Glucose uptake in normal and ischemically jeopardized myocardium measured by ^{18}F-fluorodeoxyglucose and Positron Emmision Tomography

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1. INTRODUCTION

The function of the heart is to provide a continuous supply of nutrients and oxygen to all tissues of the body. A constant myocardial production of energy to maintain cardiac contractile work is therefore essential for the organism. Using aorto-coronary sinus catheterization Bing was the first to show that the source of energy production in the human heart is its extraction of free fatty acids (FFA), glucose, lactate, ketone bodies and aminoacids (Bing et al. 1947, Bing 1954). The relative contribution of these substrates to energy production in normal human myocardium was later found to be determined by substrate competition, hormonal status and cardiac demands (Lassers et al. 1971, Wisneski et al. 1985b, Gertz et al. 1988, Camici et al. 1989b, Ferrannini & Santore 1993). FFA, glucose and lactate were demonstrated to be the quantitatively most important fuels for the heart.

The unique role of glucose as a small, but important source of energy in ischemically jeopardized myocardium has been the focus of intense experimental and clinical research (Neely et al. 1975, Camici et al. 1989a, Taegtmeyer 1994, Stanley et al. 1997, Apstein 2000). Most of the knowledge in this field has been generated using in vitro animal models where the multiple physiological and biochemical factors determining cardiac energy conversion may be controlled. Aorto-coronary sinus measurements of substrate extraction in healthy subjects and in patients with ischemic heart disease have contributed to the understanding of human cardiac metabolism, although this technique provides global measures of net myocardial substrate exchange. Positron emission tomography (PET) and the glucose analogue ^{18}F-fluorodoxyglucose (^{18}FDG) was first introduced by Phelps and co-workers (Phelps et al. 1978) as a tool for the non-invasive measurement of *regional* myocardial glucose uptake in humans.

The main objective of this thesis was to validate ^{18}FDG and PET imaging for the measurement of regional glucose uptake in normal and ischemically jeopardized myocardium *in vivo* with special reference to normal-physiological variability. Furthermore, the clinical role of diagnostic glucose metabolism-blood flow PET imaging was evaluated in relation to outcome after coronary artery bypass surgery in patients with severe ischemic heart disease after a prolonged strategy of medical treatment.

1.1. GLUCOSE METABOLISM IN THE NORMAL HEART

Glucose is delivered to the myocardium through the coronary vasculature and transported into the cardiomyocyte by carrier-mediated facilitated membrane transport (**Figure 1**). Within the cytosol glucose is phosphorylated to glucose-6-phosphate (G6P) by hexokinase and depending on metabolic conditions directed towards energy production (glycolysis and/or glucose oxidation) or storage (glycogen) (Buxton 1991). Cardiac metabolism of G6P may also occur through the pentose phosphate pathway (purine nucleotide synthesis), although the flux through this pathway is small (Zimmer 1996). ATP is generated from anaerobic (glycolysis) as well as aerobic (glucose oxidation) combustion, and the total ATP yield from glucose per extracted oxygen atom is energetically more advantageous than from FFA (Opie 1991, Korvald et al. 2000). Myocardial glucose uptake during fasting is at its minimum suppressed by a high arterial concentration of FFA (Ferrannini & Santore 1993), but may be increased by exercise or left atrial pacing (Gertz et al. 1988, Camici et al. 1989b). During euglycemic hyperinsulinemic glucose clamp (DeFronzo et al. 1979) myocardial FFA uptake is completely abolished and the major part of energy production in the heart may be ascribed to glucose degradation (Ferrannini & Santore 1993).

The initial experience with cardiac PET imaging suggested that regional left ventricular myocardial ^{18}FDG uptake is somewhat heterogeneous in young healthy subjects (Marshall et al. 1983b). Following the development of quantitative ^{18}FDG-PET imaging by which absolute myocardial glucose uptake could be measured (Huang et al. 1980, Ratib et al. 1982) it was later demonstrated that myocardial glucose uptake recorded during euglycemic hyperinsulinemic glucose clamp in normally contracting myocardium of patients with ischemic heart disease displayed considerable interindividual variability with a relative dispersion of 44% (Gerber et al. 2001). A normal variation in myocardial blood flow and/or insulin sensitivity was suggested to explain this observation, yet measurements of insulin sensitivity, myocardial blood flow and insulin stimulated glucose uptake in healthy subjects have never been performed. Furthermore, normal reference values have never been re-

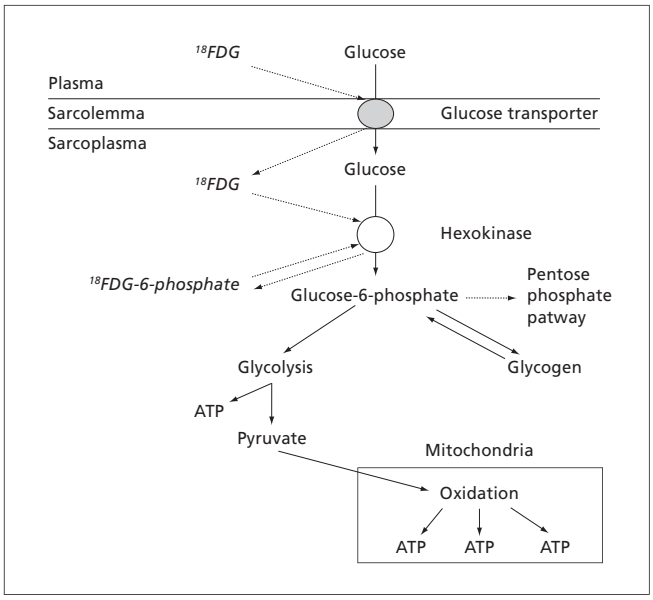

Figure 1. Myocardial glucose and ^{18}FDG metabolism. Glucose is taken up by the myocyte from plasma, phosphorylated and mainly metabolized by combustion for energy production (glycolysis and/or oxidation) or by storage (glycogen synthesis). ^{18}FDG is taken up by the myocardium similar to glucose, yet not further metabolized once it is phosphorylated.

ported in healthy subjects age-matched to the target age for the development of ischemic heart disease (Levy et al. 1990).

1.2. GLUCOSE METABOLISM IN ISCHEMICALLY JEOPARDIZED MYOCARDIUM

During moderate low-flow ischemia it has been demonstrated in animal experiments that myocardial glucose uptake plays an important role in preserving the viability of the tissue. Although FFA continues to be the major source of energy during such conditions (Kobayashi & Neely 1979, Lopaschuk & Saddik 1992), uptake of glucose appears to conserve the tissue by maintaining cellular membrane function (Weiss & Lamp 1987) and delaying the decrease in intracellular free energy yield (Eberli et al. 1991, Cave et al. 2000). The relative contributions of glycolysis, glucose and FFA oxidation for energy production are related to the severity of ischemia (Neely et al. 1975). During severe myocardial ischemia, glycolysis is inhibited by accumulation of lactate and protons (Opie 1991) and substrate oxidation arrested while the tissue deteriorates.

Following coronary reperfusion the contractile function of the myocardium remains depressed for a prolonged period despite restoration of blood flow – a condition interpreted as "myocardial stunning" (Braunwald & Kloner 1982). This phenomenon may partly be alleviated by increased supply of glucose and insulin enhancing myocardial glucose uptake (Eberli et al. 1991, Johnston & Lewandowski 1991, Tamm et al. 1994). Maintained glucose oxidation during myocardial reperfusion appears to be the biochemical mechanism responsible for this protective effect. Whereas glucose uptake is increased late after reperfusion, ^{18}FDG uptake appears to be reduced during early reperfusion (Buxton & Schelbert 1991, McFalls et al. 1994). The interpretation of the ^{18}FDG technique under these conditions has therefore been questioned (Liedtke et al. 1992).

In patients with heart failure of ischemic and non-ischemic etiology whole-body insulin resistance has been identified as an independent prognostic risk factor (Swan et al. 1997, Paolisso et al. 1999). It was therefore suggested that disturbances in insulin mediated myocardial metabolism might impair energy supply (Swan et al. 1997). However, previous studies using cardiac ^{18}FDG-PET imaging have been conflicting with regard to the relationship between whole-body insulin sensitivity and cardiac glucose uptake (Paternostro et al. 1996, Utriainen et al. 1998, Yokoyama et al. 1999).

Schelbert and co-workers were the first to evaluate myocardial glucose metabolism during acute regional myocardial ischemia using ^{18}FDG and PET (Schelbert et al. 1980). They found that pacing induced regional myocardial ischemia in dogs with a partially ligated coronary artery was accompanied by a much smaller reduction in regional myocardial ^{18}FDG uptake than the reduction of blood flow assessed by ^{13}N ammonia ($^{13}NH_3$). The term "metabolism-blood flow mismatch" was proposed to describe this condition. Similar patterns of myocardial mismatch were found in patients who had recently suffered a myocardial infarction, even though they had no signs of ongoing myocardial ischemia (Marshall et al.

Table 1. Myocardial glucose metabolism-blood flow PET-mismatch and viable myocardium in historical perspective.

Author	Image acquisition	Image analysis	Normal values	Mismatch definition	Viability of dysfunctional myocardium
Schelbert et al, 1980	^{18}FDG/$^{13}NH_3$ PET	Semiquantitative Normalization to peak ^{18}FDG and peak $^{13}NH_3$ uptake	NA	^{18}FDG/$^{13}NH_3$ ratio >1 in hypoperfused myocardium	–
Marshall et al, 1983	^{18}FDG/$^{13}NH_3$ PET	Semiquantitative Normalization to peak ^{18}FDG and peak $^{13}NH_3$ uptake	N = 10 Age 24-32 y ^{18}FDG and $^{13}NH_3$	^{18}FDG-$^{3}NH_3$ difference >mean + 2SD in normals	–
Tillisch et al, 1986	^{18}FDG/$^{13}NH_3$ PET	Semiquantitative Normalization to peak ^{18}FDG and peak $^{13}NH_3$ uptake	N = 10 Age 24-32 y ^{18}FDG and $^{13}NH_3$	^{18}FDG-$^{3}NH_3$ difference >mean + 2SD in normals in hypoperfused myocardium	1) Normal ^{18}FDG and $^{13}NH^{3}$ uptake 2) Decreased $^{13}NH_3$ uptake and ^{18}FDG-$^{3}NH_3$ difference >mean + 2SD in normals
Tamaki et al, 1989	^{18}FDG/$^{13}NH_3$ PET	Visual evaluation	N = 20 Mean age 45 y Only $^{3}NH_3$	Hypoperfused myocardium with "definitely higher" ^{18}FDG uptake	Hypoperfused myocardium with "definitely higher" ^{18}FDG uptake
Porenta et al, 1992	^{18}FDG/$^{13}NH_3$ PET	Semiquantitative Normalization to peak $^{13}NH_3$ uptake	N = 11 Mean age 24 y ^{18}FDG and $^{13}NH_3$	^{18}FDG-$^{3}NH_3$ difference >mean + 2SD	–
Knuuti et al, 1993	^{18}FDG PET/ Sestamibi SPECT	Semiquantitative Normalization to peak Sestamibi Quantitative glucose uptake	NA	–	Relative ^{18}FDG uptake >90% Absolute glucose uptake >0.42 μmol/min/g
Vom Dahl et al, 1994	^{18}FDG/$^{13}NH_3$ PET	Visual uptake scoring system: 1 normal, 2 slight reduction, 3 severe reduction, 4 background	NA	^{18}FDG uptake score ≥2 and $^{13}NH_3$-^{18}FDG ≥1	1) ^{18}FDG uptake score ≥2 and $^{13}NH_3$-^{18}FDG ≥1 2) ^{18}FDG uptake score ≥2 and $^{13}NH_3$-^{18}FDG <1
Grandin et al, 1995	^{18}FDG/$^{13}NH_3$ PET	Semiquantitative Normalization to peak $^{13}NH_3$ uptake in each slice Quantitative glucose extraction (glucose uptake/MBF) normalized to remote	Yes	^{18}FDG/$^{13}NH_3$ ratio >1.2	Normalized absolute glucose extraction >100%
Gerber et al, 2001	^{18}FDG PET	Quantitative glucose uptake normalized to uptake in normally contracting myocardium	NA	–	Normalized absolute glucose uptake >45% of peak

Semiquantitative: circumferential profile analysis; NA: not available; y: years.

1983b). Such dysfunctional myocardial regions were later shown to improve their contractile function after coronary artery bypass surgery (CABG) in patients with chronic ischemic heart disease (Tillisch et al. 1986). Conversely, no change was observed in myocardial segments in which both ^{18}FDG and $^{13}NH_3$ uptake were decreased – so-called "metabolism-blood flow match". The pathophysiologic mechanism responsible for the "mismatch" pattern in reversibly dysfunctional myocardium remains unknown and no clear definition of this scintigraphic pattern neither by relative nor absolute PET imaging criteria has been established. Historically, a variety of ^{18}FDG imaging criteria has been used to identify reversibly dysfunctional myocardium of which the relative diagnostic power to predict recovery of contractile function is unsettled (**Table 1**), see detailed discussion in section 4.3., page 16. Nevertheless, identification of this so-called "viable myocardium" – using ^{18}FDG and $^{13}NH_3$ PET imaging appeared to be a promising diagnostic tool in the clinical management of patients with chronic ischemic heart disease and reduced left ventricular function.

The specific aims of the thesis were:

1. To assess the myocardial ^{18}FDG-$^{3}NH_3$ uptake relation in healthy subjects age-matched to the target age for the development of ischemic heart disease (Study I).
2. To assess factors determining variability of insulin stimulated myocardial glucose uptake in healthy subjects (Study II).
3. To validate ^{18}FDG and PET for quantitation of regional myocardial glucose uptake in normal and post-ischemic myocardium (Study III).
4. To study glucose uptake and intermediate glucose metabolism in post-ischemic myocardium (Study III & IV).
5. To assess the association between whole-body insulin sensitivity and insulin stimulated myocardial glucose uptake, including prognostic implications in patients with ischemic heart disease and heart failure (Study V).
6. To compare myocardial ^{18}FDG uptake to indices of viable myocardium by dobutamine echocardiography and Sestamibi-SPECT (Study VI).
7. To assess the myocardial ^{18}FDG-$^{3}NH_3$ uptake relation and its relation to outcome in patients with chronic ischemic heart disease and reduced left ventricular function after a prolonged strategy of medical treatment undergoing CABG (Study VII).

2. MATERIAL

Human protocols conformed with the principles outlined in the Declaration of Helsinki and were approved by the local ethics committee. All participants gave their informed consent. The animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996).

2.1. HEALTHY SUBJECTS

Stratified by age a total of 30 healthy subjects (23 men and 7 women) were recruited from the database of the Copenhagen City Heart Study (Study I and II) (Nyboe et al. 1989). Data acquired in healthy subjects were in part also reported in Study V and VII. The subjects were randomly selected according to the following criteria: ≥ 50 years of age, no history of cardiovascular disease, normal blood biochemistry including lipid status and blood glucose, normal resting blood pressure, normal electrocardiogram at rest, normal exercise test and normal echocardiography. The likelihood of coronary artery disease was < 5% in all subjects (Diamond & Forrester 1979).

2.2. ANIMALS AND PATIENTS WITH ISCHEMICALLY JEOPARDIZED MYOCARDIUM

Adult mongrel dogs were anesthetized after an overnight fast with sodium pentothal (2 mg/kg, i.v.) and morphine (1 mg/kg, i.v.), intubated, and ventilated with air supplemented with oxygen. Anesthesia was maintained with increments of sodium pentothal and morphine. Femoral arteries were exposed, and 7F catheters advanced into the abdominal aorta for arterial blood sampling and blood pressure recording.

Open chest preparation (Study III): A left lateral thoracotomy was performed, and the heart suspended in a pericardial cradle. Two diagonal branches of the left anterior descending coronary artery were isolated, and ligatures placed loosely around the proximal portions. The largest epicardial vein draining from the myocardial region between the two branches (intervention region) was cannulated distal to the ligatures for venous blood sampling. The coronary sinus was cannulated to obtain blood from global myocardium. A left atrial appendage catheter was inserted for injection of microspheres, dye and potassium chloride.

Closed chest preparation (Study IV): The left carotid artery was exposed and a 7F catheter advanced under fluoroscopic guidance to the ostium of the left anterior descending coronary artery (LAD). A 3F Fogarty balloon catheter was passed through the 7F catheter into the LAD and the tip placed distal to the first diagonal branch and visualized by contrast medium (Angiovist; Berlex, Wayne, NJ). The guiding catheter was disengaged and the balloon was briefly inflated (2 min) with contrast medium/saline. Appropriate balloon positioning was confirmed by a corresponding wall motion abnormality during inflation with two-dimensional (2D) echocardiography. After post-ischemic measurements with PET (day 1 or day 2 post-ischemia) a left lateral thoracotomy was performed and the heart suspended in a pericardial cradle to obtain myocardial biopsies.

Patients with ischemic heart disease (Study V, VI, VII): Patients referred for coronary angiography at Rigshospitalet, Copenhagen, were studied. One group of patients (Group A, **Table 2**) with a myocardial area with abnormal contraction subtended by a totally occluded coronary artery was studied as a model for potentially viable myocardium (Study VI). Patients with diabetes and severe left ventricular dysfunction were excluded. A second group of patients (Group B, Table 2) were prospectively included according to the following inclusion criteria: 1) a history of medically treated ischemic heart disease of >6 months duration 2) a left ventricular ejection fraction < 45% as measured by radionuclide cardiography and 3) a clinical indication to perform CABG (Study V and VII). The decision to perform CABG was based on clinical and angiographic criteria according to the recommendations derived from the CASS study (Alderman et al. 1983). Exclusion criteria were a history of a recent myocardial infarction, unstable angina pectoris and chronic

Table 2. Study groups.

	Group A	Group B
Patient characteristics		
Number of patients	17	45
Mean age, years (SD)	59 (9)	64 (8)
Males	15	41
Mean duration of IHD, years (SD)	NA	8.5 (7)
Mean LVEF, % (SD)	45 (7)	31 (7)
Prior MI	14	39
Diabetes	–	10
Hypercholesterolemia	7	23
Hypertension	6	15
Coronary angiography		
1-vessel disease	0	0
2-vessel disease	12	12
3-vessel disease	5	33
Symptoms		
CCS class III-IV	7	32
NYHA class III-IV	2	13

SD: standard deviation; IHD: ischemic heart disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association; NA: not available; Group A: Study VI; Group B: Study V (n = 29) and VII (n = 45).

atrial fibrillation. In study V patients with a history of diabetes or fasting blood glucose >6.5 mM were excluded. Accordingly data acquired in 29 of the Group B patients were reported in both Study V and VII.

The patients were consecutively included in the period 1994-1998 according to the study inclusion criteria and the patients are thus representative of the natural history of ischemic heart disease in addition to referral and treatment strategy of the period. In the subsequent 6 years medical and surgical treatment of patients with ischemic heart disease has undergone a substantial development improving both symptom relief and lifetime expectancy. Results obtained in this work that could have potentially clinical implications should therefore be interpreted accordingly.

3. METHODS

Medication taken by the patients was continued throughout the investigations. In patients with ischemic heart disease the regional left ventricular contractile function was evaluated by 2 dimensional echocardiography and global contractile function by radionuclide cardiography (Study V & VII). Coronary anatomy was evaluated by coronary angiography (Study V-VII). Regional myocardial ^{18}FDG and $^{13}NH_3$ uptake, quantified glucose uptake, blood flow and hyperemic blood flow were evaluated by PET using a left ventricular 16 segment model (Pierard et al. 1987, Schiller et al. 1989). In both healthy subjects and cardiac patients ^{18}FDG studies were performed after an overnight fast during a hyperinsulinemic euglycemic glucose clamp according to DeFronzo and co-workers (DeFronzo et al. 1979) and $^{13}NH_3$ studies following a light carbohydrate containing breakfast. Animal studies were performed after an overnight fast.

3.1. POSITRON EMISSION TOMOGRAPHY

Measurements of myocardial ^{18}FDG and $^{13}NH_3$ uptake, blood flow and insulin stimulated glucose uptake by PET were performed according to tracer kinetic principles as reviewed elsewhere (Schelbert 1991). In brief, the positron emitting tracer (^{18}FDG or $^{13}NH_3$) is injected intravenously during steady state conditions, while a time sequence of cardiac images is acquired simultaneously by the positron emission tomography – so-called dynamic image acquisition. The arterial delivery (input function) and myocardial retention of the tracer as a function of time are recorded by assigning regions of interest (ROIs) to the left atrial blood pool and the myocardium on the reoriented PET images (**Figure 2**). Time activity curves thus generated are entered into tracer kinetic models to calculate myocardial blood flow or insulin stimulated myocardial glucose uptake; i.e. *quantitative PET imaging* (see 3.1.2 and 3.1.3). Following extraction to the tissue the tracer is cleared from the blood and thereupon accumulated tracer activity in the myocardium reflects the relative distribution of glucose uptake or myocardial blood flow (Figure 2) – i.e. *semiquantitative PET imaging* (see 3.1.1). Semiquantitative imaging is performed by delayed recording of a single PET image – so-called static image acquisition.

The terminology and principles of the semiquantitative and quantitative PET methods used in this work are shown in **Table 3**. Semiquantitative imaging provides information about the relative distribution of tracer uptake throughout the myocardium in percentage of the highest tracer uptake of the left ventricle (Figure 2). Consequently, globally increased or decreased myocardial glucose uptake or blood flow will not be detected using this method. This limitation of the semiquantitative method was recently illustrated in heart transplant patients in whom relative myocardial $^{13}NH_3$ uptake during vasodilation with dipyridamole was found to be completely normal (Kofoed 1998). Yet absolute hyperemic myocardial blood flow of the left ventricle quantitated by tracer kinetic modeling was severely reduced correlating with the severity of transplant related coronary artery disease detected by intracoronary ultrasound. Furthermore, using semiquantitative imaging it cannot be determined

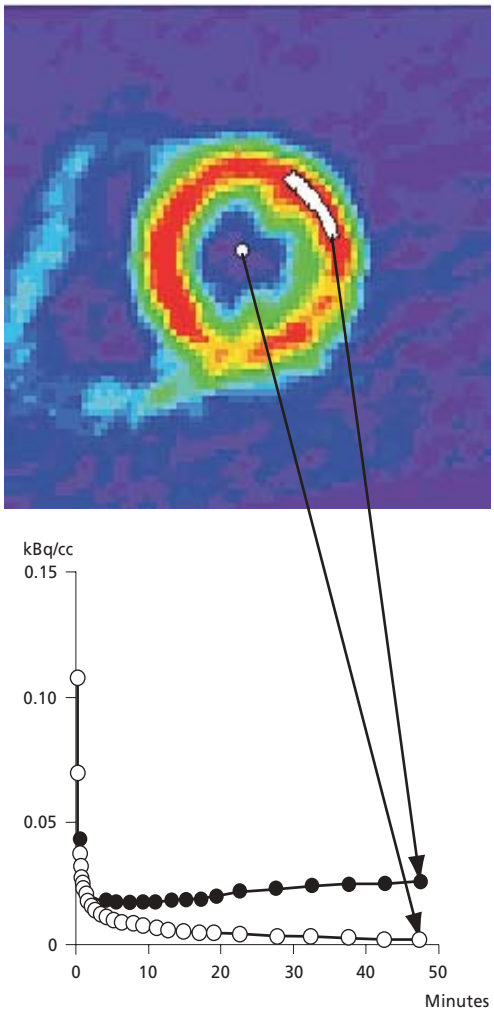

Figure 2. Semiquantitative and quantitative ^{18}FDG PET imaging. Relative ^{18}FDG uptake may be evaluated semiquantitative by visual inspection of the color-scale seen on the short axis image (top panel) and by circumferential profile analysis (see section 3.1.1). The image is acquired approximately 50 minutes after ^{18}FDG injection, where most of the tracer has been cleared from the blood. A vague outlining of the right ventricle can be appreciated at the left. For quantitative evaluation, regions of interest (see arrows) are assigned to the myocardial tissue (closed circles) and to the blood pool cavity (open circles) for generation of time activity curves from injection time (T = 0) to 50 minutes after injection (bottom panel). Absolute glucose uptake is calculated using a tracer kinetic model. For details see text.

if a regional reduction in relative tracer uptake reflects truly decreased myocardial blood flow or glucose uptake or relatively increased uptake in remote myocardium. Interestingly, in the pioneering work of Vanoverschelde and co-workers it was demonstrated in patients with ischemic heart disease that relatively decreased $^{13}NH_3$ uptake in collateral dependent dysfunctional myocardium reflected increased quantitated myocardial blood flow in remote myocardium rather than decreased blood flow in the dysfunctional region (Vanoverschelde et al. 1993). However, it is evident that quantitative imaging is logistically and computationally complex making it less suitable for general clinical use. Consequently, in the current thesis for evaluation of normal-physiological and pathophysiological aspects of myocardial glucose uptake quantitative methods were used (II, III, IV, V), whereas the logistically simpler semiquantitative methods were used in the clinical evaluation of myocardial contractile dysfunction (I, V, VI, VII). In study V both semiquantitative and quantitative methods were used as the focus of the study included both clinical and pathophysiological aspects. A hybrid semiquantitative method was used in study VI combining PET and SPECT (single photon emission computerized tomography) for logistical reasons (see 3.1.1). The relative merits of semiquantitative and

Table 3. Terminology of myocardial ^{18}FDG and $^{3}NH_3$ PET imaging.

Parameter	Study number	Image acquisition	Image analysis	Anatomical model	Units
SEMIQUANTITATIVE					
^{18}FDG uptake	I	Static ^{18}FDG	Circumferential profile analysis Normalization to Peak tracer uptake	16 LV segments	%
$^{3}NH_3$ uptake	I	Static $^{3}NH_3$	Circumferential profile analysis Normalization to Peak tracer uptake	16 LV segments	%
1) ^{18}FDG-$^{3}NH^{3}$ uptake relation 2) Glucose metabolism-blood flow relation	V, VII (I)	Static ^{18}FDG & $^{3}NH_3$	Circumferential profile analysis Normalization to peak tracer uptake Comparison with normal values Reduced uptake: Uptake < (mean –2SD)	16 LV segments Global LV	1) Segments with PET-normal, PET-mismatch, PET-match. PET-reverse mismatch 2) % of LV with PET patterns
^{18}FDG-$^{3}NH_3$ uptake difference	I	Static ^{18}FDG & $^{3}NH_3$	Circumferential profile analysis Normalization of 18FDG to peak $^{3}NH_3$ Calculation of uptake difference	16 LV segments	%
^{18}FDG uptake ad modum Knuuti See section 3.1	VI	Static ^{18}FDG & Sestamibi SPECT	Assignment of regions of interest Normalization to segment with peak Sestamibi uptake	16 LV segments	%
QUANTITATIVE					
^{18}FDG metabolic rate	III	Dynamic ^{18}FDG	Curve fitting analysis RC corrected Patlak plot	Intervention/ remote regions	μmol/min/g
1) Glucose metabolic rate 2) Glucose uptake	II, IV, V	Dynamic ^{18}FDG	Curve fitting analysis LC corrected RC corrected Patlak plot 3-compartment model (IV)	16 LV segments Intervention/ remote regions	μmol/min/g
Myocardial blood flow	II, IV, V	Dynamic $^{3}NH_3$	Curve fitting analysis RC corrected 2-compartment model	16 LV segments Intervention/ remote regions	ml/min/g

Study numbers indicates the studies in which each type of data is reported. For details see 3.1.
LV: left ventricular; SD: standard deviation; RC: recovery coefficient; LC: lumped constant.

quantitative PET imaging for clinical diagnostic purposes will be discussed in section 4.3.

Relative myocardial ^{18}FDG and $^{13}NH_3$ tracer distribution evaluated by semiquantitative image analysis are termed "^{18}FDG and $^{13}NH_3$ uptake" (Table 3). Furthermore, the relationship between ^{18}FDG and $^{13}NH_3$ uptake assessed by circumferential profile analysis is termed "the myocardial ^{18}FDG-$^{13}NH_3$ uptake relation". In study I the term "myocardial glucose metabolism-blood flow relation" was used synonymously with the "myocardial ^{18}FDG-$^{13}NH_3$ uptake relation". In addition to ^{18}FDG and $^{13}NH_3$ uptake the so-called "^{18}FDG-$^{13}NH_3$ uptake difference" was also calculated in study I (Porenta et al. 1992). Finally myocardial ^{18}FDG uptake "ad modum Knuuti" was calculated as explained in 3.1.1. All of these terms are used to acknowledge that semiquantitative image analysis does not take into account the partial volume effect (see 3.1.4), effects of regional myocardial differences of tracer redistribution late after tracer injection (see 4.1) and the lumped constant (see 5.1).

In the original work of Ratib and co-workers (see 3.1.2) the quantitative term "myocardial metabolic rate of glucose" (Study IV) was used to designate the unidirectional flux of glucose into the myocyte by membrane transport and subsequent phosphorylation (Ratib et al. 1982). Accordingly, the corresponding transport and phosphorylation of ^{18}FDG was termed myocardial ^{18}FDG metabolic rate (Study III). In subsequent publications the shorter "myocardial glucose uptake" instead of "myocardial glucose metabolic rate" was adopted to denote myocardial membrane transport and phosphorylation of glucose (II, V) i.e. myocardial ^{18}FDG metabolic rate corrected by the lumped constant (see 5.1).

3.1.1. Semiquantitative PET image analysis

For clinical evaluation of contractile dysfunction (I, V, VII) a semiquantitative yet computationally simple estimate of ^{18}FDG and $^{13}NH_3$ uptake based on circumferential profile analysis was used (Porenta et al. 1992). In brief, for each of 6 short axis slices 60 equally spaced radial profiles were acquired. The peak pixel value (kBq/cc) from each profile was recorded and the relative tracer distribution of the entire left ventricle was represented by a total of 360 pixel values (60 profiles for each of the 6 short axis slices). Pixels with a value in the maximal 5% were given the value 100%, and the remaining pixels normalized accordingly. In addition to the myocardial ^{18}FDG and $^{13}NH_3$ uptake this method also permits the calculation of the so-called "myocardial difference" (Study I). This parameter is calculated by normalization of both ^{8}FDG and $^{13}NH_3$ uptake to pixel values in the maximal 5% of the $^{13}NH_3$ study and subsequently subtraction of ^{8}FDG and $^{13}NH_3$ uptake (Porenta et al. 1992).

In patient studies (Study V and VII) ^{18}FDG and $^{13}NH_3$ uptake

Table 4. Myocardial glucose metabolism-blood flow PET patterns.

PET pattern	^{18}FDG uptake	$^{13}NH_3$ uptake
Normal	Normal	Normal
Reverse mismatch	Decreased	Normal
Mismatch	Increased/normal	Normal/decreased
Match	Decreased	Decreased

were categorized as decreased if uptake was < 2 standard deviations below the corresponding mean uptake in healthy subjects (Porenta et al. 1992). Accordingly, in the patients the following glucose metabolism-blood flow PET patterns were recorded: PET-normal (normal $^{13}NH_3$ and ^{8}FDG uptake), PET-mismatch (reduced $^{13}NH_3$ and normal ^{18}FDG uptake), PET-match (reduced $^{13}NH_3$ and ^{18}FDG uptake) and PET-reverse mismatch (normal $^{13}NH_3$ and reduced ^{18}FDG uptake) (see **Table 4**). In study VII the global left ventricular extent of these PET patterns were related to global left ventricular contractile function measured by radionuclide cardiography. To evaluate differences of regional myocardial ^{18}FDG and $^{13}NH_3$ uptake related to normal-physiology and pathophysiology of regional coronary anatomy and contractile function average ^{18}FDG and $^{13}NH_3$ uptake values were calculated in 16 left ventricular myocardial segments (Schiller et al. 1989), (Study I and V). The same segmental model was used in studies involving quantitative imaging in humans (Study II and V).

In study VI regional relative ^{18}FDG uptake was calculated by manual assignment of 16 regions of interest on short axis images. The analysis was performed manually as software for circumferential profile analysis was not available at the time of the study. Furthermore, relative regional ^{18}FDG uptake was normalized to the segment with peak Sestamibi uptake (see 3.4), as the cyclotron at Rigshospitalet could not yet produce the $^{13}NH_3$ tracer for PET imaging at the time of the study. The threshold value of ^{18}FDG uptake to predict subsequent recovery of contractile function after revascularization was determined in a subgroup of patients (N = 8). A receiver operating characteristic analysis revealed an optimal operation point of 90% of ^{18}FDG uptake in accordance with previously published values (Knuuti et al. 1993).

3.1.2. Myocardial glucose uptake

Myocardial glucose uptake was measured using ^{18}FDG. This compound is a glucose analogue, which similar to glucose is transported into the cytosol and phosphorylated by hexokinase (Figure 1). Once phosphorylated ^{18}FDG is not further metabolized and myocardial glucose uptake may thus be assessed by the amount of tracer trapped in the cytosol. Accordingly, glucose uptake measured by ^{18}FDG reflects membrane transport and phosphorylation and cannot specifically trace subsequent degradation of glucose in various downstream pathways (e.g. glycolysis, glycogen synthesis, and glucose oxidation). In the current work the term "myocardial glucose uptake" is used to denote the combined flux of glucose through membrane transport and phosphorylation (see Table 3). In Study III and IV the term "glucose metabolic rate" was used synonymously with myocardial glucose uptake. A small fraction of myocardial ^{18}F-G6P is dephosphorylated by glucose-6-phospatase to ^{18}FDG, which is lost to the bloodstream. A tracer kinetic model for the quantitation of tissue glucose uptake using radiolabelled deoxyglucose was initially proposed by Sokoloff for studies of glucose uptake in the brain (Sokoloff et al. 1977). This 3-compartment model was extended to account for the potential role of ^{18}F-deoxy-G6P dephosphorylation in ^{18}FDG PET studies and subsequently validated for quantitative PET imaging in canine myocardium (Huang et al. 1980, Ratib et al. 1982) (**Figure 3**) (Study IV). Estimation of the individual rate constants (k_1-k_4) was found to be less useful due to a large individual parameter variation (Ratib et al. 1982, Gambhir et al. 1989). In contrast, estimation of the fractional utilization constant K* – a rate constant describing the fractional rate at which ^{18}FDG is transported across the capillary and cell membranes and then phosphorylated – was found to be a more robust parameter:

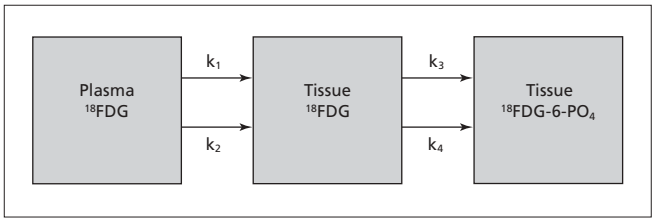

Figure 3. Three-compartment model for absolute quantitation of myocardial ^{18}FDG uptake. The rate constants k_1-k_4 represent the rate of exchange of material between compartments. For details see text.

Equation 1: $K^* = (k_3 \times k_1) / (k_2 + k_3)$ (ml/min/g)

A simplified approach was therefore later suggested by Gambhir based on the graphical analysis developed by Patlak (see Equation 2) describing the irreversible uptake of a tracer into one compartment (Patlak et al. 1983, Gambhir et al. 1989), (Study II, III, V). Within the first 50 minutes after injection of ^{18}FDG dephosphorylation of ^{18}F-G6P is assumed to be zero and the tracer is considered irreversibly trapped in one compartment. Plotting the instant ratio at time t of tissue (Am(t)) to plasma (Cp(t)) tracer concentration against the ratio of the integrated arterial tracer concentration $\int_0^t Cp(s)\,ds$ to the current arterial concentration Cp(t) a straight line may be recorded at later scan times.

Equation 2: $$Am(t)/Cp(t) = [(k_3 \times k_1)/(k_2 + k_3)]/Cp(t)\int_0^t Cp(s)\,ds + W$$

The slope of this line calculated by linear regression analysis is identical to the fractional utilization constant K* (Equation 1). W represents the intercept at the y-axis and is a function of the steady-state volume of the reversible compartments and the effective plasma volume. Data points within the 15-42 minute time interval after tracer injection was used to derive K* and linearity was confirmed by visual analysis. The Patlak approach is computationally much simpler than the 3-compartment model and provides very similar estimates of glucose uptake (Gambhir et al. 1989). Myocardial glucose uptake is calculated using the equation:

Equation 3: Glucose uptake = $1/LC \times (K^* \times C_{glu})$ µmol/min/g

where C_{glu} is the plasma concentration of glucose and LC the so-called "lumped constant". The lumped constant was introduced by Sokoloff to "lump together" all factors accounting for kinetic differences between glucose and ^{18}FDG with respect to membrane transport and phosphorylation (Sokoloff et al. 1977). Aspects with regard to the stability of the lumped constant will be discussed in detail in section 5.1. In study III the term "^{18}FDG metabolic rate" is used to designate glucose uptake quantified by ^{18}FDG and not corrected by the lumped constant (see Table 3).

3.1.3. Myocardial blood flow

Myocardial blood flow was measured using N-13 ammonia ($^{13}NH_3$). This tracer is delivered to and extracted by the myocardium in proportion to blood flow and the first-pass extraction fraction is nearly 100% (Schelbert et al. 1979, Schelbert et al. 1981). In the myocytes $^{13}NH_3$ is metabolized and thus trapped in the tissue mainly in the form of ^{13}N-glutamine (Krivokapich et al. 1984). The net myocardial retention of the tracer, however, is only about 60-80% within normal physiological flow values and inversely related to myocardial blood flow (Schelbert et al. 1981). A 2 compartment model was therefore developed incorporating a correction for the variable tissue retention (Renkin-Crone model) (Renkin 1959, Crone 1963, Schelbert et al. 1981, Krivokapich et al. 1989, Nienaber et al. 1991). Using this model excellent correlations have been demonstrated between myocardial blood flows measured by $^{13}NH_3$-PET on one hand and blood flow measured by radiolabelled microspheres (dogs) and Oxygen-15 water-PET on the other (humans) (Kuhle et al. 1992, Nitzsche et al. 1996). Furthermore, myocardial blood flow reserve measured by $^{13}NH_3$-PET correlates with the extent of coronary vascular disease (Di Carli et al. 1995b, Kofoed et al. 1997). In addition,

similar close correlations have been reported in animal experimental studies evaluating the validity of $^{13}NH_3$ for the measurement of myocardial blood flow during severe ischemia and pharmacologically induced hyperemia (Bol et al. 1993). On the other hand, it is not known to what extent these findings may apply in patients with ischemic heart disease.

In the current work we measured myocardial blood flow at rest and after intravenous dipyridamole infusion (Study II and V).

3.1.4. Technical limitations

The spatial resolution of current positron emission tomographs limits the accuracy of cardiac PET imaging. The infield spatial resolution of most available whole-body tomographs is around 7-9 mm. The recorded regional tracer concentration is only identical to the true concentration if the myocardial thickness is twice the spatial resolution of the tomograph used (Hoffman et al. 1979). In human studies this is rarely the case and the amount of tracer detected by the tomograph is therefore less than what is actually accumulated in the myocardium – a phenomenon known as the partial volume effect. Depending on the technical characteristics of the tomograph a correction for the partial volume effect (so-called recovery correction) may be applied if the myocardial thickness is known. The size of the normal myocardial wall in end-diastole is approximately 10 mm and under such conditions a correction of 10-20% of tissue uptake is required in most tomographs as a consequence of the partial volume effect. In ischemic myocardium the myocardial wall thickness may often be below 10 mm accentuating this problem in patients studies. If a uniform recovery correction factor throughout the left ventricle is used under such conditions this will result in an underestimation of tracer uptake in regions with thinning of the myocardial wall. Reliable and absolute measures of myocardial thickness in all regions of the left ventricle are rarely available and the overall wall thickness is therefore assumed to be 10 mm (Study V). In the animal studies (Study III & IV) regional wall thickness was estimated using a previously validated fitting algorithm (Porenta et al. 1995). In one study regional recovery correction factors were applied based on echocardiography and magnetic resonance imaging measurements (Study II).

Another consequence of the limited spatial resolution of PET tomographs is the activity spillover effect. The activity spillover effect is the phenomenon that tracer activity recorded by the tomograph may be "misplaced" to adjacent structures. Depending on the direction of the spillover glucose uptake or flow may be overestimated (spillover from the left ventricular cavity to the myocardium) or underestimated (spillover from myocardium to the left ventricular cavity. Activity spillover between adjacent high and low uptake myocardial regions may also occur. The special problem of spillover form both the left ventricular and right ventricular cavity into the septum may partly be solved if an input curve is generated from the right ventricular cavity and incorporated in the model (Hove et al. 1998). In the current thesis calculation of myocardial glucose uptake by the 3-compartment model (Study IV) and myocardial blood flow by the 2-compartment model (Study II, IV, V) were corrected for activity spillover from the input function to the myocardium by inclusion of the spillover fraction as an additional parameter in the model (Ratib et al. 1982, Kuhle et al. 1992). Glucose uptake calculated by Patlak graphical analysis is independent of the activity spillover from arterial input to the myocardium (Gambhir et al. 1989). Activity spillover from myocardium to the input function at later times was minimized by the use of atrial input functions (Hove et al. 2004).

3.2. WHOLE-BODY INSULIN SENSITIVITY

In study II and V whole-body insulin sensitivity was measured according to DeFronzo and co-workers (DeFronzo et al. 1979) and was defined as the mean glucose delivery rate (μmol/min/kg of body weight) needed to maintain a steady state during the second hour of a hyperinsulinemic euglycemic glucose clamp (Paternostro et al. 1996).

3.3. INVASIVE MEASUREMENTS

To evaluate the relationship between regional myocardial glucose uptake quantified by ^{18}FDG and intermediate glucose metabolism in a canine model of regional ischemia-reperfusion (Study III & IV) invasive measurements of regional myocardial substrate flux, glycolytic intermediates and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were performed.

Myocardial substrate flux. Arterial (A) and regional coronary venous (V) plasma substrate concentrations (glucose, lactate, FFA) were measured using standard laboratory methods (Bergmeyer et al. 1974, Gutmann & Wahlefeld 1974, Okabe et al. 1980). To increase accuracy arterial and venous blood samples for each time point were drawn in triplicates and the mean value was used for subsequent calculations. Regional myocardial blood flow was measured using radiolabelled microspheres (Heymann et al. 1977), allowing simultaneous measurement of myocardial glucose uptake by ^{18}FDG PET and by the Fick principle. Net substrate uptake was calculated according to the Fick principle as $U = F \times (A-V)$, where F is plasma flow (microsphere flow × (1-Hct)). To measure myocardial glucose oxidation, [U-^{14}C]glucose was infused into a peripheral vein and, arterial and coronary venous blood samples were drawn after equilibration. Samples were subsequently analyzed to determine the amount of $^{14}CO_2$ produced (Wisneski et al. 1985a).

Glycolytic intermediates and GAPDH. Multiple transmural myocardial biopsies (50-100 mg each) were obtained by high speed drill with a 2 mm diameter stainless steel needle and were frozen immediately in liquid N_2. Biopsies were taken progressively from apex to base of the heart to minimize blood flow disruption to subsequent biopsies, sites being closed with dried compressed sponge plugs. Pooled samples were homogenized and glycolytic metabolites were assayed using standard spectrophotometric methods (Bergmeyer 1974). Biopsy contents of GAPDH protein and enzyme activity were determined as described in detail in (IV).

3.4. DOBUTAMINE CONTRACTILE RESERVE AND SESTAMIBI-UPTAKE

Dobutamine echocardiography. Two-dimensional echocardiographic recordings were obtained at rest and at each 3 minute stage of dobutamine infusion at rates of 5-10-20-30 and 40 μg/kg/minute (Carstensen et al. 1995). Infusion was terminated at the following endpoints: 85% of the age-corrected heart rate, intolerable angina pectoris, obvious stress induced wall motion abnormalities, maximal drug infusion rate or severe side effects (ventricular tachycardia, hypotension, anxiety). Regional LV contractile function was qualitatively evaluated and improvement of contraction during dobutamine infusion in segments that were hypo- or akinetic at baseline was considered indicative of contractile reserve (Study VI & VII).

Sestamibi-SPECT. Myocardial technetium-99m-methoxyisobutyl isonitrile (Sestamibi) uptake was evaluated using single photon emission computerized tomography (SPECT) performed following intravenous infusion of Sestamibi. Regional Sestamibi uptake was evaluated by visual image analysis and myocardial segments with Sestamibi uptake >50% of the maximal value was considered as having preserved uptake (Study VI). The myocardial segments with the highest regional Sestamibi uptake was defined as normal and reference region for normalization of ^{18}FDG uptake. In all patients this segment was contracting normally and was subtended by an angiographically normal coronary artery.

4. MYOCARDIAL ^{18}FDG PET IMAGING IN HEALTHY SUBJECTS

Since cardiac substrate selection is highly versatile, standardization of metabolic conditions is required in order to evaluate myocardial glucose uptake reliably. As a consequence of the glucose-free fatty acid cycle myocardial glucose uptake is suppressed by high plasma levels of FFA during fasting (Randle et al. 1963, Lassers et al. 1971,

Nuutila et al. 1992). Cardiac glucose uptake in the fasted state can be evaluated in animal models, because relatively high doses of ^{18}FDG can be injected, whereas limited doses may be given to humans. Accurate ^{18}FDG imaging during fasting may only be feasible in a fraction of human subject as a consequence of an unfavorable signal-to-noise ratio (Berry et al. 1991). The hyperinsulinemic euglycemic glucose-insulin clamp procedure was therefore introduced to improve PET image quality and to provide metabolic steady state conditions for quantitative evaluation of myocardial glucose uptake (DeFronzo et al. 1979, Knuuti et al. 1992). Physiologic hyperinsulinemia abolishes myocardial extraction of FFA and increases glucose extraction substantially (Ferrannini & Santore 1993). Accordingly, insulin stimulated myocardial glucose uptake recorded during glucose-insulin clamp may be considered the near maximal capacity of the tissue to utilize this substrate at rest.

Based on the initial experience of Schelbert and co-workers (Schelbert et al. 1980) it was found that a differentiated metabolic profile of ischemically jeopardized myocardium could be obtained by relating regional ^{18}FDG uptake to myocardial blood flow measured by $^{13}NH_3$. Semiquantitative PET imaging therefore became widely used in clinical studies to determine the myocardial ^{18}FDG -$^{13}NH_3$ uptake relation. Despite the importance of using appropriate normal reference values pointed out by Porenta and co-workers (Porenta et al. 1992), most clinical studies have been performed without comparing to normal reference values. Furthermore, combined measurements of ^{18}FDG and $^{13}NH_3$ uptake have only been performed in a small number of healthy subjects and primarily in subjects younger than the typical age for the development of ischemic heart disease (≥50 years), see **Table 5**. Quantitative PET imaging was expected to improve the diagnostic accuracy, yet a substantial variability of insulin stimulated absolute glucose uptake was noted in normally contracting myocardium (Gerber et al. 2001). For clinical evaluation of reversibly dysfunctional myocardium, a variety of ^{18}FDG PET imaging criteria has been developed (Table 1). However, it remains unresolved to what extent normal values are needed and further more which of these techniques (semiquantitative or quantitative) should be preferred in clinical diagnostic ^{18}FDG PET imaging. We therefore evaluated cardiac metabolism during hyperinsulinemic euglycemic glucose-insulin clamp in relation to myocardial blood flow in healthy subjects age-matched to the target age for the development of ischemic heart disease (≥50 years) (Levy et al. 1990) using semiquantitative (Study I) and quantitative (Study II) ^{18}FDG and $^{13}NH_3$ PET imaging. Subsequently the relative merits of semiquantitative and quantitative clinical ^{18}FDG PET imaging are discussed.

4.1. THE MYOCARDIAL ^{18}FDG-$^{13}NH_3$ UPTAKE RELATION

The aim of the study was to assess the ^{18}FDG -$^{13}NH_3$ uptake relation using PET in healthy subjects age-matched to the target age for the development of ischemic heart disease.

Determination of the relationship between myocardial glucose metabolism and blood flow by PET has for several years been considered a valuable diagnostic tool in the clinical management of patients with chronic ischemic heart disease and impaired left ventricular function (for review see Chapter 7, page 22). Based on the uptake of ^{18}FDG and $^{13}NH_3$ the myocardium is categorized into four different glucose metabolism-blood flow PET patterns: PET-nor-

Table 5. Values of combined ^{18}FDG and blood flow PET imaging in healthy subjects.

Author	Subjects (N)	Mean age, years	Substrate conditions	PET image acquisition	Regional ^{18}FDG	Regional blood flow	^{18}FDG and blood flow comparison	Mismatch criteria
De Landsheere et al, 1989	10	26	Oral glucose loading	Static ^{18}FDG Static potassium-38	84-107% uptake	81-96% uptake	^{18}FDG and blood flow Ratio 1.02-1.12	Ratio >1.2
Gropler RJ et al, 1990	7	25	Fasting Oral glucose loading	Static ^{18}FDG Dynamic ^{15}O-water PET	^{18}FDG uptake 20% increased in post-lateral wall	No significant differences	NA	NA
Berry et al, 1991	17	36	Oral glucose loading	Static ^{18}FDG Static $^{13}NH_3$	NA	NA	Modified ^{18}FDG/$^{13}NH_3$ ratio 20% increased in the postero-lateral wall	NA
Porenta et al, 1992	11	24	Oral glucose loading	Static ^{18}FDG Static $^{130}NH_3$	No significant differences	10-15% lower in postero-lateral wall	^{18}FDG-$^{3}NH_3$ difference 22% in the postero-lateral wall	^{18}FDG-$^{3}NH_3$ difference >mean + 2SD
Blanksma et al, 1995	7	NA	Oral glucose loading	Dynamic ^{18}FDG Dynamic $^{13}NH_3$	Increased glucose uptake lateral-baseal segment	Decreased blood flow inferior segment	NA	Glucose up take-dipy blood flow >95% confidence interval
Gerber et al, 1996	6	24	Euglycemic hyperinsulinemic glucose-insulin clamp	Dynamic ^{18}FDG Dynamic $^{13}NH_3$	No significant differences 0.53 μmol/min/g uptake lateral-baseal segment	No significant differences 0.88 ml/min/g	NA	NA
Kofoed et al, 2001	23	64	Euglycemic hyperinsulinemic glucose-insulin clamp	Static ^{18}FDG Static $^{13}NH_3$	^{18}FDG uptake 10-15% increased in infero-lateral wall	$^{3}NH_3$ uptake 10% decreased in infero-lateral wall	^{18}FDG uptake 25% higher than $^{13}NH_3$ uptake in the infero-lateral wall	NA
Kofoed et al, 2002	20	64	Euglycemic hyperinsulinemic glucose-insulin clamp	Dynamic ^{18}FDG Dynamic $^{13}NH_3$	No significant differences 0.46 μmol/min/g	No significant differences 0.63 ml/min/g	NA	NA

N: number of subjects; Semiquantitative: circumferential profile analysis; NA: not available; y: years; dipy: dipyridamole.

mal, PET-mismatch, PET-match and PET-reverse mismatch (Table 4). Patients with ischemic heart disease who have large myocardial areas with PET-mismatch appear to benefit more from revascularization compared with patients in whom the PET-match pattern dominates. The pathophysiologic and clinical significance of PET-reverse mismatch remains to be investigated (see Chapter 6, page 20). However, controversy exists with regard to the definition of "normal" and "reduced" tracer uptake and thus how PET patterns should be identified. Visual scoring systems are the clinically most widely used methods for identifying these patterns in patients (vom-Dahl et al. 1994, Auerbach et al. 1999). However, computerized circumferential profile analysis of relative ^{18}FDG and $^{13}NH_3$ uptake in young healthy subjects showed that ^{18}FDG uptake is slightly enhanced compared with $^{13}NH_3$ uptake in the normal left ventricular lateral wall (Berry et al. 1991, Porenta et al. 1992). Based on these observations Porenta and co-workers concluded that visual analysis of ^{18}FDG and $^{13}NH_3$ distribution in the myocardium might cause interpretative errors and that a reference base of normal values is necessary in order to discriminate abnormal tracer uptake from the normal regional tracer heterogeneity (Porenta et al. 1992). It was furthermore suggested that normal tracer uptake values in patients could be defined as uptake values within 2 standard deviations from the mean value in healthy subjects.

In healthy elderly men we found that the myocardial ^{18}FDG-$^{13}NH_3$ uptake relation shows regional heterogeneity primarily characterized by high ^{18}FDG uptake and low $^{13}NH_3$ uptake in the left lateral ventricular wall (**Figure 4**). This "mismatch" of relative ^{18}FDG and $^{13}NH_3$ uptake in normal myocardium was observed in all subjects, but appeared to be most prominent in middle-aged men. Implementing the so-called "myocardial ^{18}FDG-$^{13}NH_3$ uptake difference" calculation in which both ^{18}FDG and $^{13}NH_3$ uptake are normalized to pixel values in the maximal 5% of the $^{13}NH_3$ study (Porenta et al. 1992, Di Carli et al. 1994, Di Carli et al. 1995a) the ^{18}FDG-$^{13}NH_3$ uptake "mismatch" appeared even more pronounced. In middle-aged men the ^{18}FDG-$^{13}NH_3$ uptake difference in the left lateral ventricular wall was found to be almost 50% (**Figure 5**). Interestingly, comparing our values for the ^{18}FDG-$^{13}NH_3$ uptake difference with those previously reported in younger subjects it may be estimated that approximately 78% of our middle-aged and old healthy subjects would be categorized as having a "pathologic" mismatch (>mean value + 2 standard deviations) in the left lateral ventricular wall (Porenta et al. 1992). Our findings support the conclusion of Porenta that normal reference values are needed to accurately identify myocardial regions with "pathologic" as opposed to "physiologic" glucose metabolism blood flow mismatch in patients with ischemic heart disease (Porenta et al. 1992). Future studies are required to evaluate to what extent our findings are reproducible by repeated measures within the same subjects. The degree of physiologic mismatch of ^{18}FDG and $^{13}NH_3$ uptake in the left ventricle was age-dependent, stressing that reference values for heart disease patients referred for glucose metabolism-blood flow PET imaging should be obtained in age-matched healthy subjects.

In healthy middle-aged men (50-65 years) we found that myocardial $^{13}NH_3$ uptake in the left lateral ventricular wall was significantly lower than in elderly men ($\geq$ 65 years), $p < 0.05$. The mechanisms responsible for this phenomenon are not known. It is unlikely that the finding reflects myocardial vascular disease, because the relative distribution of $^{13}NH_3$ uptake was unchanged after dipyridamole infusion. Aging of the heart is characterized by a loss of ventricular myocytes and hypertrophy of the remaining viable cells (Olivetti et al. 1995). Although the myocardial vascular bed undergoes changes resulting in increased stiffness of the vessel walls (Wei 1992), the global vasodilatory capacity of the coronary arteries remains unaffected by aging (Czernin et al. 1993). Irrespective of the age-dependency of the relative $^{13}NH_3$ uptake in the left lateral ventricular wall it has been a consistent finding in healthy subjects that $^{13}NH_3$ uptake is

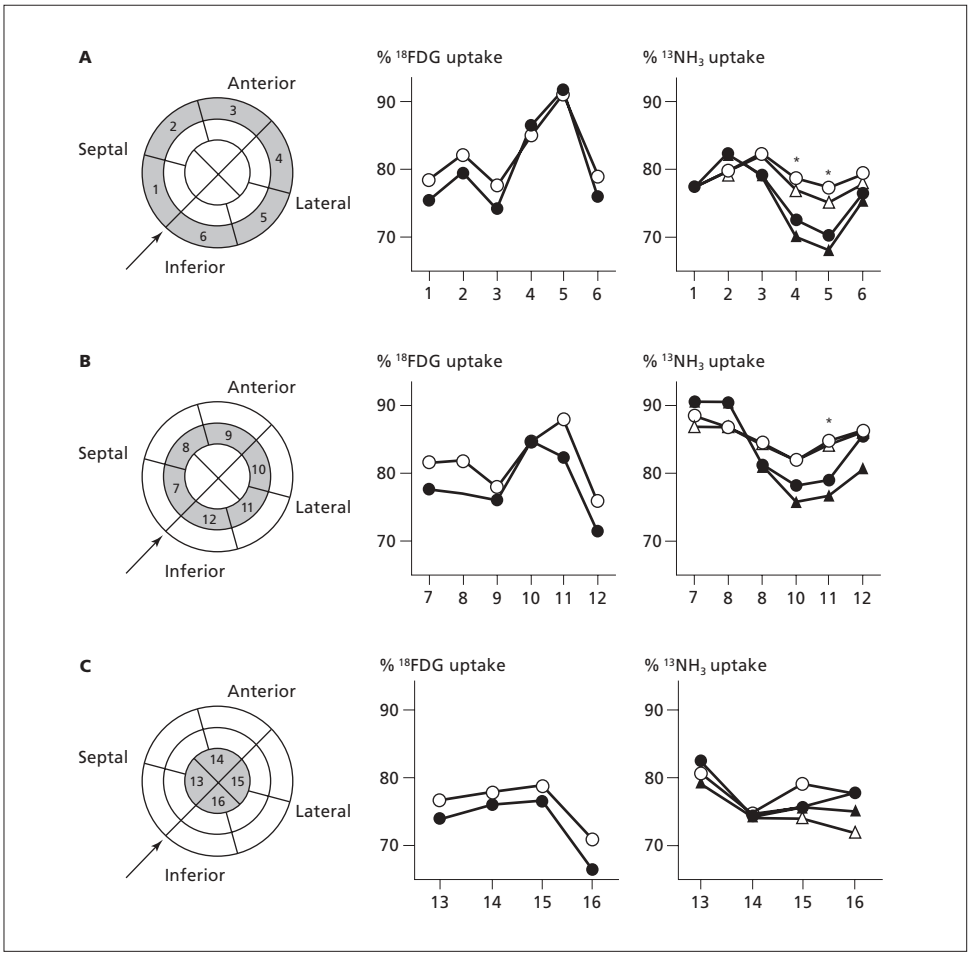

Figure 4. Regional myocardial ^{18}FDG and $^{13}NH_3$ uptake. **A:** basal short axis segments 1 to 6; **B:** midventricular short axis segments 7 to 12; **C:** apical short axis segments 13 to 16. The arrow indicates the location of the posterior insertion of the right ventricular free wall onto the interventricular septum. Average relative tracer uptake (percentage of peak uptake) is given. Circles: at rest, triangles: during dipyridamole. Closed symbols: young men (50-65 years), open symbols: old men ($\geq$ 65 years). *: $p < 0.05$ compared with regional uptake in young men. Note the "mismatch" pattern in segments 4, 5, 10 and 11.

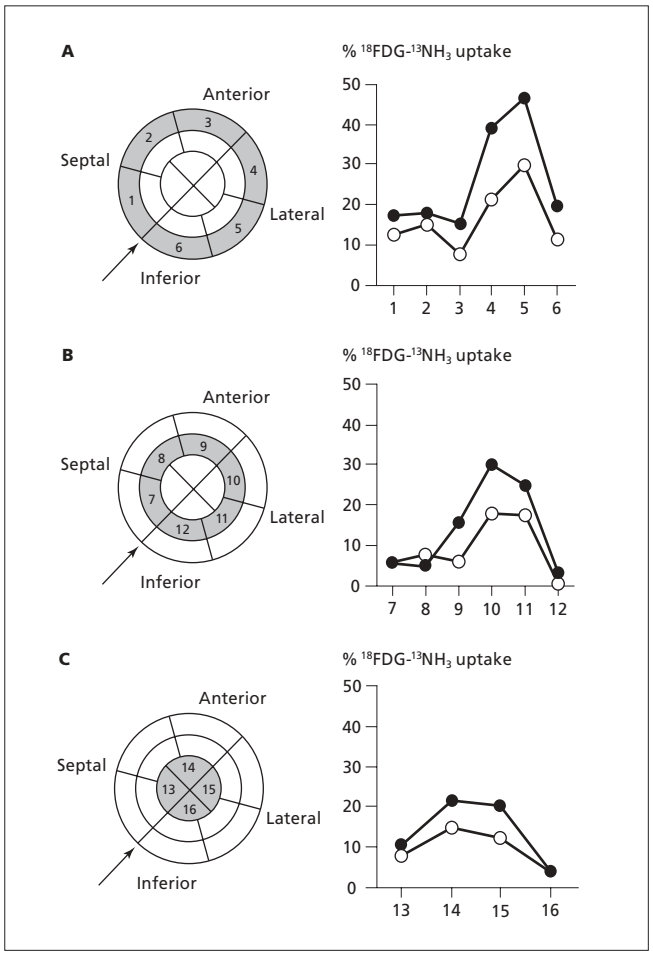

Figure 5. Regional myocardial ^{18}FDG-$^{13}NH_3$ uptake difference: **A:** basal short axis segments 1 to 6; **B:** midventricular short axis segments 7 to 12; **C:** apical short axis segments 13 to 16. The arrow indicates the location of the posterior insertion of the right ventricular free wall onto the interventricular septum. Average uptake difference is given. Closed circles: young men (50-65 years), open circles: old men (≥ 65 years).

relatively decreased in this region (Berry et al. 1991, Porenta et al. 1992, de Jong et al. 1995). We found that dipyridamole induced submaximal coronary hyperemia, which is uncoupled from regional metabolic regulatory mechanisms did not change the relative uptake profile of $^{13}NH_3$ throughout the myocardium. This finding could suggest that other factors than regional differences of coronary vascular function are responsible for the reduced relative $^{13}NH_3$ uptake in the left lateral ventricular wall. Semiquantitative PET image analysis is logistically simple, however the drawback of this approach is that is does not account for effects of regional myocardial differences of tracer redistribution. De Jong and co-workers demonstrated that low $^{13}NH_3$ uptake in the left ventricular lateral wall was not associated with low myocardial blood flow calculated by quantitative image analysis in young healthy subjects (de Jong et al. 1995). They suggested that the defect recorded by semiquantitative image analysis was caused by back-diffusion of ^{13}N metabolites to the blood stream. Accordingly, when comparing data from Study I and Study II we also found that low relative $^{13}NH_3$ uptake in the left lateral ventricular wall is associated with myocardial blood flow similar to the remainder of the left ventricle. Why ^{13}N metabolites diffuses back to the blood stream more vigorously in the left lateral ventricular wall compared to other regions of the myocardium remains unknown. It may therefore be argued that reliable evaluation of myocardial blood flow semiquantitatively or quantitatively using $^{13}NH_3$ PET cannot be performed in the left lateral ventricular wall. On the other hand if appropriate normal values are available this limitation of the method could be accounted for.

In all subjects myocardial ^{18}FDG uptake was increased in the left ventricular lateral wall compared with other regions of the myocardium. Regional recovery correction to account for the partial volume effect is usually not performed in semiquantitative PET imaging, as accurate measures of regional wall thickness rarely are available. Interestingly, in Study II it was found that when absolute quantitation of insulin stimulated glucose uptake and myocardial blood flow were performed in our healthy subjects without implementation of regional recovery correction factors glucose uptake and blood flow were concordantly increased in the left lateral myocardial wall (personal communication). This finding appears to suggest that regionally increased myocardial ^{18}FDG uptake in the left ventricular lateral wall is mainly due to the partial volume effect and not related to a regional Crone-Renkin effect of low flow resulting in increased glucose extraction.

In Study II it was demonstrated that whole-body insulin sensitivity is an important factor partly determining the intra- and inter-individual variability of absolute insulin stimulated myocardial glucose uptake. We therefore evaluated to what extent the intraindividual variability of ^{18}FDG and $^{13}NH_3$ uptake is influenced by whole-body insulin sensitivity. Whereas the intraindividual variability of $^{13}NH_3$ uptake was unrelated to insulin sensitivity, the intraindividual variability of ^{18}FDG uptake was inversely related to whole-body insulin sensitivity ($r = 0.50$, $p < 0.05$, unpublished observation) similar to findings in Study II. Thus, whereas the high ^{18}FDG uptake in the left lateral wall most likely is a consequence of the partial volume effect and to a smaller extent variability of myocardial insulin sensitivity, the low $^{13}NH_3$ uptake probably is caused by a substantial redistribution of ^{13}N metabolites.

Conclusions. In healthy elderly subjects the so-called "PET-mismatch" pattern, which is considered indicative of reversibly depressed contractile function in patients with ischemic heart disease, may be found in entirely normal myocardium. Accordingly, semiquantitative cardiac ^{18}FDG/$^{13}NH_3$ PET images should be interpreted with caution especially in middle-aged men with ischemic heart disease. Age-matched normal reference values are required to discriminate between physiologic and pathologic glucose metabolism-blood flow relations.

4.2. INSULIN STIMULATED MYOCARDIAL GLUCOSE UPTAKE

The aim of the study was to assess factors determining variability of insulin stimulated myocardial glucose uptake in healthy subjects.

Quantitation of myocardial glucose uptake by PET using curve fitting has provided important insight into the pathophysiology of myocardial ischemia in chronic ischemic heart disease (Gerber et al. 1996, Maki et al. 1996, Marinho et al. 1996). However, in patients with ischemic heart disease a considerable variability of glucose uptake in normally contracting myocardium appears to limit the diagnostic value of the quantitative method to identify viable myocardium (Gerber et al. 2001). Variability of insulin stimulated myocardial glucose uptake has only been reported in relatively small groups of healthy subjects mainly below 50 years of age and without concomitant measurements of myocardial blood flow (Hicks et al. 1991, Marinho et al. 1996, Gerber et al. 1996, Yokoyama et al. 1999). In these studies the interindividual variation of insulin stimulated myocardial glucose uptake expressed as the relative dispersion were between 11 and 23%. A substantially higher relative dispersion (44%) was recently found in a large group of patients with ischemic heart disease, in whom insulin stimulated myocardial glucose uptake was recorded in normally contracting myocardium (Gerber et al. 2001). It was hypothesized that this was due to a normal variation in myocardial blood flow and/or in myocardial insulin sensitivity. In general terms, either limitations of tissue perfusion or tissue permeability could be responsible for regional or global variability of insulin stimulated cardiac glucose uptake. In skeletal muscle vascular reactivity and the ability of the tissue to take up glucose are interrelated (Baron et al. 2000). We therefore evaluated regional and

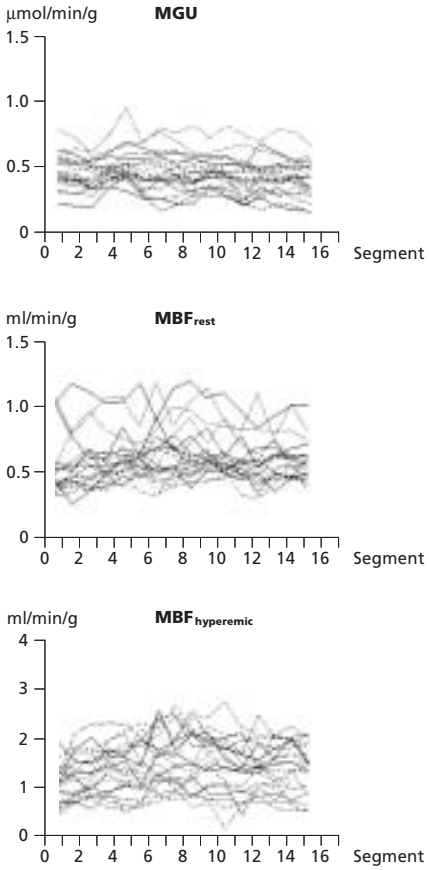

Figure 6. Regional insulin stimulated segmental myocardial glucose uptake (MGU), myocardial blood flow at rest (MBF_{rest}) and hyperemic myocardial blood flow ($MBF_{hyperemic}$) in each subject. For segmental model see Figure 3.

global variability of insulin stimulated myocardial glucose uptake in relation to resting myocardial blood flow, hyperemic blood flow and whole-body insulin sensitivity.

In our studies insulin stimulated myocardial glucose uptake, myocardial blood flow and hyperemic blood flow were found to be fairly homogenous in the left ventricular wall (**Figure 6**) in accordance with previous findings (Gerber et al. 1996, Marinho et al. 1996, Yokoyama et al. 1999). Hicks and co-workers found a 13% higher insulin stimulated myocardial glucose uptake in the left ventricular lateral wall compared with the septum (Hicks et al. 1991). This discrepancy between our results and the previously reported left ventricular heterogeneity of uptake during clamp may be explained by differences in PET equipment used, the method of regional recovery correction and/or differences in characteristics of the study groups. In our study group intraindividual variation of regional insulin stimulated myocardial glucose uptake within the left ventricle was found to be inversely related to whole-body insulin sensitivity indicating that low insulin sensitivity is associated with increased myocardial heterogeneity. However, a more important factor responsible for the discrepant results appears to be the regional recovery correction algorithm used in our study, which accounts for normal-variation of regional myocardial wall thickness throughout the left ventricle (Freiberg et al. 2004). As mentioned in section 4.1 quantitation of insulin stimulated myocardial glucose uptake and myocardial blood flow without recovery correction showed a concordantly increase in the left lateral wall compared to all other myocardial regions (personal communication). The interindividual variation of global insulin stimulated myocardial glucose uptake level was somewhat more pronounced than the difference in glucose uptake between segments (intraindividual variation) (**Figure 7**).

Global insulin stimulated myocardial glucose uptake was linearly correlated with whole-body insulin sensitivity, whereas no relation was found between glucose uptake and myocardial blood flow at rest (Figure 7). These findings suggest that limitation of tissue permeability rather than tissue perfusion determines insulin stimulated glucose uptake in normal human myocardium. Similarly, coronary delivery of glucose was not a primary determinant of uptake in normal myocardium in animal experimental studies, in which blood flow and ^{18}FDG retention were quantified invasively during glucose-insulin clamp (Fallavollita 2000). On the other hand, in our studies it cannot be excluded that insulin infused during the clamp procedure induced coronary vasodilation during ^{18}FDG imaging, explaining the lack of correlation between insulin-stimulated myocardial glucose uptake and blood flow at rest. Interventional studies are required to evaluate this issue as controversy exists with regard to a possible coronary vasodilatory effect of insulin (Ferrannini & Santore 1993, McNulty et al. 2000b, Iozzo et al. 2002).

By multivariate linear regression analysis we found that insulin stimulated myocardial glucose uptake was independently related to coronary reactivity as evaluated by dipyridamole induced hyperemic myocardial blood flow (Figure 7). The coronary capacity for nitric oxide synthesis might explain this association since glucose uptake in skeletal muscle appears to be stimulated by nitric oxide through a signaling pathway distinct from that of insulin (Higaki et al. 2001). Possibly both coronary vasodilatory function and myocardial capacity for the uptake of glucose may be modulated by endothelial derived nitric oxide (Buus et al. 2001). However, further studies are needed using either nitric oxide donors (nitroglycerin) or synthase inhibitors (NG-monomethyl-L-arginine) to evaluate the

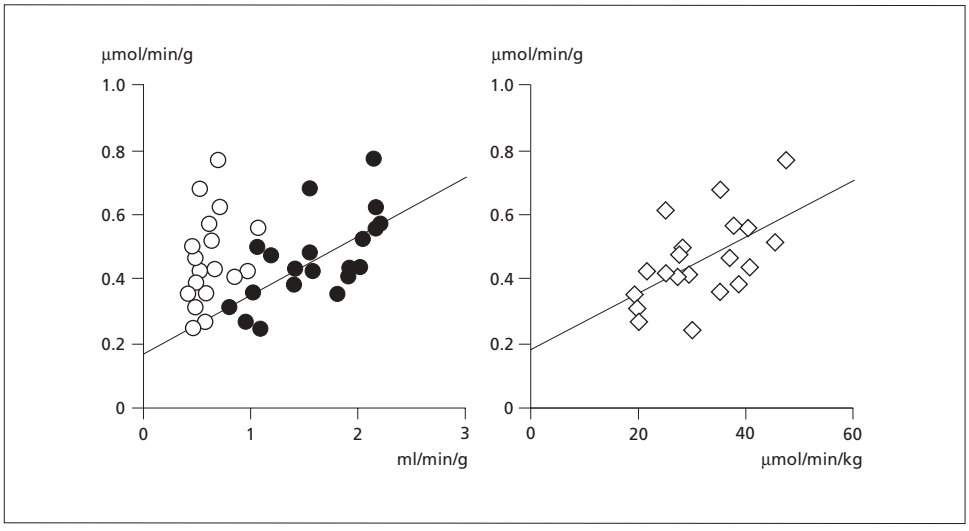

Figure 7. Left panel: relationship between left ventricular insulin stimulated myocardial glucose uptake (y-axis) and left ventricular myocardial blood flow (x-axis). Closed circles: hyperemic myocardial blood flow Open circles: myocardial blood flow at rest. The relation was y = 0.18x + 0.17; r = 0.63; p < 0.005. Right panel: relationship between left ventricular insulin stimulated myocardial glucose uptake (y-axis) and whole-body insulin sensitivity. The relation was y = 0.009x + 0.19; r = 0.56; p < 0.01.

mechanism responsible for the observed relation between myocardial glucose uptake and coronary vasodilatory function.

In Study I it was demonstrated that $^{13}NH_3$ uptake in the left lateral ventricular wall was significantly lower in middle-aged men compared to older men. In contrast absolute myocardial blood flow was found to be fairly homogenous and no correlation was found between intra-individual variability of resting myocardial blood flow, hyperemic blood flow and age. This apparent discrepancy is probably explained by an age-dependent trend toward substantial redistribution of ^{13}N metabolites in the left lateral ventricular wall accounted for by quantitative curve fitting analysis as discussed in 4.1. In accordance with previous findings a trend towards increasing blood flow at rest and decreased myocardial blood flow reserve in the left ventricle with advanced age was noted (Czernin et al. 1993), however this did not reach statistical significance. No correlation was found between left ventricular glucose uptake and age. Similarly left ventricular insulin stimulated glucose uptake was not related to the rate pressure product which is considered a rough estimate of cardiac work. Although it might be expected that such a relation would exist as a consequence of the metabolic autoregulation maintaining energy supply for cardiac work (Depre et al. 1999), our finding probably reflect that the rate pressure product merely is a surrogate marker of cardiac work.

In the current work the so-called lumped constant was assumed to be 1 (see section 3.1.2 and 5.1). However, the value of this factor has been shown to vary as a function of the plasma insulin concentration (Botker et al. 1997, Ng et al. 1998). Accordingly, it is likely that part of the recorded interindividual variability of insulin stimulated myocardial glucose uptake is reflecting interindividual variation of plasma insulin concentration at the time of measurements and myocardial insulin sensitivity resulting in interindividual variation of the lumped constant. Interestingly, Ng and co-workers found an inter-individual relative dispersion of the lumped constant determined invasively during euglycemic glucose-insulin clamp of about 7% in patients with ischemic heart disease (Ng et al. 1998). For obvious ethical reasons the corresponding value in our healthy subjects is not available. Yet future studies possibly using the method developed by Kuwabara and co-workers might provide non-invasive estimates of the lumped constant variability in our healthy subjects (Kuwabara et al. 1990).

Conclusion. Regional insulin stimulated myocardial glucose uptake is fairly homogenous in healthy elderly subjects. Interindividual variability appears primarily to be related to the variability of coronary vascular reactivity and tissue insulin sensitivity. These factors need consideration when insulin stimulated myocardial glucose uptake is evaluated in patients with ischemic heart disease.

4.3. CLINICAL, DIAGNOSTIC ^{18}FDG PET IMAGING

The main purpose of clinical ^{18}FDG PET imaging has been to predict outcome following surgical revascularization in patients with severe ischemic heart disease and left ventricular contractile dysfunction (for detailed discussion see Chapter 7, page 22). The improvement of left ventricular contractile function has been widely used as a surrogate marker of post-surgical morbidity and mortality. Accordingly, the identification of PET-mismatch or PET-normal patterns in dysfunctional myocardium was used to predict recovery of contractile function after revascularization. Using semiquantitative PET imaging the overall positive and negative predictive value of ^{18}FDG PET imaging in 12 studies including a total of 332 patients was found to be 76% and 86% for the prediction of mainly regional recovery of left ventricular contractile function after revascularization (Bax et al. 1997). A subsequent European multicenter study using quantitative ^{18}FDG PET imaging without myocardial blood flow evaluation including 178 patients recruited from 6 centers reported a somewhat lower diagnostic accuracy (Gerber et al. 2001). In that study it was determined that the diagnostic power of quantitative ^{18}PET imaging was rather poor and that normalization of absolute myocardial glucose uptake to uptake in remote normally contracting myocardium was required to produce diagnostic information. On the other hand, no normal values in age-matched healthy subjects were available in that study. Those findings overall, appears to indicate that the highest diagnostic accuracy may be achieved by semiquantitative as compared to quantitative ^{18}FDG PET imaging. However, the scintigraphic criteria (semiquantitative or quantitative) with the highest diagnostic accuracy remains to be determined.

In most studies using semiquantitative ^{18}FDG PET imaging either visual scoring systems or arbitrary threshold values of relative myocardial tracer uptake was used to identify PET-patterns of abnormal myocardial ^{18}FDG uptake in relation to blood flow. In the current work we found that in healthy subjects age-matched to the target age for the development of ischemic heart disease ^{18}FDG uptake was high and $^{13}NH_3$ uptake low in the left lateral ventricular wall (Figure 4). When using visual scoring systems or arbitrary threshold values of tracer uptake this "mismatch" of relative ^{18}FDG and $^{13}NH_3$ uptake in normal myocardium could be misinterpreted as representing metabolic adaptation in dysfunctional but viable myocardium reducing the positive predictive value of the method. In studies including reference values of ^{18}FDG uptake the mean ^{18}FDG uptake plus 2 standard deviations is generally used to define the upper limit of normal derived from generally accepted statistical principles. Interestingly, the myocardial ^{18}FDG-$^{13}NH_3$ uptake difference method (Porenta et al. 1992) may result in a more conservative estimate of "mismatch" as the "physiological" mismatch of ^{18}FDG and $^{13}NH_3$ uptake in the left lateral ventricular wall appears to be even more pronounced using this method (Figure 5). The "difference" methods was used in some of the pioneering publications on myocardial viability PET imaging which suggested a high diagnostic power of PET with regard to symptoms and prognosis (Di Carli et al. 1994, Di Carli et al. 1995a). Accordingly, it remains undetermined whether the diagnostic power of semiquantitative PET may be enhanced if a higher limit of normal such as for example mean normal value plus 2.5 standard deviations is used.

In the current study we found that the interindividual variability of insulin stimulated myocardial glucose uptake was 29%. The corresponding value in the European multicenter study mentioned above was 44% in normally contracting remote myocardium of patients with ischemic heart disease (Gerber et al. 2001). Whether the diagnostic power of quantitative PET imaging may be enhanced to a level comparable to what is achieved with semiquantitative imaging using age-matched normal values remains to be investigated. However, this appears to be unlikely as this probably also would require matching of patients and healthy subjects with regard to coronary vascular reactivity and whole-body insulin sensitivity.

Conclusion. Based on an overview of the literature the highest diagnostic accuracy appears to be achieved by semiquantitative as compared to quantitative ^{18}FDG PET imaging. Enhanced diagnostic power of semiquantitative imaging will most likely be provided if age-matched normal reference values are used. Possibly, a more conservative strategy should be preferred in the selection of diagnostic criteria for the identification of ^{18}FDG and $^{13}NH_3$ mismatch in dysfunctional myocardium. However, at this stage of clinical ^{18}FDG imaging the key issue is not related to which method of data acquisition, data analysis or criteria of viability that should be used. The main unanswered question as will be discussed in section 7.5 (page 27) appears to be which patients should be evaluated and whether assessment of myocardial viability is useful in practical clinical decision-making.

5. GLUCOSE METABOLISM IN POST-ISCHEMIC MYOCARDIUM

Angina pectoris is the main clinical manifestation of ischemic heart disease corresponding to a transient episode of acute regional myocardial ischemia. Studies in patients suffering an acute myocardial infarction have suggested that increased myocardial supply of glu-

cose may provide tissue salvage and thus clinical benefit especially in patients receiving reperfusion therapy (Fath-Ordoubadi & Beatt 1997, Diaz et al. 1998). Yet, it has been argued that a prolonged increase in glycolytic flux in ischemically jeopardized myocardium might be deleterious as a consequence of lactate accumulation (Rovetto et al. 1975, Apstein 2000). A more comprehensive understanding of the mechanisms determining glucose uptake in post-ischemic myocardium might therefore be useful.

Following regional myocardial ischemia a prolonged, but reversible contractile dysfunction is observed – i.e. myocardial stunning (see 7.1 page 22). In animal models this phenomenon has been shown to be associated with abnormalities of cardiac metabolism (Buxton & Schelbert 1991, Buxton et al. 1992). After 24 hours of reperfusion regional myocardial glucose uptake – specifically non-oxidative glucose metabolism – is enhanced suggesting a role for glycolytic ATP in the post-ischemic recovery of contractile function (Schwaiger et al. 1989, Buxton & Schelbert 1991, McNulty et al. 2000a). Similarly, Camici and co-workers found that ^{18}FDG uptake was increased in ischemically jeopardized myocardium after an acute episode of exercise-induced angina pectoris in cardiac patients (Camici et al. 1986). On the other hand, myocardial glucose uptake measured by ^{18}FDG was found to be reduced in reperfused areas compared with that in remote myocardium early after reperfusion (Buxton & Schelbert 1991, McFalls et al. 1994). The mechanism responsible for this early impairment of myocardial glucose uptake is not known and the question was raised whether this finding reflected limitations of ^{18}FDG to trace glucose in early reperfusion rather than truly impaired glucose metabolism (Liedtke et al. 1992, Doenst & Taegtmeyer 1998). We evaluated the validity of ^{18}FDG as a tracer of glucose uptake in a canine model of post-ischemic myocardium and related ^{18}FDG findings to measures of intermediate myocardial glucose metabolism (Study III & IV).

5.1. THE LUMPED CONSTANT

The aim of the study was to validate ^{18}FDG and PET for quantitation of regional myocardial glucose uptake in normal and post-ischemic myocardium.

^{18}FDG and glucose differs with respect to kinetic properties of membrane transport and phosphorylation. For the measurement of glucose uptake by ^{18}FDG a correction factor was therefore proposed to account for these differences – the so-called lumped constant (LC) (Sokoloff et al. 1977) – which is defined as the ratio of the steady state fractional extractions of ^{18}FDG (K^*) and glucose (K).

Equation 4: $$LC = K^*/K$$

The factor lump together 6 variables, which are all, assumed to be constant under biological steady state conditions

Equation 5: $$LC = \lambda V^*_{max} K_m / \phi V_{max} K^*_m$$

where λ is the ratio of the distribution volumes of ^{18}FDG and glucose in the tissue, ϕ is the fraction of glucose that is metabolized after phosphorylation, K_m and V_{max} are the half-saturation concentration and maximum velocity for phosphorylation of glucose by hexokinase (assuming first order kinetics) and the superscripted terms the equivalent values for ^{18}FDG.

The stability of the LC in myocardial tissue was initially evaluated in vitro using an isolated perfused rabbit septum model (Krivokapich et al. 1982, Marshall et al. 1983a, Huang et al. 1987). In this preparation the LC was virtually constant, yet at supraphysiologic levels of coronary blood flow, cardiac work or plasma insulin the LC decreased (Krivokapich et al. 1987). Similarly, Ratib found that the LC was stable within a broad range of myocardial glucose uptake and blood flow levels in dogs (in vivo) (Ratib et al. 1982). These findings are in contrast with studies performed in isolated working rat heart preparations in which the LC was found to vary considerably probably as a function of the relative control strength of myocardial membrane transport carrier and hexokinase (Ng et al. 1991, Hariharan et al. 1995, Botker et al. 1999). Under conditions of transport limitation (low plasma glucose and insulin concentration) the LC appeared to rise to a maximum equal to the transporter coefficient for ^{18}FDG, whereas it decreased to a minimum equal to the phosphorylation coefficient during phosphorylation limitation (high plasma glucose and insulin concentration) (Crane et al. 1983). In an isolated rat heart perfused in vitro with red blood cell- and FFA-free buffer solution using glucose as the sole initial substrate, the LC was found to vary from 0.3 to 1.2 under extreme experimental conditions (supraphysiological concentrations of plasma insulin, lactate or keton-bodies). A mathematical model was developed by Kuwabara in brain tissue and validated by Botker in the perfused rat heart predicting the value of the LC based on ^{18}FDG time activity curve analysis and assuming fixed values of transport and phosphorylation ratios for ^{18}FDG and glucose (Kuwabara et al. 1990, Botker et al. 1997, Botker et al. 1999). Still, the validity and relevance of this approach in vivo remains to be determined. In patients with ischemic heart disease Ng and coworkers demonstrated that the LC determined invasively did not change significantly in response to hyperinsulinemia (Ng et al. 1998). Ng, who also performed the initial glucose-perfused rat heart experiments (Ng et al. 1991), suggested that the large variability of the LC in vitro probably reflects the high near-saturated levels of tissue glucose, which is rarely found in vivo.

In the vast majority of studies exploring myocardial glucose uptake in humans by ^{18}FDG the LC has been assumed to be 0.67, this value originating from the work of Ratib and co-workers who compared ^{18}FDG and glucose uptake in normal canine myocardium by the Fick principle (Ratib et al. 1982). On the other hand we found the LC to be 1.1-1.4 in a similar model (Study III), values close to those recently reported in humans (Ng et al. 1998). In the study by Ratib and co-workers myocardial glucose uptake was calculated as the product of myocardial *whole blood* flow and the arterio-venous *plasma* glucose concentration difference. This calculation assumes equal plasma and whole blood glucose concentrations and rapid equilibration of glucose across the red blood cell membranes. However, in dogs glucose concentrations in plasma and red blood cells were found to be 150 and 35 mg/dl, respectively (Somogyi 1933). More recently values of 4.4, 1.5 and 3.2 mM were observed for canine plasma, red blood cells and whole blood (Higgins & Garlic 1982) which indicates a low glucose transport capacity. In addition glucose uptake by red blood cells was 4.4 nmol/ml cells/5 min at 37°C (Wagner et al. 1984). Thus, the rate of membrane glucose transport in red blood cell is far below cardiac uptake, and myocardial glucose uptake is derived almost exclusively from the plasma. We therefore estimated cardiac glucose uptake as the product of plasma blood flow and the arterio-venous plasma glucose concentration difference. By the use of whole blood flow and plasma glucose difference myocardial glucose uptake is overestimated by a factor corresponding to 1/1-Hct thus underestimating the LC.

Using an erroneous value of the LC may have some impact on interindividual variability of myocardial glucose uptake measurements as mentioned in 4.2. However, the stability of the factor under normal and pathophysiologic conditions is essential for both qualitative and quantitative ^{18}FDG studies as recently illustrated (Wiggers et al. 1999). Initially it was demonstrated in rabbit and rat that the LC was unaffected by myocardial ischemia (Marshall et al. 1983a, Schneider et al. 1991). However, in an extracorporeally perfused pig model [U-^{14}C]2-deoxyglucose accumulation in myocardial biopsies did not correlate with changes in regional myocardial glucose uptake assessed by [5-^{3}H]glucose within the first hour of reperfusion (Liedtke et al. 1992). In the perfused working rat heart preparation the stability of the LC during global ischemia appeared to be dependent on pre-ischemic feeding conditions and during reperfusion the LC fell from >1.0 to <.2 (Doenst & Taegtmeyer

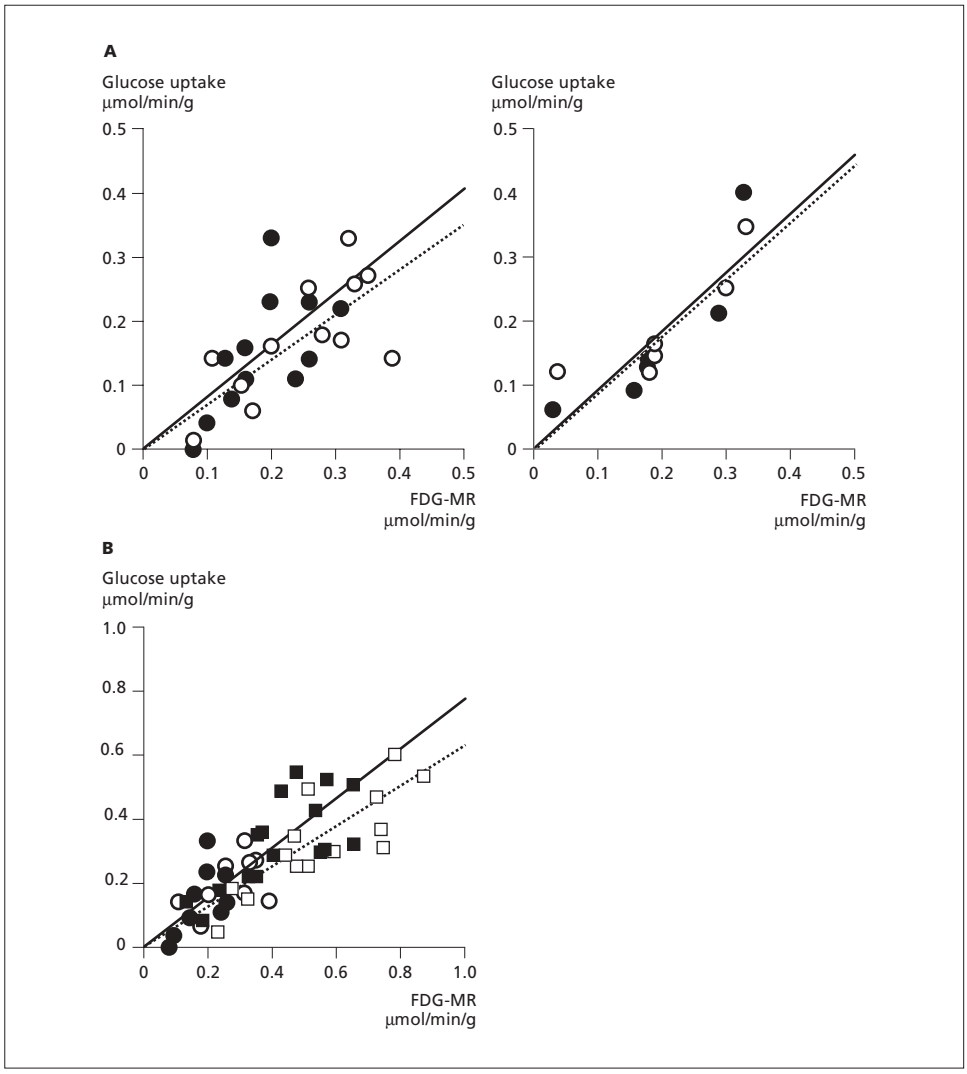

Figure 8. A: Relationship between ^{18}FDG metabolic rate (FDG-MR) and glucose uptake measured invasively by the Fick principle in the ischemia/reperfusion group (left) and in controls (right). **B:** Extended data range with experiments with dichloroacetate shown as squares. Intervention region: closed symbols, bold line. Remote: open symbols, dashed line.

1998). It was therefore important to evaluate the stability of the LC during reperfusion in vivo (Study III). We found that glucose uptake quantified by ^{18}FDG (^{18}FDG metabolic rate) in both reperfused and remote myocardium correlated linearly with glucose uptake and oxidation measured by the Fick principle (**Figure 8** and **Figure 9**). Quantified ^{18}FDG uptake was reduced 20 ± 4% in reperfused compared with remote myocardium similar to the decrease in glucose oxidation (26 ± 6%), while glucose uptake measured invasively showed no change (Kofoed et al. 2000b). However, no significant differences were found in the LC between reperfused and remote myocardium, or between reperfused myocardium and myocardium of control animals (Figure 8). Our observations suggest that there may be a reduction in the LC in reperfused compared with remote myocardium which is masked by experimental errors of the model. Nevertheless, the reduction of the LC is much smaller than that demonstrated in the perfused rat heart. Overall, we found that quantified ^{18}FDG uptake reflected regional glucose metabolism in normal and reperfused myocardium.

Conclusion. Glucose uptake in vivo may be measured quantitatively in normal and post-ischemic myocardium by ^{18}FDG PET and the LC is approximately 1. Variability of the LC observed by others in vitro probably illustrates the sensitivity of the method to extreme metabolic variations.

5.2. INTERMEDIATE GLUCOSE METABOLISM

The aim of the study was to evaluate the relationship between glucose uptake and intermediate glucose metabolism in post-ischemic myocardium.

Maintained glycolysis in early reperfusion has been shown to play a crucial role in the functional and metabolic recovery of post-ischemic myocardium (Lopaschuk et al. 1990, Mallet et al. 1990, Jeremy et al. 1993). Early after an acute ischemic event myocardial glucose uptake appears to be either increased (Myears et al. 1987, Tamm et al. 1994) unaltered (Liedtke et al. 1988) or decreased (Renstrom et al. 1989, Lopaschuk et al. 1990). These discrepancies prob-

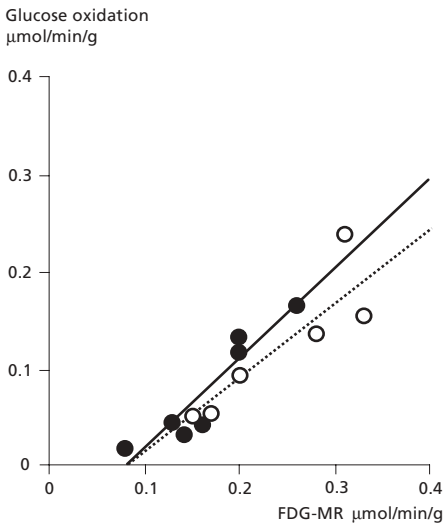

Figure 9. Relationship between ^{18}FDG metabolic rate (FDG-MR) and glucose oxidation in post-ischemic (closed circles, bold line) and remote (open circles, dashed line) myocardium.

ably reflect differences of the experimental models used, substrate and hormonal conditions in addition to severity of ischemia and duration of reperfusion. In models of prolonged *no-flow* ischemia the presence of necrosis in reperfused tissue complicates the interpretation of the metabolic changes. Furthermore, in globally perfused isolated heart preparations cardiac denervation and absence of hormones, substrates and blood components may also influence post-ischemic myocardial metabolism. We evaluated myocardial glucose metabolism in fasting, anesthetized dogs 2-3 and 24 hours after brief low-flow regional ischemia (20-25 min). The absence of necrotic tissue was confirmed by triphenyltetrazolium chloride staining. This protocol was selected to induce reversible functional and biochemical changes of the myocardium in vivo (Kloner et al. 1981, McFalls et al. 1994).

Regional myocardial glucose uptake measured by ^{18}FDG was reduced during early reperfusion in post-ischemic compared with remote myocardium, but glucose uptake was not significantly different from that of control animals (**Figure 10**). Buxton also found myocardial glucose uptake to be similar in post-ischemic and increased in remote myocardium during early reperfusion compared to baseline (Buxton & Schelbert 1991). Following an acute ischemic event the adrenergic tone is increased and an overall increase in myocardial glucose uptake is to be expected (Doenst & Taegtmeyer 1999). The relative reduction in glucose uptake in post-ischemic myocardium compared to remote areas might therefore reflect an inability of the tissue to increase uptake in response to the augmented adrenergic tone. This hypothesis is supported by the sustained reduction of glucose uptake in post-ischemic myocardium after dobutamine stimulation (McFalls et al. 1994).

At 24 hours of reperfusion the myocardial glucose uptake was found to be homogenous in our model (Study IV), in accordance with previous findings (McFalls et al. 1995). In an experimental protocol of more severe ischemia (3 hours of coronary occlusion) Buxton and others found increased levels of glucose uptake in post-ischemic myocardium at 24 hours of reperfusion (Schwaiger et al. 1989, Buxton & Schelbert 1991, McNulty et al. 2000a). Evidently, the severity of ischemia plays an important role in determining characteristics and time-course of myocardial glucose uptake during reperfusion (Terrand et al. 2001).

Even after coronary occlusions of limited duration myocardial glycogen contents remain depleted for at least 24 hours (Schwaiger et al. 1989, McNulty et al. 2000a) and within this time frame ^{18}FDG uptake is likely primarily to reflect glycolytic flux. Accordingly, low

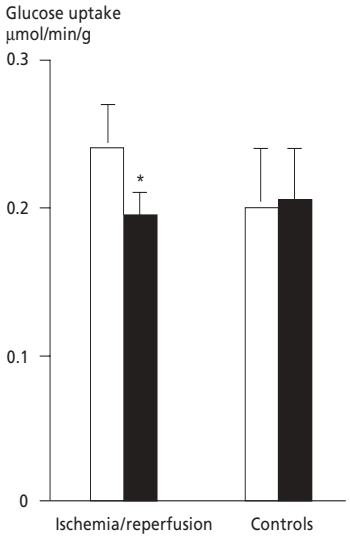

Figure 10. Glucose uptake measured by ^{18}FDG in remote (open bars) and post-ischemic myocardium (closed bars) at 2 hours of reperfusion (left panel) and in control animals (right panel), *: $p<0.01$ compared to remote. In control animals no coronary occlusion was applied.

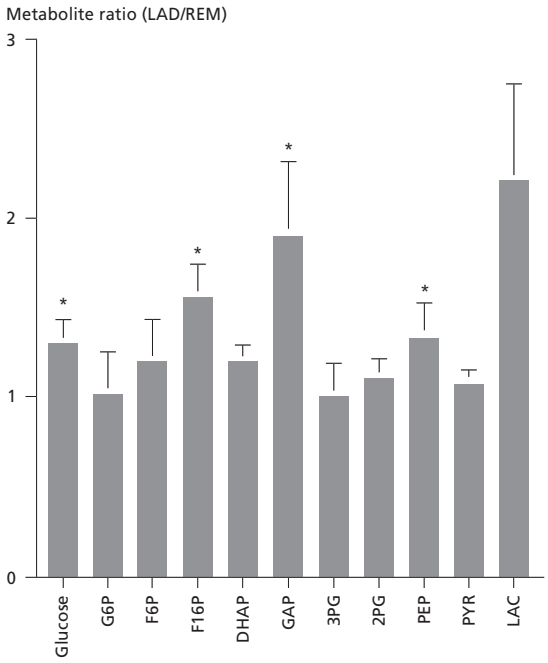

Figure 11. Crossover plot of glycolytic intermediates from biopsy samples taken 3 hours after a 20-min period of ischemia in the territory of the left anterior descending artery (LAD). Metabolite ratio (LAD/REM) = metabolite concentration in post-ischemic (LAD) territory divided by metabolite concentration in the remote territory (REM). G6P: glucose-6-phosphate; F6P: fructose-6-phosphate; F16P: fructose-1,6-bisphosphate; DHAP: dihydroxyacetone phosphate; GAP: glyceraldehyde-3-phopshate; 3PG: 3-phosphoglycerate; 2PG: 2-phosphoglycerate; PEP: phosphoenolpyruvate; PYR: pyruvate; LAC: lactate. Average and standard error of the mean are given. *: $p<0.05$ vs mean ratio = 1.

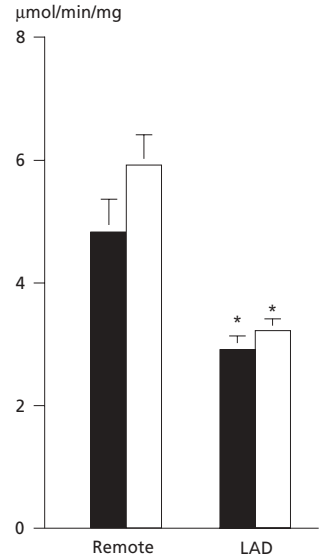

Figure 12. Absolute myocardial activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH, closed bars) and reaction V_{max} (open bars) after 3 hours of reperfusion in remote and post-ischemic (LAD) tissue. *: $p<0.01$ vs remote. No significant differences were found at 24 hours of reperfusion (data not shown). Average and standard error of the mean are given.

myocardial glucose uptake measured by ^{18}FDG after 3 hours of reperfusion was associated with a decrease in net lactate uptake and glucose oxidation corresponding to an overall impairment of glycolytic flux. Analysis of biopsy material obtained early after reperfusion revealed an accumulation of glyceraldehyde-3-phosphate (GAP) in post-ischemic tissue (**Figure 11**) probably corresponding to a decrease in the activity and V_{max} of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (**Figure 12**). However, the interpretation that GAPDH is "rate-limiting" under these conditions should be exercised with caution, since the studies of Kacser and Burns have

shown that metabolic control is shared by all enzymes of the pathway (Kacser & Burns 1979). Similarly it may be inappropriate to suggest that the observed decrease in myocardial glucose uptake estimated by ^{18}FDG reflects an "upstream" consequence of GAPDH inhibition. It is important to appreciate that FDG traces only glucose transport and phosphorylation, and does not distinguish between subsequent alternate fates of glucose such as glycolysis and incorporation into glycogen. Reduction of myocardial glucose uptake by ischemia and reperfusion could thus be independent of effects on glycolysis, reflecting alterations in glycogen synthesis and/or glucose transport. On the other hand while glycogen stores are replenished (Schwaiger et al. 1989, McNulty et al. 2000a), the number of glucose transporters are increased during reperfusion (Sun et al. 1994) suggesting that, at least at the onset of reperfusion, these pathways would be more likely to enhance than depress glucose uptake. We therefore believe that our results are consistent with an increased contribution of GAPDH to regulate glycolytic flux in early reperfusion. At 24 hours of reperfusion the activity of the enzyme was restored, no accumulation of glyceraldehyde-3-phosphate was found and cardiac glucose uptake was homogenous.

The reduction of enzyme activity in early reperfusion was not caused by degradation of the enzyme since the ratio of GAPDH protein between remote and post-ischemic myocardium was similar during early and late reperfusion. The enzyme could not be reactivated in vitro, and the decreased V_{max} (Figure 12) together with an unaltered K_m (data not shown) was consistent with non-competitive inhibition probably induced by covalent modification. Our data do not provide a mechanistic explanation for the inhibition of GAPDH activity in reperfused myocardium. Probable mechanisms are that of covalent modification by reactive oxygen species (Janero et al. 1994) or ADP-nitrosylation by nitric oxide released at reperfusion (Dimmeler et al. 1992).

Inasmuch as similar metabolic changes can be assumed to take place in human myocardium after an acute ischemic event, strategies to overcome the inhibition of flux through glycolysis should be developed. In our dog model glucose oxidation and net lactate extraction in post-ischemic myocardium could be normalized by stimulation of the pyruvate dehydrogenase enzyme activity by infusion of dichloroacetate (Schöder et al. 1998). The possible beneficial effect of glucose-insulin-potassium administered to patients with an acute myocardial infarction (Diaz et al. 1998) might in part be mediated by reversal of the glycolytic flux inhibition.

Conclusion. Myocardial glucose uptake, net lactate uptake and glucose oxidation are reduced early after regional ischemia. The impaired glycolytic flux appears to some extent to be caused by non-competitive inhibition of GAPDH activity. Inhibition of this enzyme is probably caused by covalent modification as a consequence of the reperfusion injury. The potential clinical implications of these findings remain to be determined.

6. INSULIN SENSITIVITY AND ISCHEMIC HEART DISEASE

The aim of the study was to assess the association between whole-body insulin sensitivity, PET-patterns of myocardial ^{18}FDG and $^{13}NH_3$ uptake and insulin stimulated myocardial glucose uptake, including prognostic implications in patients with ischemic heart disease and heart failure.

Animal experimental studies have suggested that maintained myocardial glucose uptake during the course of ischemia-reperfusion plays an important role in preserving viability and contractile function of the tissue (Cave et al. 2000, McNulty et al. 2000a). In accordance, whole-body insulin resistance has been identified as an independent prognostic risk factor in patients with heart failure (Swan et al. 1997, Paolisso et al. 1999). Impairment of insulin mediated whole-body glucose uptake as part of the so-called "metabolic syndrome", initially proposed by Reaven, has for a long time been considered an important factor in the development and progression of coronary atherosclerosis (Reaven 1988, Korpilahti et al. 1998, Haffner 1999). In addition, whole-body insulin sensitivity seems to be reduced in patients with congestive heart failure including that of non-ischemic etiology, and it was therefore suggested that disturbances in insulin mediated myocardial metabolism might impair energy supply to the myocardium resulting in deterioration of the tissue (Swan et al. 1997). This hypothesis is supported by poor long-term survival in patients with low insulin-mediated whole-body glucose uptake and heart failure caused by heart valve dysfunction (Paolisso et al. 1999). On the other hand, impaired whole-body insulin sensitivity mainly reflects decreased insulin stimulated glucose uptake in skeletal muscle, and there is no solid evidence that low whole-body insulin sensitivity is associated with impairment of insulin stimulated glucose uptake in the heart. Impaired whole-body insulin sensitivity is accompanied by either normal or decreased myocardial glucose uptake (Paternostro et al. 1996, Utriainen et al. 1998, Yokoyama et al. 1999). Patient characteristics such as a history of diabetes, coronary artery disease and heart failure in addition to limitations in the methodology used to determine myocardial glucose uptake might account for these inconsistent results. The PET reverse-mismatch pattern (see Chapter 4.1) has been suggested to reflect regionally impaired myocardial insulin sensitivity in non-diabetic patients with chronic ischemic heart disease and heart failure (Perrone-Filardi et al. 1994, Schwaiger & Pirich 1999, Yamagishi et al. 1999). However, the pathophysiologic and clinical significance of this PET pattern remains unknown.

The relationship between whole-body insulin sensitivity, PET-patterns of myocardial ^{18}FDG and $^{13}NH_3$ uptake and insulin stimulated myocardial glucose uptake in non-diabetic patients with ischemic heart disease and heart failure was evaluated (Study V). Low whole-body insulin sensitivity was defined by a glucose delivery rate below the mean value minus 1 standard deviation determined in control subjects (glucose delivery rate less than 21 μmol/min/kg). This threshold value was selected to identify patients with low whole-body insulin sensitivity, but without subclinical diabetes mellitus (Paternostro et al. 1996). In addition to demographics, left ventricular function, angiographic findings and symptoms, the patient groups were matched with regard to medication including ACE-inhibitors, β-blockers, digitalis/diuretic and nitrates. Myocardial patterns of ^{18}FDG and $^{13}NH_3$ uptake (Table 4)) were determined as described in section 3.1.1 (page 9) by comparing to uptake values obtained in age-matched healthy subjects (Study I). Although semi-quantitative ^{18}FDG and $^{13}NH_3$ PET imaging may provide clinically useful information as discussed in section 3.1, and 4.3, the pathophysiological correlates of these scintigraphic patterns cannot be derived using this methodology. We therefore evaluated regional myocardial insulin stimulated glucose uptake and blood flow using quantitative PET imaging in our patients and compared with normal values obtained in healthy subjects (Study II). To discriminate between effects of impaired myocardial insulin sensitivity on one hand and myocardial ischemia or infarction on the other in myocardial segments with abnormal contractile function is very difficult (Paternostro et al. 1996, Holmvang et al. 1999). Quantitative PET

Table 6. Patterns of ^{18}FDG and $^{13}NH_3$ uptake in relation to whole-body insulin sensitivity.

PET pattern	Low whole-body insulin sensitivity (N = 15)	Normal whole-body insulin sensitivity (N = 14)
Normal	41% (96/232)	47% (97/206)
Reverse mismatch	26% (61/232)*	13% (27/206)
Mismatch	8% (18/232)	5% (11/206)
Match	25% (57/232)*	35% (71/206)

N: number of patients. Percentage of segments are given.
*) $p < 0.05$ vs normal whole-body insulin sensitivity.

measurements were therefore only performed in non-infarcted normokinetic myocardium with normal $^{13}NH_3$ uptake (i.e. PET-normal and PET-reverse mismatch segments).

We found that the PET-reverse mismatch pattern was more frequently observed in patients with low whole-body insulin sensitivity compared to those with normal whole-body insulin sensitivity ($p<0.05$), **Table 6**. In this patient group left ventricular ejection fraction was reduced after CABG, and to some extent PET reverse mismatch was found to be predictive of outcome within 7 months after coronary artery bypass surgery. The percentage of normoperfused myocardial segments with PET reverse mismatch predicted the occurrence of a major adverse cardiac event with a positive and negative predictive value of 55% and 88%, respectively. Although these values are insufficient for clinical diagnostic purposes, our finding could have important clinical implications. It might be interesting to perform a large scale clinical trial evaluating to what extent identification of PET reverse mismatch by semiquantitative imaging could be useful in management of patient with ischemic heart disease considered for coronary artery bypass surgery.

The pathophysiological correlates of our semiquantitative findings are shown in **Figure 13**. In normokinetic myocardium with normal relative $^{13}NH_3$ uptake (i.e. PET-normal and PET-reverse mismatch segments) absolute myocardial blood flow at rest was similar to blood flow measured in age-matched healthy subjects. In contrast, insulin stimulated myocardial glucose uptake in PET-normal myocardium was increased in patients with normal whole-body insulin sensitivity, but in patients with low whole-body insulin sensitivity similar to uptake in healthy subjects. These findings are most likely explained by a generalized defect in insulin mediated tissue glucose uptake involving both skeletal and cardiac muscle metabolism in patients with heart failure. Evidently, in the failing heart with preserved insulin sensitivity an increased left ventricular end-diastolic pressure resulted in "supranormal" insulin stimulated myocardial glucose uptake, whereas myocardial glucose uptake is disproportionately low in relation to cardiac work when insulin sensitivity was impaired. In myocardial segments with the PET reverse mismatch pattern insulin stimulated glucose uptake was severely reduced (Figure 13). The pathophysiologic mechanism responsible for this finding remains unknown. In the current study the LC was set at the value of 1. However, as mentioned in 4.2, page 14 regional LC determined by the method developed by Kuwabara and co-workers could provide further insight into the metabolic state of myocardium with the PET reverse mismatch pattern (Kuwabara et al. 1990). In Study III and IV it was shown that regional glucose metabolism is impaired after short periods of myocardial ischemia (Knight et al. 1996, Kofoed et al. 2000b). It could therefore be speculated that in patients with chronic ischemic heart disease low insulin mediated glucose uptake in normally perfused myocardial regions reflects downward regulation of glucose metabolism as a consequence of brief episodes of regional myocardial ischemia. On the other hand we mainly observed PET reverse mismatch in patients with low whole-body insulin sensitivity and it could therefore reflect regional accentuation of the generalized defect of insulin sensitivity. Overall, these findings suggest that in addition to accelerating coronary atherosclerosis which is well-documented in patients with the "metabolic syndrome", insulin resistance may also exert a deleterious effect by impairing insulin mediated glucose uptake in the myocardium of patients with ischemic heart failure. Our data appear to support the hypothesis that cardiac "glucose metabolic reserve" defined as the ability of the tissue to increase glucose uptake in response to increased demand or ischemia may be an important factor determining outcome in patients with ischemic heart failure.

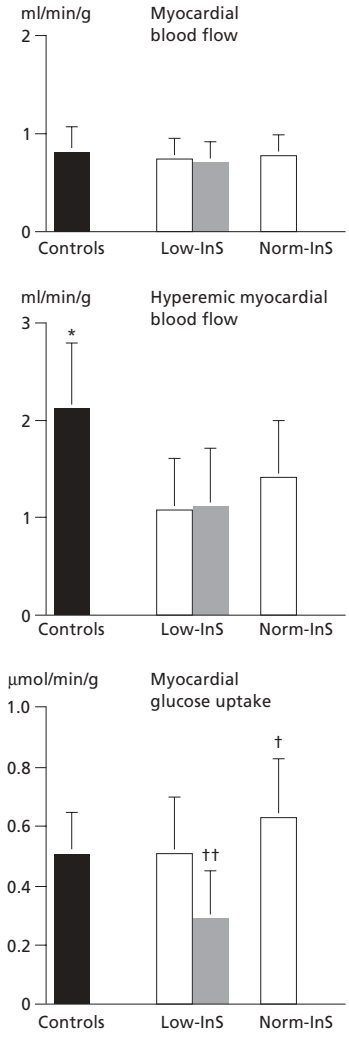

Figure 13. Myocardial blood flow at rest, hyperemic blood flow and insulin stimulated glucose uptake in normokinetic segments. *Controls:* healthy subjects (closed bars). *Low-InS:* patients with low whole-body insulin sensitivity. *Norm-InS:* patients with normal whole-body insulin sensitivity. Open bars: PET-normal segments. Shaded bar: PET-reverse mismatch segments. *: $p<0.01$ vs patients; †: $p<0.001$ vs controls; ††: $p<0.001$ vs PET-normal segments in patients with low whole-body insulin sensitivity myocardial glucose uptake in low and normal whole-body insulin sensitivity patients.

It was a major breakthrough in the treatment of patients with heart failure when β-blocker therapy was shown to improve long-term prognosis in these patients (Packer et al. 1996). Interestingly, it was recently found that the effect of the β-blocker carvedilol appeared to be dependent on the extent of insulin resistance before initiation of treatment in patients with heart failure primarily of ischemic etiology (Refsgaard 1999). Improvement of left ventricular contractile function following carvedilol treatment was mainly observed in patients with a minor reduction in insulin sensitivity whereas no change was observed in severely insulin resistant patients. These findings suggest that a preserved cardiac "glucose metabolic reserve" in patients with heart failure is required to improve prognosis using β-blocker treatment.

Conclusion. Global and regional insulin stimulated myocardial glucose uptake is impaired in patients with ischemic heart disease, impaired left ventricular ejection fraction and low whole-body insulin sensitivity. In these patients the myocardium appears to be unable to increase myocardial glucose uptake in response to an increased demand. This abnormality of cardiac metabolism is predictive of a worse outcome after CABG in patients with ischemic heart disease and heart failure.

7. MYOCARDIAL VIABILITY

Regional myocardial ischemia is accompanied by impairment of left ventricular contractile function, and until the early seventies it was believed that akinesia of a left ventricular segment at rest observed after an episode of myocardial ischemia was indicative of irreversible necrosis. However, in 1975 Heyndrickx demonstrated that pro-

longed contractile dysfunction observed in post-ischemic canine myocardium could be fully reversible (Heyndrickx et al. 1975). In addition, it was found that contractile function could recover after CABG in patients with ischemic heart disease and chronically impaired left ventricular function (Bourassa et al. 1972, Popio et al. 1977). Based on these experimental and clinical observations the concept of a reversible LV contractile dysfunction or "viable myocardium" was founded. Although regionally preserved or enhanced myocardial ^{18}FDG uptake in relation to $^{13}NH_3$ uptake appeared to be a frequent finding, the pathophysiologic substrate of viable myocardium was subsequently found to be rather complex.

Within the last 20 years, identification of viable myocardium in the clinical setting to predict outcome after CABG has been a field of intense clinical research in patients with chronic ischemic heart disease and impaired left ventricular contractile function. In the nineteen eighties large scale clinical trials had documented a small yet significant survival benefit of CABG compared to medical therapy especially in patients with multi-vessel coronary artery disease, a reduced left ventricular ejection fraction (LVEF) and various degrees of angina pectoris (Alderman et al. 1983, Passamani et al. 1985, Pigott et al. 1985, Vigilante et al. 1987, Bounous et al. 1988, Yusuf et al. 1994). However, this long-term survival benefit of CABG compared to medical therapy in these high-risk patients appeared only to be present if the in-hospital peri-operative mortality was less than 7% (Alderman et al. 1983, Pigott et al. 1985). At that time it was therefore considered of paramount importance to develop presurgical methods that could identify patients with a high likelihood of increased survival after CABG, despite a potentially high surgical risk. The hypothesis was subsequently put forward that a recovery of left ventricular contractile function after CABG as a consequence of increased blood flow in dysfunctional but viable myocardium was a strong indicator for improved survival. Accordingly, identification of viable myocardium was therefore suggested to be clinically useful to select patients who would benefit the most from CABG.

7.1. PATHOPHYSIOLOGY OF VIABLE MYOCARDIUM

Myocardial ischemia can be defined as an imbalance of coronary oxygen supply and myocardial demand. During the development of coronary atherosclerosis myocardial ischemia occurs at times of increased demand as a consequence of an impaired myocardial blood flow reserve. At more advanced stages of coronary artery disease a stenosis may restrict myocardial blood flow even at rest and result in myocardial ischemia at basic cardiac demands. In addition progression of coronary blood flow restriction may also occur acutely during an acute coronary syndrome. Contractile work cannot be maintained during myocardial ischemia as a consequence of low energy supply and if the normal balance of oxygen supply and demand is not restored within a few hours the tissue deteriorates. However, ischemically jeopardized myocardium may assume a biologic state in which contractile function is impaired for a prolonged period of time (months) even without development of myocardial necrosis – i.e. reversible contractile dysfunction.

Two concepts – myocardial stunning and myocardial hibernation – have been proposed to describe the pathophysiologic characteristics of reversible contractile dysfunction (Heyndrickx et al. 1975, Diamond et al. 1978, Braunwald & Kloner 1982, Rahimtoola 1985). Myocardial stunning can be defined as a delayed recovery of contractile function after acute myocardial ischemia despite normalization of regional blood flow. Initially demonstrated in canine hearts after 5-15 minutes of coronary occlusion (Heyndrickx et al. 1975), myocardial stunning was subsequently reported in patients with ischemic heart disease (Sabia et al. 1992, Ambrosio et al. 1996).

Myocardial hibernation was originally postulated by Rahimtoola to develop in patients with chronic ischemic heart disease as a consequence of persistent myocardial ischemia transforming into a chronic condition in which "a new state of equilibrium is reached whereby myocardial necrosis is prevented" (Rahimtoola 1985). This equilibrium was postulated to be achieved by a downregulation of contractile function in response to coronary hypoperfusion (perfusion-contraction match). Furthermore, hibernating myocardium was thought to be stable throughout a prolonged period of time, and when coronary revascularization was performed contractile function would recover.

Whereas chronically reversible contractile dysfunction in patients with ischemic heart disease may occur in several clinical scenarios, it is evident that the pathophysiology of viable myocardium is complex and most often involves a combination of stunning and hibernation (Schelbert & Buxton 1988, Bolli 1992, Heusch & Schulz 2001). By definition myocardial blood flow is normal subtending stunned myocardium whereas the flow to hibernating myocardium is reduced. In patients with chronic ischemic heart disease several studies, however, have demonstrated that transmural myocardial blood flow at rest measured quantitatively with PET in reversibly dysfunctional myocardium is frequently within the near-normal range, although blood flow reserve is severely impaired (Vanoverschelde et al. 1993, Gerber et al. 1996, Maki et al. 1996, Marinho et al. 1996). Furthermore, although some functional and metabolic adaptation is detected initially during moderate hypoperfusion in chronically instrumented animals, prolonged myocardial hypoperfusion (12-48 hours) does not result in a state of balanced perfusion-contraction match, but rather in a progressive development of regional myocardial necrosis (Schulz et al. 1993, Kudej et al. 1998, Schulz et al. 2001). These observations appear to challenge the original concept of hibernating myocardium as the primary mechanism by which chronically reversible contractile dysfunction develops (Rahimtoola 1985). Repetitive stunning progressing into chronic myocardial stunning was subsequently proposed to be a more likely mechanism for the development of reversible contractile dysfunction (Vanoverschelde et al. 1993), and this hypothesis has been supported by data derived in several animal experimental studies (Liedtke et al. 1995, Fallavollita & Canty 1999, Kofoed et al. 2000a). On the other hand, a reduced myocardial blood flow at rest has also been recorded in viable myocardial segments consistent with a state of myocardial hibernation in patients with ischemic heart disease (vom-Dahl et al. 1994, Haas et al. 2000). Whether this latter finding reflects a state of truly compensatory perfusion-contraction match in response to persistent ischemia at rest remains unknown. Recent animal experiments report that a reduced blood flow at rest in coronary arteries subtending reversible dysfunctional myocardium may not be a result of "classic" hibernation, but could be a secondary compensatory mechanism occurring in chronically stunned myocardium to improve an otherwise exhausted myocardial flow reserve (Fallavollita & Canty 1999, Fallavollita et al. 2002).

7.2. GLUCOSE UPTAKE IN VIABLE MYOCARDIUM

In the vast majority of clinical studies performed to evaluate viable myocardium by PET glucose uptake it has been estimated using semiquantitative ^{18}FDG PET imaging – for review see Di Carli 1998. Viable myocardium in patients with ischemic heart disease was found by Tillisch and co-workers to have an ^{18}FDG uptake after oral glucose loading equal to or slightly lower than uptake in the myocardium of healthy subjects (Tillisch et al. 1986). In approximately 40% of viable segments myocardial $^{13}NH_3$ uptake was decreased while ^{18}FDG uptake was relatively higher consistent with a pattern of glucose metabolism-blood flow mismatch (PET-mismatch). In the rest of the viable segments both myocardial blood flow and ^{18}FDG uptake were normal (PET-normal). Identification of PET-mismatch was subsequently considered the strongest indicator of viable myocardium (Bax et al. 1997, Di Carli 1998). On the other hand, non-viable segments were consistently found to have concordantly reduced ^{18}FDG and $^{13}NH_3$ uptake (PET-match). Under fasting conditions a relatively higher level of ^{18}FDG uptake in viable myocardium in relation to $^{13}NH_3$ uptake was reported in patients

with ischemic heart disease (Tamaki et al. 1989, Lucignani et al. 1992, Maki et al. 1996). However, due to poor image quality of ^{18}FDG images during fasting this imaging procedure has never become widespread.

Why myocardial glucose uptake is normal or relatively increased in the face of a severe reduction in contractile work in reversibly dysfunctional myocardium remains unknown. Schelbert & Buxton initially hypothesized that the increased glucose uptake in viable myocardium reflected stimulation of anaerobic glycolysis in response to a state of chronic myocardial ischemia (Schelbert & Buxton 1988). This hypothesis was later supported by the finding of increased glycolysis, but also glycogen synthesis during sustained low flow ischemia in dogs (McNulty 1996). The recent detection of glycolytic intermediates in tissue biopsies obtained from reversibly dysfunctional myocardium in patients with ischemic heart disease also supports the concept of an increased anaerobic glycolysis (Vogt et al. 2002). Schelbert & Buxton pointed out that it would appear unlikely that such a condition would persist indefinitely. Other investigators have argued that ongoing ischemia appears unlikely in viable myocardium with near-normal myocardial perfusion at rest (Vanoverschelde et al. 1993, Vanoverschelde et al. 1997). Alternative explanations for the high glucose uptake and glycogen contents in reversibly dysfunctional myocardium are a sustained post-ischemic activation of glycogen synthase during chronic stunning and a shift in substrate preference from FFA to glucose (McNulty & Luba 1995, Bolukoglu et al. 1996). Histologic examination of myocardial biopsies obtained in dysfunctional myocardium has provided additional information with regard to the possible mechanism of increased glucose uptake in viable myocardium (Depre & Taegtmeyer 2000). Changes in the tissue consistent with a dedifferentiation process promoting a fetal phenotype have implied that adult myocardial tissue may have an increased reliance on glucose for energy provision similar to what is seen in the fetal heart.

7.3. HETEROGENEITY OF POTENTIALLY VIABLE MYOCARDIUM

As reviewed in section 7.1 it is evident that the pathophysiology of viable myocardium is complex most likely involving a combination of both stunning and hibernation. Accordingly, at any given time point resting myocardial blood flow may be normal or decreased, myocardial flow reserve may be slightly or severely reduced and ^{18}FDG uptake may be normal or relatively increased in reversibly dysfunctional myocardium. Whether this continuum of pathophysiological conditions may influence the clinical diagnosis of viable myocardium remains unresolved.

To assess viable myocardium in patients with chronic ischemic heart disease several other image modalities of less logistic complexity and cost than PET have been developed (Dilsizian & Bonow 1993, Bax et al. 1997). In early studies of reversible myocardial contractile dysfunction reversibility could be unmasked by inotropic stimulation with epinephrine during ventriculography in patients with ischemic heart disease (Horn et al. 1974, Nesto et al. 1982). Infusion of low doses of dobutamine during simultaneous recording of contractile function with echocardiography – dobutamine echocardiography (see 3.4, page 11) – was therefore suggested as an alternative method for identification of viable myocardium (Cigarroa et al. 1993). In addition, myocardial retention of technetium-99m-methoxyisobutyl isonitrile (Sestamibi, see 3.4, page 11) as visualized by single photon emission computerized tomography (SPECT) was also proposed as an indicator of myocardial viability (Beanlands et al. 1990, Marzullo et al. 1992) Although ^{18}FDG PET, dobutamine-echocardiography and Sestamibi-SPECT tested in separate studies appear to provide approximately the same level of diagnostic accuracy (Bax et al. 1997) it should be appreciated that these methods reflect distinctly different physiologic properties of the myocardium.

The aim of our study was to evaluate to what extent the pathophysiological complexity of reversible contractile dysfunction may influence clinical diagnosis of viable myocardium by semiquantitative ^{18}FDG-PET, dobutamine echocardiography or Sestamibi-SPECT.

Potential reversible contractile dysfunction was evaluated in a selected group of patients with ischemic heart disease (Study VI). An area of abnormal myocardial contraction subtended by a totally occluded coronary artery was defined as a "target area" of potentially viable myocardium. This relatively simplified model was chosen to limit the number of pathophysiological variables. In this study the acquired ^{18}FDG data were the first cardiac PET images ever recorded in Denmark (1994). At the time of the study, as mentioned in section 3.1.1, page 9, the $^{13}NH_3$ tracer was not yet available for clinical use. Accordingly, relative myocardial ^{18}FDG uptake was related to blood flow in identical myocardial areas estimated by SPECT-Sestamibi. This hybrid method of PET/SPECT had at the time of the study recently been extensively evaluated in patients with ischemic heart disease for the assessment of viable myocardium (Knuuti 1993). Using this method myocardial segments are not categorized with regard to the glucose metabolism-blood flow relation, but reversible contractile dysfunction may be characterized by an ^{18}FDG uptake >90% (Knuuti et al. 1993). We found an identical threshold value of ^{18}FDG uptake > 90% to predict subsequent recovery of contractile function after revascularization using this methodology. This was confirmed by a receiver operating characteristic analysis in a subgroup of the patients (N = 8) undergoing CABG and re-examined with echocardiography 3 months later.

Relative ^{18}FDG uptake in potentially viable myocardium was normally distributed ranging from 34% to 150% with approximately one third of the myocardial segments having ^{18}FDG uptake indicative of viable myocardium. This reflects a continuum of myocardial glucose uptake in potentially viable myocardium. Depre and coworkers previously reported a linear correlation between ^{18}FDG uptake and the fraction of dedifferentiated cardiomyocytes detected in myocardial tissue biopsies obtained in dysfunctional myocardium during coronary surgery (Depre et al. 1995). Thus the continuum observed in our study may reflect a variable proportion of dedifferentiated cardiomyocytes. Within this continuum of ^{18}FDG uptake a striking degree of heterogeneity was observed with respect to dobutamine contractile reserve and Sestamibi uptake (**Figure 14**). At levels of ^{18}FDG uptake >90% only half of the myocardial segments had preserved Sestamibi uptake and dobutamine contractile reserve. Absence of dobutamine contractile reserve in areas of the myocar-

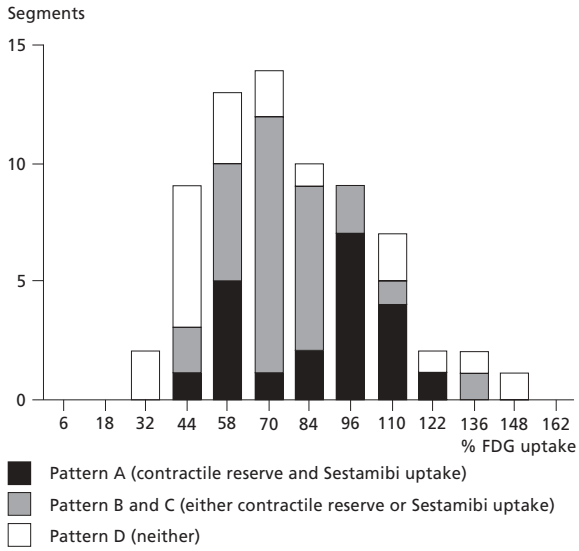

Figure 14. Patterns of dobutamine contractile reserve and Sestamibi uptake in relation to ^{18}FDG uptake. Note that pattern A is more frequent above the 90% ^{18}FDG threshold level. Conversely, pattern D is more frequently observed at ^{18}FDG uptake levels <51%.

dium with preserved ^{18}FDG uptake was previously reported in patients with ischemic heart disease (Chan et al. 1996, Melon et al. 1997). In collateral dependent reversibly dysfunctional myocardium recent animal experiments have demonstrated that preserved dobutamine contractile reserve is an infrequent finding (Fallavollita et al. 2002). Although Sestamibi SPECT may reflect cellular viability it has been a consistent finding that Sestamibi uptake underestimates the extent of viable myocardium compared with ^{18}FDG PET (Altehoefer et al. 1994, Soufer et al. 1995). In non-viable myocardium (^{18}FDG uptake below 90%) the tissue was very heterogeneous, yet at low levels of ^{18}FDG uptake (<51%) a large proportion of segments did not have either residual dobutamine contractile reserve or Sestamibi uptake. The heterogeneity of the tissue most likely reflects different stages of myocardial stunning, myocardial hibernation or both, illustrating the complex pathophysiology of potentially viable myocardium. However, it should be stressed that methodological limitations such as the use of semiquantitative image analysis, tissue attenuation artifacts using SPECT, and misalignment between image modalities could have influenced our findings. Furthermore, although studies of regional myocardial pathophysiology in reversible dysfunctional myocardium may have basic scientific interest, probably a more clinically relevant parameter is an evaluation of the global left ventricular function following CABG (see section 7.4).

Conclusion. Dysfunctional, but potentially viable myocardium subtended by an occluded coronary artery represents a continuous metabolic spectrum with a high degree of heterogeneity with regard to contractile reserve and Sestamibi uptake. This finding probably reflects the complex pathophysiology of reversibly dysfunctional myocardium and stresses the importance of a deeper insight into the connection between clinical results and pathophysiology of potentially viable myocardium.

7.4. CORONARY ARTERY BYPASS SURGERY AND CLINICAL MYOCARDIAL VIABILITY TESTING

In accordance with the results of several large-scale trials conducted in the nineteen eighties it has been generally accepted in clinical practice that patients with multivessel coronary artery disease, impaired left ventricular contractile function and no other serious comorbidity should be referred for CABG irrespective of symptom severity (Yusuf et al. 1994). This is because a survival benefit was documented compared to medical therapy especially in patients with such angiographic findings. The mechanism responsible for the improved survival was suggested to be a post-surgical increase in global left ventricular ejection fraction, as this parameter in general already had been identified as a very important prognostic factor. However, open-heart surgery in patients with reduced left ventricular ejection fraction had for many years been associated with a substantially increased perioperative risk. It was therefore suggested that among high-risk patients with low left ventricular ejection fraction in whom the surgeon was reluctant to do CABG, identification of large amounts of viable myocardium preoperatively would predict improvement of contractile function and thus survival if surgery was performed. On the other hand, if only small amounts of viable myocardium was found, the likelihood of the patient improving prognosis should be considered low and accordingly speak strongly against surgery.

The hypothesis that implementation of myocardial viability testing could be useful in clinical decision-making has been explored in a large number of studies mostly in small patient groups and primarily evaluating segmental indices of viability (Bax et al. 1997). However, the clinical relevance of minor regional improvements in contractile function after CABG with no effect on global left ventricular contractile function remains unknown. To implement myocardial viability testing in clinical decision-making based on solid scientific evidence, studies preferably randomized are required including a substantial number of patients with multivessel disease and low left ventricular ejection fraction referred for CABG. Surgery should be performed either in a randomized fashion or independently of viability data. The peri-operative mortality and post-surgical outcome including cardiac symptoms, left ventricular ejection fraction, and long-term survival should be evaluated blindly. Although other methods to identify myocardial viability have been developed (see section 7.3) the main focus of this review is the clinical use of the ^{18}FDG method. In this context only a few papers of clinical relevance have been published (**Table 7**). The listed studies are characterized by the following: myocardial viability evaluated by ^{18}FDG imaging, included patient groups (N ≥ 35) with multi-vessel disease, left ventricular ejection fraction <45% referred for CABG, in whom post-surgical global left ventricular ejection fraction and possibly also survival have been related to pre-operative myocardial viability. All studies including ours were observational.

The aim of our study (VII) was to assess the ^{18}FDG-$^{13}NH_3$ uptake pattern and its relation to outcome after CABG in patients with chronic ischemic heart disease, reduced left ventricular function following a prolonged strategy of medical treatment. The general patient management strategy in Denmark at the time of the study (1994-1998) was one of initial medical treatment followed by invasive investigation and treatment only when medication could no longer reduce cardiac symptoms to an acceptable level. It was therefore of relevance to evaluate myocardial viability in that particular

Table 7. Clinical evaluation of myocardial viability with 18FDG-PET in high-risk patients undergoing CABG.

		Pre-CABG					CABG	Post -CABG			
Author	N	duration of IHD mean (m)	CCS≥3 N (%)	NYHA≥3 N (%)	LVEF mean %	^{18}FDG viability >25% of LV N (%)	peri-operative mortality N (%)	improvement ≥5% of LVEF N (%)	CCS improved ≥1 class N (%)	NYHA improved ≥1 class N (%)	survival % (y)
Vom Dahl et al, 1994	37	NA	NA	NA	34	NA	0 (0)	10/37 (27)	NA	NA	NA
Pagano D et al, 1998*	35	≥30	14 (40)	35 (100)	23	24/29 (83)	2 (5.7)	17/29 (59)	9/9 (100)	20/20 (100)	NA
Wiggers et al, 2000*	46	50	13 (28)	15 (32)	35	NA	Such patients not included	7/46 (15)	Mean Improved CCS 0.8	Mean Improved NYHA 0.5	NA
Pasquet et al, 2000	66	NA	NA	34 (51)	28	37 (62)	0 (0)	28/59 (47)	NA	NA	NA
Bax et al, 2001	47	NA	9 (20)	38 (80)	30	22 (49)	0 (0)	21/47 (45)	NA	7/38 (18)	NA
Kofoed et al, 2002	45	102	32 (71)	13 (29)	31	2 (4)	1 (2)	2/30 (7)	18/30 (60)	23/30 (77)	77 (3)

CABG: coronary artery bypass grafting; IHD: ischemic heart disease: LVEF: left ventricular ejection fraction; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association; N: number of patients; m: months; y: years; NA: not available.
*) Viability data was available during the selection of patients for CABG.

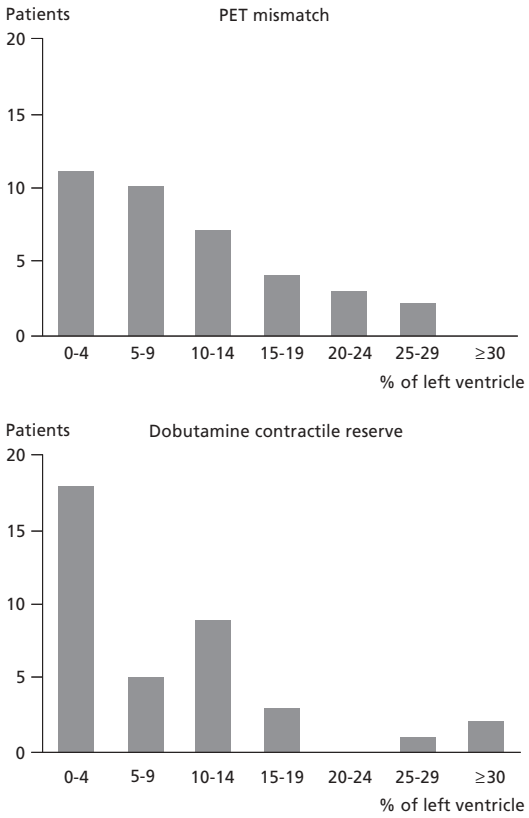

Figure 15. Number of patients with different amounts (%) of left ventricular myocardial viability evaluated by positron emission tomography (PET mismatch) and dobutamine echocardiography (dobutamine contractile reserve).

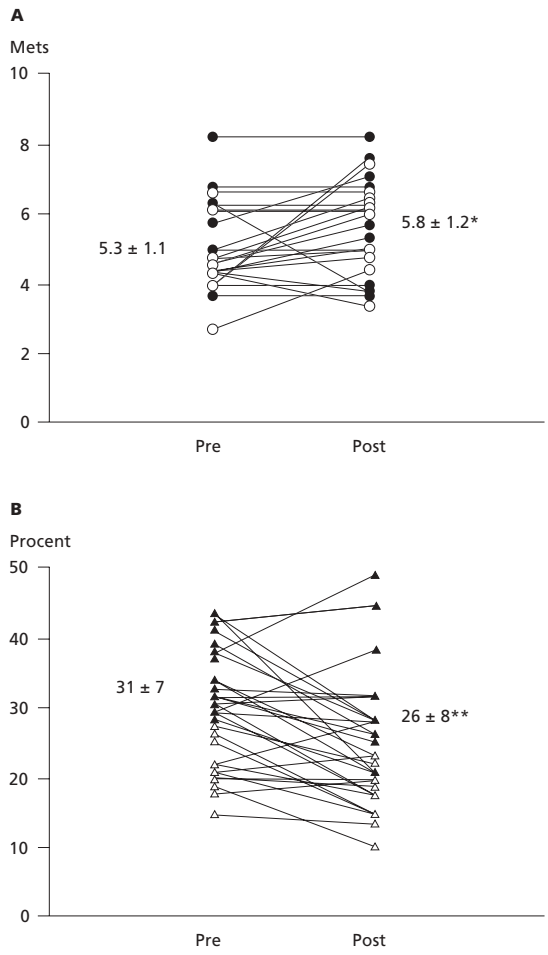

Figure 16. A: Exercise capacity and **B:** Left ventricular ejection fraction before (pre) and 7 months after (post) coronary artery bypass grafting in event-free survivors (n = 30). *: p < 0.05, **: p < 0.0005. Closed symbols: patients with LVEF ≥ 30%. Open symbols: patients with LVEF < 30%.

patient group, as such patients were representative of contemporary clinical practice. To minimize selection bias myocardial viability data was not made available in the clinical decision process and the indication to perform surgery was an integrated decision-process involving angiographic findings, symptoms and clinical judgment. In our patients the mean duration of ischemic heart symptoms was 9 years, and left ventricular extent of myocardial viability measured by PET and dobutamine-echocardiography was < 30% in most patients (**Figure 15**). Thus, the amount of dysfunctional, but viable myocardium was rather scarce. On the other hand, serious surgical complications were rare during CABG and the perioperative mortality rate only 2%, suggesting that CABG could be performed with a reasonable degree of safety in these potentially high-risk patients. At 7 months after CABG angina pectoris and heart failure symptoms improved in most event-free patients and a small increase in exercise capacity was noted (**Figure 16**, top). No relation was found between left ventricular extent of viable myocardium and improvement of symptoms or exercise capacity after CABG. Left ventricular ejection fraction decreased in event free survivors, independent of symptomatic benefit (Figure 16, bottom) and no relationship was found between indices of viable myocardium and changes in left ventricular ejection fraction 7 months after CABG (**Figure 17**). Nevertheless, the 3-year survival for our study group was 77%, which is comparable to surgical treatment results of similar patients from other cardiac centers (Elefteriades et al. 1997, Luciani et al. 2000). In patients with a reduced LVEF to 30% and multivessel disease treated medically in the era of ACE-inhibitors, 3-year survival rates are in the range of 60-70% (Digitalis Invest Group 1997, Pitt et al. 2001).

In the previously reported studies (Table 7) the proportion of patients with clinically relevant amounts of viable myocardium defined as an improvement of left ventricular ejection fraction of ≥5% after CABG was highly variable ranging from 15-59%. The amount of viable myocardium necessary to produce a detectable improvement in left ventricular ejection fraction was initially suggested to be at least 25% of the left ventricular myocardium (Tillisch et al. 1986). The percentage of patients with potential myocardial viability of this magnitude has been reported to range from 20% to 60% among patient groups referred for viability tests as part of a pre-surgical diagnostic evaluation (Christian et al. 1997, Auerbach et al. 1999, Schinkel et al. 2002). However, it should be noted that recovery of global left ventricular contractile function after CABG was not confirmed in any of these studies. This large variability could reflect differences in methodology used to identify viable myocardium, but may also be a function of the referral pattern and patient management strategy at the individual site. The time lag between the initial ischemic event and the time of referral for viability testing could be of importance as viable myocardium might not persist indefinitely (Schelbert & Buxton 1988). Recent retrospective data in small patient groups have suggested that viability of dysfunctional myocardium might only be maintained for a limited period of time (Beanlands et al. 1998, Schwarz et al. 1998). A prolonged strategy of medical treatment could therefore reduce the overall prevalence and left ventricular extent of viable myocardium and thereby the clinical benefit of CABG. In the listed papers (Table 7) it was only possible to extract information about the pre-surgical duration of ischemic heart disease in the work of Wiggers (Wiggers et al. 2000) and Pagano (Pagano 1998). However, in these two studies some selection bias must be accounted for as the study design excluded patients with surgical complications (Wiggers), 2 patients had PCI instead of CABG (Wiggers) and viability data were available for the surgeon before decision to operate was made (Wiggers and Pagano). It is obvious that some patients with small amounts of myocardial viability were not referred for surgery in these studies. Yet, in the studies by Pagano,

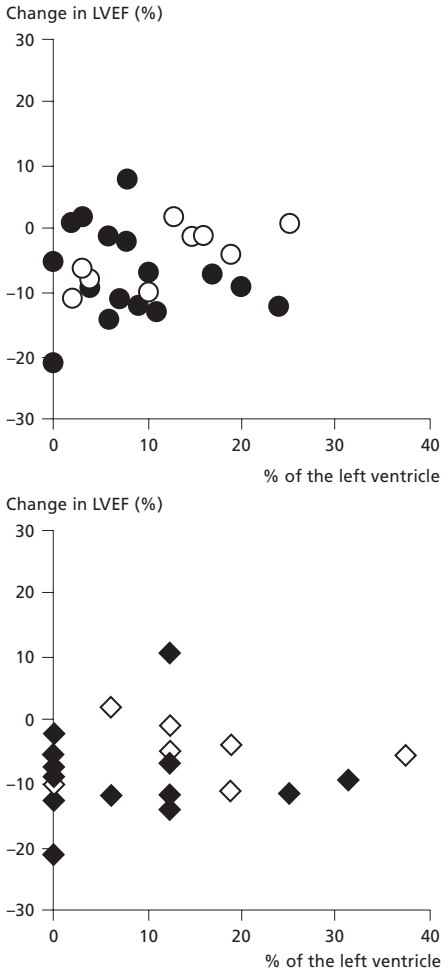

Figure 17. Relationship between the extent of myocardial viability by PET and by dobutamine echocardiography (DE) and change in left ventricular ejection fraction 7 months after coronary artery bypass grafting. Circles: mismatch. Squares: DE contractile reserve. Open symbols: patients with LVEF <30%.

Wiggers and Kofoed an increasing duration of ischemic heart disease from 30 to 102 months was associated with a decreasing proportion of patients with improved LVEF ≥5% after CABG.

Despite a low proportion of patients with post-surgical increase in LVEF was found in our study, a substantial symptomatic benefit together with an acceptable long-term cardiac survival were achieved by CABG in our high risk patients. These findings appear partly to challenge the assumption that patients with impaired left ventricular contractile function benefit from CABG because of an increase in left ventricular function. On the other hand, our results correspond to the recent report of Samady and co-workers who found no relationship between changes in left ventricular ejection fraction early after CABG and clinical outcome (Samady et al. 1999). They suggested that additional mechanisms not related to global left ventricular function may be responsible for the beneficial symptomatic and prognostic effects of CABG. Recent retrospective data suggest that improved survival after CABG in patients with left ventricular dysfunction most likely is achieved by a reduction in the frequency of sudden cardiac death rather than death from progressive heart failure (Veenhuyzen et al. 2001). Accordingly, although improvement of left ventricular function may be absent, revascularization of small regions of dysfunctional but viable myocardium could contribute to an extended life-time expectancy and possibly also symptom relief after CABG (Di Carli et al. 1995a). A recent meta-analysis including data from 24 mostly retrospective, non-randomized studies suggested a strong association between myocardial viability by pre-surgical testing and improved survival after CABG (Allman et al. 2002). Specifically, if patients with myocardial viability were not revascularized, a substantially higher mortality was recorded when compared to similar patients undergoing surgery. Furthermore, the data suggested that surgery in patients with viable myocardium was associated with better survival compared to surgery in patients without viable myocardium. In the study by Allman post-surgical LVEF and symptoms, in addition to the amount of LV myocardial viability were not available, and the interpretation of these retrospective data including possible clinical implications remains a subject of discussion (Bonow 2002). The concept that revascularization of viable myocardium irrespective of improvement in global left ventricular contractile function results in improved prognosis after CABG needs to be confirmed in a prospective randomized trial.

The relative symptomatic profile of the patients – predominantly angina pectoris or symptoms of heart failure – was only available in some of the previous comparable studies (Table 7). No apparent relationship could be found between the pre-surgical relative symptomatic profile of the patients and post-surgical outcome. A variable fraction of patients had severe angina pectoris and as in our study the patient groups from these observational studies most likely reflect the general symptomatic profile of patients referred for CABG at the individual site. It has been argued that the symptomatic profile of patients with multi-vessel ischemic heart disease and left ventricular contractile dysfunction should be a determinant factor in the selection of treatment strategy including diagnostic myocardial viability testing. In patients with severe angina pectoris surgery will of cause frequently be indicated to achieve pain relief irrespective of the likelihood of a concomitant prognostic gain of the procedure. In contrast, in patients who do not have angina pectoris, but rather symptoms of congestive heart failure the decision to perform surgery has been recommended to be guided by viability testing. Interestingly, in the meta-analysis by Yusuf and co-workers including data from all previous large-scale randomized trials 2649 patients were randomized to either CABG or medical treatment and most patients had angina pectoris except 297 (11.2%) who were without chest pain. In the post-hoc subgroup analysis of this study, the survival benefit of surgery compared to medical therapy was similar among all classes of chest pain severity. Evidently this finding needs confirmation in a prospective randomized trial, but nevertheless appears to suggest that the relative symptomatic profile should possibly not be a determinant factor in the process of deciding to operate or not high risk patients with multi-vessel disease and impaired left ventricular function. Future studies are required in which both the symptomatic profile of the patients and the duration of ischemic heart disease is accounted for when the value of clinical myocardial viability testing is evaluated (for further discussion see 7.5).

In most of the studies in which the perioperative mortality at that time had been recorded (Table 7) it was found to be well below the 7% value required to maintain a survival benefit of CABG compared to medical therapy as originally reported (Alderman et al. 1983, Pigott et al. 1985). The hypothesis that implementation of myocardial viability testing could be useful in clinical decision-making in high-risk patients was originally developed because the perioperative mortality at the time frequently exceeded 7%. Evidently current surgical techniques has improved substantially during the last 20 years, and in most large volume centers the peri-operative mortality is substantially below 7% even in high risk patients (Luciani et al. 2000). Consequently, in this setting of considerably improved surgical techniques further studies are needed to resolve the possible role of clinical viability testing.

Overall we believe that our study has several important clinical implications. First, since one of the corner stones in the treatment strategy of patients with ischemic heart disease is to preserve left ventricular contractile function, detection of myocardial viability should apparently not await aggravation of cardiac symptoms. Secondly, CABG can be performed with a reasonable degree of safety in patients with low ejection fraction and small amounts of viable myocardium. Thirdly, a substantial symptomatic benefit together

with an acceptable long-term cardiac survival may be achieved by CABG despite low levels of viable myocardium. However, the development of modern cardiology has substantially changed the characteristics of patients referred for coronary angiography compared to the current study (see 7.5) and future studies may elucidate the general clinical applicability of our findings.

Conclusion. When left ventricular function is reduced after a prolonged conservative strategy of medical treatment, areas of myocardial viability are scarce and improvement of left ventricular function after CABG can rarely be expected in patients with ischemic heart disease and multi-vessel disease. Nevertheless, a substantial symptomatic benefit together with an acceptable long-term cardiac survival was achieved after CABG. Although our study provides important insights into the relationship between myocardial viability and outcome after CABG it cannot determine in general whether myocardial viability testing is clinically useful in the management of high-risk patients with ischemic heart disease.

7.5. FUTURE PROSPECTS OF CLINICAL MYOCARDIAL VIABILITY TESTING

The possible future role of clinical myocardial viability testing remains unsettled. The current practice of evidence-based cardiology is that all patients with chest pain and risk factors of ischemic heart disease, patients with positive exercise-ECG, patients with a non-ST segment elevation myocardial infarction and patients with recurrent ventricular tachycardia or extramural cardiac arrest in whom ischemic heart disease is suspected are referred for coronary angiography irrespective of the relative symptomatic profile. If coronary angiography reveals surgical graftable 3-vessel coronary artery disease together with a reduced left ventricular contractile function and if there are no contraindications (e.g. advanced age, severe renal failure, previous debilitating cerebrovascular disease, malignant illness etc) the patient will often be referred for surgical or percutaneous revascularization in order to extent life-time expectancy and improve symptoms (Yusuf et al. 1994). The indication will of course be further strengthened by the severity of any cardiac symptoms and the final decision to revascularize will always be a process integrating overall findings and the individual wishes of the patient. With the current surgical technique the operative mortality may be expected to be moderate and myocardial viability testing may therefore only be useful in a small subset of these patients. On the other hand, denying a patient from the above mentioned referral groups the potential benefit of CABG on the basis of small amounts of viable myocardium does not appear to be supported by scientific evidence (Ståhle 2000, Tawakol & Gewirtz 2001, Bach 2003).

In a small group of patients with ischemic heart disease the primary manifestation of the disease resulting in referral for invasive coronary evaluation is clinical signs of congestive heart failure without chest pain. These patients may either be patients without a previous ischemic event, patients with a previous acute myocardial infarction treated medically or patients previously revascularized (CABG or PCI). In this particular patient group there are no large-scale randomized trials specifically evaluating whether CABG provides improved relief of heart failure symptoms and extended life-time expectancy compared to optimized, modern medical therapy. In this setting it is possible that myocardial viability testing could be clinically useful. Accordingly, appreciating that the management of this selected group of patients with symptoms of heart failure without angina pectoris is difficult and at the present time not evidence-based three large-scale randomized trials in the UK (Cleland et al. 2003), Canada (Beanlands et al. 2003) and the US (Joyce et al. 2003) are underway exploring this issue.

8. SUMMARY

In this thesis glucose uptake in normal and ischemically jeopardized myocardium was studied using ^{18}FDG and PET. Furthermore, the value of myocardial glucose metabolism-blood flow PET imaging in the management of patients with ischemic heart disease and impaired left ventricular function was evaluated.

In healthy subjects age-matched to the target age for the development of ischemic heart disease a regionally increased ^{18}FDG uptake compared with myocardial blood flow measured by $^{13}NH_3$ uptake – so-called PET-mismatch – was found in the posterolateral segments of the left ventricle especially in middle-aged men. Consequently, age-matched normal reference values are necessary in order to discriminate between physiologic and pathologic glucose metabolism-blood flow relations. Interindividual variability of left ventricular insulin stimulated myocardial glucose uptake was primarily related to the variability of coronary vascular reactivity and tissue insulin sensitivity in healthy elderly subjects.

In animal experiments it was demonstrated that ^{18}FDG uptake accurately reflects glucose metabolism in post-ischemic myocardium. Glycolytic flux was impaired early after acute regional myocardial ischemia probably as a consequence of a non-competitive inhibition of glyceraldehyde-3-phosphate dehydrogenase.

Low whole-body insulin sensitivity was associated with abnormalities of regional and global insulin stimulated myocardial glucose uptake and could to some extent predict a poor outcome after CABG in non-diabetic patients with chronic ischemic heart disease and heart failure. This finding emphasizes the prognostic importance of insulin stimulated myocardial glucose uptake in patients with ischemic heart disease.

In chronically dysfunctional, but potentially "viable" myocardium a substantial degree of heterogeneity with regard to ^{18}FDG uptake, contractile reserve and Sestamibi uptake was found, probably reflecting a complex pathophysiology.

When left ventricular function is reduced after a prolonged strategy of medical treatment, areas of myocardial viability are scarce and improvement of left ventricular function after CABG can rarely be expected in patients with multivessel ischemic heart disease. Nevertheless, substantial symptomatic benefit together with an acceptable long-term cardiac survival were achieved after CABG. Myocardial viability testing does not appear to contribute to the management of such patients.

In conclusion, quantitation of cardiac glucose uptake by ^{18}FDG and PET provides valuable insight into the pathophysiology of ischemically jeopardized myocardium. Conversely, the clinical value of myocardial viability testing using ^{18}FDG PET imaging is limited in patients with ischemic heart disease and impaired left ventricular function following a prolonged strategy of medical therapy.

9. FUTURE PERSPECTIVES

Quantitative cardiac ^{18}FDG PET imaging may be a valuable tool in future studies exploring regulatory mechanisms of cardiac glucose uptake, pathophysiology of ischemically jeopardized myocardium and novel pharmacological principles of treatment in patients with ischemic heart disease. Further studies will be required to fully resolve the important question of whether assessment of myocardial viability with PET is clinically useful in selected patients with ischemic heart disease for coronary revascularization. Within the field of non-invasive cardiac imaging several new modalities are under development, which shows great promise for future research in this field.

The regulation of glucose uptake in normal myocardium has been extensively studied in vitro. However, it is not known to what extent the observations made in these experimental studies can be extrapolated to conditions in the human heart. It would for example be interesting to explore whether the association between insulin stimulated myocardial glucose uptake and coronary reactivity observed in our healthy subjects is mediated by coronary nitric oxide synthesis.

Although numerous animal experimental studies have demonstrated that supply of glucose to ischemically jeopardized myocardium conserves the tissue and improves post-ischemic recovery of contractile function, this effect has never been shown in humans.

The recent introduction of acute percutaneous coronary intervention in patients with acute myocardial infarction may be an interesting model for the study of this issue during controlled myocardial reperfusion. It would be highly interesting to evaluate the effect of increased coronary glucose supply by a glucose-insulin clamp on regional myocardial glucose uptake, blood flow and contraction in reperfused human myocardium.

Recently a new group of drugs – peroxisome proliferator-activated receptor-gamma agonists – was shown to increase tissue insulin sensitivity (Olefsky 2000). Future studies in patients with low whole-body insulin sensitivity and ischemic heart disease may explore whether these new drugs are able to restore normal insulin stimulated myocardial glucose uptake and thus possibly improve the outcome after CABG.

The role of myocardial viability testing has been extensively evaluated world-wide and many investigators have concluded that myocardial viability testing provides clinically relevant information, which is helpful in the decision for or against CABG in patients with ischemic heart disease and impaired left ventricular function. However, this question remains unresolved and awaits the results of three large-scale randomized trials underway evaluating the relative merits of surgery versus medical therapy in relation to myocardial viability testing in patients with heart failure of ischemic aetiology (Beanlands et al. 2003, Cleland et al. 2003, Joyce et al. 2003). These studies appear to have the potential to provide definite answers with regard to the future role of clinical myocardial viability testing.

Within the field of non-invasive cardiac imaging several promising methods are developing which may further contribute to our understanding of the physiology and pathophysiology of the human heart. With the introduction of a combined PET/CT tomography it may become possible to perform paired evaluation of coronary anatomy, contractile function, myocardial blood flow and myocardial glucose uptake non-invasively. Furthermore, dual head SPECT imaging is now well established as a reliable alternative to the very expensive PET equipment. Possibly this will result in a much larger number of patients who may undergo myocardial viability testing, facilitating future clinical research in this field. Cardiac magnetic resonance imaging (MRI) has also undergone a rapid development towards a very powerful non-invasive tool both for clinical and research applications. The high temporal and spatial resolution of this technique enables accurate non-invasive measures of regional cardiac structure and function in addition to measurements of myocardial perfusion and myocardial viability by contrast enhancement. Cardiac MRI spectroscopy also shows great promise in the field of metabolic imaging by measurements of for example high-energy phosphate metabolites. Finally instrumentation for three dimensional echocardiography imaging has now become commercially available possibly enhancing the diagnostic power of this technique. Within the field of echocardiographic image analysis the development of tissue Doppler imaging and myocardial strain imaging may prove useful in future studies of patients with heart disease.

ABBREVIATIONS

CABG: coronary artery bypass grafting
PCI: percutaneous coronary intervention
^{18}FDG: ^{18}F-fluorodoxyglucose
^{18}FDG uptake: ^{18}F-fluorodoxyglucose uptake evaluated by semiquantitative image analysis
FFA: free fatty acids
LAD: left anterior descending artery
LC: lumped constant
LV: left ventricular
$^{13}NH_3$: ^{13}N ammonia
$^{13}NH_3$ uptake: ^{13}N ammonia uptake evaluated by semiquantitative image analysis
PET: positron emission tomography
SPECT: single photon emission computerized tomography

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