses, immediately followed by 10 mL saline flushes. Emission associated with WAT-PET and AC-PET was captured from the start of injection with initial time-frames of not more than 5s per frame during the first minute and successively longer time-frames. A scan with [15O]-H2O comprised up to 5.5 minutes and a scan with 1-[11C]-acetate took 5 min in animals and volunteers and 30 min in patients.

The duration of a FDG-PET scan was 50 min, starting with time-frames of 60s for the first minutes and followed by successively longer time-frames. The preparations associated with FDG-PET included a glucose loading, 75 g glucose in water consumed 1 h before the scan start. Blood glucose was assessed frequently and small amounts of rapidly acting insulin were given intravenously to maintain normoglycemia, if needed. [18F] in plasma was sampled frequently during the scan from a preheated hand vein.

Blood pressure and heart rate was recorded frequently before and during all PET scans.
Graphical Regions of Interest

Regions of interest (ROIs) were invariably defined in the short axis view on a summed image from 2-5 minutes after injection of 1-[11C]-acetate at the first or only occasion. Small circular ROIs were positioned centrally in the right and left ventricular cavities. In the human studies, a large ROI was positioned in the left lung in an image plane at the level of the left atrium. In the animal studies, the entire lung parenchyma was enclosed by ROIs. The myocardial wall was divided into segments with a fixed ROI width of 10 mm. The number of myocardial segments varied depending on the study. In the animals (Paper I) a single ROI at a midventricular level was used to analyze the impact of myocardial activity spill-over on the calculations of cardiac output. In the AMI study (Paper III) the myocardial wall was divided into 4 segments encompassing the infarct centre, remote undamaged tissue and two border regions in between. In the evaluation of effects of revascularisation on patients (Paper IV) the myocardial wall was divided into 16 segments to enable comparison of regional PET data with two-dimensional echocardiography57.

![Image of the heart with graphical regions of interest using [1-11C]-acetate PET in a patient with chronic ischemic cardiomyopathy.](image)

To minimize the effects of patient motion, the emission data from all other scans was realigned to the index scan, the first (or only) AC-PET scan performed in an individual, by a series of automated manoeuvres58,59. All ROIs defined in the index scan were then copied to all other emission images of scans performed at the same or other occasions in the same individual. The positioning of ROIs on the additional scans was checked visually and cor-
rected if needed. Time-Activity curves (TACs) were obtained from all ROIs and exported to a standard PC for further analysis.

Statistical methods

Differences between two groups were evaluated by paired and unpaired Student t-tests (Papers II and IV), where appropriate, or by non-parametric tests (Paper III). Differences between several groups were evaluated by a one-way ANOVA approach followed by a planned comparison of individual groups (Papers II and IV). In Paper III, Friedman two-way analysis of variance by ranks followed by Wilcoxon's matched-pairs signed ranks test was applied to determine significant differences between the three points of time. Kruskal-Wallis analysis of variance followed by Mann-Whitney U test was applied to determine significant differences between the myocardial regions at the same time-point.

Univariate correlations were evaluated with non-parametric Spearman rank tests (Paper III) or by a combination of Pearson tests and simple linear regression analysis (Papers I-IV). Multivariate techniques included piecewise linear regression analysis (Paper I) and multiple linear regression analysis (Paper IV).

Values are presented as mean ± standard deviation (SD), unless otherwise stated. A two-sided P-value less than 0.05 was considered statistically significant.
Results

Measurements of Cardiac Output

In the animal experiments, $\text{CO}_{\text{thermo}}$ ranged from 2.1 – 8.2 L/min. $\text{CO}_{\text{PET}}$ determined from both RV and LV were linearly related to $\text{CO}_{\text{thermo}}$ (see Fig. 4) with slopes close to 1 (LV: $r=0.98$, RV: $r=0.96$, both $p<0.001$). Interobserver reproducibility was $r=0.98$, $p<0.001$ and interobserver variability was 6%. The main error sources were related to the partial volume effects induced by small ventricular cavities and spillover of activity from the LV wall in situations with high MBF.

In the CHF study (Paper II), SVI with both tracers correlated ($r=0.91$, $p<0.001$, see Fig. 5) with an estimated standard error of 4 mL/m$^2$. SVI measured with AC-PET was significantly different between all groups (ANOVA: $p<0.001$).

![Graph showing the relationship between CO by thermodilution and RV-CO_PET](image_url)
Figure 4. Diagram showing the relation of cardiac output measured with invasive thermodilution and with non-invasive PET in 24 animal experiments. Upper panel: linear regression analysis. Lower panel: Bland-Altman plot.

\[ y = 0.0441x - 0.5574 \]
\[ n = 24, \ r = 0.15, \ p = 0.43 \]

Figure 5. Diagram showing the replicability of stroke volume index measurements with [1-11C]-acetate (SVIAC) and [15O]-H2O PET (SVIWAT) in 26 patients with symptoms of severe heart failure (Group 1, n=17) or mild-moderate heart failure (Group 2, n=9).
Relation of pulmonary tracer retention towards LV diastolic function

In the animal experiments, PCWP range was 6-14 mmHg and total pulmonary extravascular acetate retention was 2.7-8.5% of the injected dose. When normalized to baseline, pulmonary acetate retention was correlated to PCWP (r=0.56, p=0.01) and linearly correlated to left ventricular input resistance (PCWP divided by COthermo, r=0.91, p<0.001, see Fig. 6). When both pulmonary acetate retention and stroke volume were normalised to baseline, a piecewise linear relation was found (r=0.95, p<0.001).

In the patients investigated in Paper II, LungAC-SUV correlated with echocardiographic parameters of LV diastolic function and was proportionally more increased in patients with a restrictive LV filling pattern. LungAC-SUV correlated with rLW (r=0.78, p<0.001, see Fig. 7) and both were elevated in patients with NYHA class III, compared to patients with NYHA class II (p<0.05 for both).

![Diagram showing the relation of early pulmonary retention of [1-11C]-acetate and left ventricular input resistance (PCWP/COthermo) in 20 animal experiments. Solid line is line of regression.](image-url)
PET in acute myocardial infarction

In the AMI study, the evaluation of the global hemodynamic parameters showed that stroke volume increased over time (p=0.003), while lung water was initially high, dropped after 24h and again increased at 3 weeks, compared to 24h. Lung water at 3 weeks correlated with ischemia duration, residual stenosis in the infarct-related artery and residual wall motion abnormality during low-dose dobutamine echocardiography.

There was a persistent gradient of decreasing perfusion closer to the infarct center with a tendency towards improvement over time in all affected regions, reaching significance only in the border-infarct region (p = 0.03) and mainly after the 24h time-point.

The level of oxidative metabolism within the perfused tissue, as defined by $k_{mono}$, decreased successively closer to the infarct zone ($\chi^2 = 23.1, p < 0.001$) with significant differences between all regions. Accordingly, the relative transmural oxygen utilization (expressed as fraction of the transmural $r$MMRO$_2$ in the remote region) showed a similar pattern with gradual reduction from the remote to the infarct region (Fig. 8). The regional oxygen extraction, relative to the remote region, also showed a significant gradient with lower values closer to the infarct center (Fig. 8).
Figure 8. Relation of transmural Myocardial blood flow (MBF$_{\text{WAT}}$), oxidative metabolic rate (MMRO$_2$) and oxygen extraction (OEF) at 3 hours after start of thrombolytic treatment in 8 patients. Symbols and error bars show mean ± SD fraction of the remote region. KWA = Kruskal-Wallis analysis of variance.

Transmural glucose utilization at 24 h was also reduced with a prominent gradient closer to the infarct center. When normalized to the remote area there was a close correlation to the simultaneous perfusion in all affected regions. This pattern included the infarct center ($r = 0.86$, $p = 0.01$) but glucose utilization was relatively more reduced than perfusion in all patients, resulting in a significantly lowered relative glucose extraction closer to the infarct.

Relative values of oxygen extraction at 3 h and glucose extraction at 24 h in the infarct region tended to correlate ($r = 0.64$, $p = 0.11$), but oxygen extraction was slightly lower ($44 ± 22\%$ vs. $63 ± 19\%$, $p = 0.06$).

From 24h to 3 weeks, the relative glucose utilization increased from $78 ± 15\%$ to $87 ± 6\%$ in the border remote region ($p = 0.03$), from $48 ± 19$ to $64 ± 14\%$ in the border infarct region ($p = 0.01$) and from $36 ± 28\%$ to $45 ± 20\%$ in the infarct region ($p = 0.09$). As the relative perfusion also tended to increase in all regions, the relative glucose extraction was not significantly changed in any region and a gradient from remote to infarct was still evident (Fig. 9).
The perfusable tissue fraction, PTF, in the remote region was virtually unchanged over time with a mean intra-individual coefficient of variation (SD/mean of the three measurements) of 4.8 ± 1.4%. The relative PTF in the border regions and the infarct region (expressed as fraction of the PTF in the remote region) is summarized for all regions and time-points in Fig. 5. PTF was initially significantly reduced closer to the infarct zone, but gradually recovered in all affected regions (p < 0.05 for all) and the difference across the regions was no longer significant at 3 weeks.

**Figure 9.** Relation of transmural Myocardial blood flow ($\text{MBF}_{\text{m WAT}}$), glucose metabolic rate (MMGlu) and glucose extraction (GluEF) at 3 weeks after thrombolytic treatment. Symbols and error bars show mean ± SD fraction of the remote region. KWA = Kruskal-Wallis analysis of variance.
Figure 10. This diagram shows the evolution of the Perfusable Tissue Fraction (PTF) after acute myocardial infarction in various regions over time. Values were obtained in 8 patients with \[^{15}\text{O}\]H\(_2\)O PET and are expressed as the mean ± SD fraction of the remote region at 3 h, 24 h and 3 weeks after start of trombolytic treatment. KWA = Kruskal-Wallis analysis of variance. Within-region variation over time was tested with Friedman two-way analysis of variance.

Figure 11. Global myocardial glucose utilization at 24h and 3 weeks after AMI in 8 patients treated with trombolysis. Glucose utilization increased by \(42 ± 23\%\) (p<0.001).
A non-linear relationship of relative PTF and MMRO$_2$ at 3h was found. Within the infarct region, the $k_{mono}$ at 3h correlated with the relative values of PTF at 3h ($r = 0.96$, $p < 0.001$), at 24h ($r = 0.79$, $p = 0.04$) and at 3 weeks ($r = 0.75$, $p = 0.05$). A similar relationship of relative oxygen extraction at 3h was found towards relative PTF at 3h ($r = 0.83$, $p = 0.01$) and 3 weeks ($r = 0.90$, $p = 0.002$). The relative values of the various indices of perfusion, glucose utilization and glucose extraction within the infarct region were less consistently correlated to the dynamics of PTF.

The global myocardial glucose utilization invariably increased from 24h to 3 weeks after AMI ($40.8 \pm 7.0$ versus $57.0 \pm 6.0 \mu$mol/min/100 grams, $p < 0.001$), as seen in Fig. 11. This metabolic alteration occurred at unchanged global MBF, blood glucose levels and LV minute work and the increase was seen in the remote as well as the infarct-related regions.

Oxidative metabolism within the infarcted region at 3h was found to be highly predictive of pulmonary oedema formation and residual wall motion abnormality at 3 weeks after infarction.

**PET in chronic ischemic cardiomyopathy**

After surgical revascularisation, the NYHA class improved by at least one step in 8 patients, from class IIIB to IIIA in 6 patients, was unchanged in 1 and deteriorated in 1 patient ($p=0.001$). Anginal symptoms decreased in 16 patients and 15 were completely free of angina at follow-up ($p<0.001$). Peak exercise capacity increased from $62.8 \pm 15.8\%$ to $76.1 \pm 18.0\%$ of the expected exercise capacity (difference $13.3 \pm 11.7\%$, $p < 0.001$). LVEF increased by a mean $2.7 \pm 3.6\%$ ($p = 0.007$), but an increase of ≥5% was noted in only 5 patients. Changes in LVEF were not correlated with changes in exercise capacity or NYHA class.

Alterations of cardiovascular function at rest were relatively small for the entire cohort. Significant improvements were seen in variables related to LV volumes and systemic vascular resistance, but these changes were not directly correlated with outcome variables.

Changes in SVI and LVEF correlated linearly ($r = 0.78$, $p < 0.001$). After adjustment for changes in preload (LVEDVI) and afterload (systemic vascular resistance), the correlation increased to a partial $r = 0.86$. Changes in LVEF were also associated with changes in myocardial efficiency, as assessed by the WMI ($r = 0.73$, $p < 0.001$).

The pulmonary acetate retention index changed in inverse correlation towards exercise capacity by univariate analysis ($r = -0.55$, $p = 0.01$) and remained the best predictor by multivariate analysis. Exercise capacity before
surgery and change in pulmonary acetate retention index together explained most of the variation in exercise capacity after surgery (r = 0.87, adjusted r² = 0.75, p < 0.001).

The patients with significantly reduced heart failure symptoms (NYHA class reduction by at least one step, n = 8) also had a larger reduction of pulmonary acetate retention, compared to those with poorer outcome (-0.33 ± 0.38 vs 0.11 ± 0.31 SUV, p = 0.02).

A total of 272 segments were evaluated by echocardiography. 65 segments (24%) improved at least one step, fulfilling the criteria for dysfunctional but viable segment. 56 segments (21%) decreased function by at least one step. Almost half of the segments with initially normal wall motion had reduced wall motion at follow-up. All but one patient had at least one viable but dysfunctional segment, but the count was not significantly associated with changes in LV-EF, exercise capacity or NYHA class. The patients with NYHA class improvement of at least one step (n = 8) had significantly more myocardial segments with normal wall motion after surgery (p = 0.001).

Myocardial blood flow and oxygen utilization

The largest difference between segment groups before surgery was found for the MMRO₂%. Among the initially hypokinetic segments, those with reduced wall motion after surgery had relatively lower MMRO₂% (p = 0.01). A strong trend was seen between the two groups with initially normal function (p = 0.07) and the two initially akinetic groups (p = 0.05). A similar relation was not obvious for MMRO₂ in absolute terms.

Initially akinetic segments with improved wall motion had higher absolute MBF than those that remained akinetic (p < 0.001). Initially hypokinetic segments with improved or stable wall motion had higher relative MBF than those in which function deteriorated (p = 0.01).

In the segments with MBF% > 70%, absolute MBF decreased from 0.767 ± 0.212 to 0.724 ± 0.220 mL/min/mL (n = 142, p = 0.036) and the segments with MBF% ≤ 70% increased from 0.436 ± 0.186 to 0.462 ± 0.216 (n = 105, p = 0.038). No significant change in MMRO₂ was seen in the well-perfused segments, but the low-perfused segments increased from 2.59 ± 1.37 to 2.80 ± 1.34 umol/min/g (p = 0.005).

Increased MMRO₂% in viable segments was associated with a simultaneous increase of the MBF% of approximately the same proportion. As seen in Figure 12, this was in sharp contrast to the non-viable segments, in which relatively increased oxygen utilization was associated with an unchanged or lowered relative perfusion.
Figure 12. Relation of change in segmental MBF% and MMRO$_2$% after CABG in 17 patients with chronic ischemic cardiomyopathy. Segments with MBF% in upper quartile (> 87.5%) and lower quartile (< 55.6%) were removed to minimize regression to the mean. Changes in MMRO$_2$% were followed by similar changes in MBF% in viable segments but not in non-viable. Solid lines are lines of regression.

Decreased MMRO$_2$% in viable segments after surgery was common and was investigated separately. This phenomenon was more pronounced in the NYHA class improvers and was found mainly in the segments with full recovery of wall motion. As can be seen from Table 4, there were distinct differences towards the patients without substantial NYHA class improvement, both regarding the number of segments with normal wall motion after surgery ($p = 0.001$) and the metabolic reaction to surgery in these segments.
Table 4. Characteristics of segments with normal wall motion after CABG in patients with significant functional improvement (NYHA ≤ II) and patients with little or no functional improvement (NYHA III). WMS: echocardiographical wall motion score. MMRO$_2$%: oxygen utilization indexed to segment with highest perfusion. *: $P \leq 0.01$ compared to pre.

<table>
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<th>NYHA III (n=9)</th>
<th>P-value</th>
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<td>WMS post</td>
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<td>MMRO$_2$% post</td>
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<td>94.7 ± 19.1*</td>
<td>0.17</td>
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<tr>
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<td>10.6 ± 14.9</td>
<td>&lt; 0.001</td>
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Before surgery, the global MMRO$_2$% was associated with the pulmonary acetate retention index ($r = -0.59$, $p = 0.01$) and peak exercise capacity ($r = 0.61$, $p = 0.009$). While there was no significant correlation of global MBF indices towards changes in outcome parameters by univariate analysis, a model with changes in LVEF as dependent and MBF%, MMRO$_2$% and changes in LVEDVI as independent variables achieved an overall $r = 0.81$ (adjusted $R^2 = 0.57$, $p = 0.01$). A high MBF% indicated better outcome (partial $r = 0.78$, $p < 0.001$) and a low MMRO$_2$% indicated worse outcome (partial $r = -0.67$, $p = 0.006$). Obviously, an increased LVEDVI indicated worse outcome (partial $r = -0.59$, $p = 0.02$).

On the global level, mean MBF% was more reduced than MMRO$_2$% both before and after surgery ($p < 0.001$). The (MBF%-MMRO$_2$%) index had a range of -27% to 5%. This variation itself, by univariate analysis, correlated with subsequent changes in LVEF ($r = 0.67$, $p = 0.003$) and changes in the myocardial efficiency ($r = 0.76$, $p < 0.001$, see Figure 13). Furthermore, the (MBF%-MMRO$_2$%) index contributed significantly (partial $r = -0.54$, $p = 0.03$) in association with myocardial efficiency to the prediction of changes in pulmonary acetate retention.

Changes in the global MMRO$_2$% were directly and inversely proportional to the percentual change in LVEDVI ($r = -0.80$, $p < 0.001$), as seen in Fig. 14. Similar correlations were found for changes in the global MMRO$_2$% towards LVESVI. Patients with increased global MMRO$_2$% (n = 9) had a more prominent improvement in peak exercise capacity ($19 \pm 10$ vs $7 \pm 10\%$, $p = 0.02$).
Figure 13. Scatterplot of the balance of microcirculatory and metabolic heterogeneity (MBF% – MMRO2%) before surgery in relation to subsequent changes in myocardial efficiency, defined by the Work-Metabolic Index. Solid line is line of regression.

Figure 14. Relation of simultaneous changes in myocardial oxidative metabolic heterogeneity (MMRO2% index) and LV end-diastolic volume (LVEDVI). Solid line is line of regression.
Discussion

Role of PET in evaluation of congestive heart failure

In Paper I it was shown that PET allows highly accurate and reproducible measurements of cardiac output in animals. A high replicability of cardiac output and stroke volume measurements with different PET tracers in humans was confirmed in Paper II. Paper II also indicated a high accuracy of first-pass PET in differentiating patient groups according to symptom severity. In Paper IV, the simultaneous changes of LVEF and stroke volume index were highly correlated. The stroke volume index, as measured with PET, therefore seems to be a reliable and reproducible indicator of LV systolic function. Because virtually no tracer is lost from the site of intravenous injection to the right ventricular region, any injectable tracer can be used in this context. This is potentially an important contribution to the use of PET in cardiology.

The pulmonary retention of both [1-11C]-acetate and [15O]-H2O was investigated as indicators of pulmonary congestion. Either tracer seems to enable a quantitative assessment of subclinical pulmonary oedema formation. This provides an opportunity for PET to investigate both the cause and the consequence of a diastolic LV dysfunction that might be of use in clinical decisions.

The diagnosis of heart failure in clinical practice relies heavily on evaluation of the LVEF. This single value carries high prognostic power, because it incorporates both the stroke volume and the filling volume. However, in up to 40% of patients presenting with symptoms of congestive heart failure LVEF is within the normal range, raising a suspicion of an isolated diastolic LV dysfunction. Doppler-echocardiographic assessment of the transmirtal inflow is generally regarded as the non-invasive diagnostic test of choice in this subgroup, but the criteria for diagnosis is a matter of debate. The current studies indicate that dynamic PET scanning with diffusible tracers provides assessment of both cardiac output regulation and pulmonary congestion in feasible and accurate terms. According to the definition of
heart failure, this capacity could put PET directly at the core of diagnosis. However, more studies are needed to define the possible clinical role of PET in this context.

Role of PET in evaluation of ischemic cardiomyopathy

The main finding of the PET studies in acute myocardial infarction was that the information from a single cardiac PET scan potentially enables an integrated analysis of cardiac function, spanning from the molecular level to the level of overall hemodynamic function. Additionally, this study indicates that preservation of myocardial oxidative metabolism is an important therapeutic goal in acute myocardial infarction beyond restoration of epicardial vessel patency.

In the early phases of AMI the perfusable tissue fraction seems to reflect microvascular patency rather than fibrosis. This finding is potentially important, because quantitative and non-invasive indicators of the endothelial component in reperfusion injury are needed. More work on validating this finding is warranted.

Glucose utilization increased significantly in all of the myocard over time. This increase occurred unrelated to changes in cardiac work load and blood glucose levels and therefore seems to indicate that the shift in myocardial substrate preference towards fatty acid utilization in association with severe acute ischemia is a global phenomenon even in humans. This phenomenon was not directly associated with the chosen outcome parameters. It might be important because fatty acid utilization occurs at a higher oxygen cost, compared to glucose, potentially increasing the metabolic burden in the infarct area.

After the beginning of the thrombolytic era numerous researchers have focused on earliest possible complete reperfusion of the infarct related coronary artery. In a previous PET study the recovery of LV-contractile function was highly dependent on adequate myocardial tissue perfusion. However, achievement of TIMI grade 3 flow in the epicardial infarct related artery does not seem to be enough. In a trial with 11 patients with metabolism/perfusion mismatch and TIMI grade 3 flow in the infarct related artery, six of seven with PTCA showed LV-function recovery compared to none out of four patients with no PTCA. Furthermore, in a recent study multivariate analysis revealed that oxidative metabolism in the successfully reperfused myocardium was the only significant predictor for recovery of global systolic LV-function at three months after acute myocardial infarction. The results of Paper III, demonstrating that the oxidative metabolism at 3 h is highly predictive of residual myocardial fibrosis, pulmonary oedema forma-
tion and contractile dysfunction at 3 weeks seems to fit into the same concept. Thus it might be suggested that only patients with both TIMI grade 3 flow and an early adequate level of oxidative metabolism will show a complete recovery of myocardial functions while those with poor oxidative metabolism will need further early treatment measures despite re-established TIMI grade 3 flow.

PET allows a detailed evaluation of the development of myocardial microcirculation and metabolism together with simultaneous assessment of global hemodynamic parameters. PET technology might be one way to test new treatment modalities in acute myocardial ischemia before embarking on large-scale clinical trials.

In Paper IV it was shown that the beneficial effects of surgical revascularisation in chronic ischemic cardiomyopathy were related to altered LV loading conditions rather than an isolated improvement of systolic function. Recovery of physical capacity and reduction of heart failure symptoms was associated with a more homogenous distribution of myocardial oxygen utilization. Poor myocardial microcirculatory function prior to surgery was found to reduce the likelihood of recovery, probably as a consequence of more severe fibrosis or advanced remodeling in those areas.

It seems that beyond the restoration of wall motion in discrete segments, revascularisation starts a chain reaction involving all myocard. As previously described, several different abnormal tissue patterns are known to coexist in chronic ischemic cardiomyopathy. These patterns include tissue with hypertrophy due to increased workload, repetitive stunning, hibernation and scar. All patterns might coexist within the same wall segment, but the results of the segmental analysis indicate that AC-PET can be used to characterize the predominant pattern of most segments.

A previous study with 11C-acetate PET during dobutamine-induced stress has shown that viable dysfunctional myocard subtended by stenosed epicardial vessels possesses an oxidative metabolic reserve. From the current material, it seemed that a majority of hypofunctioning segments reacted to revascularization by utilizing at least some of that reserve and, as a consequence, improved the internal cardiac work needed to maintain diastolic function. On the global level, this was associated with improved LV filling function and reversed remodeling.

A subpopulation of hypofunctioning segments had a relatively undamaged microcirculatory function (high relative MBF) in combination with a relatively lowered oxygen utilization and could therefore be said to be truly hypometabolic. This is a pattern indicative of repetitive stunning and, on the global level, was associated with improved LVEF. These segments, in addition to internal work production, apparently regained contractile capacity enough to increase the external work.
A substantial fraction of the well-perfused and viable segments exhibited reduced relative MBF and MMRO2 indices after surgery. What most of these segments had in common was that they had intact oxygen utilization before surgery and either maintained or obtained normal wall motion after surgery. Because this phenomenon was much more common in patients with substantial NYHA class improvement, the finding is probably associated with a load reduction. If substantial amounts of previously non-functioning myocard partake in wall tension build-up after surgery, the undamaged myocard might be able to produce more external work at a lower metabolic cost. This seems to be an important finding for several reasons. It is probably the mechanism of improved myocardial efficiency, as defined by the Work-Metabolic Index. It is also an indication that surgical revascularization arrests and possibly reverts the vicious circles of heart failure (as defined in the introducing chapter of this thesis). Finally, it seems to be the dominant mechanism of symptom reduction in heart failure in this patient category.

These findings were made possible by the use of an extended AC-PET method with which myocardial perfusion and oxidative metabolism as well as relevant indices of global hemodynamic function were quantified and evaluated in context. Noteworthy, LVEF by radionuclide angiography and regional wall motion by 2D-echocardiography did not change in relation to physical performance. These methods are widely available and generally trusted as surrogate markers in evaluation of heart failure therapy, but apparently their use without supplementary investigations could be questioned in some instances.

Is there a place for quantitative PET in cardiology?

As evidenced by the findings reported in this thesis and by many others, quantitative PET is undisputedly a powerful tool in heart failure research. However, only FDG-PET has found a way into clinical routine. The PET technique is currently undergoing a rapid dissemination into routine healthcare in many industrialized countries and, as a consequence, costs are reduced. This process is driven by the use of FDG-PET in the management of malignant diseases and the fact that the isotope $^{18}$F has a sufficiently long half-life to support transportation of the tracer from the cyclotron site to satellite scanning centres.

FDG-PET is clinically useful in cardiac studies of patients with LV insufficiency due to chronic ischemic disease. The combination of a regionally lowered perfusion and preserved metabolic activity in a segment with reduced motility indicates a high likelihood of functional recovery after revascularisation. Gold standard evaluation of LV metabolism with FDG requires simultaneous intravenous administration of glucose and insulin to minimize myocardial fatty acid utilization, which is demanding and prolongs the pro-
Additionally, the protocol requires knowledge of regional myocardial perfusion. There is currently no clinically useful $^{18}$F-tracer of myocardial perfusion. In PET centers with access to a cyclotron, perfusion is commonly evaluated with the tracer $^{13}$N-ammonium. In the absence of a cyclotron, perfusion is evaluated with standard gamma camera protocols for myocardial scintigraphy.

AC-PET has also been found of use in the diagnosis of viable but dysfunctional myocard with results that are equal or superior to the FDG protocol. The study is performed in 30 minutes and there is no substrate dependency. In PET centres with an on-site cyclotron, this translates into cost reduction. However, the diagnostic work-up requires the use of kinetic modeling for which commercial software is not yet available, thereby limiting the clinical acceptance of the AC-PET approach. With the prospect of integrating more relevant parameters of cardiac function into a single scan, this situation might change. The studies reported in this thesis suggest that further validation and refinement of the AC-PET method could be well rewarded.
Conclusions

Extensions to the use of PET in cardiology were developed, validated and applied in clinical studies. Cardiac output can be assessed with dynamic PET using any injectable tracer.

Stroke volume index is a relevant indicator of LV systolic function in patients with heart failure.

PET measurements of radiolabelled water and acetate lung retention provide quantitative indices of pulmonary adaptations in patients with heart failure even at rest.

PET studies in evaluation of treatment in acute myocardial infarction and chronic ischemic cardiomyopathy are feasible and provide a detailed survey of cardiac functions from the molecular level to the level of global hemodynamics.

Assessment of the myocardial distribution and magnitude of perfusion and oxidative metabolism by [1\textsuperscript{-11}C]-acetate PET is highly predictive of regional and global outcome in ischemically compromised hearts.
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