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TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS

– A clinical and experimental study

Håvard Bersås Nordgaard, MD

Department of Circulation and Medical Imaging

The Faculty of Medicine

Norwegian University of Science and Technology

Trondheim, Norway

Transitt-tid blodstrømsmåling og analyse av skjærekrefter i bypass-graft ved koronar hjertekirurgi. En eksperimentell og klinisk studie.

Bakgrunn

Avhandlingen ”Transit-time flowmetry and wall shear stress analysis of coronary artery bypass grafts – A clinical and experimental study” er en studie av funksjonen i nye bypass-årer i ulike situasjoner, samt av skjærekrefter i disse under ulike eksperimentelle intervensjoner. I Norge utføres årlig ca. 3000 bypass-operasjoner pga. koronar hjertesykdom (angina pectoris). Ved åpen hjertekirurgi sys da erstatningsårer forbi de trange partier på hjertets egne kransarterier. Korrekt vurdering av forsnevringen i kransarteriene og intraoperativ kvalitetskontroll av åreforbindelsen (anastomosen) er viktig for at bypass-årer holder seg åpne. Doktoravhandlingen er basert på fire arbeider som alle er publisert i anerkjente internasjonale tidsskrifter. Arbeidet er en blanding av studier på hjertekirurgiske pasienter og dyreeksperimentelle studier.

Resultater

I den første studien ble et stort pasientmateriale med 1390 blodstrømsmålinger analysert. Ulike typer bypass-graft til de forskjellige kransarteriene på hjertet ble sammenlignet. Hovedfunnet var økende blodstrøm ved økende antall anastomoser (opptil tre) fra den samme erstatnings-åre og når denne er vene. ”Pulsatility index”, som til en viss grad indikerer motstand i åresystemet, var uavhengig av antall anastomoser, men hadde høyere verdi på høyre side av hjertet sammenlignet med venstre side.

I en annen klinisk studie ble de to mest anvendte transitt-tid blodstrømsmålere sammenlignet på samme bypass-åre. Undersøkelsen viste at MediStim flowmeter systematisk ga høyere pulsatility index-verdier enn Transonic flowmeter, selv om mengde blodstrøm per tidsenhet var lik. Årsaken var ulik filtrering av blodstrømssignalene i flowmetrene. Det bør derfor etableres retningslinjer for fortolkning og rapportering ved anvendelse av de respektive blodstrømsmålere.

Det er kjent at konkurrerende blodstrøm fører til at bypass-graft hyppigere går tett eller får mindre kaliber. Dette forekommer når innsnevringen av kransarterien er mindre uttalt enn forventet og ikke begrenser blodstrømmen i hvile. I en grisemodell ble transitt-tid blodstrømsmåling ved forskjellig grad av konkurrerende blodstrøm studert, med og uten innsnevring i anatomosen. Resultatet var at konkurrerende blodstrøm har en stor innvirkning på målingene, mens en innsnevring i anastomosen på inntil 75 % ikke ga noen begrensning av blodstrømmen i bypass-åren.

I den fjerde studien ble varierende grad av konkurrerende blodstrøm studert med avansert datasimulering, såkalt ”computational fluid dynamics”, på bakgrunn av en ny grisemodell. Her ble spesielt skjærekreftene (”shear stress”) mellom blodstrøm og årevegg beregnet. Resultatet var at full konkurrerende blodstrøm induserer ugunstige skjærekrefter i bypass-åren på grunn av redusert og retningsskiftende blodstrøm. Ved mindre grad eller fravær av konkurrerende blodstrøm var skjærekreftene gunstigere på grunn av høyere og mer retningsstabil blodstrøm. Ugunstige skjærekrefter kan føre til endotel-dysfunksjon, som er en viktig årsak til intima-hyperplasi og åreforkalkning. Disse funn indikerer at konkurrerende blodstrøm med ledsagende endotel-dysfunksjon er en negativ faktor i forhold til langtids holdbarhet av bypass-årer ved koronar hjertekirurgi.

Navn kandidat:	***Håvard Bersås Nordgaard***
Institutt:	***Institutt for sirkulasjon og bildediagnostikk (ISB)***
Hovedveileder:	***Professor Rune Haaverstad, ISB/NTNU og Universitetet i Bergen***
Biveiledere:	***Overlege PhD Dag Ole Nordhaug, ISB/NTNU og St. Olavs Hospital*** ***Overlege PhD Idar Kirkeby-Garstad, St. Olavs Hospital*** ***Post. doc. Lasse Løvstakken, ISB/NTNU***

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden philosophiae doctor (PhD).
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1. ACKNOWLEDGEMENTS

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Above all, I want to thank my wonderful Marit and our beautiful children, Magnus, Synnøve and Henrik, for their love and support. I will always be there for you.

2. LIST OF PAPERS

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

I. Transit-time blood flow measurements in sequential saphenous coronary artery bypass grafts. Nordgaard H, Vitale N, Haaverstad R. Ann Thorac Surg 2009 May;87(5):1409-15

II. Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model. Nordgaard H, Nordhaug D, Kirkeby-Garstad I, Lovstakken L, Vitale N, Haaverstad R. Eur J Cardiothorac Surg 2009 Jul;36(1):137-42

III. Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery. Nordgaard H, Vitale N, AstudilloR, Renzulli A, Romundstad P, Haaverstad R. Eur J Cardiothorac Surg 2010 May;37(5):1063-7.

IV. Impact of competitive flow on wall shear stress in coronary surgery: Computational fluid dynamics of a LIMA-LAD model. Nordgaard H, Swillens A, Nordhaug D, Kirkeby-Garstad I, Van Loo D, Vitale N, Segers P, Haaverstad R, Løvstakken L. Cardiovascular Research June 2010; In press

3. ABBREVIATIONS

BFI	blood flow imaging
CFD	computational fluid dynamics
CABG	coronary artery bypass grafting
CO	cardiac output
CX	circumflex artery
ECG	electrocardiogram
FFR	fractional flow reserve
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LIMA	left internal mammary artery
LMS	left main stem
MI	myocardial infarction
MVR	mitral valve replacement
MVr	mitral valve repair
OPCAB	off-pump coronary artery bypass
OM	obtuse marginal
OSI	oscillatory shear index
PCI	percutaneous coronary intervention
PDA	posterior descending artery
PI	pulsatility index
PL	posterolaterale branch
RCA	right coronary artery
SD	standard deviation
SSVG	sequential saphenous vein graft
SVG	saphenous vein graft
TTFM	transit-time flow measurement
WSS	wall shear stress

4. INTRODUCTION

4.1 Coronary artery bypass grafting (CABG)

CABG is one of the most frequently performed surgical procedures worldwide, with approximately 600,000 – 700,000 operations conducted annually. In Norway, 2859 patients underwent CABG in 2008 [Norsk Nasjonalt Hjertekirurgiregister 2008]. There has been a trend towards a decreased number of pure CAGB procedures over the last five years, after a maximum of 3430 operations in 2004. At the same time, there has been an increased number of combined CABG and aortic valve procedures. Since the mid-90s, percutaneous coronary intervention (PCI) has been done considerably more frequently than CABG worldwide. In 2008, a total of 11242 PCI procedures were performed in Norway, but this activity has also stabilised over the past five years (Figure 1) [Norsk Nasjonalt Hjertekirurgiregister 2008].

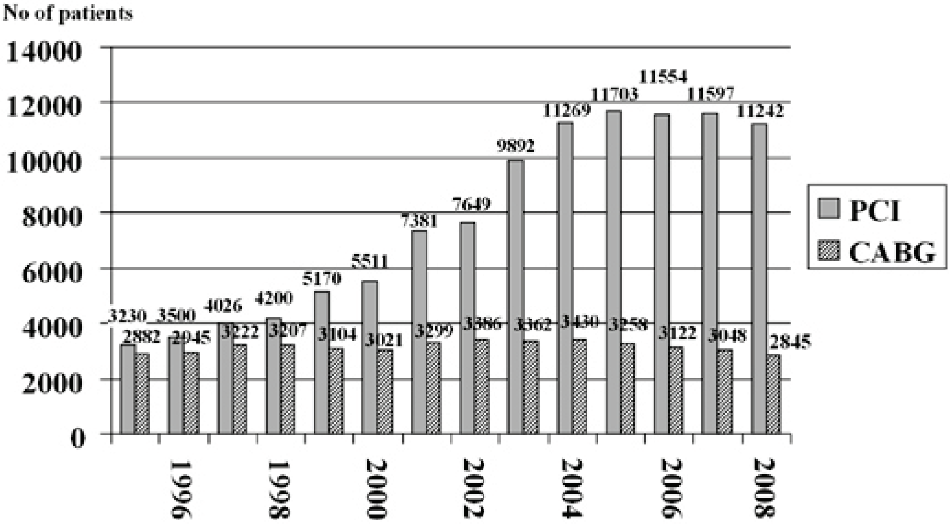

Figure 1. CABG and PCI in Norway 1995 – 2008. http://www.legeforeningen.no/thorax. Reproduced with permission from The Norwegian Association for Cardiothoracic Surgery.

PCI with stenting has replaced CABG in most cases with one- or two-vessel disease and in patients presenting with acute coronary syndrome, whereas CABG is still considered as best practise in most patients with triple-vessel or left main vessel disease and with impaired left ventricular function [Eagle et al 2004; Serruys et al 2009; Patel et al 2009].

Patients with complex coronary anatomy and calcified lesions are more often treated by CABG, as PCI in such cases are technically less feasible [Haaverstad 2009]. Moreover, patients undergoing CABG nowadays often have a higher operative risk due to old age and comorbidities. On-pump CABG is still the technique most widely performed when surgical revascularisation is considered. In Norway, off-pump CABG is usually reserved for patients with a heavily calcified wall of the ascending aorta. The cannulation and cross-clamping may increase the risk of calcium emboli. In 2007, only 20 off-pump coronary artery bypass (OPCAB) operations were performed in Norway [Haaverstad 2009].

The use of the left internal mammary artery (LIMA) and the great saphenous vein are still the most common procedures of surgical myocardial revascularisation. The LIMA-to-LAD has a superior long-term patency versus other conduits and improves long-term survival and freedom from reinterventions [Cameron et al 1996; Goldman et al 2004; Sabik et al 2005].

Currently, vein grafting is often carried out by the sequential grafting technique, in which one or more side-to-side anastomoses are performed in addition to the distal end-to-side anastomosis. The obvious advantages of sequential vein grafting are shorter limb incisions and fewer proximal anastomoses with better utilisation of the vein graft segment. However, sequential vein grafts may also carry more blood flow to the myocardium compared to single vein grafts, although solid evidence for this is still warranted [Christenson et al 1998; Dion et al 2001; Vural et al 2001; Kandemir et al 2007]. Furthermore, some data suggest that the long-term patency of side-to-side anastomoses are better than the patency of end-to-side anastomoses [Kieser et al 1986]. Sequential grafting may also optimise haemodynamic conditions like flow pattern and wall shear stress [Frauenfelder et al 2007].

Graft failure is a concern after CABG. Improvement of the early as well as the long-term graft patency is frequently addressed. Nowadays it is common to perform intraoperative quality assessment of the bypass grafts. Several technologies are available, but transit-time flowmetry is the most widespread method. The aim of intraoperative graft assessment is to detect and thereby to revise technical of grafts and anastomoses, thus improve clinical outcome and avoid re-interventions.

Table 1. Possible causes of early graft failure after CABG.

Reported findings	**References**
Failure of prox. or dist. anastomosis	[D'Ancona et al 2000]
Overstretched graft	[D'Ancona et al 2000; Tokuda et al 2007]
Graft dissection	[Walpoth et al 1998; Tokuda et al 2007]
Obstructing intimal flap	[Walpoth et al 1998; D'Ancona et al 2000; Tokuda et al 2007]
Intramural haematoma	[Walpoth et al 1998; D'Ancona et al 2000]
Kinked or twisted graft	[D'Ancona et al 2000; Tokuda et al 2007]

In CABG, the flow within bypass grafts may be influenced by the function of native coronary arteries. Competitive flow may be seen when grafting is performed on coronary vessels with low-grade stenosis. Clinically, competitive flow is assumed to occur frequently in CABG, as coronary arteries with a luminal area stenosis of 50-70 % are often grafted. Most studies on graft function have shown better long-term patency when they are directed distally to severe stenoses rather than beyond non-significant lesions [Villareal et al 2000; Hirotani et al 2001; Sabik et al 2003; Bezon et al 2003; Berger et al 2004; Nakajima et al 2007; Botman et al 2007; Sabik et al 2008; Kawamura et al 2008].

The “string phenomenon” of the LIMA graft, which displays a threadlike structure on the angiogram, is assumed to be caused by competitive flow. However, there is limited knowledge of the underlining patho-physiological and biomechanical mechanisms of competitive flow in CABG. By addressing why grafts often fail during competitive flow conditions, essential information with great consequences may be achieved. This may subsequently facilitate the development of surgical, pharmacological and genetic interventions for improvement of coronary grafts patency.

4.2 Coronary haemodynamics

Because this thesis deals with blood flow and wall shear stress in coronary bypass grafts, some basic fundamental anatomical and physiological concepts of the coronary circulation will be presented.

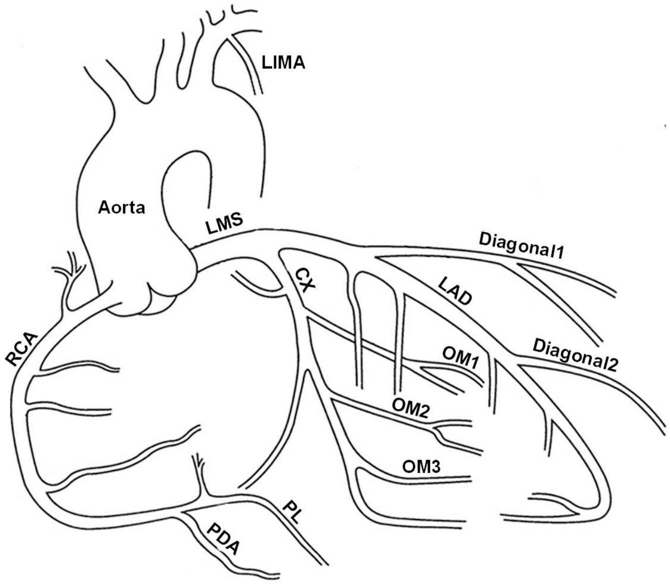

Figure 2. *The coronary artery tree. LMS = left main stem; CX = circumflex artery; LAD = left anterior descending artery; OM = obtuse marginal; LIMA = left internal mammary artery; RCA = right coronary artery; PDA = posterior descending artery; PL = posterolateral artery. Modified figure from: http://www.meddean.luc.edu/lumen/meded/Radio/curriculum/Vascular/Coronary_artery.jpg*

Coronary blood flow, autoregulation and stenosis

At rest, the total coronary flow is 180-250 ml/min, i.e. 5-10 % of the total cardiac output [Naidu et al 2001]. The primary regulatory mechanism of coronary blood flow is determined by the local myocardial metabolism by release of adenosine and other vasodilator mediators. At rest, the myocardium already has an extremely high oxygen extraction. The higher oxygen demand during increased cardiac work load or ischaemia is normally met by increased coronary blood flow. Thus, there is a nearly linear relationship between the myocardial metabolic demand and the coronary blood flow. Healthy individuals can increase coronary flow up to four-to-six fold [Naidu et al 2001; Spaan et al 2006]. Other important control mechanisms are the neurogenic and hormonal systems, which are generally more vasoconstrictive than vasodilatory.

The vascular endothelium acts as control system by determining the vascular tonus. The blood flow induced *wall shear stress* (WSS) increases the release of several mediators from the intact endothelium, particularly the vasodilatory molecule nitric oxide (NO). However, in damaged endothelium such as in patients with atherosclerosis, the release of NO is reduced and the release of the vasoconstrictive endothelin-1 is increased [Opie et al 2004].

Coronary blood flow is inversely related to the peripheral vascular resistance. The vascular resistance is very low in the *epicardial* coronary arteries due to these large branches. Thus, only a minimal pressure drop exists between the ascending aorta and the distal end of healthy major coronary arteries. The smaller coronary branches are arterioles embedded deeply into the myocardium and are also called *resistance arteries.* They can adjust coronary blood flow according to the metabolic demands of the myocardium through the metabolic, neurogenic and vascular control systems (*autoregulation*).

The coronary arteries provide stable myocardial perfusion when the systolic pressure ranges between 50 - 180 mmHg, allowing a relatively constant blood flow. If the systolic perfusion pressure drops below 50 mmHg, the vasodilatory effect controlled by the coronary autoregulation is gradually lost [Gould et al 1974; Opie et al 2004]. An estimated 70 % diameter reduction, equivalent to a 90–95 % decrease in luminal area, is required to decrease the *basal, resting* coronary blood flow [Gould et al 1974].

Coronary flow varies considerably from rest to exercise. During exercise, the coronary flow is already impaired when the internal diameter is reduced beyond 30 % [Gould et al 1974]. The coronary flow is further influenced by the collateral blood flow, the vascular spasm and a multiple or extensive stenosis, as well as the degree of turbulence across the stenosis.

The impact of a stenosis on blood flow *cannot* directly be explained in the context of Poiseuille's law due to the coronary autoregulation, the vessel tortuosity and the pulsatile flow that is present in-vivo. Moreover, the law was based upon a Newtonian fluid, i.e. an homogenous fluid with constant viscosity like water and not blood. The law relates the flow Q to the length of the internal radius r of the vessel, according to the following formula:

$Q = \frac{\pi r^4 \Delta P}{8 \eta L}$, with viscosity η, length L and pressure difference ΔP [Opie et al 2004]. The equation states that the dominant factor on the flow Q is the internal radius r of the vessel.

The coronary flow pattern is pulsatile due to the myocardial contraction and relaxation. During systole, the subendocardial coronary branches are much more compressed than the epicardial branches [Yada et al 1993]. Hence, most of the coronary flow occurs in the diastolic phase of relaxation, most pronounced for the left coronary artery. The right coronary artery has a more equal volume flow both in systole and diastole. The heart rate also affects coronary blood flow as bradycardia extends the diastole, thus increases the coronary flow. Tachycardia prolongs the systolic phase of the cardiac cycle, thus reduces the coronary flow [Opie et al 2004].

Wall shear stress and endothelial dysfunction

The blood flow through arteries is mostly laminar with a parabolic profile: the highest blood velocity in the centre and the lowest velocities close to the vessel wall. The laminar blood flow may be considered as a series of layers that move with different velocities, but in the same direction. The friction between these layers generates the shear stress of blood. The WSS is the friction of blood flow against the vessel wall (Figures 3-5).

For a Newtonian fluid, the WSS τ is proportional to the wall shear rate ($\frac{\partial v}{\partial y}$, the change in flow velocity across the vessel) and the blood viscosity μ, given by: $\tau = \mu \cdot \frac{\partial v}{\partial y}$. The wall shear stress is defined as the shear stress at $y = 0$, i.e., at the vessel wall (Figure 3).

The WSS may also be calculated in terms of volume flow Q and vessel radius R by applying Poiseuille's law: $\tau = \frac{4 \mu Q}{\pi R^3}$. Thus, small changes in radius R greatly influence WSS τ (Figure 4). This formula is easy to use for estimating WSS because flow and dimensions can be measured non-invasively, for instance by ultrasound imaging. However, as for Poiseuille's law, the formula has several major assumptions: a) stiff, straight and smooth vessels; b) Newtonian fluid; c) laminar, steady, non-pulsatile flow and d) zero velocity at the vessel wall.

In healthy arteries at rest, the time-average WSS over a cardiac cycle typically varies within an approximate range of 1-7 Pa. A time-average WSS < 1-1.5 Pa is considered as low. Non-physiological elevated WSS is reported to be > 7 Pa and is usually seen in a narrowed lumen (Figure 4) [Malek et al 1999; Chatzizisis et al 2007].

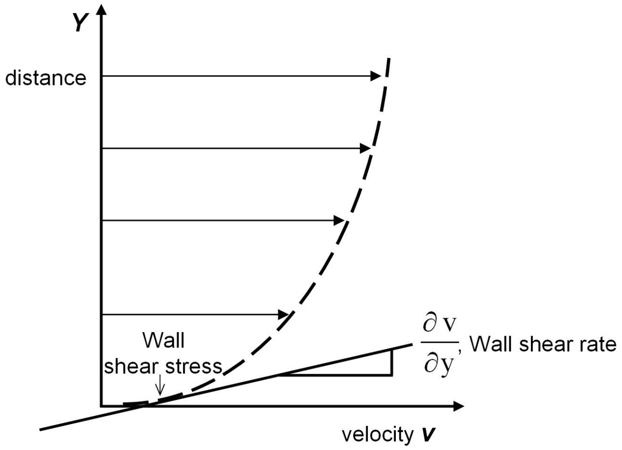

Figure 3. *The **wall** shear stress is defined as the shear stress at y = 0.*
Y is the distance within the flow profile in relation to the vessel wall.

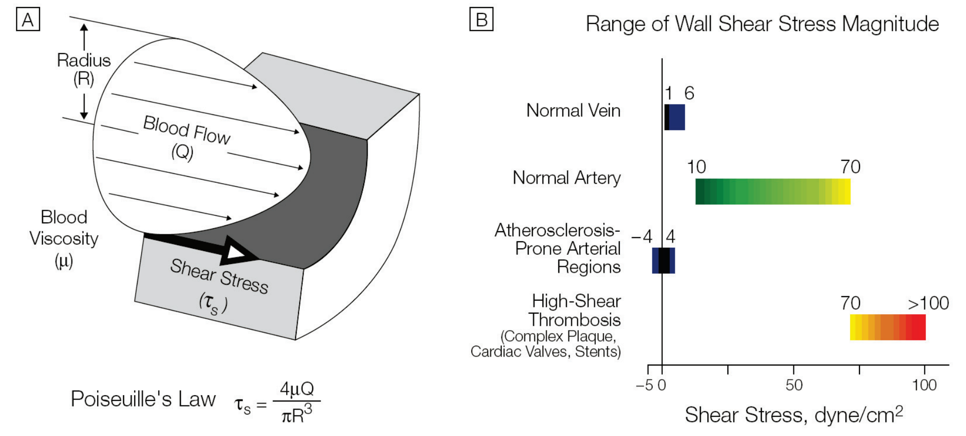

Figure 4. *(A) The frictional WSS acting on the endothelial surface. (B) Range of WSS magnitudes in different regions (1 Pa = 10 dyne/cm^2).*

With permission: Malek et al, Hemodynamic shear stress and its role in atherosclerosis. JAMA 282 (1999): 2035-2042. Copyright © (1999) American Medical Association. All rights reserved.

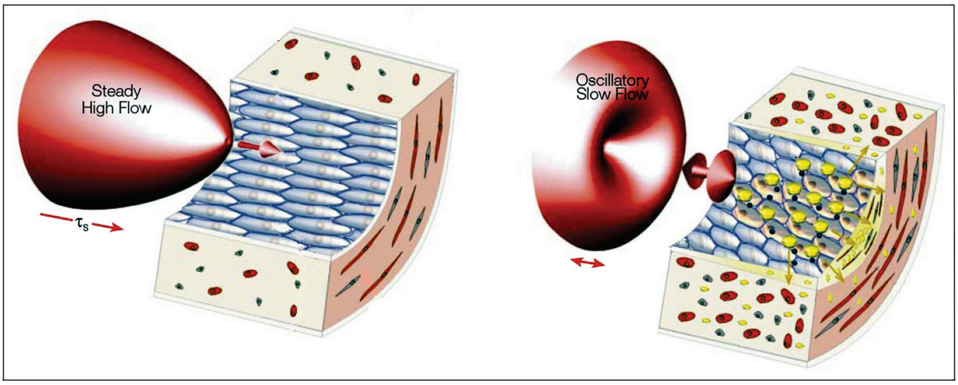

Figure 5. *Steady, high flow versus oscillatory, slow flow. The left panel shows a steady high blood flow,which induces a high uni-directional shear stress, considered as athersclerosis-protective. The right panel shows a presumably atherogenic situation with slow, unsteady blood flow, inducing a bi-directional (oscillatory) shear stress.*

Modified figure with permission: Malek et al, Hemodynamic shear stress and its role in atherosclerosis. JAMA 282 (1999): 2035-2042. Copyright © (1999) American Medical Association. All rights reserved.

An established index for assessing the changes in direction and magnitude of WSS is the oscillatory shear index (OSI). It is given by the following equation:

$$\mathrm{OSI} = \frac{1}{2} \cdot \left(1 - \frac{\left| \int_{0}^{T} \tau \, dt \right|}{\int_{O}^{T} |\tau| \, dt} \right),$$

where T is the time of an entire cardiac cycle, and τ is the WSS vector [Ku et al 1985]. The numerator and the denominator display the total WSS (the sum of all positive and negative WSS vectors) and the sum of all absolute values of the same WSS vectors over a cardiac cycle, respectively. The OSI varies between 0 and 0.5, where 0 indicates a completely unidirectional shear force, and 0.5 indicates a purely unsteady, oscillatory shear force with a net amount of zero WSS. Regions of high OSI are prone to *endothelial dysfunction* and atherogenesis [Ku et al 1985; Kassab et al 2006; Davies 2009].

Next to WSS, the other basic mechanical force acting within vessels is the transmural pressure. This acts perpendicular to the vessel wall and stretches the wall. Although there is a wide discrepancy between the extremely small force generated by the normal WSS (1-7 Pa) and the transmural arterial blood pressure (100 mmHg = 13332 Pa), WSS has a major and well-documented influence on endothelial function [Malek et al 1999; Davignon et al 2004; Slager et al 2005; Chatzizisis et al 2007; Stone et al 2007; Katritsis et al 2007; Davies 2009; Koskinas et al 2009]. All endothelial cells throughout the cardiovascular system are constantly exposed to WSS generated by the blood flow. Further, WSS varies in magnitude and direction, depending upon the geometry of the vessel, blood viscosity and flow pattern. Healthy and intact endothelium is crucial for efficient control of vascular resistance and function [Opie et al 2004; Davignon et al 2004; Chatzizisis et al 2007]. WSS exerts its effects through the conversion of mechanical stress to biochemical response, also described as a mechano-transduction [Davies 1995]. Thus, the endothelium triggers the metabolic reactions by synthesising vasoactive mediators in response to WSS changes.

The endothelium attempts to adapt to local flow conditions [Kassab et al 2006]. Vasoactive mediators regulate the adaptation to sudden changes in WSS, whereas sustained and prolonged changes of WSS induce a slow, structural wall remodelling that is mediated by the activation of several genes [Slager et al 2005; Kassab et al

2006; Davies 2009]. In regions with high and steady blood flow, where WSS varies within a physiologic range, the endothelial cells express various athero-protective genes and suppress several pro-atherogenic ones, inducing endothelial stability. In contrast, regions with oscillatory and slow blood flow where low WSS occurs, have suppressed the athero-protective genes. Thus, as the pro-atherogenic genes are up-regulated, atherosclerosis is promoted [Chatzizisis et al 2007].

Generally, vessel regions with low and oscillating WSS are non-optimal and appear to be at high risk of endothelial dysfunction and vascular disease. These conditions are particularly found in specific regions like the inner wall of curved segments and in outer wall of bifurcations. On the other hand, regions exposed to steady blood flow with moderate-to-high and unidirectional WSS remains relatively disease free [Asakura et al 1990; Malek et al 1999; Feldman et al 2002; Slager et al 2005; Kassab et al 2006; Reneman et al 2006; Chatzizisis et al 2007; Stone et al 2007; John 2009; Davies 2009; Koskinas et al 2009].

The most important endothelium derived relaxing mediator is the short-living NO. This is a vasodilator that is mainly liberated from healthy endothelial cells and exerts a protective action on the vessel wall [Opie et al 2004; Davignon et al 2004; Chatzizisis et al 2007]. However, in situations where the endothelium is dysfunctional, as in coronary artery disease, the release of NO is reduced. Simultaneously the synthesis of vasoconstrictors, like endothelin-1, is increased. The endothelial dysfunction, characterised by impaired endothelial-dependent vasorelaxation, is associated with well-documented risk factors for atherosclerosis, such as smoking, hypercholesterolaemia, obesity, and diabetes mellitus [Opie et al 2004; Davignon et al 2004; Chatzizisis et al 2007].

5. STUDY OBJECTIVES

Paper I

Routine TTFMs were performed in a large group of patients by the same surgeon. The grafts considered for analysis were LIMA-LAD, single saphenous vein grafts (SVGs), double sequential SVGs, and triple sequential SVGs. The aim was to study TTFMs of different sequential SVGs in relation to single grafts, and to investigate how graft flow is related to patient characteristics and haemodynamics.

Paper II

Nine pigs underwent off-pump coronary artery bypass surgery with the LIMA grafted to LAD. TTFMs of the LIMA graft were recorded under the following four flow conditions (Figure 6):

A. No competitive flow; the proximal LAD totally occluded (the *baseline* condition), mimicking an ideal situation for placing the graft distal to a totally occluded coronary artery.

B. Partial competitive flow; partial occlusion of the LAD to half its full flow, mimicking a situation in which the anastomotic site was placed distal to a significant stenosis, providing about half the volume flow compared to the full flow.

C. Fully competitive flow; no occlusion of the proximal LAD, mimicking a situation in which a graft was placed distal to a moderate (or less than critical) stenosis.

D. Stenotic anastomosis with no competitive flow; mimicking a typical site of surgical error (the toe of the anastomosis).

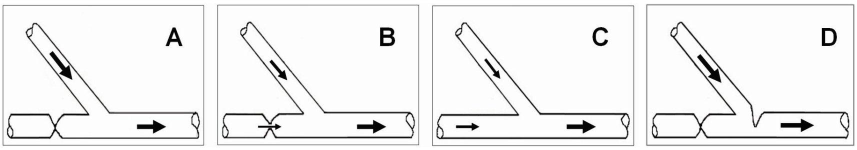

Figure 6. *A schematic layout of the four investigated flow conditions on each pig.*

The aim was to assess the influence on graft flows due to competitive flow and stenotic anastomosis in LIMA-LAD anastomoses. Sub-analysis of TTFMs was of particular interest in this project.

Paper III

The objective was to compare the flow signals produced by the two most commonly used transit-time flowmeters, manufactured by MediStim ASA and Transonic Inc., both having the same guidelines regarding the level of Pulsatility index (PI).

In the first part of the study a MediStim (VeriQ) or a Transonic (HT331) flowmeter were directly compared by applying two flow probes simultaneously on coronary bypass grafts. In the second part we aimed to investigate whether the PI is influenced by different technical characteristics with regards to variation of filter settings within the flowmeter.

Paper IV

In an experimental porcine model a LIMA-LAD anastomosis was performed to investigate wall shear stress (WSS) during competitive flow conditions. By applying computational fluid dynamics, WSS in a 3-D LIMA-LAD model were investigated during three different flow conditions (Figure 6):

A. No competitive flow; simulation of an ideal situation
B. Partial competitive flow; simulation of a significant LAD stenosis
C. Fully competitive flow; simulation of a no-significant LAD stenosis

The aim of the study was to explore the influence of competitive flow on WSS within the coronary grafts and vessels, and to analyse how different flow conditions may trigger endothelial dysfunction and subsequent graft failure.

6. METHODOLOGICAL CONSIDERATIONS

6.1 Transit-time flow measurements

Almost every cardiac intervention, including valve repair and PCI, are routinely followed by a reliable assessment to ensure adequate technical results. However, in CABG, this kind of evaluation is not always a routine procedure, although technical failures is quite common even if the operation is performed by an experienced surgeons [D'Ancona et al 2000; Hol et al 2004].

The intention of intraoperative graft assessment is to reduce the risk of early graft failure and thereby achieve optimal surgical results. Ideally, an intraoperative quality assessment has the following characteristics:

- Simple and quick application
- Easy interpretation
- Surgeon or technician independent
- Provision of both anatomical and physiologic information
- Inexpensive
- Applicable for all relevant vessels
- Highly sensitive
- Highly reliable and specific

TTFM of bypass grafts is the most commonly used method for intraoperative quality assessment in CABG. The theoretical basis of the transit-time method has been known for more than 40 years, but it has only been applied in clinical practice since the early 1990s. Initially, this *delay* was due to several technical difficulties, like the extremely short “transit-time” of a few nanoseconds and the complexity and stability of the electronic network. The progress in electronic technology solved these problems. The first commercial transit-time flowmeter was introduced by Transonic Inc. in 1983 (Personal communication with Arne Grip, former CEO, MediStim ASA, Oslo). Later, TTFMs were proven to be an accurate method for intraoperative verification of bypass grafts [Matre et al 1994; Beldi et al 2000]. A common misunderstanding is that the TTFM method is based on the Doppler principle, as erroneously asserted by some authors [Wolf et al 2003]. TTFMs are based on the ultrasonic transit-time principle according to the following formula:

$V = \frac{(t_{up} - t_{down}) \cdot c^2}{4 \cdot L \cdot \cos\theta}$, in which V = velocity of the blood flow; t_{up} and t_{down} = the up- and down-stream transit-times, respectively; L = distance between the transducer and the reflector; c = ultrasound or phase velocity; θ = angle between the flow direction and the line formed by the transducers (Figure 7) [Christensen 1988].

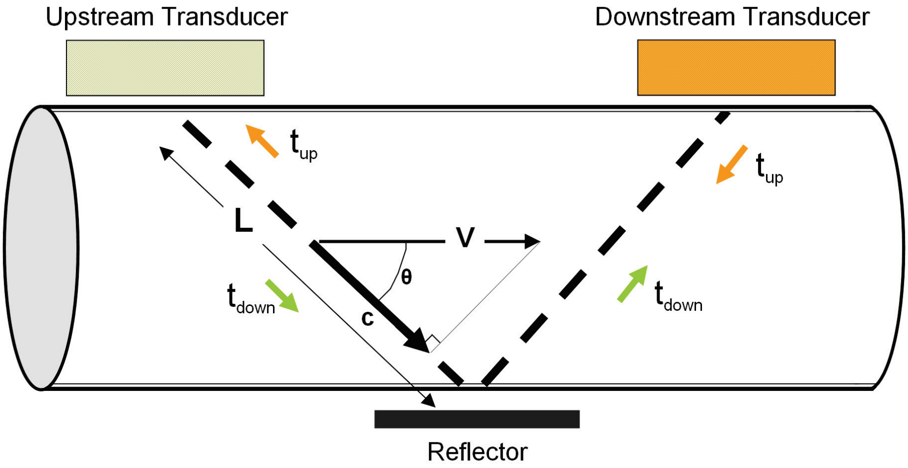

Figure 7. *The transit-time flow principle.*

The perivascular transit-time flow probes used in coronary surgery are composed of two transducers placed at a specific angle with a metal reflector on the opposite side of the vessel (Figures 7 and 8). The two transducers act as the transmitter and the receiver for the ultrasound beams. The ultrasound beam transmitted through the vessel is wide enough to cover the entire flow diameter. When the beams are transmitted through the blood, there is a difference between the upstream and downstream transit-time (time of flight or time difference), which is proportional to flow velocity. The average cross-sectional flow velocity is calculated. Larger time differences are correlated with higher flow velocities.

Procedure

The timing of TTFMs during the operation is dependent on the CABG technique employed:

(1) In on-pump CABG, the measurements are usually done after discontinuation of the cardio-pulmonary bypass circulation. Measuring the LIMA-

LAD flow is also recommended before removal of the aortic clamp because this time point has no collateral flow. Some cardiac surgery units register graft flow both before and after application of diluted papaverine, particularly within vein grafts. Some surgeons recommend repeated flow measurements as well as when the sternal edges are approximated during chest closing in order to assure correct graft position and absence of graft kinking.

(2) In OPCAB, the arterial grafts are usually assessed both immediately after they have been constructed and before chest closure. For vein grafts, the assessment may be performed as with on-pump surgery.

The final measurements should be carried out under stable haemodynamic conditions. The hook of the flow probe connected to the flowmeter is placed around the bypass graft. The graft should fit within the flow probe because the ultrasound beam must illuminate the entire graft.

When assessing a pedicled LIMA graft, a short segment of the graft should be skeletonised to fit the probe hook. By measuring the graft both before and after application of papaverine into the vein graft, the flow reserve for the individual graft is also measured. For the LIMA graft, papaverine is usually applied only externally, which is not as efficient as when it is given intraluminally.

In order to obtain a correct interpretation of the blood flow patterns, an ECG recording should be combined with flowmetry to differentiate systole from diastole.

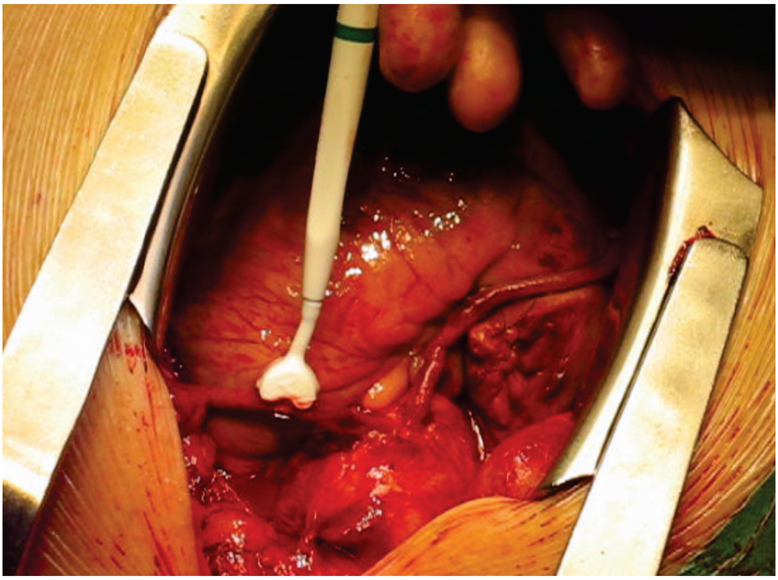

Figure 8. *A transit-time flow probe is placed around a vein graft after weaning off the cardio-pulmonary bypass circulation.*

Interpretation

There is a poor correlation between mean volume flow and the quality of the anastomosis [Jaber et al 1998; D'Ancona et al 2001; Nordgaard et al 2009]. At rest, the graft flow is not reduced until the luminal stenosis is severe.

The flow pattern in a bypass graft should mainly be *diastolic* as in a coronary artery. Different indicators have been introduced for the quality assessment in CABG. The most important are:

a) Diastolic filling % (DF%), which is calculated as

$$\mathrm{DF\%} = \frac{|V_D|}{(V_{S,abs} + V_{D,abs})} * 100\% ,$$

where VD and VS is diastolic- and systolic volume flows, respectively. The DF% is only calculated when an ECG signal is connected to the flowmeter with sufficient quality for defining systole and diastole. The DF% is perhaps the most important indicator for TTFM interpretation [Morota et al 2002]. A DF % < 50 is suspicious of disturbed graft flow because it represents a systolic graft flow pattern [Becit et al 2007].

b) Insufficiency % is the percentage retrograde flow:

c) Pulsatility index (PI) is calculated according to the following formula:

$$\mathrm{PI} = \frac{\max \mathrm{volumeflow} - \min \mathrm{volumeflow}}{\mathrm{mean\,volumeflow}}$$

The PI has been described as an indicator of peripheral vascular resistance [Louagie et al 1994; D'Ancona et al 2000; Becit et al 2007], although the sensitivity and specificity are unknown. Peripheral resistance is governed by many factors, and PI is not sufficiently specific to distinguish between stenoses of different severity. Only very severe stenoses may produce significantly higher PIs [Evans et al 1980].

Several TTFM cut-off values have been suggested as indicators of adequate graft flow [D'Ancona et al 2001; Kim et al 2005; Di Giammarco et al 2006]. The largest prospective study on TTFMs was performed by Tokuda et al., who measured blood flow by the MediStim flowmeter in 261 bypass grafts, and correlated the results obtained with 3-month postoperative coronary angiography. They found that mean flow <15 ml/min, PI > 5 and insufficiency % > 4 % in grafts to the left coronary system had a higher incidence of graft failure. The failure of grafts to the right coronary artery was predicted with mean flow < 20 ml/min, PI > 4.7, and insufficiency % > 4.6 % [Tokuda et al 2007].

The most commonly used transit-time flowmeters, manufactured by MediStim ASA (Oslo, Norway) and Transonic Systems Inc. (Ithaca, NY, USA), use a default low-pass filter at 20 Hz and 10 Hz, respectively. They filter the signals differently, which yields different wave forms (Figure 9) [Proakis et al 1995]. The different maximum and minimum peak flows that are registered may influence the PI value.

Although several scientific papers have compared the available flowmeters and concluded that they are accurate and precise with regard to volume flow, the issue of different flow patterns has not previously been addressed [Laustsen et al 1996; Beldi et al 2000; Cikirikcioglu et al 2006]. However, the latter is important because smoother flow pattern and low PI are indications of good flow, in contrast to spiky flow pattern and higher PI, which are associated with poor flow [Jaber et al 1998; D'Ancona et al 2001; Kim et al 2005].

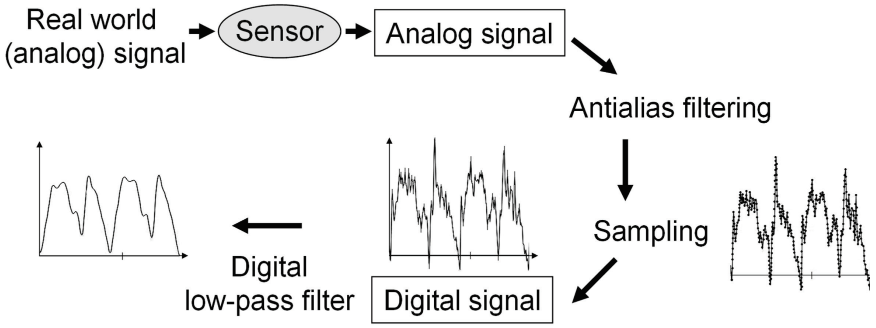

Figure 9. *A simplified scheme of signal processing in the flowmeter. The signal processing determines how the flow signals are visualised on the screen. The analog signal is digitally sampled at a sufficiently high frequency according to the Nyquist-Shannon sampling theorem. Further, the flowmeters use a low-pass filter to smooth the signals and attenuate noise.*

Definitions: Analog signal: A "real world" continuous signal in time and amplitude with total precision.

Antialias Filtering: A low-pass filter of the analogue signal to reduce the aliasing-effect, so the sampling rate can beat least twice the maximum frequency of the signal. All signals above the cut-off frequency are totally attenuated.

Sampling: To convert the continuous analogue signal to a "digital" form. The sampling rate (samples per second) must be sufficient to reproduce the same analogue signal as a digital signal. To reproduce the full information of the signal, it is necessary to sample at twice the maximum frequency in the signal of interest, known as the Nyquist-Shannon sampling theorem.

Digital signal: A signal with limited precision defined by sampling of the analogue signal and discrete in both time and amplitude.

Limitations

The commercial success of TTFMs in coronary surgery is probably due to the clinical importance and interest of blood flow rate in coronary bypass grafts. The goal of a surgeon is to perform a revascularisation that will bring as much blood flow as possible to the ischaemic myocardium. Further, flowmetry is simple and quick to carry out. The measurements are angle- and vessel-size independent; thus, the flow assessment is not too biased by the operator. However, several important limitations should be acknowledged.

The interpretation of TTFMs may be difficult in some cases and may generate confusion and uncertainty. It provides purely physiological information, which for many surgeons is less convincing than anatomical information. Also, it cannot point out where the problem is located. Flow values and curves cannot be standardised because of the great variability among patients (sex, races, etc.). Thus, the interpretation of graft quality is to a large extent surgeon dependent.

6.2 Computational fluid dynamics (CFD)

A CFD model may be applied to investigate the WSS distribution in arteries [Krams et al 1997; Lei et al 2001; Boutsianis et al 2004; Frauenfelder et al 2007; Stone et al 2007]. CFD is a subfield within fluid mechanics in which numerical methods and algorithms are used to analyse and solve problems that involve fluid flows; in particular, the Navier-Stokes equations govern how the motion of fluids is treated. The numerical tools can be used to obtain a better understanding of local haemodynamic and mechanical forces in arteries, including native coronary arteries and bypass grafts [Krams et al 1997; Lei et al 2001; Boutsianis et al 2004; Frauenfelder et al 2007].

The CFD technique allows parameters, such as vessel wall conditions and inlet flow velocity, to be changed easily, so that they can simulate theoretical and realistic conditions. Additionally, the CFD technique may be use to estimate shear stress and other important haemodynamic factors. These characteristics make CFD to an appropriate tool for research of vessel disease aetiologies, for instance intimal hyperplasia, atherosclerosis and subsequent failure of coronary bypass grafts.

Our study group developed 3-D CFD simulations of the LIMA-LAD model based on a geometric model and TTFMs (Figure 10). Details are presented in Paper IV [Nordgaard et al 2010].

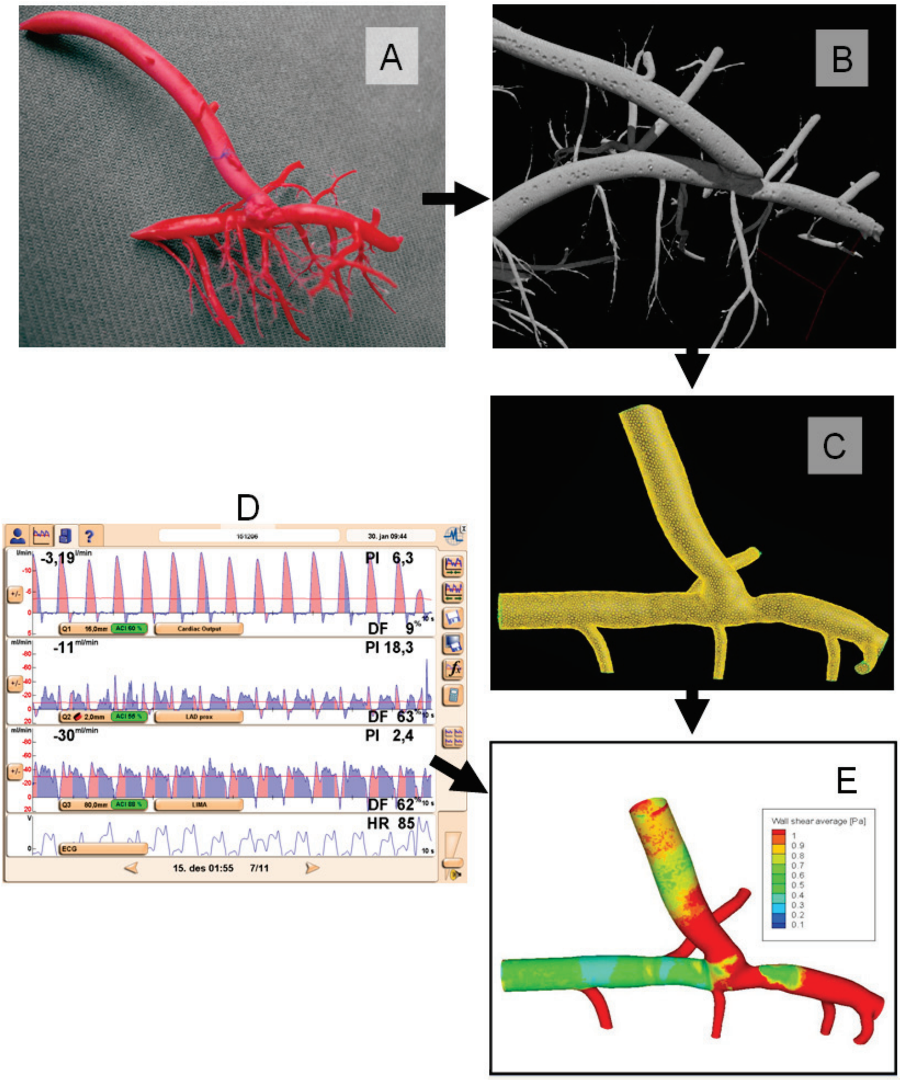

Figure 10. *The acquisition of the CFD simulation of the LIMA-LAD model.*
A: Resin cast of the vessel lumen. A methyl-methacrylat-based resin was injected into the LIMA graft and the surrounding tissue was removed with potassium hydroxide.
B: 3-D micro-CT. The cast was scanned using a high resolution micro-CT.
C: Geometric mesh. The cast was generated to a tetrahedral grid of 1 058 405 elements.
D: Simultaneous TTFMs of the LIMA and the LAD together with ECG and cardiac output. The TTFMs were used for calculation of the flow behaviour.
E: CFD simulations

Limitations of CFD simulations

There are several potential sources of errors that may cause simulations to differ from true conditions. The most common sources of error are as follows [Versteeg et al 2007]:

- Input data error: If the geometry and the flow data that come from *in vivo* measurements are inaccurate.
- Boundary conditions error: The model is simplified. All flow properties are generally not exactly known because they are estimated. For instance, flow data are needed at locations where the fluid enters and leaves the geometric model.
- Discretisation error: Errors that occur when the entire numerical flow data are transferred into small discrete domain of space and time, known as *grid* or *mesh,* as algebraic expressions. These errors are intrinsic and of most concern to the CFD model. They are mainly dependent on the quality and distribution of the grids used in the simulation.
- Modelling error: The real flow may involve complicated flow patterns that are not perfectly described by current scientific theories, for instance in turbulence modeling.

In paper IV, we compared the flow pattern in the CFD model with the one seen by epicardial ultrasound imaging as a qualitative validation.

6.3 Surgical procedures and experimental set-up

CABG and experimental set-up in the clinical setting (papers I, III)

A median sternotomy was performed in all cases and the LIMA was harvested with its pedicle. The greater saphenous vein was placed in a heparin solution with 0.05 % papaverine after harvesting. Cardio-pulmonary bypass circulation was instituted with moderate hypothermia (34 °C). The heart was arrested by infusion of antegrade crystalloid or cold blood cardioplegia. In OPCAB operations (paper I: n = 61, 11 % of all patients) the target vessel was snared with 4-0 Prolene (Ethicon, NJ, USA) proximal to the coronary arteriotomy. After 3-5 minutes of ischaemic preconditioning, the snare was released, and an epicardial stabiliser was applied to pull the heart and immobilise the vessel site chosen for grafting. After arteriotomy, an intracoronary shunt (CardioThoracic System, CA, USA) was positioned into the vessel lumen.

Grafting was attempted on all vessels measuring ≥ 1 mm and with >50 % stenosis on the angiogram. The surgical plan was to carry out sequential grafting any time it was considered feasible and the LIMA was always grafted end-to-side to the LAD. The single SVG anastomosis was constructed end-to-side. In the sequential SVG, the distal end-to-side anastomosis was constructed before the side-by-side anastomoses. All LIMA and vein anastomoses were sutured with 7-0 Prolene. The proximal anastomoses were generally performed after release of the aortic cross-clamp and by applying a side-biting clamp on the ascending aorta.

The final TTFMs were done at a stable haemodynamic condition 10-15 minutes after weaning off CPB. In off-pump patients, the measurements were done after completion of all distal anastomoses and removal of the cardiac stabilizer. Three- or four mm flow probes connected to a transit-time flowmeter (Medi-Stim ASA, Oslo, Norway) were used. Both for single and sequential SVG, the flow probe was placed 2-4 cm below the proximal anastomosis. The LIMA flow was assessed by applying the probe around a skeletonised area. In all grafts both mean graft flow and PI were registered.

CABG and experimental set-up in the animal model (papers II, IV)

A total of 11 Noroc pigs (hybrid of ¼ Duroc, ¼ Yorkshire and ½ Norwegian landrace) were operated upon. Animals of 65-70 kg weight were chosen because at that size the dimensions of the coronary vessels are similar to humans, and the myocardium has a relatively good tolerance to ischaemia. One pig died due to ventricular fibrillation before completion of the investigation protocol. A second pig was excluded from the study because it was haemodynamically unstable, making measurements unreliable for statistical analysis.

Details of anaesthesia and the animal instrumentation are presented in Paper II and 4 [Nordgaard et al 2009; Nordgaard et al 2010].

Pigs are quite intolerant to myocardial ischaemia and prone to ventricular fibrillation. Ventricular fibrillation happened also during our experiments, especially when making the anastomosis. The heart was promptly defibrillated, and in most of the cases, the heart converted into sinus rhythm with a haemodynamically stable condition. These events likely do not influence results because the pigs returned to haemodynamic stability long before and during all measurements.

Amiodarone 150 mg and hexamethonium chloride 20 mg/kg (Hexamethonium, Sigma-Aldrich, MO, USA) were given to avoid arrhythmias. Hexamethonium chloride is a ganglionic blocker, which paralyses the autonomic nervous system (sympatholytic and parasympatholytic), thus contributing to a more stable pig model. This ganglion blocker provides a stable heart rate throughout the experiment and presumably avoids ventricular fibrillations [Nordhaug 2003].

The pig was chosen as an animal model because the anatomy and physiology of its cardiovascular system are very similar to humans. Nonetheless, the pig model has normal coronary arteries with good run-off and no collateral flow, a very different condition from patients with severe coronary disease. When planning the experimental studies, we concluded that non-animal research models were unsuitable to the purposes of our investigations. The minimum number of animals required for meaningful results was utilised, and we aimed to reduce any pain to the animals during the experiments. All experimental protocols were approved by the Norwegian Animal Experiments Authority. All animals received care in compliance with the European Convention on Animal Care, and the investigation conformed to the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

All pigs underwent OPCAB surgery with a LIMA-to-LAD anastomosis. After sternotomy, the LIMA was harvested with its pedicle. The LAD was identified and investigated visually and sometimes with ultrasound images to identify diagonal arteries. An epicardial stabiliser (Axius Vacuum Stabilizer, Guidant, CA, USA) was applied to immobilise the LAD. Proximal to the anastomotic site, approximately 15-20 mm (dependent on diagonals/ anatomy), the LAD was dissected from the epicardial tissue in order to apply a 2-3 mm flow probe around the vessel. Adjacent to this flow probe, another short area was dissected in order to fit an adjustable vascular occluder (In Vivo Metric, CA, USA). A 16-mm flow probe was placed around the pulmonary trunk to monitor cardiac output. The flow through the pulmonary trunk was also used to define systole and diastole because the flowmeter was not always able to read and interpret the ECG from the pig (Figure 11).

Prior to coronary arteriotomy, ischaemic preconditioning was performed. Then, the LAD was snared distally and proximally with 4-0 Prolene (Ethicon, NJ, USA) to allow a coronary arteriotomy. An intracoronary shunt (CardioThoracic System, CA, USA) was positioned into the vessel lumen. Then, the LIMA was grafted to the LAD end-to-side and sutured with a continuous 7-0 Prolene to create patent anastomoses without technical failures. Patency of the anastomosis was confirmed with epicardial ultrasound imaging (Figures 12 and 13). Upon completion of the anastomosis, a short segment of the LIMA was skeletonised, and a flow probe was applied, at approximately 4-5 cm from the anastomosis, to assess graft flow. Another flow probe was placed around the proximal LAD to assess competitive flow (Figure 11). All animals were stabilized for 30 min before the experimental protocol was carried out.

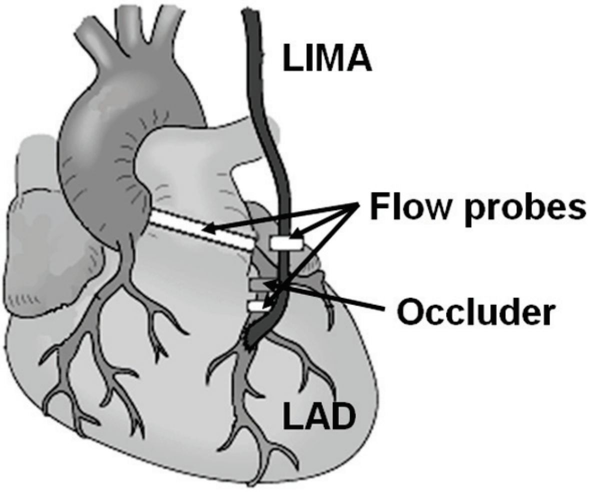

Figure 11. *A schematic layout of the positions of flow probes and the vascular occluder. Modified figure from Nordgaard et al. Eur J Cardiothorac Surg 36 (2009): 137-142.*

Epicardial ultrasound imaging

A GE Vivid 7 scanner (GE Vingmed, Norway) with an i13L linear array mini-transducer (GE Healthcare, WI, USA) was used. This scanner is capable of operating at frequencies 7-14 MHz. We applied ultrasound imaging extensively for visualisation of the anastomosis and the blood flow (Figure 12-13). In paper II, ultrasound imaging was used to calculate the stenosis at the toe of the anastomosis (Figure 14).

We used a new imaging modality named “blood flow imaging” (BFI). It is based on conventional colour Doppler imaging, but, in addition, shows the speckle pattern of the blood flow with a very high frame rate. It visualizes the blood flow in any direction of the two-dimensional image plane without limitations imposed by aliases (the velocity aliasing or the angle-dependency). Using slow motion display of subsequent speckle images, the movement of speckle pattern can be tracked by the human eye. This new BFI provides a more intuitive display of the flow conditions, making interpretation easier than conventional colour Doppler imaging [Lovstakken et al 2008].

In addition to the assessment of coronary graft anastomosis, ultrasound imaging may be useful to locate intra-myocardial coronary vessels, for evaluation of severity of coronary stenoses, identification of the arteriotomy site (to avoid plaques or stented segments), as well as assessment of the ascending aorta [Haaverstad et al 2002; Dessing et al 2004; Budde et al 2006; Lovstakken et al 2008; Ibrahim et al 2008; Budde et al 2009].

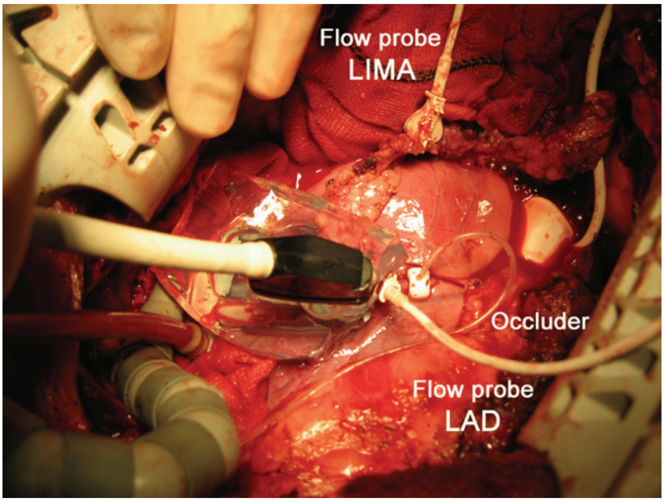

Figure 12. *Intraoperative photo of the pig heart with flow probes and occluder. Epicardial ultrasound imaging of the LIMA-LAD anastomosis is being performed with the stabiliser placed on the epicardial tissue. The geometry and blood flow were assessed before and after constructing a stenotic anastomosis, as well as with and without competitive flow.*

Figure 13. *Simultaneous TTFM and epicardial ultrasound imaging on a patent LIMA-LAD anastomosis.*

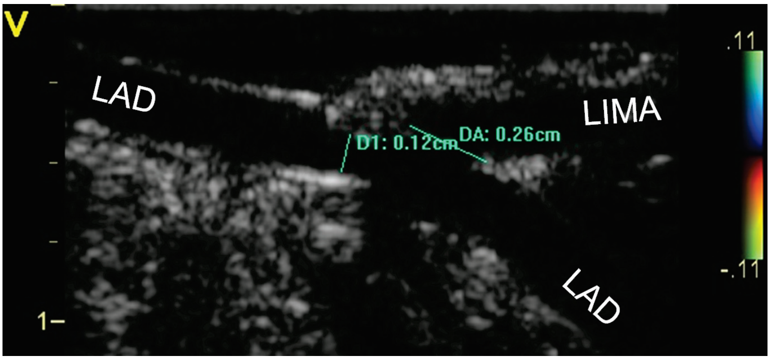

Figure 14. *The luminal dimensions for estimating the extent of the stenoses were measured by epicardial ultrasound imaging. D1 = the vessel diameter of the stenotic toe; DA = diameter of the anastomotic inlet. A circular lumen was presumed. The formula for calculating the luminal stenosis:*

$$\text{Stenosis \%} = \left(1 - \frac{\text{Area D1}}{\text{Area DA}}\right) \times 100 \quad = \left(1 - \frac{\pi\left(\frac{\text{D1}}{2}\right)^2}{\pi\left(\frac{\text{DA}}{2}\right)^2}\right) \times 100$$

6.5 Statistical analysis

Data are presented as either the arithmetic mean ± one standard deviation for normally distributed data or the median with range for data that were not normally distributed. In paper III, the values are expressed as geometric mean and 95 % confidence interval after logarithmic transformation. P-values less than 0.05 were considered significant. Statistical analysis in Papers I-III was performed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA). In paper III, STATA for Windows version 10 (StataCorp, College Station, Texas, USA) and Excel were also used.

In paper I, the flow values were compared utilising a linear mixed regression model. The pair-wise post-hoc comparisons were adjusted for multiple comparisons using the Bonferroni technique. Categorical variables were analysed using a chi-square test, and continuous variables were analysed using a two-tailed Student's t-test with equal or unequal variances based on the findings of an initial F-test for equality of variance.

In paper II, Friedman’s tests for non-normally distributed variables were applied. If the Friedman’s test revealed significant changes, post hoc analyses by Wilcoxon signed-ranks were performed without correction for multiple comparisons. Instead of using the Bonferroni correction for multiple comparisons, we chose to report uncorrected P-values for the Wilcoxon signed-ranks, so the readers may more easily assess the relevance of the statistical differences described [Perneger 1998].

In paper III, a logarithmic transformation of the collected flow data was performed to achieve normal distribution. Two-sample t-tests were used on data with no repeated measurements, while a random effects model was used to account for repeated measurements on same individuals. The grafts were nested into LIMA-LAD, single SVGs and double sequential SVGs to the left and right coronary arteries. The comparisons between grafts from two different cardiac centres were performed using two sample t-tests except for the single SVGs to the left coronary artery, where a random effects model was used to account for repeated measurements. Wilcoxon signed ranks tests were used to compare the simultaneous flow assessments on the same grafts.

7. SUMMARY OF RESULTS

7.1 Paper I

Within the single vein graft group there were no differences between flows within grafts to different target vessels except for diagonals, which had the lowest flow. The blood flow increased substantially from single to double and further to triple sequential vein grafts. Graft flow was higher in males versus females. Lower age and higher left ventricular ejection fraction were associated with higher mean graft flows. The aortic pressure did not influence on graft flow. The mean PI of vein grafts to the right coronary system was significantly higher than the mean PI of vein grafts to the left coronary system (PI ± SEM: 2.40 ± 0.06 and 2.00 ± 0.05, respectively). Similar PI values were found between gender and groups of vein grafts within each coronary system (Figure 15).

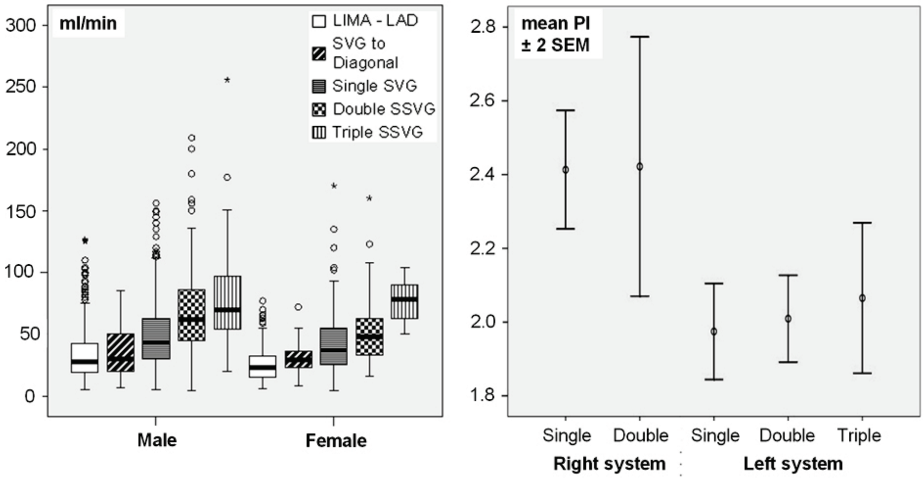

Figure 15. *Left: Box-plot of the blood flows in different coronary bypass grafts. The bottom and top of the boxes show the 25th and 75th percentile, and bands near the middle of the box are the 50th percentile (the median). The ends of the vertical lines indicate the minimum and maximum values. Points outside the ends of the lines represent suspected outliers.*

Right: Mean PI ± 2 SEM in single SVGs, double and triple sequential SVGs, divided by right and left coronary system.

Modified figure from Nordgaard et al. Ann Thorac Surg 2009; 87: 1409-1415

7.2 Paper II

Competitive flow reduced the mean LIMA graft flow more than by a stenotic anastomosis, which was assessed to be 75 % ± 11 % luminal stenosis as measured by ultrasound. Reduction of the graft flow due to competition was particularly evident during diastole. The systolic flow remained unchanged. Competitive flow decreased both diastolic and systolic maximum peak flows, making the flow curve look smoother. Moreover, competitive flow increased retrograde flow. The PI and rate of insufficiency % (retrograde flow as a fraction of total flow) were more increased by competitive flow than by stenosis. Diastolic filling % was substantially reduced during competitive flow compared with both stenosis and baseline.

7.3 Paper III

The Transonic flowmeter calculated substantially lower PI values than the MediStim flowmeter. A systematic and constant increase of PIs occurred when the filter setting was raised from 5 Hz to 100 Hz. Under various filter settings (5 Hz, 10 Hz, 20 Hz, 30 Hz, 50 Hz and 100 Hz) the proportion of the changes depended on the level of the PI values. Major changes were seen between the filter levels when the PI was high, typically seen when the flow curves were spiky with high and low peaks. Minor changes were observed when the PI was low, typically seen when the flow curves were smoother (Figure 16).

Nineteen coronary bypass grafts were assessed simultaneously by the MediStim (VeriQ) and Transonic (HT331) flowmeters. The differences in calculation of PI between the two flowmeter increased as the flow pattern became more spiky. Thus, the differences between the flowmeters are more pronounced when the flow curve is spiky, typically seen in situations with poor graft flow and high resistance, situations where flow analysis is critical.

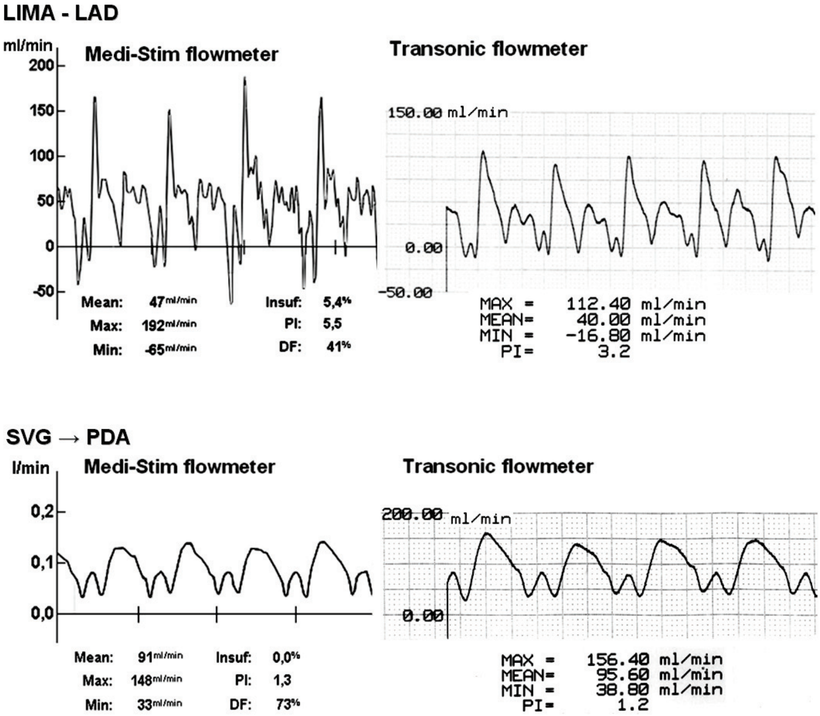

Figure 16. *Simultaneous graft flow measurements with the MediStim and Transonic flowmeters [Nordgaard et al 2009].*

The upper panel shows a LIMA-to-LAD with flow pattern with sharp peaks. The PI values are 5.5 and 3.2 as calculated by the MediStim and Transonic flowmeters, respectively.

The lower panel shows a single SVG to PDA with smoother flow pattern, thus similar PIs in both flowmeters; PI 1.3 and 1.2 in the MediStim and Transonic flowmeter, respectively.

7.4 Paper IV

High competitive flow resulted in substantial lower WSS and more oscillatory shear stress in the LIMA graft compared to the two other flow conditions. Partial competitive flow resulted in WSS and OSI values that were similar to the no-competitive flow condition (Table 2; Figure 17 and 18).

Table 2. WSS and OSI in the LIMA graft found during one cardiac cycle.

Competitive flow	WSS [Pa]	OSI
High	0.3-0.6	0.15-0.35
Partial	0.6-3.0	<0.05
None	0.9-3.0	<0.05

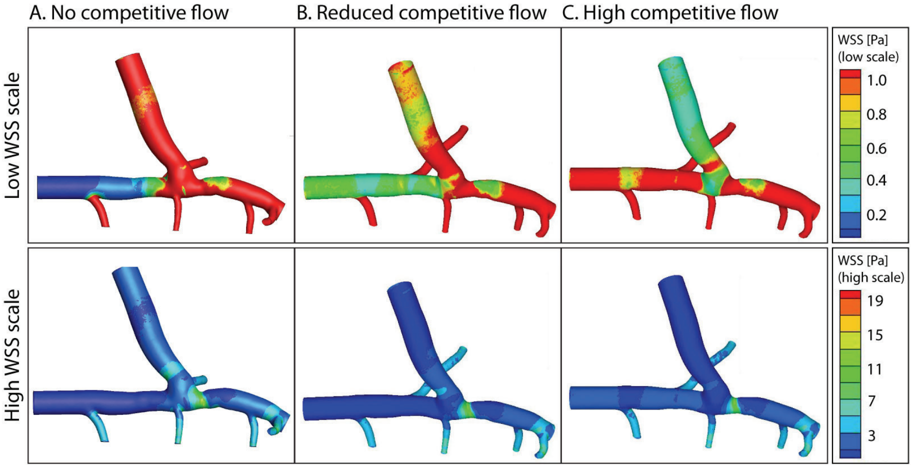

Figure 17. *The time-average distribution of the WSS in the LIMA–LAD model during one cardiac cycle. The upper and lower panels show the WSS in two different scales: 0.1 – >1 and 1 – >19 Pa, respectively.*

(A) No competitive flow shows WSS > 1 Pa in the LIMA graft. In comparison, lower WSS is seen during partial reduced competitive flow (B). Substantial lower WSS in the LIMA graft is seen during high competitive flow (C). Higher WSS is shown at the toe of the anastomosis where a moderate narrowing of the vessel lumen had formed.

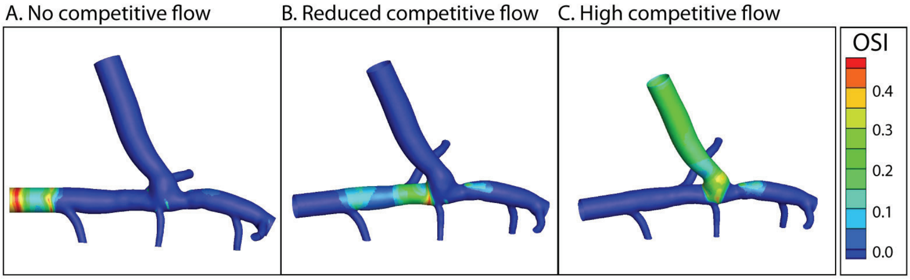

Figure 18. *The time-average oscillatory shear index (OSI) distribution during one cardiac cycle. Higher OSI values are found in LIMA graft and within the anastomosis during high, unimpaired competitive flow (C), while reduced (B) and no competitive flow (A) lead to very low OSI values.*

8. DISCUSSION

Transit-time flowmetry as intraoperative quality assessment

Coronary bypass graft failure is a troubling complication that may cause various problems, including refractory angina pectoris, myocardial infarction, arrhythmia, heart failure, and premature death. *Early* graft failure is related to technical problems involving the bypass grafts and anastomoses, which are difficult to detect during surgery by visual assessment, palpation or conventional cardiac monitoring. Thus, to avoid early graft failure, intraoperative graft assessment is required. *Late* graft failure may be caused by both technical failures and other factors. We know that long-term patency is dependent on competitive flow, pathology of the target vessel, type of graft (venous or arterial) and time since CABG [Sabik et al 2005]. However, the exact pathophysiological reason for graft failure has been difficult to define.

The first study of this thesis included flow measurements of 1390 coronary bypass grafts that were operated on and assessed by the same senior surgeon. Thus, operator-related biases were minimised due to all procedures being conducted by the same surgeon and the same protocol of flow measurements being applied to all patients. This continuity was essential for the statistical analyses.

A detailed statistical analysis of the patient characteristics and all flow values gave important insights in the haemodynamic behaviour of different bypass grafts. Sequential vein graft flow was higher as compared to single bypass grafts, with flow substantially increasing from single versus double and triple sequential vein grafts. However, the differences were not two or three-fold higher, as one would expect if the resistance to flow were only determined by the peripheral coronary resistance. Other factors, such as the length of the grafts and the flow pattern in the anastomoses themselves, must contribute significantly to the total resistance.

In terms of the Poiseuille's law, the flow resistance is proportional to the length of the conduit. Sequential bypass grafts are longer conduits, hence they produce more resistance. Another possible explanation may be the interaction between the two distal anastomoses. Flow disturbance caused by myocardial contractions or competitive flow close an anastomosis may impair the flow into the other anastomosis.

The lowest flow was found in vein grafts to diagonals, which usually are small vessels with a limited peripheral vascular bed compared to other coronary branches.

Mean graft flows were higher in men vs. women, probably due to men having larger coronary arteries and larger ventricular mass [Levy et al 1987]. Higher graft flow was generally seen in younger patients and in patients with good left ventricular ejection fraction. A possible explanation may be that younger patients have larger and more dynamic coronary vessels than older patients, which may allow a better run-off.

Reduced ejection fraction indicates congestive heart failure, which may reduce coronary flow due to the reduction of the coronary vascular bed caused by myocardial infarction, fibrosis and cardiomyopathy.

The aortic pressure did not influence on graft flow. However, no patients had hypotension at the time of measurement. The mean blood pressure was around 90 mmHg during the flow measurements suggesting that the coronary auto regulatory mechanism was intact.

The LIMA-LAD grafts showed lower flow compared to vein grafts directed to the LAD. Lower flow is probably because of smaller dimensions and some degree of spasm in the LIMA grafts, since no vasodilators (e.g. papaverine) were used routinely.

In study I similar PI values for single and sequential vein grafts were found. This observation was unexpected because the PI is thought to reflect peripheral resistance; hence, one would hypothesise that sequential grafts provide lower PIs compared to single grafts. Thus, flow pattern and thereby PI are determined by more factors than the run-off.

Higher PIs were found in vein grafts directed to the right coronary system, which usually has higher systolic peaks and a more equal systolic and diastolic flow pattern as compared to the left coronary system. Although the difference in PI values reached statistical significance, the numeric difference was small. Our findings are in contrast to Kim et al who suggested cut-off values for insufficient graft flow of PI > 3 to the left and > 5 to the right coronary artery [Kim et al 2005].

Graft flow alterations induced by competitive flow and stenotic anastomoses

Firstly, the comparisons of the different levels of competitive flows revealed that competitive flow reduced the LIMA graft flow, mainly because of decreased diastolic flow, whereas the systolic flow remained unchanged. Secondly, partial competitive flow induced the same effect as fully competitive flow on both mean and diastolic flow, although not to the same extent. Thirdly, retrograde flow and PI increased only under fully competitive flow. We also found that competitive flow caused a smoother flow pattern with less sharp peaks compared with the flow pattern at no competitive flow.

The LIMA graft flows were not significantly altered by a 75 % ± 11 % stenosis of the lumen of the anastomosis. Hence, our observations are in line with previous flow studies concluded that substantial hemodynamical effects at rest are seen only in a critical stenotic anastomosis [Jaber et al 1998; Jaber et al 1998].

The question how to distinguish competitive flow from a severe stenotic anastomosis is an important issue because both conditions may alter the graft flow. In addition, numerous other causes may alter the graft flow, such as graft dissection, kinking, torsion and spasm, as well as high coronary resistance due to small target vessels [Walpoth et al 1998; D'Ancona et al 2000; Wolfe 2001; Tokuda et al 2007]. The consequences of even tighter stenotic anastomoses were not investigated. Naturally, the graft flow will abruptly decrease due to a tighter stenosis. In these situations, other studies have reported a systolic dominant flow pattern, similar to our findings with competitive flow conditions [Morota et al 2002].

TTFM of grafts flows and pattern may be difficult to interpret, especially in situations when graft flow is lower than expected. When competitive flow is suspected, one manoeuvre is to block the native flow while measuring the graft flow. Such block may be conducted by snaring the target coronary artery proximal to the anastomosis. If a significant competitive flow is present, the temporary occlusion of the native flow will induce an increase of graft flow [D'Ancona et al 2001]. However, there is concern that the temporary occlusion of a coronary artery proximal to an anastomosis may cause injury of the vessel [Hangler et al 2001]. Temporary clamping of grafts directed to collateral coronaries may also aid in the interpretation of graft flow. Another simple and practical technique to assess competitive flow in the LIMA graft is to measure the flow before and after removal of the aortic cross-clamp. If the LIMA flow decreases substantially following removal of the aortic clamp, competitive flow may be present.

Alternatively, epicardial ultrasound may be used [Haaverstad et al 2002]. In our study, the Blood flow imaging (BFI) modality was applied to evaluate the patency of the anastomosis by looking at its geometry and function as well as the degree of stenosis [Lovstakken et al 2008]. We believe that this technique has a great potential for intraoperative assessment during CABG because it is non-invasive and can easily detect stenoses and competitive flow.

Comparison of the Transonic and the MediStim flowmeters

The majority of published data regarding clinical TTFM have been obtained with the MediStim flowmeter [Goel et al 2003; Kim et al 2005; Hassanein et al 2005; Gwozdziewicz et al 2006; Nordgaard et al 2009].

In our clinical series, we found a trend towards lower PI values provided by the Transonic flowmeter versus the MediStim flowmeter. When we used both flowmeters simultaneously on the same grafts, the Transonic flowmeter gave systematically lower PI values. Furthermore, the difference was highly dependent upon the flow pattern: sharp peaks led to remarkable differences between the two flowmeters, while smoother flow pattern revealed similar PI values. In other words, the difference between the flowmeters became greater as PI increased (Figure 16).

The graft flow assessment at different filter settings revealed a systematic and constant increase of PIs when the filter in the flowmeter was gradually raised from 5 Hz to 100 Hz. Progressively higher filter settings led to a flow pattern with sharper peaks, which caused higher PIs. On the contrary, lower filter settings produced smoother flow pattern and lower PIs. The change of PI became greater when the flow curves had sharp peaks, and these peaks were filtered away at lower filter settings.

Coronary bypass graft patency and failure

Several studies with early postoperative coronary angiography demonstrate graft failure in the range of 4-14 % [Sanz et al 1990; Goldman et al 1991; Alderman et al 1998; D'Ancona et al 2000; Desai et al 2006; Tokuda et al 2007]. Early graft failure is associated with low and disturbed graft flow, which is commonly related to technical problems with the graft or anastomosis, both correctable if recognised intraoperatively [Nwasokwa 1995]. A post-mortem study of 517 coronary bypass grafts in 223 patients with fatal outcome within 30 days of CABG, discovered that 55 % of the patients had technical failures in the grafts or anastomoses that were not recognised intraoperatively [Weman et al 1999].

In a 10-year prospective study on graft patency in 1254 patients who were followed-up by repeated angiograms the most important predictors of long-term graft patency were the *early* patency as well as the size of the peripheral vascular bed [Goldman et al 2004]. Therefore, intraoperative evaluation of graft patency should be mandatory.

Ultimately, the majority of SVGs occlude or become substantially narrowed after 10-15 years [Fitzgibbon et al 1996; Motwani et al 1998]. Unlike LIMA grafts, SVGs are subject to intimal hyperplasia, atherosclerosis, progressive stenosis and occlusion [Motwani et al 1998]. During the first year 12-20 % of the SVGs occlude. Intimal hyperplasia occurs mainly one month to five years after surgery [Nwasokwa 1995]. Atherosclerotic lesions that are also haemodynamically significant appear after about 3-5 years [Nwasokwa 1995; Goldman et al 2004]. At approximately 10 years, 50 % of all SVGs are occluded, and half of the remaining grafts are expected to be severely narrowed due to atherosclerosis [Nwasokwa 1995; Fitzgibbon et al 1996; Motwani et al 1998]. Vein graft failures are believed to be the most common reason for recurrent coronary symptoms following CABG [Nwasokwa 1995; Fabricius et al 2001; Goldman et al 2004].

Numerous studies have shown that about 10 % of all LIMA grafts are occluded within 10-15 years. When LIMA occlusions occurs the mechanism seems to be different from vein graft occlusions [Nwasokwa 1995; Shimizu et al 2000; Goldman et al 2004; Berger et al 2004; Desai et al 2004; Sabik et al 2008]. A characteristic lesion observed in the LIMA is the “string phenomenon”, a longitudinal narrowing of the LIMA lumen to less than 1 mm over a length of 3-5 cm. The rate of the string phenomenon has not been ascertained yet, but it has been estimated to happen in 2 % of CABG patients [Villareal et al 2000]. Competitive flow in the LIMA is believed to cause the string phenomenon, which is considered an early sign of graft failure [Siebenmann et al 1993; Nasu et al 1995; Kawasuji et al 1996; Hashimoto et al 1996; Pagni et al 1997; Pagni et al 1997; Hirotani et al 2001; Gaudino et al 2002; Sabik et al 2003; Bezon et al 2003; Nakajima et al 2004; Berger et al 2004; Sabik et al 2005; Botman et al 2007; Sabik et al 2008].

Biological properties of the LIMA graft are crucial determinants of its resistance to atherosclerosis. The LIMA is an elastic artery and has an enhanced endothelial function compared to vein grafts, as shown by greater production of vasodilating mediators like NO [Nishioka et al 1998]. The LIMA characteristic of higher basal release of vasodilating mediators is likely to play a vital role in maintaining the superior vascular patency. In that respect, a promising step in improving vein graft patency has been introduced by the so-called “no-touch” method during vein harvesting. Early reports on this technique have shown better early- and long-term graft patency compared to conventional vein harvesting [Souza et al 2002].

During conventional vein harvesting, the tissue around the saphenous vein is removed and often exposed to high-pressure distension to overcome spasm and leakages. The no-touch method involves harvesting the vein with minimal handling with the intention of conserving the perivascular adipose tissue. Conserving the perivascular tissue may protect the vein by reducing the circumferential stress [Kassab et al 2006] as well as maintain *long-term* sufficient endothelial function [Dashwood et al 2005]. Regarding the acute effects, conventional vein harvesting induces considerable endothelial injury and reduced NO production compared to the no-touch method [Dashwood et al 2005].

As mentioned in chapter 4.2, the shear stress induced by blood flow on the endothelium triggers its biochemical responds; thus, it is a major contributor to endothelial function. An unfavourable WSS induces an endothelial dysfunction, which induces vascular disease such as intimal hyperplasia and atherosclerosis. In paper IV, we studied the WSS under competitive flow conditions. At high competitive flow, such as when a graft is placed distal to the non-significant coronary stenosis, very low and oscillatory WSS was found. This unfavourable WSS may explain the LIMA string phenomenon and reduced graft patency by competitive flow.

The WSS pattern observed under partial competitive flow, simulating the clinical condition of a conduit grafted distal to the significant coronary stenosis, was comparable to the no competitive flow condition (Figure 17 and 18). We found very low and oscillatory WSS during high competitive flow, which simulates a non-significant coronary stenosis. The WSS pattern during partial competitive flow, simulating significant coronary stenosis, was comparable to the condition with no competitive flow. Thus, the WSS pattern changed greatly upon the degree of competitive flow. Our findings indicate that bypass grafts may tolerate a certain degree of competitive flow, which is probably the most frequent situation. In contrast, the unfavourable WSS caused by high competitive flow probably has an adverse impact on graft patency. Thus, our findings are in line with other studies reporting the relationship of graft patency and competitive flow [Siebenmann et al 1993; Nasu et al 1995; Kawasuji et al 1996; Hashimoto et al 1996; Pagni et al 1997; Pagni et al 1997; Hirotani et al 2001; Gaudino et al 2002; Sabik et al 2003; Bezon et al 2003; Nakajima et al 2004; Berger et al 2004; Sabik et al 2005; Botman et al 2007; Sabik et al 2008]. The consequences of low and oscillatory WSS may very likely be the LIMA string phenomenon and subsequent LIMA graft failure [Kassab et al 2006; Reneman et al

2006; Chatzizisis et al 2007; Stone et al 2007; John 2009; Davies 2009]. Moreover, another additional explanation for the changes seen at competitive flow conditions is based on the fact that WSS influences on homeostasis and vessel lumen dimensions [Gusic et al 2005; Kassab et al 2006]. The physiological responds may explain, in part, the aetiology of the string phenomenon of the LIMA graft: The endothelium maintains a sufficient WSS by affecting the vessel radius ($\tau = \frac{4\mu Q}{\pi R^3}$, radius R greatly influences WSS τ. See Chapter 4.2). At a low and oscillatory WSS, as under high competitive flow, the vessel narrows in order to increase the WSS, and hence, the endothelial function.

9. MAIN CONCLUSIONS

- The statistical analyses of the 1390 flow measurements concluded that the graft flow in vein grafts increase gradually from single to double and up to triple sequential bypasses. The PIs of vein grafts to the right coronary system were significantly higher than in grafts to the left coronary system. However, no PI differences exist between single, double and triple sequential vein grafts. In addition, higher graft flow should be expected in males compared to female patients.

- TTFMs cannot detect minor or moderate technical failures in the anastomoses because they are not haemodynamically significant. However, competitive flow influences the TTFMs early and substantially. During transit-time flowmetry the surgeon should particularly be aware of the severity of the coronary stenosis, the size of the target coronary vessel and the influence of competitive flow. These considerations are essential before final interpretations of TTFMs are made.

- Although the transit-time flowmeters from MediStim ASA and Transonic Inc. have presented the same guidelines regarding the PI values, they are not directly comparable due to their different default filter settings. The level of filter settings in the flowmeter determines the shapes in the flow curves, which results in different PI values. Thus, it is important to refer to the type of flowmeter used when presenting transit-time flow values.

- Competitive flow, which is known to influence negatively on graft patency, induces low and oscillatory wall shear stress (WSS). The levels of WSS found in our computational fluid dynamics model are supposed to have damaging effects on the endothelium, inducing endothelial dysfunction. Thus, the low and oscillatory WSS seen during high competitive flow may explain the reduced long-term patency of bypass grafts and the LIMA "string phenomenon". A lower level of competitive flow may be better tolerated due to a higher and more unidirectional shear stress, similar to the ideal situation with no competitive flow.

10. PROSPECTS OF FUTURE RESEARCH

Further developments within intraoperative quality assessment in CABG

There is a need for dedicated instruments designed for intraoperative quality assessment, for instance scanning areas prior to incisions. The widespread use of new technology will largely depend on the cost, ease and sensitivity of the method. Transit-time flowmetry may remain the cornerstone for intraoperative quality assessment of CABG, but using it in combination with ultrasound imaging may provide better and more reliable information in the future. This new approach with epicardial ultrasound and TTFMs needs to be validated in clinical studies.

Graft patency

Improvement of the long-term patency of grafts, especially vein grafts, must remain an important aim for future research. Preservation of endothelial function is probably essential for long-term patency. Thus, better knowledge of endothelial function, especially in vein grafts, is mandatory. Does the conventional way to harvest a vein by removing the surrounding tissue reduce the endothelial function and hence the long-term patency? A better understanding of WSS and endothelial function, atherosclerosis and intimal hyperplasia may lead us to improved operative strategies, for instance keeping the surrounding tissue around the vein grafts. Better knowledge may also guide us to a biological or pharmacological approach, such as gene therapy.

There is a need for clinical studies on the impact of WSS and other biomechanical forces in different flow conditions and different bypass grafts. Changes in surgical practice will only occur if favourable results can be demonstrated in humans.

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Appendix

Article in Press:
Trachiotis GD. Value of diastolic flow with transit-time flow meters in coronary artery bypass surgery.
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Paper I

Transit-Time Blood Flow Measurements in Sequential Saphenous Coronary Artery Bypass Grafts

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Background. **Little information is available on transit-time flow measurements of sequential saphenous vein grafts. The aim of the study was evaluation of mean blood flow and pulsatility index of sequential saphenous vein grafts in a large population of patients operated on with coronary artery bypass grafting.**

Methods. **In 581 patients 1,390 grafts were nested into left internal mammary artery to left anterior descending artery, single vein grafts, or double and triple sequential vein grafts, and analyzed.**

Results. **Within the single vein graft group there were no differences between flow of grafts to different target vessels except for diagonals (diagonal versus obtuse marginal, $p < 0.001$; versus posterior descending artery, $p = 0.035$; versus right coronary artery, $p = 0.003$). Flows measured in single vein grafts were significantly lower than in double ($p < 0.001$) and triple sequential vein grafts ($p < 0.001$). Flows were lower in double versus triple sequential vein grafts ($p = 0.017$) and higher in men versus women ($p < 0.001$). Mean pulsatility index of vein grafts were lower in the left versus the right coronary system, 2.0 ± 0.01 and 2.4 ± 0.06, respectively ($p < 0.001$). Between sex and groups of vein grafts within each coronary system, mean pulsatility index had similar values.**

Conclusions. **Blood flow increases from single to double and up to triple sequential grafts. Single grafts directed to diagonals have the lowest flow. Graft blood flows are higher in male versus female patients. Single, double, and triple saphenous vein grafts have similar pulsatility indexes. Pulsatility index of grafts to the right coronary system is significantly higher than that of grafts to the left coronary system.**

(Ann Thorac Surg 2009;87:1409–15)

Coronary artery bypass graft (CABG) surgery is an established treatment for angina pectoris of ischemic origin and can increase life quality and expectancy as well as reduce ischemic complications [1, 2]. Long-term results depend on the patency of grafts [3]. Vein grafts show poor long-term patency and limit the long-term success of CABG. Approximately 60% to 70% of saphenous vein grafts (SVGs) will be narrowed or closed down within a decade; in contrast, 90% of internal mammary artery grafts remain patent at 10 years [4–6].

Angiography is still the gold standard for intraoperative graft assessment, but it is rarely carried out routinely because of logistics and lack of time. Nowadays, transit-time flow measurement is the most common method for intraoperative assessment of CABG. Several studies have reported blood flows in arterial and saphenous vein graft (SVG) by transit-time flowmetry [7–12]. Nonetheless, little information is available regarding sequential SVGs, which together with left internal mammary artery (LIMA) to left anterior descending artery (LAD), are still the routine conduits for surgical myocardial revascularization.

To assess the performance of sequential SVGs, a comparisons of mean blood flows and pulsatility index (PI) of single versus sequential SVGs was carried out by the retrospective analysis of results obtained in a large population of patients operated on with CABG by a single surgeon.

Material and Methods

From 2000 to 2005, 595 consecutive patients were operated on by the same senior surgeon (R.H.). Routine transit-time flow measurements of all grafts were carried out at the end of the procedure as a quality control. Patients' clinical characteristics are presented in Table 1. The grafts considered for analysis were LIMA to LAD, single SVG, and double and triple sequential SVG. Altogether, 347 (60%) patients received a sequential SVG.

Of the 595 patients, 14 patients (2%) were excluded

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Table 1. Patients' Clinical Characteristics[a]

Variable	Total	Male	Female	*p* Value
Patients (N)	581	445	136	<0.001[b]
Age (y)	66 ± 10	65 ± 10	70 ± 9	<0.001[b]
Coronary vessel disease				<0.084[b]
1 VD	66	42 (9%)	24 (18%)	
2 VD	97	73 (16%)	24 (18%)	
3 VD	238	181 (42%)	57 (41%)	
LMS only	8	7 (2%)	1 (1%)	
1 VD + LMS	13	10 (2%)	3 (2%)	
2 VD + LMS	42	33 (7%)	9 (7%)	
3 VD + LMS	117	99 (22%)	18 (13%)	
Unstable angina	230 (41%)	181 (40%)	49 (36%)	0.3[c]
Distal anastomoses	3.4 ± 1.2	3.5 ± 1.2	3.1 ± 1.3	0.001[c]
Euroscore	5 ± 3	4 ± 3	6 ± 3	<0.001[b]
BMI (kg/m^2)	27 ± 4	27 ± 4	26 ± 5	0.6[b]
Left ventricular EF	0.63 ± 0.15	0.62 ± 0.14	0.65 ± 0.16	0.049[b]
Redo	29 (5%)	23 (5%)	6 (4%)	0.7[c]
On-pump CABG	436 (75%)	353 (79%)	83 (61%)	<0.001[c]
Off-pump CABG	61 (11%)	42 (9%)	19 (14%)	0.1[c]
CABG + AVR	73 (13%)	41 (9%)	32 (24%)	<0.001[c]
CABG + MVR/ MVr	11 (2%)	8 (2%)	3 (2%)	0.8[c]

[a] Mean values are ± 1 standard deviation. Probability value refers to male versus female. [b] Student's *t* test for equality of mean. [c] χ^2 test.

AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass grafting; EF = ejection fraction; LMS = left main stem stenosis; MVR = mitral valve replacement; MVr = mitral valve repair; VD = vessel disease.

from the analysis because of missing data. In the remaining 581 patients, a total of 1,552 grafts were constructed. Of these, 162 grafts (10%) were excluded from further analyses: 15 grafts with a mean flow less than 15 mL/min and PI greater than 5 as a result of a poor peripheral vascular bed (2 sequential SVGs, 3 LIMA-LAD, 10 single SVGs) [13], 10 grafts made of different (right internal mammary artery, radial) or composite (Y graft, quadruple sequential SVG) conduits, and 137 grafts with incomplete flow data. Thus, the analysis was carried out on 1,390 grafts.

All data were entered into a single clinical database according to the regulation of the Norwegian Social Science Data Services. The local ethical committee granted approval to this study on the basis of a quality control; therefore no informed consent was required.

Table 2. Mean Blood Flow and Pulsatility Index Values

		Male			Female		
Graft	Target Vessel	N (grafts)	Flow (mL/min)	PI	N (grafts)	Flow (mL/min)	PI
Single LIMA	LAD	386	34 ± 22	2.4 ± 0.9	109	27 ± 15	2.2 ± 0.8
Single SVG	Diagonal	60	36 ± 18	1.9 ± 0.8	15	32 ± 17	1.6 ± 0.3
	PDA	200	47 ± 26	2.5 ± 1.5	59	42 ± 28	2.2 ± 1.0
	OM	78	54 ± 29	2.1 ± 1.0	24	48 ± 26	2.0 ± 0.7
	RCA	37	56 ± 32	2.3 ± 1.6	19	49 ± 22	2.1 ± 1.1
	Posterior-lateral	12	54 ± 33	2.8 ± 1.7	0	. . .	. . .
	LAD	20	56 ± 25	2.1 ± 0.8	9	51 ± 23	1.9 ± 0.9
Double SSVG	PDA-posterior	33	62 ± 32	2.3 ± 1.0	8	50 ± 26	3.0 ± 1.5
	OM-OM	57	62 ± 33	2.1 ± 0.9	13	44 ± 20	1.9 ± 0.5
	Diagonal-diagonal	9	74 ± 42	1.9 ± 0.9	0	. . .	. . .
	OM-diagonal	153	73 ± 33	1.9 ± 0.9	43	56 ± 28	2.1 ± 1.2
Triple SSVG	Left coronary artery system	37	84 ± 44	2.1 ± 0.7	9	75 ± 19	2.0 ± 0.7

Mean values are ± 1 standard deviation.

LAD = left anterior descending artery; LIMA = left internal mammary artery; OM = obtuse marginal; PDA = posterior descending artery; PI = pulsatility index; RCA = right coronary artery; SSVG = sequential saphenous vein graft; SVG = saphenous vein graft.

Table 3. Estimated Mean Flows[a]

	Males				Females			
			95% CI				95% CI	
Graft	N	Mean Flow (mL/min)	Low	High	N	Mean Flow (mL/min)	Low	High
LIMA to LAD	386	35	32	38	109	26	22	31
SVG to Diagonal	60	42	36	49	15	34	26	41
Single SVG	347	50	47	53	111	42	37	46
Double SSVG	252	69	65	72	64	60	55	65
Triple SSVG	37	81	74	89	9	73	64	81

[a] Covariates appearing in the model are evaluated at the following values: age = 66 years; left ventricular ejection fraction = 0.63; mean arterial pressure = 68 mm Hg.

CI = confidence interval; LAD = left anterior descending artery; LIMA = left internal mammary artery; SSVG = sequential saphenous vein graft; SVG = saphenous vein graft.

Operative Technique

The approach to the heart was through a median sternotomy in all cases. A pedicled LIMA was harvested by diathermia. The greater saphenous vein was stored in heparin solution with 0.05% papaverine after harvesting. Cardiopulmonary bypass was performed with moderate hypothermia (34°C). The heart was arrested by infusion of antegrade and retrograde crystalloid or cold blood cardioplegia. In off-pump operations the target vessel was snared with 4-0 pledgeted polypropylene suture (Prolene; Ethicon, Somerville, NJ) proximal to the coronary arteriotomy. After 3 to 5 minutes of ischemic preconditioning, the snare was released and an epicardial stabilizer applied to pull the heart and immobilize the vessel site chosen for grafting. After arteriotomy an intracoronary shunt (CardioThoracic System, Cupertino, CA) was positioned into the vessel lumen.

Grafting was attempted on all vessels measuring 1 mm or more in diameter with a 50% or greater stenosis. The surgical policy was to carry out sequential grafting any time it was considered feasible. The LIMA was always grafted to the LAD end-to-side. The single SVG anastomosis was also constructed end-to-side, whereas in the sequential SVG the distal end-to-side anastomosis was constructed before the side-by-side anastomosis. All LIMA and vein anastomoses were sutured with 7-0 Prolene. The proximal anastomoses were made after release of the aortic cross-clamp and by applying a side-biting clamp on the ascending aorta.

Transit-Time Flow Measurements

Grafts were assessed in stable hemodynamic conditions 10 to 15 minutes after cardiopulmonary bypass discontinuation. In off-pump patients, the flow measurements were recorded after completion of all distal anastomoses. Mean systemic arterial blood pressure during measurements was 68 ± 8 mm Hg.

Measurements were carried out by 3- or 4-mm flow probes connected to a transit-time flowmeter (Medi-Stim ASA, Oslo, Norway). Both for single and sequential SVGs the flow probe was placed about 2 cm below the proximal anastomosis. The LIMA flow was assessed by applying the probe around a skeletonized distal site.

In all grafts the flow measurements included mean flow and the PI. The PI is a dimensionless positive number that is considered as an indicator of peripheral vascular resistance. This is automatically calculated by the flowmeter according to the following formula: PI = [maximum volumetric peak flow − minimum volumetric peak flow]/mean volumetric flow.

Based on work by Belboul and coworkers [14], mean flows and PIs were divided according to patients' sex, target vessel, and left and right coronary circulation. The intermediate coronary branch was considered as diagonal. Because the posterior descending and posterior-lateral branches originated from the right coronary artery in most cases, they were considered part of the right coronary system.

Table 4. Factors Influencing Blood Flow in Coronary Artery Bypass Grafts[a]

Factors	Flow Estimate	SEM	t Ratio	*p* Value
Male	8.7	2.4	3.7	<0.001
EF	−0.23	0.06	−3.56	<0.001
Age	0.21	0.10	2.12	0.034
LIMA to LAD	−46	4	−11.9	<0.001
Single SVG	−39	5	−7.9	<0.001
SVG to diagonal	−31	4	−7.9	<0.001
Double SSVG	−13	4	−3.1	0.002
Triple SSVG	0			
Intercept	61.3	11.9	5.2	<0.001

[a] The table shows the fixed factors influencing the flow in all coronary bypass grafts according to the linear mixed model. Triple SSVG is the reference level (N = 1,390).

EF = ejection fraction; LAD = left anterior descending artery; LIMA = left internal mammary artery; SEM = standard error of the mean; SSVG = sequential saphenous vein graft; SVG = saphenous vein graft.

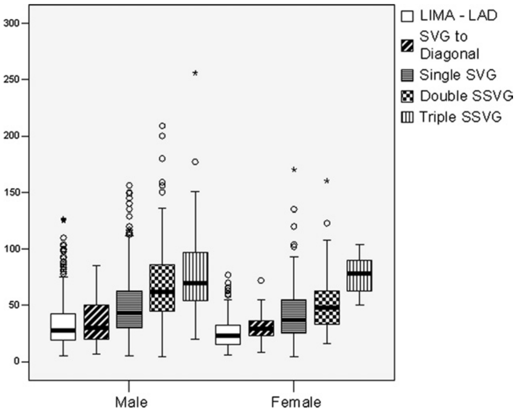

Fig 1. Transit-time blood flows in different coronary bypass grafts (581 patients; 1,390 grafts) in a box plot diagram. All triple sequential saphenous vein grafts (SSVGs) were directed to the left coronary artery system. (LAD = left anterior descending artery; LIMA = left internal mammary artery; SVG = saphenous vein graft.)

Statistical Analysis

Data are presented as the mean ± 1 standard deviation. All data were reviewed retrospectively. The grafts were naturally nested into four groups: LIMA-LAD, and single, double, and triple sequential SVGs. Comparison of flow values within these groups and overall comparison among the groups were done using a linear mixed model. Sex, age, blood pressure, and ejection fraction were initially included in the model, and statistically nonsignificant terms were sequentially removed. The mixed model also incorporated correlation of grafts within each patient [15]. Pairwise post-hoc comparisons were adjusted for multiple comparisons using the Bonferroni technique. Categorical variables were analyzed using a χ^2 test, and continuous variables using a two-tailed Student's t test with equal or unequal variances based on the findings of an initial F test for equality of variance. A probability value of less than 0.05 was considered significant. Statistical analysis was performed by SPSS for Windows 15 (SPSS Inc, Chicago, IL).

Results

Of the 1,390 grafts constituting the study, 1,385 were found satisfactory at the transit-time flow measurements control, whereas 5 grafts (0.4%; 2 LIMA-to-LADs, 3 single SVGs to obtuse marginal, posterior descending, and LAD) required revision of the anastomosis because of unexpected low flows and high PIs attributable to technical failure or incorrect placement of the anastomosis. After revision both flows and PI were within satisfactory ranges.

Graft Flow

Mean flow values of grafts directed to different target vessels are shown in Table 2. In Figure 1, the box plots depict flow values when categorized in LIMA-to-LAD, single SVG, and double and triple sequential SVGs, whereas Table 3 shows the estimated mean values from the statistical model. Within the single SVG group there were no significant differences between flows in grafts directed to different target vessels except for the diagonal (diagonal versus obtuse marginal, $p < 0.001$; diagonal versus posterior descending artery, $p = 0.035$; diagonal versus right coronary artery, $p = 0.003$). This behavior was taken into consideration for further analysis by grouping together all single SVGs, whereas those directed to the diagonal were treated as an additional group. Within the double sequential group the target vessels of the grafts made no significant difference ($p = 0.093$).

Table 4 shows the fixed factors influencing the flow in all CABGs according to the linear mixed model. Overall, graft flows were 9 mL/min higher for men than for women ($p < 0.001$). Age and left ventricular ejection fraction also made significant contributions to the model. Flow was not significantly influenced by the perfusion pressure ($p = 0.115$).

The pairwise post-hoc comparison showed flows in single SVGs were significantly lower when compared with double ($p < 0.001$) and triple sequential SVGs ($p < 0.001$; Fig 1, Table 3). Flows in single SVG to diagonal were significantly lower than flows in double and triple sequential SVG ($p < 0.001$, respectively). Flows in double sequential SVGs were significantly lower than those in triple sequential SVGs ($p = 0.017$).

Pulsatility Index

Mean PI values of grafts directed to different target vessels are shown in Table 2. Figure 2 shows PI values in single and sequential SVG to the left and right coronary system. Overall, the mean PI ± standard error of the mean of SVG to the left or right coronary system were 2.0 ± 0.05 and 2.4 ± 0.06, respectively, with the difference

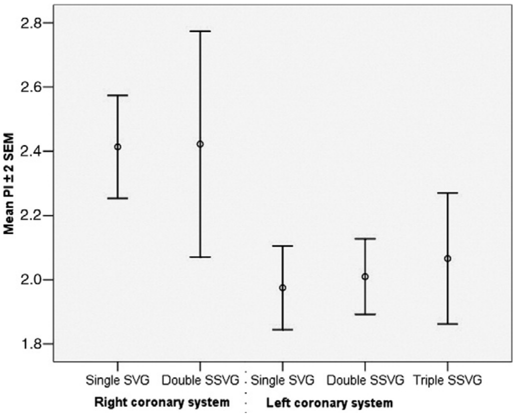

Fig 2. Pulsatility index (PI) in single saphenous vein grafts (SVGs) and double and triple sequential saphenous vein grafts (SSVGs), divided by right and left coronary system presented in a box plot diagram. (SEM = standard error of the mean.)

being significant ($p < 0.001$). There were no significant differences between PI values for any type of grafts within the single and double SVG group to the left or right coronary system ($p < 0.001$). Moreover, PI values of single versus double versus triple SVG group within the left coronary system were not significantly different ($p = 0.244$). Similarly, PI values of single versus double SVGs to the right coronary system were also not significantly different ($p = 0.126$). Pulsatility index values were similar for men and women ($p = 0.534$).

Comment

Although several clinical series have demonstrated that the sequential bypass grafting technique has excellent long-term results [16–18], this technique remains a controversial one. This is particularly true considering that the majority of studies on sequential technique go back at least a decade, when transit-time flowmetry was unavailable.

Our study analyzed routine recordings of intraoperative transit-time flow measurements of sequential SVGs in a large population of patients operated on by one surgeon. Thus, the same surgical technique of coronary artery grafting and standard of measurements were applied in all patients, avoiding operator-related biases at the time of statistical analysis of the outcome.

The first finding was an increased blood flow in sequential SVG compared with single SVG. This observation was consistent for both male and female patients, with male patients exhibiting the highest flows. Specifically, male patients were predicted to have a graft blood flow 8.7 mL/min higher than women of the same age and left ventricular ejection fraction. The blood flow increased according to the number of distal anastomoses: from a lower flow in single SVGs to a higher flow in double sequentials and up to the highest flow in triple sequentials. The trend was confirmed by our linear mixed model predicting that in patients of the same age, sex, and left ventricular ejection fraction, a triple sequential graft has 13 and 39 mL/min flow higher than double sequential and single SVG, respectively. This behavior is recognized to be caused by decreased total resistance, better run-off, and minimized impedance difference.

The variables generally used for evaluation of the flow rate are graft quality and diameter, and the resistance posed by the native coronary vessel. If one considers that the diameters of SVGs are relatively constant for a given patient, and the resistance posed by an SVG is negligible when compared with that of its coronary counterpart, the resistance of the native coronary vessels remains the principal determinant of the flow rate [17]. Therefore, if individual resistances of the grafted coronaries are assumed to be equivalent, a double sequential graft should pose only half of the resistance of an individual graft. Thus, the single SVGs are more resistant than sequential conduits, and are expected to have a lower flow compared with the sequential ones. Although all the differences among the three flow values reached statistical significance, flows in double and triple sequential SVGs were not twofold or threefold higher, respectively, compared with flows in single SVGs. This observation is consistent with the conclusion by Gwozdziewicz and coworkers [19] that blood flow through an individual bypass is comparable with that through the distal segment (end-to-side anastomosis) of a double sequential bypass. A likely explanation may be the relation between the capacity of the graft and the blood flow velocity in the graft. Although a sequential SVG would be able to provide a blood supply two or three times larger than a single SVG, this will not occur because blood flow velocity should be similarly high. The native coronary blood flow velocity is relatively fixed because it is dependent on the cross-sectional area of the coronary lumen and regional left ventricular mass [20].

Within the single SVG group, grafts directed to diagonal branches exhibited significantly lower flows than those directed to other target vessels, and this held true both for men and women. The explanation is that diagonals may be vessels of a smaller diameter and with less peripheral flow reserve, thus posing a higher coronary resistance. Significantly lower flows of single grafts to diagonals were also reported by Hassenein and colleagues [21]. Overall, flows were significantly higher in men versus women because the former are assumed to have coronary arteries of larger diameter than the latter as well as larger ventricular mass [22].

Surprisingly, and in contrast to comparable studies [9–12], we measured a lower flow in the LIMA-LAD grafts compared with vein grafts directed to the LAD. We believe this may be caused by some degree of spasm of the LIMA graft, as no vasodilators (eg, papaverine) were used routinely.

With regard to the PI, our results show that single, double, and triple SVGs all had similar PI values without significant differences among the three groups. The only difference was the higher PI in the right coronary system compared with the left, and this was true both for male and female patients. These findings are opposite to what one could expect as sequential grafts provide higher flows owing to a reduced peripheral vascular resistance. Thus, sequential grafts should theoretically provide lower PIs compared with single SVGs. Nonetheless, our data indicate that the increased blood flow from single to sequential SVGs is not associated with a decrease of PI. The likely explanation is that the shape of the flow curves of the single and sequential grafts are similar, resulting in similar PI values. Thus PI, a dimensionless number derived from an equation considering the maximum and minimum peaks and mean flow measurements, will change concomitantly with marked changes of the flow curve. This is typically seen as a gross increase of resistance in the bypass grafts (ie, technical failure of the anastomosis, graft kinking or torsion) or coronary arteries (ie, small diameter, poor runoff). This is in line with the reports by Morota and coworkers [23], who showed a large increase of PI as a consequence of a progressive tightening of the LIMA-LAD graft in the pig causing a reduced mean flow. On the other hand, the right coronary system had significantly higher PI values compared with the left across all the graft types because of a more spiky and systolic flow pattern, indicating higher vascular resistance in the right system. However, it is also known that blood flow to the right coronary artery takes place during systole as a result of minor compression of the epicardial vessels during right ventricular contraction [13].

The limitations of our study are, first, that total flow measurements were taken in sequential grafts by applying the probe about 2 cm distal to the aortic anastomosis; therefore the assessment of flow characteristics such as the systolic and diastolic patterns of each distal anastomosis could not be carried out. On the other hand, Gwozdziewicz and coworkers [19] reported that grafting a sequential graft proximal to the larger artery in sequence did not appear to have a significant effect on the blood flow in the distal segment of a sequential graft. Second, coronary flow reserve was not investigated as injection of papaverine in the bypass grafts was not carried out routinely. Third, exclusion of the few grafts with PI greater than 5 and mean flow less than 15 mL/min was done because of poor runoff as assessed by the combined information from the angiogram and the limited peripheral vascular bed seen in the surgical field. However, this issue was not confirmed by postoperative angiography as this was not performed routinely. A follow-up angiography would have been needed to prove the long-term outcome of sequential grafts.

On clinical grounds the reason to carry out transit-time flow measurements is as first-line quality control of CABG, with the aim to rule out all the likely causes of early graft failures. Ideally flow measurements should be followed by an angiogram later in the patient's follow-up. Unfortunately an angiogram performed on a routine basis in a patient without recurrent angina is just wishful thinking, because it is costly, difficult, and impractical owing to the heavy caseloads of the catheterization laboratories. We are aware that clear cutoff transit-time flow values to predict the patency for different types of grafts to different target vessels have not been defined, owing to a wide variability among patients and among different grafts. Nonetheless flow measurements remain the most applied specific investigation readily available on graft performance, and may be considered proof of a satisfactory surgical job. In our unit transit-time flow measurements of each graft are part of the operation report.

In conclusion, at retrospective analysis, sequential SVGs had a significantly higher blood flow compared with single SVGs, with flow increasing from single SVG to double and triple sequential SVG. Single SVGs directed to diagonals had the lowest flow. Blood flows in single and sequential grafts were higher in men versus women. Single, double, and triple SVGs had similar PIs. The PI of grafts directed to the right coronary system was significantly higher compared with grafts to the left coronary system.

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INVITED COMMENTARY

Sequential grafting techniques during coronary artery bypass grafting (CABG) have been in use for decades and have been adopted by different surgeons to varying extents. Purported advantages have included efficient use of available conduits, potentially improved graft patency rates attributable to presumed higher flow rates, and the need for fewer proximal anastomoses for sequential aortocoronary grafts. Intraoperative transit time graft flow measurement and calculation of the pulsatility index have likewise been available for many years and have been adopted by some surgeons as a quality control measure.

Nordgaard and coauthors [1] have provided a retrospective analysis of intraoperative transit time flow measurements from a consecutive cohort of CABG patients operated on at a single center by a single surgeon using a standardized technique during a 5-year time period. The stated objective of this report was to compare the mean flow rates and the pulsatility indices in single grafts with those of double and triple sequential grafts. Sequential grafting techniques were preferred and were used for saphenous vein grafts (SVG) whenever feasible. Routine transit time flow measurements using a standardized technique were used for quality control. Results were tabulated for left internal mammary artery-left anterior descending artery and for SVG-diagonal, other single SVG grafts, and double and triple sequential grafts.

There were 581 evaluable patients with a total of 1552 grafts, of which 1390 were evaluated. Some patients and some grafts were excluded from analysis, most often because of inadequate data. Nordgaard and coauthors based their analysis on previous authors' findings, dividing the data according to gender, target vessel, and left or right coronary systems.

Among the pertinent findings were that measured mean graft flows increased with the number of recipient vessels. Single grafts had the lowest mean flows, followed by double sequential grafts, whereas triple sequential grafts had the highest mean flows. These findings persisted after statistically controlling for gender, recipient vessel, and left or right coronary system grafting. Interestingly, the magnitude of increased flow compared with single grafts was less than double for double grafts or triple for triple sequential grafts. The authors offer some theoretical geometric and physiologic explanations for this finding.

The authors have provided a thorough analysis of a considerable amount of mean flow and pulsatility index data from a consecutive cohort of patients in which surgeon and technique biases were minimized. The findings suggest that sequential grafts do result in higher proximal vein flows and that triple sequential grafts carry the highest proximal flows.

The authors also correctly point out several limitations to their study: Some patients and some grafts were not included, and the technique used only measured total graft flow, so nothing could be said about the relative proportions of flow into each recipient vessel. Flow reserve was not evaluated. Follow-up angiographic data and patient outcome data that would indicate the adequacy or durability of revascularization are not provided. The authors do suggest that from their experience, transit time mean flow and pulsatility index measurement might be considered as useful intraoperative graft quality control measures.

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Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model☆,☆☆

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Abstract

Objective: To assess whether coronary graft flow patterns are affected differently by native coronary competitive flow or by stenosis of the coronary anastomosis. **Methods:** Nine pigs (65–70 kg) underwent off-pump grafting of the left internal mammary artery to the left anterior descending artery (LAD). Transit-time flow patterns in the mammary grafts were recorded under four different conditions: (1) baseline flow (proximal LAD occluded), (2) full competitive flow, (3) partial competitive flow and (4) after creation of a stenosis in the anastomosis. Competitive flow was achieved by an adjustable occluder on the left anterior descending artery. The mean luminal stenosis of the anastomosis was 75 ± 11%, calculated by epicardial ultrasound. Mean flow, systolic and diastolic antegrade and retrograde flow during different flow conditions were calculated as ratios of baseline flow and compared. Different derived flow indexes were calculated and compared in the same manner. Friedman's test and post hoc analyses by Wilcoxon signed-ranks were performed without correction for multiple comparisons. **Results:** Mean graft flow was more reduced by competitive flow than by a stenotic anastomosis of 75 ± 11%. Competitive flow significantly decreased diastolic antegrade flow and both diastolic and systolic maximum peak flows, but increased retrograde flow, compared with baseline and stenosis. Furthermore, competitive flow and stenosis could be distinguished by analysis of several derived indexes. Pulsatility index (maximum − minimum flow/mean flow) and insufficiency percent (retrograde flow as fraction of total flow) was increased significantly more by competitive flow than by stenosis. Diastolic filling percent was significantly reduced at competitive flow compared with stenosis and baseline. **Conclusions:** The mammary graft flow was significantly reduced by native coronary competitive flow, but marginally decreased by a stenotic anastomosis of 75% mean luminal stenosis. Reduction of graft flow due to competition was particularly evident in diastole. A detailed flow pattern analysis may differentiate between competitive flow and stenosis of the anastomosis.

Keywords: Heart surgery; CABG; Anastomosis; Coronary graft assessment; Transit-time flow measurement; Epicardial ultrasound

1. Introduction

Transit-time blood flow measurement has gained popularity for assessing patency of coronary bypass grafts. It is easy and convenient for intra-operative use and provides accurate graft flow measurements with few sources of technical error [1]. However, clear cut-off values to predict the patency for different types of grafts to different target vessels have not been reported because of a wide variability among patients and grafts. Generally, a mean graft flow of under 10–15 ml/min, pulsatility index >5 and a poor diastolic flow pattern have been accepted as indicating poor graft performance, necessitating further investigation of the graft and the anastomosis [2]. When interpreting transit-time flow measurements, it is important to take the hemodynamic conditions of the coronary system into consideration. Thus low flow within bypass grafts might have numerous causes, such as high coronary resistance, small target vessels, kinking, dissection or spasm in the graft, competitive flow and anastomotic failure. Hence the use of graft flow for assessing the anastomosis may give unreliable results and lead to unnecessary revisions.

This study aimed to assess the impairment of graft flows due to competitive flow from the coronary artery or stenosis

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of the coronary anastomosis, as well as the extent of their impact. Transit-time flow patterns were measured at four different flow conditions in a left internal mammary artery (LIMA) to left anterior descending coronary artery (LAD) in a porcine model.

2. Materials and methods

Ten Noroc pigs (hybrid of 1/4 Duroc, 1/4 Yorkshire and 1/2 Norwegian landrace, weight 65—70 kg) underwent off-pump coronary artery bypass grafting (OPCAB) with LIMA-to-LAD anastomosis through a median sternotomy. One pig was excluded from the study because of hemodynamic instability throughout the study so that nine animals were included in the final analysis. The animals received good care in accordance with the European convention on animal care and Norwegian national regulations. Approval was given by the Norwegian ethics committee on animal research. All animals were treated by the same anesthesiologist and surgical team. At completion of the experiments, the animals were killed with an intravenous injection of high dose pentobarbital and potassium chloride.

2.1. Anesthesia and surgical technique

All pigs received premedication with intramuscular azaperone 4 mg/kg and ketamine 0.20 mg/kg. Anesthesia was induced with intravenous atropine 1 mg, fentanyl 0.01 mg/kg and pentobarbital 10 mg/kg. General anesthesia was maintained by infusions of fentanyl 0.02 mg/kg/h and midazolam 0.3 mg/kg/h. Amiodarone 150 mg and hexamethonium chloride 20 mg/kg were given to avoid arrhythmias. Full heparinization was achieved with heparin 10—20 000 IE intravenously. The pigs were ventilated with room air through a tracheotomy tube, and ventilator settings were adjusted according to blood gas measurements. Central venous catheters were introduced into both internal jugular veins for infusions and measurements of central venous pressure. A catheter was placed in the descending thoracic aorta for continuous measurement of arterial pressure. The bladder was drained through a cystotomy. After median sternotomy, the LIMA was harvested with its pedicle. A 16 mm flow transit-time flow probe (VeriQ flowmeter, Medi-Stim ASA, Oslo, Norway) was placed around the pulmonary trunk to measure cardiac output. ECG leads were connected to the flowmeter. An Axius vacuum stabilizer (Guidant, Santa Clara, CA) was applied to immobilize the LAD at the site chosen for grafting. A 2 or 3 mm flow probe was placed immediately proximal to the coronary arteriotomy to assess native coronary flow. Adjacent to this flow probe, an adjustable vascular occluder (In Vivo Metric, US) was applied to create either occlusion of the LAD or partial competitive flow (Figs. 1 and 3). Full competitive flow was achieved by complete pressure release of the vascular occluder. Ischemic preconditioning was performed by five repeated cycles of 30 s of LAD occlusion with 30 s of reperfusion in between. After arteriotomy of the LAD, an intracoronary shunt was placed in the vessel lumen. The LIMA—LAD anastomosis was then sutured with a continuous 7-0 Prolene to create patent anastomoses without technical failures. Patency of the anastomosis was confirmed with epicardial ultrasound imaging. At completion of the anastomosis, a 3 mm flow probe was also placed on the LIMA graft to assess graft flow (Figs. 1 and 3).

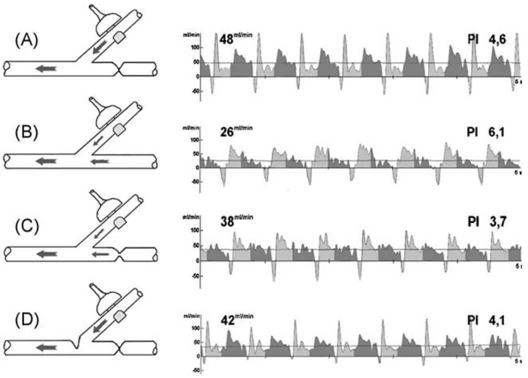


Fig. 1. Layout of the four flow conditions with typical corresponding flow curves. (A) Baseline flow with proximal LAD totally occluded. (B) Full competitive flow with no snaring of the proximal LAD. (C) Partial competitive flow with partial occlusion of LAD (approximately 50% of full competitive flow). (D) Stenotic anastomosis with no competitive flow.

2.2. Epicardial ultrasound imaging

The status of the anastomosis was assessed by epicardial ultrasound imaging before and after constructing a stenosis of the anastomosis, and with or without competitive flow.

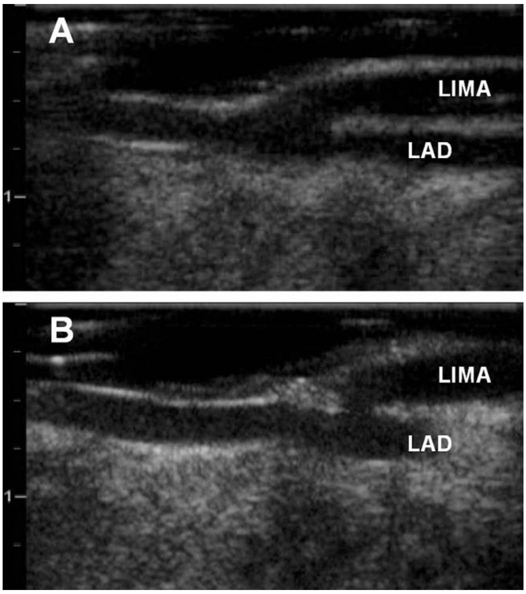


Fig. 2. B-mode ultrasound images of the same LIMA—LAD anastomosis. (A) Fully patent anastomosis. (B) Stenotic anastomosis after placement of a deep stitch at the toe.

The ultrasound imaging was performed with a GE Vivid 7 scanner (GE Vingmed, Norway) equipped with an i13L linear array probe (GE Healthcare, Waukesha, WI), capable of operating at frequencies from 7 to 14 MHz. Ultrasound gel was applied in the field of the anastomosis to get a proper stand-off, suitable for better images. The anastomosis was visualized in transverse and longitudinal scan planes using B-mode tissue imaging and a new ultrasound flow imaging modality termed 'blood flow imaging' (BFI). The BFI modality is based on conventional color Doppler imaging and can visualize blood flow in any direction of the two-dimensional image plane without limitations imposed by aliases [3] (Videos 1 and 2). The luminal stenosis was estimated with the use of MATLAB v7.0 (Mathworks Inc., USA).

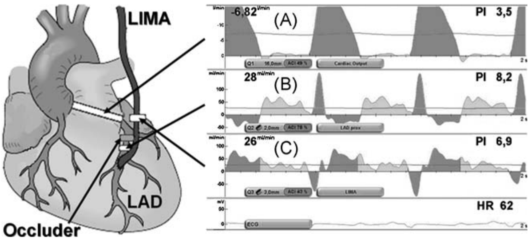


Fig. 3. Layout showing the position of the three flow probes during experiments and their corresponding flow curves by the Medi-Stim VeriQ flowmeter. (A) Pulmonary trunk flow. (B) LAD flow. (C) LIMA flow. The vascular occluder was applied around the proximal LAD to adjust competitive flow. These flow curves were recorded at full competitive flow; light gray represents diastolic flow, dark gray is the systolic flow. Antegrade and retrograde flow is the flow above and below the zero line, respectively.

2.3. Experimental protocol

Transit-time flow patterns in the LIMA grafts were recorded under four different conditions: (A) baseline flow: the proximal LAD was totally occluded; (B) full competitive flow: no occlusion of the proximal LAD; (C) partial competitive flow: partial occlusion of the LAD to roughly half its competitive flow; (D) stenotic anastomosis (Fig. 1). After a fully patent anastomosis was constructed and controlled by epicardial ultrasound, a stenosis of the anastomosis was made by placing a deep stitch at the anastomotic toe with the aim to reduce its cross sectional area (Fig. 2). The calculated mean degree of stenosis was 75 ± 11% as measured by epicardial ultrasound [3].

All flow and ultrasound measurements were made after 30 min stabilization and at similar and stable hemodynamic conditions (heart rate, cardiac output and blood pressure) after removal of the stabilizer from the epicardial surface. All recordings of flow values in the LAD, LIMA and pulmonary trunk were obtained simultaneously and stored in a database. The flow curves were analyzed off-line using the Medi-Stim 2.0 VeriQ software. The LAD flow represented the competitive flow (Figs. 1 and 3) (Videos 1 and 2).

For each flow condition five consecutive stable wavelets from each recording probe were stored for further analysis. The flow in the pulmonary trunk defined the systolic and diastolic flow phase. The following flow values were calculated in the LIMA graft under all four conditions: diastolic antegrade flow, systolic antegrade flow, total retrograde flow, diastolic maximum peak flow, and systolic maximum peak flow. The following values were used to calculate the following derived indexes:

$$\begin{aligned}
\text{Mean flow} &= \text{antegrade} - \text{retrograde flow}\\
\text{Insufficiency}\,(\%) &= (\text{retrograde flow}/\text{antegrade flow}) \times 100\\
\text{Diastolic filling}\,(\%) &= (\text{diastolic flow}/(\text{systolic} + \text{diastolic flow}) \times 100\\
\text{Pulsatility index}\,(\text{PI}) &= (\text{maximum peak flow} - \text{minimum peak flow})/\text{mean flow}.
\end{aligned}$$

This is automatically calculated by the flowmeter.

2.4. Statistics

Data were analyzed using SPSS, version 15.0 (SPSS Inc., Chicago, IL) and expressed as mean ± 1 standard deviation for normally distributed data and as median with range for data not normally distributed. Friedman's tests for non-normally distributed variables were applied. If the Friedman's test revealed significant changes, post hoc analyses by Wilcoxon signed-ranks were performed without correction for multiple comparisons. To compare the flow measurements between individual pigs, ratio values to baseline flow were calculated. A p value <0.05 was considered significant.

3. Results

The overall blood pressure, heart rate and cardiac output were 94 ± 14 mmHg, 102 ± 19/min and 7.0 ± 1.6 l/min,

Table 1
True values of mean flow and derived indexes. Median and range ($n = 9$).

Name	Baseline	Full competitive flow	Partial competitive flow	Stenosis of anastomosis	p
Mean flow	48 (35—50)	29 (3—38)*,†	38 (18—52)*	41 (19—60)	0.001
Pulsatility index	3.3 (1.6—10.1)	5.8 (2.2—12.8)*	4.0 (2.0—9.7)	3.9 (1.5—10.1)	0.006
Diastolic filling%	67 (56—85)	46 (31—58)*,†	56 (40—71)*	61 (46—75)	<0.001
Insufficiency%	2.3 (0—13.1)	9.4 (0.21—37.0)*,†	5.1 (0—14.5)	2.0 (0—14.6)	0.002

p refers to Friedman's test.

* $p < 0.05$ refers to comparison with baseline condition analyzed by post hoc test.

† $p < 0.05$ refers to comparison with a luminal LIMA—LAD stenosis of 75 ± 11%, analyzed by post hoc test.

Table 2
Flow values as ratios to baseline (=1). Baseline flow is defined as patent anastomosis with no competitive flow. Median and range (n = 9).

Flow	Full competitive flow	Partial competitive flow	Stenosis	p
Mean	0.63 (0.08–0.81)*,†	0.76 (0.51–1.17)*	0.88 (0.54–1.25)	0.001
Diastolic antegrade	0.52 (0.13–0.77)*,†	0.56 (0.50–1.07)*	0.83 (0.43–1.86)	0.008
Systolic antegrade	1.06 (0.39–1.40)	1.16 (0.49–1.54)	0.96 (0.67–2.54)	0.481
Diastolic maximum peak	0.59 (0.34–0.78)*,†	0.72 (0.40–1.08)*	0.83 (0.37–1.83)	$<$0.001
Systolic maximum peak	0.77 (0.50–1.04)*,†	0.76 (0.54–0.96)*,†	1.07 (0.71–2.83)	0.001
Retrograde	2.30 (1.15–10.55)*,†	1.37 (0.46–8.00)	0.60 (0.14–10.6)	0.018

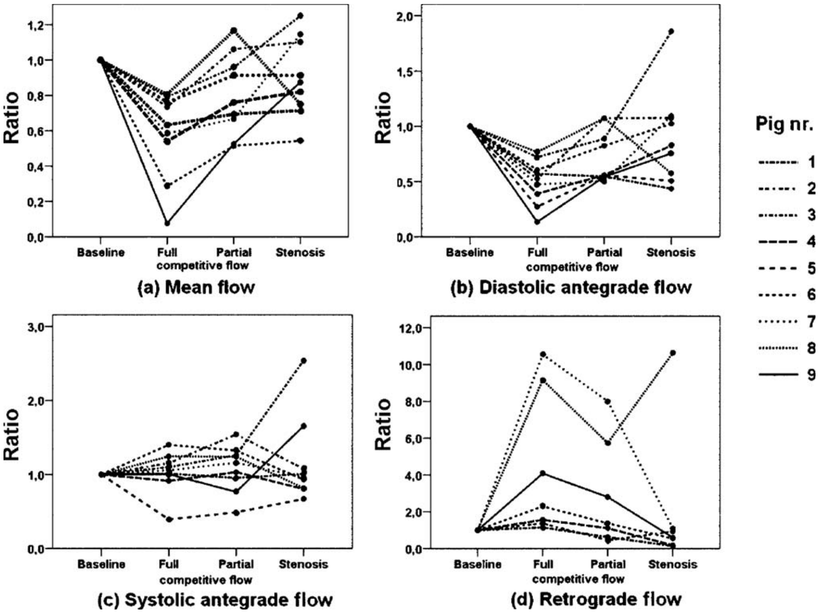
p refers to Friedman's test.
* $p < 0.05$ refers to comparison with baseline conditions analyzed by post hoc test.
† $p < 0.05$ refers to comparison with stenosis analyzed by post hoc test.

respectively. The flow values and derived indexes at all four flow conditions are presented in Tables 1 and 2. A dot plot diagram (Fig. 4) illustrates the flow ratios under the four flow conditions.

The most important findings were the reduction of diastolic flow determined by full and partial competitive flow compared with baseline flow (p = 0.008 and 0.021, respectively), whilst the stenotic anastomoses influenced either the diastolic or the mean flow (p = 0.314 and 0.285, respectively) (Fig. 4; Tables 1 and 2). The mean flow was reduced during both full and partial competitive flow compared with baseline flow (p = 0.008 and 0.051, respectively). The systolic antegrade flow was not influenced by any of the flow conditions (p = 0.481) (Fig. 3). The PI and percentage of insufficiency increased only under full competitive flow (p = 0.008, both indexes) (Table 1). The diastolic filling % was lower in full and partial competitive flow compared with baseline (p = 0.008 and 0.011, respectively). Retrograde flow occurred in early systole under all four flow conditions, but was significantly increased only during full competitive flow (p = 0.008), (Table 2). The diastolic and systolic maximum peak flows were both reduced at competitive flow (p = 0.008 and 0.011, respectively), whilst a 75% anastomotic stenosis did not affect maximum peak flows (p = 0.086 and 0.314, respectively) (Table 2).

4. Discussion

Our study produced four major findings. Firstly, competitive flow led to a significant reduction of blood flow within the LIMA graft, mainly because of a considerable decrease of the diastolic flow. Secondly, the graft flow was not significantly decreased despite a major (75%) stenosis of the anastomoses. Thirdly, higher PI was observed at full competitive flow because lower mean flows were recorded. Finally, partial competitive flow generally had the same effect as full competitive flow on both the mean and



(a) Mean flow

(b) Diastolic antegrade flow

(c) Systolic antegrade flow

(d) Retrograde flow

Fig. 4. Dot plots presenting flow values at four different flow conditions, expressed as ratio of baseline flow (=1). (a) Mean flow, (b) diastolic antegrade flow, (c) systolic antegrade flow and (d) retrograde flow.

diastolic flow, whereas retrograde flow, PI and insufficiency were significantly influenced only under full competitive flow.

Our various experimental settings evoked three different flow conditions often encountered by the surgeon in practice. Full competitive flow mimics the situation of a graft placed distal to a less than critical stenosis of the coronary vessel. This may occur when coronary vessels with less than 50—70% stenosis are grafted, although such stenosis has no hemodynamic consequences at rest. Partial competitive flow occurs when a coronary artery is grafted distal to a significant stenosis providing about half the volume flow compared with the full value. The third condition was no-flow, an ideal situation for placing the graft distally on a totally occluded coronary.

This study showed that the LIMA graft was much influenced by competitive flow, as both the full and partial competitive flow conditions significantly altered the flow patterns. Despite the superior long-term patency of mammary grafts, the effect of competitive flow on the patency of LIMA grafts is still controversial [4—15]. The narrowing phenomenon (string sign) of the distal mammary graft is believed to be associated with competitive flow [4,7,16], because the blood flow within the mammary artery is so low that it cannot meet the metabolic requirements of its cell walls, causing the graft to narrow and eventually fail.

Clinical studies of competitive flow do not measure flows because they are retrospective and based on angiographic data. The occurrence of competitive flow has been inferred from the concomitant presence of a non-significant stenosis of the grafted vessel [7,9,17]. Furthermore, other studies suggest that arterial grafts such as LIMA are more influenced by competitive flow than are saphenous vein grafts [4,7,10—16]. The non-muscular saphenous vein grafts cannot adjust their lumens in response to metabolic requirements as much as arterial grafts. Thus, the response of vein grafts to low flow is limited.

To consider the effects of stenotic anastomoses we found that a 75% luminal stenosis of the anastomosis did not reduce blood flow through the grafts. This supports the findings of Morota et al. [18] and Jaber et al. [19], who also showed that blood flow measurements remained stable when anastomotic stenoses varied from mild (<25%) to moderately severe (<75%).

Our results are in line with the patho-physiological principles underlining blood flow in stenotic vessels described by Poiseuille's law. Nonetheless, this effect of a stenosis on blood flow is reduced in the LAD because of the autoregulation within the peripheral vascular bed. The LAD is characterized by the largest lumen and most extensive peripheral vascular bed of all coronary arteries. Therefore to reduce the LAD perfusion flow by stenosis, the vessel lumen must be considerably restricted (e.g. from 80 to 90%). With such narrowing autoregulation will soon be exhausted, and any subsequent small reduction will have major hemodynamic consequences [20]. Clinically, a stenosis of the LAD <75% will reduce maximal flow capacity, causing ischemic induced chest pain during exertion. During rest a stenosis >75% may significantly reduce blood flow, which can lead to chronic myocardial hypoxia.

A practical question raised by our findings is how to distinguish between competitive flows from a stenotic anastomosis, whenever low flows are recorded after CABG, since both conditions may decrease blood flow. We found that competitive flow altered mainly the diastolic phase of graft flow, whereas the systolic flow remained unchanged. Additionally, a smoother flow pattern might be present, because the maximum peaks in systole and diastole decrease during competitive flow in LIMA—LAD anastomoses. Thus, a careful analysis of flow patterns and their timing should always be carried out in situations with low graft flow. If the flow pattern is still difficult to interpret then snaring the coronary artery proximal to the anastomotic site might be of further help. Thus D'Ancona et al. strongly recommended that graft flow should be measured with and without proximal snaring of the coronary artery [2]. With competitive flow, as we found, occlusion of the coronary artery will increase graft flow; conversely, with a flow decrease an obstruction distal to the graft may be suspected (i.e. stenotic anastomosis, coronary stenosis distal to the anastomotic site or poor run-off). Temporary clamping of grafts directed to collateral coronaries may also aid in the interpretation of blood flow.

Hangler et al. strongly warned against the use of occluders during CABG, as they found evidence of coronary endothelial injury on electron microscopy after different occluding techniques [21]. To avoid vessel snaring, many surgeons measure the flow in the LIMA graft before removing the aortic cross clamp. Alternatively, as we have reported, epicardial ultrasound is fast and efficient for assessing coronary graft anastomoses [22]. In the present study the new blood flow imaging modality was used to evaluate the patency of the anastomosis by looking at its morphology and function, and particularly the degree of stenosis [3]. We believe that this technique has a great part to play in the intra-operative assessment of CABG as it is non-invasive and can easily detect stenoses and competitive flow [22].

The main limitations of this study were that the pigs had normal coronary arteries with good run-off, and that the animal model may not be directly comparable to patients with advanced coronary disease. The measured flow values may also be different in different species. Thus, the true flow values and derived indexes may not be directly applicable to humans, although the 75% degree of anastomotic stenosis in our model still represented a failed anastomosis likely to cause stable angina. The consequences of an even tighter stenosis on graft flow were not investigated. Finally, the statistical limitations were the multiple comparisons and a limited number of measurements. The widely used Bonferroni correction for multiple comparisons is designed for use with independent multiple measurements and does not fully apply to this situation. We instead report uncorrected p values for the Wilcoxon signed-ranks, which the readers may themselves more easily assess the relevance of the statistical differences described.

In conclusion, in a porcine model, the LIMA flow was significantly reduced by native coronary artery competitive flow but marginally decreased by an anastomotic mean luminal stenosis of 75%. Reduction of graft flow due to competitive flow was particularly evident in diastole. Thus a careful analysis of flow patterns may help to discriminate between competitive flow and an anastomotic stenosis. A detailed knowledge of different flow patterns by the surgeon is mandatory for a reliable interpretation of transit-time flowmetry. In a near future epicardial tissue and Doppler imaging assessment may be performed together with transit-time flowmetry because the combined information supplied by each technique might potentially improve intra-operative evaluation of coronary grafts.

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Appendix A. Conference discussion

Dr B. Walpoth (*Geneva, Switzerland*): Thank you for presenting an interesting experimental assessment of this new device from MediStim. Basically there are some problems with what you showed. First of all, it has been shown before, secondly, it is well known to all cardiac surgeons that you will never have full competitive flow. You need a relevant stenosis in order to make a bypass. And as you have shown and which was known that if you have a stenosis of the native vessels which is not in excess of 75 to 80%, you will not have major changes in your flow measurement.

However, I fully agree with you that the addition of imaging technique is an important feature, because sometimes you measure low-flow situations in grafts without any obvious reasons, but if imaging is available it can help onsite in the operating room to make a decision.

My question is the following. You said with 75% stenosis at the toe of your anastomosis you didn't see major flow changes. You saw some changes but not as much as you would have expected. How did you assess the 75% stenosis? To obtain a correct degree of stenosis you need a biplanar angiographic evaluation and 75% might not be sufficient.

Dr Nordgaard: We used our ultrasound images of the anastomoses. The images were afterwards analyzed using the MatLab software. Several diameters of each LIMA—LAD anastomosis were measured for calculation of the degree of luminal stenosis. In the operation field we assessed the anastomosis using ultrasound imaging since our aim was creating a stenosis of a significant degree at the toe of the anastomosis.

I do not agree with your comment that full competitive flow doesn't exist in coronary surgery. Often surgeons do graft vessels with about 50% luminal stenosis. Then the hemodynamic still acts as full competitive flow because the blood flow is not influenced at this degree of stenosis.

Dr Walpoth: This is correct, yes.

Dr A. Pavie (*Paris, France*): On your presentation I would like to make a small comment, and I am a little provocative. You suggest that it is more important to have good indication to avoid competitive flow, but it is still very important to do good surgery. I am not sure that we can follow you. It is certainly important to do a good indication, but if we do good surgery, it is probably better.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejcts.2009.02.036.

Paper III

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Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery☆

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Abstract

Objective: Transit-time flow measurement is widely accepted as an intra-operative assessment in coronary artery bypass grafting (CABG). However, the two most commonly applied flowmeters, manufactured by MediStim ASA and Transonic Inc., have different default filter settings of 20 and 10 Hz, respectively. This may cause different flow measurements, which will influence the reported results. The aim was to compare pulsatility index (PI) values recorded by the MediStim and Transonic flowmeters in two different clinical settings: (1) analysis of the flow patterns recorded simultaneously by both flowmeters in the same CABGs; and (2) evaluation of flow patterns under different levels of filter settings in the same grafts. **Methods:** Graft flow and PI were measured using the two different flowmeters simultaneously in 19 bypass grafts. Finally, eight grafts were assessed under different digital filter settings at 5, 10, 20, 30, 50 and 100 Hz. **Results:** The Transonic flowmeter provided substantially lower PI as compared with the MediStim flowmeter. By increasing the filter setting in the flowmeter, PI increased considerably. **Conclusions:** The MediStim flowmeter displayed a lower PI than the Transonic, due to a lower filter setting. In the Transonic, flow signals are filtered at a lower level, rendering a 'smoother' pattern of flow curves. Because different filter settings determine different PIs, caution must be taken when flow values and flowmeters are compared. The type of flowmeter should be indicated whenever graft flow measurements and derived indexes are provided.

Keywords: CABG; Coronary graft assessment; Flowmetry; Pulsatile index; PI; Transit-time

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1. Introduction

Intra-operative assessment of graft patency is an important aspect of coronary artery bypass grafting (CABG). Transit-time flow measurement (TTFM) has been in clinical use for more than a decade and is the most applied technique for intra-operative coronary graft assessment. Transit-time technology has proven to have a high reliability and accuracy with few sources of technical errors and provides volumetric flow patterns and derived indexes, such as the pulsatility index (PI) [1–4].

The PI is considered a non-invasive method for the assessment of peripheral vascular resistance of coronary arteries [5–9], as well as in arteries of other organs (i.e. brain, kidney, placenta, eye, and so on) [5]. It was first introduced by Gosling and King [6], and was originally defined as the peak-to-peak height of the waveform divided by the mean height during a single cardiac cycle, as assessed by Doppler ultrasound. With the introduction of TTFM, the definition of PI was replaced and simplified, and at present the following formula is applied: PI = [maximum volumetric peak flow − minimum volumetric peak flow]/mean volumetric flow.

The two most commonly used transit-time flowmeters are manufactured by MediStim ASA (Oslo, Norway) and Transonic Systems Inc. (Ithaca, NY, USA) and have different default filter settings of 20 and 10 Hz, respectively. Since the level of filter settings in a flowmeter may influence the wave form, different maximum and minimum peak flows may be registered and influence the PI values [10].

The aim of this study was to assess the potential variability of the PI as calculated by the MediStim and Transonic flowmeters, and to investigate whether increase in filtering of the flowmeter signals influences flow curves and PI values.

☆ The Medical Faculty, Norwegian University of Science and Technology, has a corporate partnership with MediStim ASA.

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Table 1
Mean PI of two patient populations assessed by MediStim and Transonic flowmeter, respectively.

Graft	Group A				Group B				
	N	Mean	95% CI		*N*	Mean	95% CI		*p*
			Lower	Upper			Lower	Upper	
LIMA-LAD	482	2.1	2.1	2.2	100	1.7	1.6	1.8	<0.001
Single SVG to LCA	198	1.8	1.7	1.9	36	1.7	1.5	2.0	0.52
Double SSVG to LCA	264	1.8	1.7	1.9	19	1.4	1.0	1.8	0.03
Single SVG to RCA	317	2.1	1.9	2.2	25	1.6	1.3	2.0	0.03
Double SSVG to RCA	41	2.2	1.9	2.5	61	1.7	1.5	1.9	0.001

Group A: MediStim flowmeter; Group B: Transonic flowmeter; CI: confidence interval; LCA: left coronary artery; RCA: right coronary artery; SSVG: sequential saphenous vein graft; and SVG: saphenous vein graft.

2. Material and methods

The idea to carry out this study came to us while studying two clinical series of patients operated upon with CABG, each of them assessed by TTFM of coronary grafts by the MediStim or the Transonic flowmeter, respectively (see Table 1). The first series was operated on by RH at the University Hospital of Trondheim, Norway, whereas the second series came from the University Hospital of Catanzaro, Italy, being operated upon by AR. All single and sequential saphenous vein grafts (SVGs), and left internal mammary artery (LIMA) grafts were included. All flow measurements were carried out after weaning of cardiopulmonary bypass and after administration of protamine. Factors such subclavian artery stenosis or spasm of the LIMA graft were not taken into consideration. We observed that the PI calculated by the Transonic was generally lower than the PI by MediStim. This difference was either due to a real difference between the two flowmeters (i.e. different levels of filter setting), or it was determined by the intrinsic biases associated with a comparison between different patient populations and surgeons. Moreover, we decided to search the literature for the largest clinical series reporting PI data of coronary grafts calculated by the MediStim or Transonic flowmeters, to find out whether the trend of different PI values calculated by the two machines were consistent in other series as well (see Table 2). Most of the relevant data available were obtained by the MediStim flowmeter [11—16], whereas just two series presented by the same investigators were found reporting PI values by Transonic [17,18]. Despite differences in the amount of data, we noted a trend towards lower PI values provided by the Transonic flowmeter versus the MediStim flowmeter. Thus, we decided to carry out the following study to ascertain whether this observation held true based on the technical characteristics of transit-time flowmeters.

2.1. Digital signal processing technology in transit-time flowmeters

The transit-time flowmeters measure the time difference between an upstream and downstream ultrasonic pulse when transmitted and received by two spatially separated transducers in the flow probe. This time-delay difference can be converted to volume flow, which is displayed on-screen as a digitised signal. The flow is recorded as analogue signals that are initially digitally sampled at a sufficiently high frequency according to the Nyquist—Shannon sampling theorem [19]. Further, the flowmeter typically uses a low-pass filter to smooth the signal and attenuate noise. MediStim and Transonic flowmeters use default low-pass filters at 20 and 10 Hz, respectively. In other words, the flowmeters filter the signals differently, which may determine different flow curve patterns.

Table 2
Mean PI from different published studies.

Flowmeter	Author	Type of graft (*N*)	PI ± SD
MediStim	Becit [11]	LIMA-LAD (102)	2.32 ± 0.88
		SVG to Diagonal (48)	2.26 ± 0.81
		SVG to OM (80)	2.51 ± 0.94
		SVG to RCA (73)	2.23 ± 0.94
	Goel[*] [12]	LIMA-LAD (162)	2.71 ± 0.95
		SVG overall (224)	2.48 ± 1.04
	Gwozdziewicz [13]	SSVG (50)	1.8 ± 0.4
	Kim[***] [14]	To LCA (67)	2.4 ± 1.3
		To RCA (36)	3.1 ± 1.6
	Hassanein [15]	LIMA-LAD (421)	1.98 ± 1.08
		SVG to Diagonal (69)	1.72 ± 0.58
		SVG to OM (71)	1.88 ± 0.86
		SVG to RCA (107)	1.80 ± 1.82
	Nordgaard[**] [16]	LIMA-LAD (495)	2.4 ± 0.9
		SVG to LCA (527)[†]	2.0 (0.05 SEM)
		SVG to RCA (368)[†]	2.4 (0.06 SEM)
Transonic	Onorati [17]	LIMA-LAD (199)	1.53 ± 0.62
		SVG to RCA (102)	1.67 ± 1.20
		SVG to OM (61)	2.06 ± 0.89
		SVG to Diag (25)	2.25 ± 1.25
	Onorati [18]	LIMA-LAD (45)[a]	1.2 ± 0.4
		LIMA-LAD (45)[b]	1.0 ± 0.7
		SVG to OM[a]	1.46 ± 0.9
		SSVG to OM[b]	0.71 ± 0.4

[a] Single SVG group.

[b] Sequential SVG group.

[*] OPCAB in 36% of cases.

[**] OPCAB in 11% of cases.

[***] Only arterial grafts were used: mammary ($n = 78$), gastroepiploic ($n = 38$) and radial artery ($n = 1$).

[†] Includes values from single and sequential SVG as no PI difference was found between the groups [16].

The study protocol was divided into two steps:

(1) Controlled comparison of PI as calculated by the MediStim and Transonic flowmeters applied simultaneously on the same coronary grafts;
(2) Evaluation of changes in the flow curves and PI with different filter settings.

2.1.1. Assessment of PI in the same graft by MediStim and Transonic flowmeters

The two flowmeters were simultaneously compared in 19 coronary bypass grafts (10 single and five sequential SVGs, and four LIMA grafts) in 10 patients who were operated on by the same surgeon (RA) in the same unit (Trondheim). Two 4 mm flow probes, each connected to the respective MediStim or Transonic flowmeter, were placed next to each other on the middle segment of the grafts. Each measurement was done at a stable haemodynamic condition after weaning from cardiopulmonary bypass, and good acoustical coupling was obtained between the flow probe and the graft.

2.1.2. Assessment of PI during different filter settings

Finally, to investigate the influence of different filter settings on the flow curves, eight grafts in four patients, who were operated on by the same surgeon (RA), were assessed by gradually increasing the filter setting of the flowmeter from 5 Hz to 10, 20, 30, 50 and 100 Hz. To accomplish this, the MediStim VeriQ flowmeter was used since it is fitted to adjust the filter level. After discontinuation of the cardiopulmonary bypass and at stable haemodynamic conditions, the flow patterns of the grafts were recorded for 5—10 s at each filter level. The analysis of the flow curves was carried out using the MediStim VeriQ 2.0 software.

The complete study protocol was approved by the Regional Medical Ethics Committee on Human Research at both institutions. All data were entered into a single clinical database according to the regulations of the Norwegian Social Science Data Services.

2.2. Statistical methods

The grafts were nested into LIMA-LAD, single and double sequential SVGs to the left and right coronary arteries, respectively. In Table 1, a logarithmic transformation of the flow data was performed to achieve normal distribution. The comparisons between grafts from the two cardiac centres were performed using two sample *t*-tests except for the single SVGs to the left coronary artery, where a random effects model with random intercept using the 'xtreg' command in STATA was used. A random effects model was used to account for repeated measurements as several patients got more than one single SVG to the left coronary artery system. A Wilcoxon signed rank test was used to compare the simultaneous flow assessments in the same grafts. Bland—Altman plots of the simultaneous flow measurements were made in Excel. The PI values are expressed as geometric mean and 95% confidence interval. $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA) and STATA for Windows version 10 (StataCorp, College Station, TX, USA).

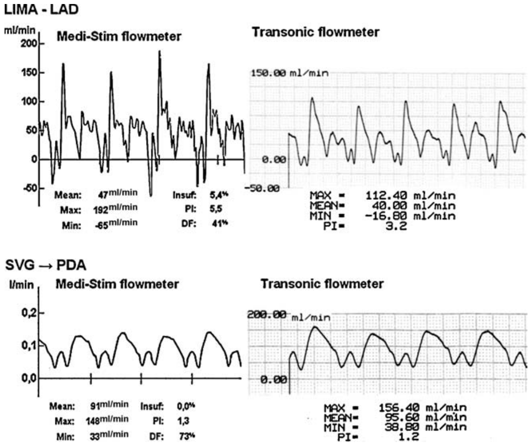

Fig. 1. Simultaneous graft flow measurements on the same graft with the MediStim and Transonic flowmeter. The upper panel shows a LIMA-LAD graft with 'spiky' flow curves. The PI values are 5.5 and 3.2 as calculated by the MediStim and Transonic flowmeters, respectively. The lower panel shows SVG to posterior descending artery (PDA). The PI values are lower and the flow curves are similar in both flowmeters PI 1.3 and 1.2 in the MediStim and Transonic flowmeter, respectively.

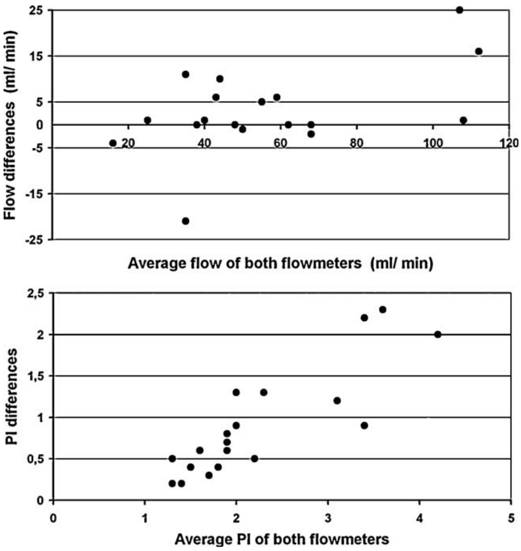

Fig. 2. Bland—Altman plots of simultaneous measurements in 19 coronary bypass grafts by the MediStim and Transonic flowmeters. The upper and lower graphs show the flow (ml/min) and PI values, respectively. Measurements (dots) above the zero line are those that the MediStim flowmeter records higher than the Transonic. The values below the zero line are measurements that the Transonic records higher than the MediStim flowmeter. There is a trend towards higher flow values in the MediStim flowmeter ($p = 0.053$; Wilcoxon sign ranks test). On the PI chart, all values were above the zero line meaning that the MediStim flowmeter always records higher PI values than the Transonic ($p < 0.001$; Wilcoxon sign ranks test). Of note, the PI differences between the two flowmeters become greater as the PI increases.

3. Results

3.1. Assessment of PI by MediStim versus Transonic flowmeter in the same grafts

The MediStim and Transonic flowmeter provided mean PI and standard deviations of 2.7 ± 1.2 and 1.8 ± 0.6, respectively ($p < 0.001$; Wilcoxon signed ranks test). Fig. 1 clearly demonstrates the difference between the two flowmeters. The Transonic flowmeter achieved systematically lower PI values. The degree of difference depended on the flow pattern. In a spiky flow curve pattern the resultant PI was high, with remarkable differences between the two flowmeters. However, with a smoother flow pattern the PI was low, and the two flowmeters produced similar values, demonstrating that the difference between the flowmeters becomes greater as PI increases (Fig. 2).

3.2. Assessment of PI under different filter settings

Typical changes in the flow pattern occurred under different filter settings. At low-filter setting, a smoother flow pattern appeared with no sharp flow spikes. By increasing the filter setting, a 'noisier' flow pattern appeared which produced higher PIs. Fig. 3 visualises the different flow curves at different filter settings with the MediStim VeriQ flowmeter, and in this case as well, the difference between filter settings becomes greater as PI increases.

4. Discussion

This study identified important differences between the two most frequently used TTFMs. Because of a lower filter setting, the Transonic flowmeter produced smoother flow curves than the MediStim, which influenced the calculation of the PIs. Specifically, PIs calculated by Transonic are lower than those calculated by MediStim.

Direct comparisons of flow and PI results of the same grafts by the two flowmeters provided evidence that the Transonic produced a lower PI than the MediStim, which was observed consistently during the testing of 19 grafts. Furthermore, PI differences between the two flowmeters seemed to be more pronounced at higher PI values, as shown in Fig. 1.

The next step in our analysis was to find out whether a lower PI was achieved by applying a lower filter setting, which produced smoother flow curves. We discovered that a constant increase in PI value occurred in concomitance with an increase in the filter setting, and that higher filter settings are characterised by a pronounced spiky pattern that determined very high maximum and low minimum peaks on the flow charts, resulting in increased PI values.

The PI is calculated automatically by the flowmeters. The MediStim flowmeter and the Transonic flowmeter measure the higher and lower peaks during a blood flow recording time of 2 and 8 s, respectively. Therefore, one would expect higher and lower peaks, resulting in higher PIs, to most likely be recorded by the Transonic flowmeter, rather than the MediStim because of its longer recording time. Interestingly, but still of unknown

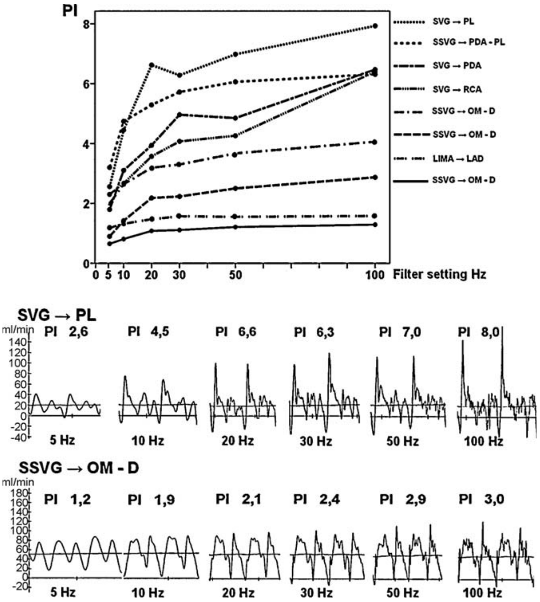

Fig. 3. The upper panel shows PI values of eight different grafts measured under various filter settings (5, 10, 20, 30, 50 and 100 Hz, respectively). The proportion of the changes depends on the level of the PI values. There are major changes between the filter levels when PI is high, minor changes when PI is low. The lower panels show two corresponding flow curves under increasing filter settings. The upper flow curves of a single saphenous vein graft (SVG) to the posterior-lateral branch (PL) present a greater increase in PI values due to higher filter settings. The lower flow curves of a sequential saphenous vein graft (SSVG) to obtuse marginal (OM) and diagonal (D) show a more moderate change in PI values due to lower filter settings. Increased filter settings lead to a spikier flow pattern, causing higher PIs. Lower filter setting results in a smoother flow pattern, and consequently a lower PI. PDA: posterior descending artery. RCA: right coronary artery.

reason, this was not the case since the Transonic produces systematically lower PIs due to its lower filter setting.

Similar outcomes, which document the differences between these two flowmeters, have only previously been published in an abstract.[1] Fifty-five grafts from 23 patients were assessed intra-operatively by both devices. On the one hand, a significantly higher PI of 2.7 was shown with the MediStim as compared with a PI of 2.2 by the Transonic. On the other hand, the differences in mean flow were also significant: it was 45.6 ml min^{-1} using the MediStim as compared with 62.1 ml min^{-1} with the Transonic. Unfortunately, the authors did not comment on these findings.

In vitro and *in vivo* comparisons of TTFMs have both shown a high accuracy and precision in regard to volumetric flow [1,3,20]. To the best of our knowledge, this variation in flow pattern as seen in different flowmeters has not been previously described, although it is highly relevant. The simultaneous comparison of the two flowmeters confirmed the differences seen clinically as presented in Table 1.

On clinical grounds, the difference in waveforms due to different filter settings may have important repercussions. The shape of the flow curve is an element which comes into play when assessing grafts that are difficult to interpret (low flows and high PI). In cases involving a failed anastomosis or a graft directed to coronary arteries with high peripheral vascular resistance, the waveform will present multiple spikes that will be higher than expected. On the one hand, a device equipped with a high filter setting will produce very spiky flow curves, making it difficult to evaluate the graft flow. On the other hand, a device with a low filter setting will smooth out most of the spikes, making the graft assessment appear to be better than it actually is.

Unfortunately, there are no clear cut-off values of mean flow and PI that allow surgeons to adequately establish the quality of a coronary graft. There has been much debate over the identification of these cut-off values, but so far, no general agreement has been reached due to the many variables involved in graft assessment [14,21,22]. The important issue of having separate cut-off values for different flowmeters has not been discussed. Therefore, based on the results of our investigation, it is important to refer to the type of flowmeter used when presenting flow values.

In conclusion, MediStim and Transonic TTFMs are not directly comparable because of their filter settings at 20 and 10 Hz, respectively. Different levels of filter settings in the flowmeters determine different shapes in the flow curves, which results in different PI values. In particular, more pronounced differences in PIs were noted when the PI was around 3. Thus, the type of flowmeter should always be reported together with the graft flows and PI.

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Corrigendum

Corrigendum to "Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery" [Eur. J. Cardiothorac. Surg. 37 (5) (2010) 1063–1067]

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The author regrets that an error appeared in the original version of this paper.

The Conclusions section of the abstract should read as follows:

Conclusions: The Transonic flowmeter displayed a lower PI than the MediStim, due to a lower filter setting. In the Transonic, flow signals are filtered at a lower level, rendering a 'smoother' pattern of flow curves. Because different filter settings determine different PIs, caution must be taken when flow values and flowmeters are compared. The type of flowmeter should be indicated whenever graft flow measurements and derived indexes are provided.

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131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.

135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.

164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
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168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
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185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.

194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.

219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS

247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS

275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
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291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY

300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2s IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON’S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
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