New approaches to monitoring of cardiac function

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“Science will always win.” - Fred Hassan, at the time chairman of the Board of Pharmacia, now Chairman of the Board and Chief Executive Officer of the Schering-Plough Corporation.

“I have never created a more fictional character than the researching ‘I’ in my doctorate /.../ a self that begins in pretended ignorance and then slowly arrives at knowledge, not at all in the fitful, chancy way I myself arrived at it, but step by step, proof by proof, according to the rules." - Sven Lindqvist, author and literature researcher.
Abstract

Left ventricular pumping performance may be described by intraventricular pressure and volume variables, usually presented as a pressure-volume plot. However, on-line monitoring of left ventricular pressure and volume with high temporal resolution requires the use of an invasive catheter technique such as, for example, the conductance catheter method. On the other hand, the very invasiveness and complexity of this approach makes it less suitable for clinical use. It is then not surprising that there has been long-felt need to make the conductance method less invasive and attempts have been made to adjust the method to clinical demands and routine in order to extract more information from pressure-volume interplay and possibly translate relevant data to their non-invasive estimates.

In the present studies, a standard five segmental conductance catheter was used in animal (pig) experiments. Segmental conductances were compared to global conductance. Since the mid-ventricular segment was shown to reflect global volume, which was also shown on theoretical basis, it was concluded that a single segmental catheter most probably could be used to estimate global left ventricular volume.

Subsequently, a thin and flexible single segmental conductance catheter was constructed and applied to an animal (pig) experimental model. Results were reproducible and very few arrhythmias were detected.

At the next stage, left ventricular isovolumic phases were investigated using the standard conductance catheter method, as well as echocardiographically derived tissue velocity doppler. Conductance was shown to decrease during isovolumic contraction, and an adjustment method was proposed in order to account for the subsequent decrease in pressure-volume loop area.

In separate experiments, the left ventricular pressure wave form during left ventricular systole was examined, and an algorithm was proposed to discriminate between the changes in afterload, preload and contractility. Results showed clearly discernible patterns of the respective load and contractility alternation.

Finally, the left ventricular continuous area was monitored continuously during the entire cardiac cycle as a measure of left ventricular volume dynamics in normal subjects and three patients with left ventricular abnormalities using echocardiographic automatic boundary detection. The left ventricular area thus obtained was plotted against its first derivative, to form a flow-volume estimates loop, in accordance with the flow-volume examinations used in respiratory physiology. Data obtained from the abnormal ventricles were presented as flow-volume estimates loops, exemplifying the possible use of the method.
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Abbreviations and terminology (most relevant)

*Much medical terminology is introduced and explained in the first paragraphs of the thesis.*

- **adrenalin**: hormone that e.g. increases heart rate and contractility
- **afterload**: load encountered by muscle during contraction
- **aorta**: main artery, leading blood from the left ventricle
- **arteriosclerosis**: calcification of artery
- **artery**: vessel leading blood from the heart
- **atrium**: chamber in the heart
- **AV**: atroioventricular
- **CAD**: coronary artery disease
- **CT**: computed tomography, 3D x-ray imaging
- **cardiac output**: blood volume pumped by the heart (per minute)
- **cardiomyopathy**: disease exclusively in heart muscle
- **CHF**: congestive heart failure
- **cardial**: relates to 'heart'
- **cardiovascular**: heart and vessels
- **conductance**: ability to lead current, opposite of electrical impedance
- **contractility**: contraction ability
- **coronary**: vessel supplying the heart with blood
- **diastole**: heart's relaxation phase
- **ECG**: electrocardiography, measuring electrical activity of the heart
- **echocardiography**: ultrasound measurement on the heart
- **EDPVR**: end-diastolic pressure-volume relationship
- **ejection fraction**: percent of ventricular volume ejected during one heart beat
- **ESPVR**: end-systolic pressure-volume relationship
- **EW**: external stroke work
- **gamma camera**: imaging technique using scintigraphy
- **hypertrophy**: abnormal growth
- **impedance**: alternating pressure divided by alternating flow
- **ischemia**: oxygen deficiency of local tissue
- **isometric**: with constant length
- **isovolumic**: with constant volume
- **mitral valve**: valve between left atrium and ventricle
- **MR**: magnetic resonance (imaging), 3D imaging technique
- **myocardium**: heart muscle
- **noradrenalin**: hormone that e.g. increases heart rate and contractility
- **papillary muscle**: situated in the ventricles, connected to atrioventricular valves
- **parallel conductance**: conductivity of tissues surrounding left ventricular blood volume
- **preload**: load encountered by muscle before contraction
- **PRSW**: preload recruitable stroke work
- **pulmonary**: relates to 'lung'
- **PV**: pressure-volume
- **PVA**: total energy, EW plus potential energy
- **SA**: sino-atrial
- **scintigraphy**: technique to detect radio-isotope decay
- **stroke volume**: ejected volume during one heart beat
- **systole**: heart's contraction phase
- **vein**: vessel leading blood to the heart
- **vena cava**: vein ending in the right atrium
- **ventricle**: chamber (in the heart)
List of publications

This thesis is based on the eight publications listed below, and will be referred to throughout this work by their roman number, respectively.


VII. E. Söderqvist, J. Hultman, G. Källner, J. Nowak and LÅ. Brodin. Assessment of acute load and contractility changes by left ventricular pressure measurements. Accepted 2006 for publication in Physiological Measurement.

VIII. E. Söderqvist, P. Cain, J. Nowak and LÅ. Brodin. Feasibility of creating estimates of left ventricular flow-volume dynamics using echocardiography Accepted 2006 for publication in Cardiovascular Ultrasound.
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Preface

In our days and in the western part of the world, cardiovascular disease is the most common cause of death. In EU, 39 % of all deaths are caused by cardiovascular disease, and in particular, 17 % of all deaths are caused by coronary heart disease. In Sweden, the figures are even greater - 47 and 22 %, respectively. (All data valid for 2004. Source: WHO.)

However, no one lives forever, and data above may not be too discouraging. It is remarkable, though, that people in productive age increasingly die from cardiovascular disease, which perhaps could be prevented. It is known, for example, that different behavioural factors, such as smoking, high blood pressure, and disturbed balance of blood fat, increase the risk of cardiovascular disease (Persson 2003). Anyhow, cardiovascular disease is common, and research in risk factors, pathophysiology, diagnosis, and therapy is getting even broader and deeper. In the following survey, a small number of cardiovascular research topics will be presented.

Firstly, the physiology and some pathophysiology of the heart, relevant for the thesis, is overviewed. Secondly, different cardiac monitoring techniques is presented. Pressure and volume measurements and analysis are in focus. Thirdly, the work is presented in terms of methods, results, discussion and conclusions.

The main focus of this thesis has been on the pumping performance of the left ventricle of the heart that pumps oxygenated blood to all the cells in the body. However, the obtained results may be applicable to the right ventricle as well.

The text is intended match a reader who is used to the research literature, but who is not familiar with medical terminology. Every such term is defined when first used. The presentation goes from a medical overview to a more detailed technological survey, and from prerequisites to conclusions. It also quite well follows the author's development and knowledge.

Huddinge 9th of November, 2006.
Aims

The pumping performance of the ventricles of the heart, both right and left, can be well described through continuous monitoring of the intraventricular pressure and volume. This type of monitoring is rarely used due to the invasiveness of the method and complexity of the procedure.

One problem regarding the presently used evaluations of the pumping ability of the heart, especially on the left side, is that they are mostly indirect, and hence that conclusions are drawn from estimates. Pressure values such as end-diastolic pressure and systolic pressure is estimated from the pulmonary artery and arterial systemic pressure, respectively. Volumes are even more complicated to estimate on-line.

The general aims have therefore been to both develop invasive measurement techniques that is harmless and accurate, and to develop other and hopefully better estimates of cardiac performance. Hence, the aims were can be summarized as:

- To develop a thin and less harmful pressure-volume catheter in order to monitor left ventricular performance
- To investigate if single segments of the conductance catheter accurately reflects acute volume changes
- To evaluate conductance data in order to determine the cause of and possibly adjust for isovolumic irregularities
- To evaluate volume and pressure data in order to extract more information, potentially useful also for non-invasive estimates of left ventricular function
- To evaluate echocardiographically obtained left ventricular continuous area, in order to improve the non-invasive detection of abnormalities in left ventricular function
(Patho-) Physiological background

Diseases influencing cardiac performance

Briefly, some frequently occurring heart diseases are presented here, with focus on cause, and effect on left ventricular performance:

- **Coronary artery disease**, CAD, develops in most cases as a result of coronary arteriosclerosis. Both predisposing heredity and factors such as age, smoking, diabetes mellitus, and disturbed lipid metabolism increase risk. CAD may lead to several different complications, such as angina pectoris, caused by constricted coronary arteries and insufficient blood supply to the heart muscle which becomes ischemic (i.e. not enough perfused and oxygenated). Myocardial infarction (heart attack) is another common complication. As the myocardium becomes hypoxic, the heart may fail to increase coronary blood flow to meet increased demands, and the characteristic pain in the chest and left arm might develop. In the chronic state, the heart might compensate through myocardial hypertrophy (myocardial growth), to increase its capacity.

- **Congestive heart failure**, CHF, is more of a symptom than a disease, and may have several different causes. CHF is therefore a state in which the heart (e.g. the left ventricle) is incapable of delivering enough blood volume (cardiac output) to meet the oxygen demands of the body. One of the causes might be myocardial infarction, with myocardial cell death and reduced pumping ability as a consequence.

- **Cardiomyopathy** is best characterised as a diffuse myocardial disease that is not attributable to pressure or volume overload, or to segmental loss of muscle function secondary to ischemic damage. The cause might be hereditary and the disease includes several subgroups such as, for example, hypertrophic cardiomyopathy, resulting in restricted diastolic filling and obstructed systolic ejection, or dilated cardiomyopathy with ventricular dilatation and impairment of systolic function.

The heart and the circulatory system

Deoxygenated blood returns through the veins to the right atrium, and flows further through the tricuspid valve into the right ventricle. It is subsequently ejected by the contraction of the right ventricle through the pulmonary valve into the pulmonary artery to be oxygenated in the lungs, in the capillaries surrounding the pulmonary alveoli. The oxygenated blood returns to the left atrium through pulmonary veins. As the mitral valve opens, the blood flows into the left ventricle and is subsequently ejected by the left ventricular contraction via the aortic valve into the aorta that branches into several arteries, arteriole, and capillaries, to supply oxygen to all cells. The cardiac valves permit only unidirectional blood flow, and prevent backflow.
Every heart beat is initiated by electrical pulses generated by specialized cells in the sino-atrial (SA) node, located in the upper part of the right atrium. The SA node-generated pulses spread through the atrial tissue causing atrial contraction, and then further down to the atrio-ventricular (AV) node and specialized conducting system in the ventricles, finally inducing ventricular contraction.

The left ventricle, basics
The contracting left ventricle supplies energy to the systemic vascular system by building up arterial pressure. As a consequence, the blood flows forward to the lower pressure compartment of the capillaries.

Since this flow normally requires a mean systemic arterial pressure of about 100 mmHg (13.3 kPa), the left ventricle, contracting at rates of 60 beats per minute at rest and increasing during exercise, is constantly exposed to high load and has to deliver enough work to overcome this load. Since about 100 ml is ejected with every beat, the required 'lifetime achievement' of the left ventricle can be calculated through multiplying pressure and volume, which expressed in Joules amounts closely to as many seconds as it has to work. This amount of work, 2500-3000 MJ, is almost equal to the work required to lift the Empire State Building one meter, or to lift an elephant from sea level up to Mount Everest peak 10 times. The power developed in the left ventricular contraction is about 2.5 W, since contraction time constitutes about 40% of the heart cycle.

The phases of the left ventricle
- **Ventricular systole:** After the electrical pulse has passed through the AV node at atrio-ventricular junction and spreads through intraventricular conducting system, the myocardium of the ventricle starts to contract. This results in a torsional (wringing) motion, accompanied by longitudinal shortening pulling the AV plane downwards towards the apex (Lundback 1986, Henein and Gibson 1999). The intracavital pressure rises and the mitral valve closes. Pressure rises until it exceeds aortic pressure - and ejection of blood into the aorta can start. Systole ends when the ventricle starts to relax. The pressure falls, and the aortic valve closes (backward flow mediated).

- **Ventricular diastole:** As the aortic valve closes, pressure in the relaxing ventricle continues to fall. When the left ventricular pressure falls below left atrial pressure, the mitral valve opens and filling from the atrium starts, accompanied by the recoil of the AV plane towards the base. Diastolic left ventricular filling is divided into two portions, rapid and slow, based on the rate of
change of ventricular volume with respect to time. The rapid filling phase is normally short, with a high filling rate, and ends when pressures in atrium and ventricle are equilibrated and slow filling ensues. Late in diastole the atrium contracts (atrial systole), and an additional small amount of blood pass into the ventricle, while the AV plane moves upwards towards the base of the heart.

- **Isovolumic or isovolumetric phases:** During short periods of time before and after the systolic ejection, both valves of the left ventricle are closed and no blood enters or leaves the ventricle. These periods are therefore called isovolumic phases: IVC for contraction and IVR for relaxation. Both are of diagnostic interest since the rates of pressure rise and fall, and changes in myocardial motion velocities during these phases may reflect myocardial ischemia. (Gibson et al. 1976).

**Left ventricular pressure, volume, and flow**

Left ventricular pressure and volume during one cardiac cycle are plotted in figure 1, to the left. The blood volume is decreasing (ejected into the aorta) during systole and increasing during diastole (flow from the left atrium). To the right, the first derivatives of pressure (dp/dt) and volume (dV/dt) are presented. Maximum dP/dt is sometimes used to estimate the contraction ability of the myocardium. dV/dt can be regarded as flow into and out from the left ventricle. This will be further explored below.

*Figure 1. To the left, pressure (P) and volume (V) are plotted against time. The pressure curve is dashed. To the right, the first derivatives, dP/dt (dashed) and dV/dt, of the data are presented.*
**Preload**

Preload on a single muscle is established by a force before the start of contraction, stretching the muscle to an initial length (Sonnenblick 1962a). For an intact heart, preload may be defined as left ventricular volume, since increasing volume stretches the myocardium, and thus the length of all the individual cardiac muscles. It has been shown that, to a certain extent, the longer the muscle, the more work can be performed by the muscle (Sonnenblick 1962a, Sonnenblick and Downing 1963). Hence, for an intact heart, the greater the volume in the ventricle at the onset of the contraction, the greater volume will be ejected (into the aorta). This is also known as Frank-Starling’s law (Frank 1895, Patterson et al. 1914).

Preload may change on a beat-to-beat basis as part of normal physiological variations, for example as a result of increased venous return when a person lies down. The increased preload will result in increased pumping ability of the left ventricle due to lengthening of muscle fibres, and the extra volume will be ejected.

On the other hand, in pathological situations, when the distensibility of the myocardium is decreased, preload may not increase sufficiently to match the needs of the tissues. For example, it has been shown that normal increase in sympathetic activity leading to increased contractility does not change the distensibility of the left ventricular myocardium (Sonnenblick et al. 1963), but ischemic heart disease does so. Through compensatory mechanisms, pathological decrease of distensibility will produce high end-diastolic pressures (Smiseth et al. 1991). In such situations, a normal increase in preload will result in a pathological increase in filling pressure, regulated to some extent by atrial contraction.

**Afterload**

Afterload is defined as the load on the single muscle when attempting to shorten. For an intact heart, afterload may be regarded as the resistance to shortening of the ventricular myocardium, and is encountered only during contraction (Sonnenblick and Downing 1963).

Sonnenblick et al. used mean aortic pressure as an estimate of afterload, but many other suggestions have been discussed, e.g. mean left ventricular pressure, peak left ventricular pressure and aortic input impedance (Noble 1979, Nichols and Pepine 1982, Piene and Myhre 1984).

Elzinga and Westerhof showed that the curve shape of left ventricular pressure changes in accordance to arterial impedance, which fact can be taken to imply that mean left ventricular pressure would be better measure of left ventricular load than peak pressure (Elzinga and Westerhof 1973, Noble 1979). Elzinga et al. used a mean value over a complete heart cycle, but a
more appropriate load characterisation would perhaps be the mean left ventricular pressure during ejection (Buoncristiani et al. 1973).

Taken together, afterload is somewhat difficult to estimate in the intact heart. A longer discussion will follow below.

**Contractility**

For a given preload and afterload of a muscle, contractility (or inotropy) may be defined as the ability to perform a certain amount of work given these premises. Contractility may be altered using pharmacological interventions, e.g. increased through infusion of noradrenalin. Contractility also changes with heart rate and nervous (sympathetic) stimulation.

In a myocardium with given preload and afterload, an increase in myocardial contractility will result in increase of the force developed by the muscle and increased velocity of contraction, but will also decrease the time of contraction (Sonnenblick 1962a). (In skeletal muscle, velocity of contraction is constant during physiological conditions.)

In the intact heart, contractility of the left ventricle is difficult to estimate. The maximum first derivative of pressure \((dP/dt)_{max}\), mostly timed within the contraction phase before opening of the aortic valve, i.e. during isovolumic contraction phase, is not affected by afterload unless aortic end-diastolic pressure is low (Mason 1969). It is, however, dependent on preload since increased preload and thus increased muscle length results in increased isometric contraction velocity (Sonnenblick 1962a, Siegel and Sonnenblick 1963). On the other hand, the maximum of the first derivative of force divided by integrated isometric force \((dT/IIT)_{max}\) should be constant (Siegel and Sonnenblick 1963). In that perspective, \((dP/dt/P)_{max}\) for the intact heart should be a better estimate; this quotient for isometric (i.e for the left ventricle: isovolumic) contraction has been shown to be almost independent of preload and afterload, but increases with heart rate, noradrenalin infusion and Ca^{2+} infusion (Siegel and Sonnenblick 1963, Mason et al. 1970, Mason et al. 1971). It should be noted that \(dP/dt\) and \(P\) should be timed within the isovolumic phase and be simultaneous.

However, Kass et al showed that the contractility indices \((dP/dt)_{max}\), \((dP/dt/P)_{max}\), and \((dP/dt)_{max}/V_{ed}\) (\(V_{ed}\) : end-diastolic volume) were all dependent on loading, although the two latter to a lesser degree (Kass et al. 1987).

Another index could be \((dP/dt/\int P)\), in concordance with the single muscle preparations mentioned above (the quotient \(dT/IIT\) being constant for constant contractility), and with intra- isovolumic limits as mentioned. Contractility indices will be further explored in sections of the pressure-volume measurements, below.
**Stroke volume and cardiac output**

The stroke volume (SV) of a normal man is about 100 ml; for a woman about 80. At rest, normal heart rate (HR) is 60 beats/min, giving a cardiac output (CO) of 4-7 litres/min. CO is regulated to be proportional to body demand of oxygen. During exercise, CO can increase to 25 litres/min, or more. CO increases or decreases mainly by changes in heart rate, although there may be present an SV regulation, too (Warner and Toronto 1960). A long term effect of exercise is an increase in SV and decrease in resting HR. Stroke volume is obviously affected by preload and contractility.

**Ejection fraction**

A commonly used measure of left ventricular performance is ejection fraction (EF), defined as stroke volume expressed as percentage of end-diastolic volume. Values above 50 % are considered to indicate normal systolic left ventricular function. (This implies that 50% of ventricular volume will not be ejected during systole and constitutes left ventricular residual volume.)

EF does not say anything about stroke volume, or cardiac output, or whether the heart ejects volume matching the systemic requirements of oxygenated blood or not, but it only implicates if the pump function is normal (Carabello 2003). EF may be calculated from ultrasound data/images.

In patients with diastolic heart failure as, for example, left ventricular hypertrophy, ejection fraction may be normal despite clear clinical signs and symptoms of diastolic heart failure (Zile et al. 2001). It seems that in these cases EF alone is not sufficiently good measure of left ventricular function, but other echocardiographic methods may be employed in order to confirm the diastolic dysfunction.

**Work of the left ventricle**

The work or power of the left ventricle depends on inotropic state of the cardiac muscle, its initial length and the afterload (Sonnenblick 1962b).

The experiments of Sonnenblick and Downing showed that for a given left ventricular preload and contractility, left ventricular work is primarily dependent on afterload (Sonnenblick and Downing 1963). These experiments, performed both on a single papillary muscle and on an intact feline heart, demonstrated that work performed by the left ventricle, or by the cardiac single muscle preparation, is a function of arterial blood pressure or afterload, whereas stroke volume is independent of arterial blood pressure (within physiological ranges). This implies that
in order to decrease left ventricular work load with sustained stroke volume and performance, arterial blood pressure has to be decreased.

**Coupling between the left ventricle and the arteries**

It should be emphasized that the left ventricle is a part of the circulatory system. Consequently, changes in either venous return or peripheral resistance or compliance will affect left ventricular performance.

For example, imagine yourself about to lift a very heavy stone. As you are preparing for this enormous task, your nervous system might signal to adrenal glands to infuse adrenalin into your circulatory system - in order to increase your muscle capacity. But as you take a big breath and finally lift the stone you discover that it is made of papier-mâché. Surprised by the lightness of the object, and your muscles already tense and in a lifting dynamic state, you will not be able to adjust the power of the muscles. Therefore the lift will be too fast and uncontrolled. You might even loose balance and fall backwards. Next time, however, you will probably not make the same mistake.

It should not be forgotten in this context, that for different people there exists a maximum weight of a real stone that is possible to lift, and probably also an ideal weight at which the stone can be lifted with speed and control.

In this example, in order to explain the muscular performance, it is necessary to describe not only the strength of the muscles or the tension before lifting, but also the shape and weight of the stone. The example thus illustrates the aspect of heart physiology regarding preload, afterload and contractility.

In order to explain left ventricular performance and function, it is necessary to include parts of the circulatory system coupled to the left ventricle and affecting its performance during diastole or systole.

**Arterial impedance**

It should be kept in mind that the arterial tree is more or less compliant to the pressure pulses. A mathematical model of the arterial tree using a three-element windkessel was proposed (Tozeren and Chien 1985), along with electrical equivalents (Piene 1984). Elzinga and Westerhof performed experiments on isolated feline hearts, in which the heart ejected into an arrangement of tubes that could be easily adjusted to desired resistance and compliance (Elzinga and Westerhof 1973). The results indicated that the arterial tree can be described by an input impedance (Noble et al. 1967), independent of the heart having its own internal impedance. In
other words, pressure waves and flow waves look different for the same heart working against arteries differing in either compliance or resistance.

Flow and pressure, and the arterial tree, may thus be described with electrical equivalents, i.e. current and voltage for flow and pressure, and resistance, capacitance and inductance for radius, compliance, and blood mass, respectively.

Further, if source impedance is calculated, i.e. mean left ventricular pressure divided by mean flow, a measure of pumping ability may be calculated. The pumping ability calculated in this way was shown to decrease during myocardial infarction (Elzinga and Westerhof 1976).

**Arterial pressure wave form and reflections**

Taking into account the results of research on afterload and arterial impedance, it is not possible to disregard the impact of the reflected pressure waves in the arterial system. Since the arterial input impedance has a frequency dependence, it also has a characteristic impedance. It has been shown that the characteristic impedance is the average of absolute impedance at frequencies > 2 Hz, and that oscillations around the characteristic impedance are due to reflections of the pressure (Noble 1979, Nichols et al. 1980).

The pressure wave propagates from the proximal aorta to the distal arteries with a pulse wave velocity of about 5 m/s. In the distal arteries, due to bifurcations and increased muscular content of the vessel walls, parts of the pulse wave are reflected. During physiological conditions, the returning wave returns to the ascending aorta during diastole, thus increasing diastolic pressure.

With age or high blood pressure, pulse wave velocity is increased due to increased stiffness of the central arteries (e.g. aorta) and the reflected waves coincide with the late phase of ventricular systole (Safar et al. 2003).

Reflections returning during ventricular systole, i.e. when the aortic valve is open, augment central aortic and left ventricular systolic pressure, but reduce central aortic diastolic pressure (Safar et al. 2003, O'Rourke and Pauca 2004). Such systolic augmentation has been shown to increase risk for coronary artery disease (Weber et al. 2004) and left ventricular hypertrophy (O'Rourke 2004).

The ascending aortic wave form can be deducted from pulse wave in the radial artery, using empirical mathematical equations (Soderstrom et al. 2002, Adji and O'Rourke 2004).

Recently, wave-intensity analysis has been applied to the investigation of arterial blood flow and pressure waves. The analysis can in a more precise way deduce origin and effect of any wave. Application of this technique to coronary blood flow has highlighted the importance of the diastolic decompression of the coronary microvasculature. This decompression is disturbed and
reduced in patients with left ventricular hypertrophy (Davies et al. 2006). A disadvantage of the method is its invasive nature of measurement, i.e. both instant pressure and flow must be measured intraarterially.

**Matching of left ventricular - aortic coupling**

Ross suggested in 1976 that there exists some form of matching between the left ventricle and arterial pressure, and that alterations in left ventricular function, e.g. acute heart failure, leads to some degree of mismatch (Ross 1976). One line of research made probable that the left ventricle normally performs at work optimum or power optimum, as a function of stroke volume (van den Horn et al. 1985, Myhre et al. 1986, van den Horn et al. 1986, Myhre et al. 1988, Toorop et al. 1988). A flaw of this concept is the fact that the authors cannot present any possible physiological regulatory mechanism.

Sunagawa and colleagues have suggested a model, based on end-systolic elastance, valid for the ventricle and corresponding elastance for the arterial tree (Sunagawa et al. 1984). Matching would then occur when slopes of these elastances are equal, transferring maximal energy from the ventricle to the arteries. However, this model does not take into account the time-varying properties of arterial elastance, which in fact has been shown to vary along with pressure (Berger and Li 1992).

Another study suggests that matching strives to adapt the system to optimal oxygen consumption (i.e. maximising of output power/oxygen consumption) by the left ventricle (Burkhoff and Sagawa 1986).

The outcome of this research is unclear, but the raised questions may have some clinical implications, for example, choice of therapy in the peri- and post-operative phases for thoracic surgery (Ross 1976).
Methods to measure and monitor left ventricular function

Overview

Apart from physical examination that include the important methodology of auscultation (i.e. listening with stethoscope), a number of more technically advanced methods are available to diagnose and differentiate heart diseases. ECG detects abnormalities in cardiac electrical activity; a number of x-ray type examinations (including computed tomography, CT) can be performed to detect coronary stenosis, hypertrophy, anatomical irregularities, etc. Using cardiac catheterisation, pressures and flows values can be obtained, whereas regional myocardial blood flow may be qualitatively determined using radio-isotope injection followed by scintigraphy using a gamma camera. The method of magnetic resonance (MR) has now quite high frame rate and may be used both to answer morphological questions and to measure flow and myocardial displacement (Persson 2003).

Below, two methods to measure left (or right) ventricular function are presented: pressure-volume measurements using a designated catheter, and cardiac ultrasound. A number of studies can be performed using these techniques. Pressure-volume measurements are invasive, and more often used in animal experiments as a reference method to evaluate, for example, ultrasound methodology.

Pressure and volume measurements

The pumping function of the cardiac ventricles can be described by simultaneously measured pressure and volume (figure 2). Pressure is plotted against volume to form a pressure-volume (PV) loop.

![Figure 2. Pressure and volume (PV) loop for one heart beat. Systole starts with a rapid pressure increase in the lower right hand corner. Blood ejection into the aorta starts between 80 and 90 mmHg.](image-url)
Pressure measurement

Pressure is measured using a transducer mounted on a catheter, positioned to measure the static part of the pressure, and hopefully not any kinetic components. Absolute pressure values of the left ventricle can only be obtained invasively. Some comments about bandwidth of fluid-filled pressure catheters and sampling frequency are made in the Discussion.

Volume measurements

Volume measurements of the left ventricle are far more difficult, since for most of the time, the valves (i.e. aortic and mitral valves) are open and the atrio-ventricular (AV) plane is moving. Hence, the volume of the left ventricle is not easy to define and measure.

Regarding spatial resolution, volume can be measured by, for example, ultrasound, magnetic resonance (MR) or computed tomography (CT), but the temporal resolution of these techniques is still not enough high for on-line monitoring. Furthermore, practical reasons limit their use in on-line, long-term measurements.

There are some other techniques, e.g. metallic radiopaque markers and sonomicrometry, but they are not used in clinical practice because of their invasiveness (Rankin et al. 1976, Vine et al. 1976).

Conductance

In 1981, Baan and co-workers presented a new volume measurement technique, which was based on conductance measurement (Baan et al. 1981, Baan et al. 1984). A weak alternating current (0.4 mA peak-to-peak, 20 kHz) between two electrodes induces an electrical field in the blood. The potential is measured by six sensing electrodes in between the two current electrodes. The six sensing electrodes thus form five segments, each one delivering a voltage output. Since the conductance of the blood itself is constant (neglecting long term changes in haematocrite) the measured voltage will be proportional to blood resistivity, and thus inversely proportional to the conductance or amount of blood between the sensing electrodes. The segmental conductances are then summed to reflect total cavity volume.

Baan and his colleagues proposed to use the method to measure blood volume in the left ventricle with the catheter positioned inside the ventricle, via the aortic valve.

Since then, improvements have been made in the calibration methods, in the positioning of the electrodes, and in electrical field characteristics (see below). However, the method is basically the same today as it was initially described.
Figure 3. The multi-electrode conductance catheter introduced by Baan et al.

- Calibration methods -

A calibration method for the conductance catheter has been proposed by Baan and his co-workers (Baan et al. 1981, Baan et al. 1984, Baan et al. 1989). The slope factor \( \alpha \) and parallel conductance \( G_p \) must be determined, and blood conductivity must be measured at least every half hour for long term studies, and after fluid injections. \( \alpha \) and \( G_p \) function as gain and offset, where \( \alpha \) is determined through a cardiac output measurement, and \( G_p \) through injection of a hypertonic bolus of saline. The bolus can be injected in the pulmonary artery, or if this is impossible, in vena cava inferior (Steendijk and Baan 2000).

In other words, the dynamic range of the conductance signal has to be multiplied with a calibration factor (\( \alpha \)) to reflect the amount of blood ejected into aorta per beat. Then, as parallel conductance is contributing with an offset to the volume signal, since current leaking out of the left ventricle will decrease the current density within the ventricle and thus decrease the measured voltage. This offset (\( G_p \)) has to be removed to allow the conductance signal to reflect 'true' volume.

Since the introduction of the conductance catheter, other calibration techniques have been described - particularly regarding the parallel conductance \( G_p \). Three different techniques are presented: 1) the dual frequency method, 2) development of the dilution technique, and 3) the volume reduction technique.

The dual frequency technique, described originally by Gawne et al. 1987, is based on the observation that surrounding structures have different frequency characteristics compared to blood: a dual frequency catheter system could then, in theory, automatically separate the two (blood from tissue), and thus calculate \( G_p \) (Gawne et al. 1987). This concept has been later
evaluated in another study that produced negative results (White et al. 1998). However, the method is still of interest in \( G_p \)-determination in mice (Feldman et al. 2000, Georgakopoulos and Kass 2000, Uemura et al. 2004). Theoretically, this technique is very elegant, since \( G_p \) can be estimated without any further manipulation that might be harmful to the patient.

The dilution technique still uses a bolus of hypertonic saline, but instead of extrapolating to the point where blood conductivity is zero, the area below the dilution curve is analysed (Kornet et al. 2000). In this way, a better reproducibility is achieved, and fewer injections are needed.

The third technique described is a development of a suction technique, where the left ventricle is emptied – the conductance thus measured is equal to \( G_p \) (Baan et al. 1984, Tachibana et al. 1997). The method is for understandable reasons not applicable in clinical use. Instead, the inflow of blood from vena cava inferior or superior is reduced, and the volume curve is extrapolated to zero (White et al. 2001), allowing calculation of \( G_p \). The procedure may save both time and decrease risk for the patient: since this is the same method to determine the slope of ESPVR (see below), \( G_p \) and ESPVR can be determined simultaneously.

- Calibration discussion -

The parallel conductance \( G_p \) has become thoroughly investigated, probably because of the difficulty to measure it accurately. For example, the saline bolus itself has been reported to effect the measured variable, as well as bolus temperature (Herrera et al. 1999). Other evaluated variables possibly affecting parallel conductance include lung insufflation, and left ventricular volume (Boltwood et al. 1989, Applegate et al. 1990, Szwarc et al. 1994, Szwarc and Ball 1998). Furthermore, different studies propose that \( G_p \) does or does not vary during the cardiac cycle, and that the slope factor \( \alpha \) varies during a heart beat (Lankford et al. 1990, Szwarc et al. 1995). The results of a recent study imply though, that \( G_p \) does indeed vary significantly during the cardiac cycle (Kornet et al. 2001).

In one early study, relative volumes were measured, but with a much lower frequency than otherwise used (McKay et al. 1984). These investigators suggested that, for current with lower frequencies, a bigger percent of the current will stay within the ventricle, due to the myocardium’s much higher impedance at lower frequencies (typically < 5kHz). These results are in favour of the dual frequency method.
**- Dual field catheters -**

Implicit in the volume calculation from conductance data, an assumption is made that the electrical field is homogeneous. Since this is not the case, especially in larger ventricles, a dual-field catheter was introduced (Steendijk et al. 1992, Steendijk et al. 1993). Proximal and distal to the existing pair of current electrodes, another electrode pair was positioned. These electrodes generate current with the same frequency, but with opposite polarity. The combination of two pairs of current electrodes was suggested to give a more homogenous field, and thus a more linear relation between true volume and volume estimate from the conductance method (Steendijk et al. 1992). This was reported to be generally true although results were not perfect, especially not for larger ventricles (Steendijk et al. 1993, Wu et al. 1997).

Regarding II and III, the small diameter of the catheter makes it impossible to add an extra pair of electrodes, and thus two extra cables inside the catheter. Hence, the dual field technique is not applicable.

**- Number of electrodes and electrode positions -**

Baan et al. introduced at first a catheter with 8 electrodes (which was later modified to include 10 or 12 electrodes), forming 5 measuring segments. However, during the 90s, studies have been carried out in mice, rats and rabbits using different types of single-segment conductance catheters (Abe et al. 1995, Georgakopoulos et al. 1998, Feldman et al. 2000). In these cases, only global volume was of interest since, for example, the analysis of PV-relations in mice are often done to relate gene products to phenotype (Feldman et al. 2000). Since a global decrease (or increase) of the heart function was expected, a single segment catheter was assumed to be sufficient to estimate left ventricular function in these settings.

In the studies mentioned here, the single segment was covering almost the entire length of the ventricle (long axis), which made it possible, at least in theory, to measure true volume. If, on the other hand, the segment is shorter than the ventricle, only the part of the volume in between the electrodes will be included. Thus, the measurement can not, even in theory, be anything else but an estimate of true left ventricular volume. Some related measurements and calculations are made in I and II.

To add to this discussion, Spinelli and Valentuzzi have performed theoretical studies on the 8-electrode conductance catheter (Spinelli and Valentuzzi 1986). They suggest that the most proximal current electrode should be positioned outside the aortic valve, and the closest measuring electrode should be positioned within the ventricle as far away as possible from the proximal current electrode. Thus, these electrode positions should constitute a compromise
between linearity (conductance to volume), and the volume not seen by the first measuring segment. A similar discussion can be made for the distal electrodes.

- **Conductance catheters in the clinic** -

Most studies using the conductance catheter are experimental and concern animal models. In the clinic, the conductance catheter is not used in daily routine, but constitutes an analytical tool for evaluation of different methods in cardiac surgery, effects of drug therapy, and so on (Caputo et al. 2000). A few studies will be mentioned here:

Only one year after introducing the conductance technique in 1981, Baan et al. reported on the use of this catheter in humans for measurements of relative volumes (i.e. without calibration) (Baan et al. 1982). Two years later, the same group introduced the technique for measurements of true volume, including calibration methods to determine the gain factor (α) and the parallel conductance (Gp) (Baan et al. 1984).

Kass et al. reported on the use of the same technique in humans, but the pressure-volume relationship was measured through inferior vena cava occlusion (Kass et al. 1988). More on this in sections below. Apart from a pressure-conductance catheter which was positioned in the left ventricle, an IVC (inferior vena cava) balloon occlusion catheter was introduced through a femoral vein.

The conductance derived pressure-volume loops were obtained in seven patients undergoing cardiac bypass surgery, implying that the catheter technique may be a useful tool for the estimation of left ventricular performance after by-pass surgery (Schreuder et al. 1991). Bishop et al. studied the conductance technique in the right ventricle (RV) and found the method applicable as well (Bishop et al. 1997a, Bishop et al. 1997b).

Another study showed no interference of conditions normally encountered during cardiac surgery (e.g. changes in heart rate, viscosity, temperature, salinity) on the conductance-measured volume (Al-Khalidi et al. 1998).

In all studies mentioned in this section, calibrations were done using of saline or glucose bolus injection for parallel conductance determination and thermodilution for α. Later on, new methods have been developed. See Calibration methods for details.

Differentiation between calibration with opened contra closed thorax are important, as the different pressure situations will affect both pressure and volume.
- **Some limitations of the conductance catheter technique** -

There are some limitations in the technique described above. For example, the calibration methods alone can not be used in patients suffering from aortic regurgitation (Dekker et al. 2002). In such cases, the amount of regurgitation has to be determined by another method. Some studies have, on theoretical grounds, pointed out some methodological problems, because some of the model concepts presupposed in the method are not true, e.g. left ventricular segments are not cylindrical in shape, electrical field is not homogenous, and the catheter is neither immobile during measurements nor positioned in the center of the left ventricle, etc. (Spinelli and Valentinuzzi 1986, Salo 1989, Woodard et al. 1989, Kun and Peura 1993). Unfortunately, most of the suggestions for corrections emanating from these studies have not been applied to experimental set-ups in vivo.

- **Concluding remarks on conductance volumetry** -

In the clinical situations, many causes of errors must be avoided and problems have to be solved. For example respiration, opened or closed chest, frequency (or dual frequency) choice, changes in blood resistivity, position and displacement of the catheter, and electrode positioning will all affect the conductance signal or the true volume itself. The quality and usefulness of the obtained data are probably correlated both to the applicability of the method (how user-friendly it could be), and to the risk for the patient.
Pressure and volume analysis
The pressure-volume (PV) loop was used for the first time for measurements of the output power in the age of steam engines. In medicine, the first man to apply the pressure-volume relations was Frank who measured these variables in frog hearts (Frank 1895). Due to misinterpretation of the data, these relations did not arouse any interest until more than half a century later, when Sarnoff (Sarnoff and Berglund 1954) popularised the use of the stroke work-preload relationship (Sagawa et al. 1988).

The PV-loop has some interesting features. First, its area is equal to performed work per heart beat. Second, for a heart with given contractility, a change in preload or afterload will change the appearance of the PV-loop, but the changes will not exceed the established limits of the end-systolic pressure-volume relationship, ESPVR, and the end-diastolic pressure-volume relationship, EDPVR (figure 4). These relations were first assumed to be independent of loading conditions (see Alternatives to ESPVR, below). However, ESPVR changes with contractility and may be used as a contractility index.

Third, the energy consumption of the heart is closely related to the PV-loop area plus the area representing the potential energy, i.e. area defined by ESPVR, the isovolumic relaxation period of the PV-loop, and a straight line from $V_0$ to $V_{ed}$ (Suga et al. 1981, Foex and Leone 1994).

Figure 4. PV-loop with principal end-systolic and end-diastolic relations.
Determination of ESPVR

The ESPVR can neither be determined from a single PV-loop, nor from a set of practically similar loops. This is because the intercept with the volume axis \( V_0 \) is not equal to zero. \( V_0 \) also changes with increasing or decreasing contractility, and with different kinds of heart diseases (Sagawa et al. 1988).

ESPVR must be determined from the upper left corner of the PV-loop, at end-systole. However, end-systole must then be defined. End-ejection would be intuitive to use, but another definition has been suggested: end-systole as the point of maximum elastance \( E_{\text{max}} = \frac{P}{V-V_0} \) (Sagawa et al. 1988). This point is in most cases close to end-ejection, but for some cases it is not. For example, in the case of low pulmonary resistance, the PV-loop measured in the right ventricle will have a pronounced rounded upper left “corner”. End-systole without the above mentioned definition of maximum elastance, will be hard to find.

Since \( V_0 \) is not known but necessary in order to calculate \( E_{\text{max}} \), an iterative algorithm is used. An accurate method to practically determine the slope of ESPVR and its intercept with the volume axis, seems to be to inflate a balloon in the vena cava inferior (i.e. to reduce preload), and thus decrease pressure in the left ventricle as much as 20 to 30 % within 6-8 beats (Kass et al. 1986). This makes it possible to determine the slope and intercept before the baroreceptors react and cause a sympathetic change in contractility (figure 5). Elevation of airway pressure in order to reduce preload has also been proposed (Haney et al. 2002).

![Diagram of PV-loop](image)

**Figure 5.** The vena cava inferior is occluded, which induces a volume decrease. The ESPVR can be calculated by linear regression. EDPVR can be determined through the same preload reduction manoeuvre, but must be fitted to an exponential function.
- External stroke work, pressure-volume area and energy consumption -

The energy imparted to the blood, i.e. external stroke work EW, equals the area of the PV-loop. The energy consumed by the heart during a cardiac cycle, excluding basal metabolism and calcium handling, is represented by the PV-loop area (EW) plus the area named potential energy in figure 6.

![Diagram of PVA = EW + Potential energy](image)

**Figure 6.** The potential energy defined as the area limited by the two straight lines and the left hand side of the PV-loop. The straight lines are calculated from the formula $E=P/(V-V_0)$, i.e. maximum and minimum elastance.

The sum of the areas, the systolic pressure-volume area (PVA), is thus closely related to myocardial oxygen consumption. A formula for use in dogs has been proposed (Sagawa et al. 1988):

$$VO_2 = 1.8 \times 10^{-5} \times PVA + 0.0018 \times E_{\text{max}} + 0.010 = A + B + C$$

where $VO_2$ denotes myocardial oxygen consumption, and $E_{\text{max}}$ is equal to the slope of ESPVR. The formula consists of three parts, where A is referring to actual tension and shortening of the myocardium, i.e. total mechanical work, B corresponds to increased energy needed for calcium handling at increased inotropy, and C constitutes the constant basal metabolism. Since energy consumption linked to calcium handling seems to increase with heart rate, a term D dependent on heart rate could be introduced (Kiyooka et al. 2002).

The quotient EW/PVA has been used in a clinical study in patients with remodelled left ventricle after myocardial infarction (Takaoka et al. 2002). Compared to a control group, EW/PVA decreased significantly.

The usefulness of this approach to the heart’s energetics is evident, but requires calibrated volume and pressure, and the determination of the ESPVR.
- Diagnosis using the PV-loop -

There are three main types (figure 7) of PV-loop alterations (Sagawa et al. 1988):

1) Increased workload as during elevated preload or afterload
2) Restriction to filling as during hypertrophy, increased tissue stiffness, pericardial restraints
3) Loss of contractility as during ischemic heart disease, metabolic, etc

The three alterations can also be mixed.

![Graphs of PV-loop alterations](image)

**Figure 7. Principal sketches of 1) elevated afterload, 2) constriction to filling, and 3) loss of contractility, respectively. The shaded lines denotes the normal situation.**

From these changes, the progress of the disease can be predicted, including mild and severe compensatory mechanism. For example, development of hypertrophy will increase contractility and thus increase the slope of the ESPVR, elevating the filling pressure and thus augmenting EDPVR.

- Alternatives to ESPVR -

It has been shown that ESPVR may be underestimated using the conductance catheter technique together with vena caval occlusion, due to alterations in parallel conductance (Applegate et al. 1990).

More disappointing, the ESPVR has been found to be non-linear and affected by loading conditions, which disqualifies ESPVR as an accurate measure of contractility (Baan et al. 1992).
Hence, it has been suggested that $V_{13}$ instead of $V_o$ should be used. $V_{13}$ is the intercept with a horizontal line in the PV-diagram at 13 kPa (about 100 mmHg).

In 1985, Glower proposed the concept of preload recruitable stroke work, PRSW (Glower et al. 1985), which is more linear, and more independent of preload and afterload, and therefore a better measure of contractility. PRSW is determined as ESPVR, i.e. through preload reduction, and is defined as the slope of the relation between end-diastolic volume (x-axis) and the external work (y-axis) of the following beat. PRSW is probably preferable to ESPVR regarding contractility.

Kass et al. proposed an empirical measure of contractility with non-invasive possibilities (Kass and Beyar 1991), defined as maximal instant power divided by the square of the preceding end-diastolic volume. This index has been evaluated and found to have non-invasive, clinical possibilities (Mandarino et al. 1998).
Ultrasound measurement of left ventricular function

Ultrasound is a non-invasive imaging technique using sound waves of 2-10 MHz, which are sent from an ultrasound transducer into the body, and are partly reflected at interfaces between tissues with different acoustic impedances. One transmitted pulse give rise to numerous reflections at different depths of the body. The returning reflected waves are registered by the same equipment, visualised and stored. About 100 pulses are required to create an image, and thus a 100 times the frame rate to achieve real-time moving images. Frame rate is number of images per second.

If the objects (e.g. the myocardium or the blood cells) are moving, the ultrasound pulse will change frequency when reflected. This frequency shift (i.e. the doppler shift) is proportional to the velocity of the object.

Since no absolute pressures can be measured by ultrasound, much effort has been made to validate estimates of left ventricular function.

Ultrasound investigations performed on the heart are summarized in the term 'echocardiography'. Below will be presented only a few types of echocardiographic procedures, relevant to this thesis.

- Ejection fraction -

Ejection fraction can be determined from 2-dimensional images, using assumptions of left ventricular geometry (Parisi et al. 1979), e.g. modified Simpson's rule for off-line determination of ejection fraction. This method was used in III and VII. The more echocardiographic projections (views) used, the better accuracy. A single-plane short-axis model was proposed for the best accuracy of on-line quantification of ejection fraction during transient events (Parisi et al. 1979).

- Continuous area measurement as estimate of volume -

During the last 15 years, it has been possible to automatically detect and measure the area of the left ventricle in each echocardiographic frame. Left ventricular area vs. time can be presented on-line as a curve, and data can be stored for off-line analysis. Area changes (short axis or apical 4 chamber view) have been shown to correlate well with changes in volume measured with the conductance catheter (Appleyard and Glantz 1990, Gorcsan et al. 1996, Chen et al. 1997, Schmidlin et al. 2000), or with other volume measures in controlled experiments (Appleyard and Glantz 1990, Aakhus et al. 1994, Oe et al. 1995). Regional myocardial dysfunction poses, however, limitations to the use of the method since linearity may be then violated (Appleyard and Glantz 1990). On the other hand, volume calculated from area using automated boundary detection seems to under-estimate true volume, the variability of the estimates being considerable (Weiss et al. 1983, Sapra et al. 1998). To summarize, it seems that measured area accurately
reflects volume changes, and that any conclusions about true volume should be done with care. This will be further discussed in connection with I, II and VIII.

- **3D measurement of volume** -

Intuitively, 3-dimensional echocardiographic data would be preferrable to 2-dimensional. On the other hand, the quantification of left ventricular function using this technique is so far less developed, i.e. no tissue or blood doppler data can be measured in 3D at present. Furthermore, most calculations have to be done off-line, which is sometimes too time consuming (Krenning et al. 2003, Monaghan 2006). Nevertheless, in some cases it might be superior. For example, determination of ejection fraction from 2D images is based on geometrical assumptions that may fail as, for example, in patients with left ventricular aneurysms (Monaghan 2006).

It is today possible to obtain 3D data with a frame rate of 25 images per second (and reported to increase), in only a few seconds measuring time. Accuracy and reproducibility in volume or ejection fraction determinations have been reported to increase compared to conventional 2D echocardiography (Monaghan 2006).

- **Myocardial velocities with tissue doppler (TVE)** -

It is possible to separate doppler shift originating from myocardial tissue and from blood, by use of low-pass filtering, since myocardial velocities are relatively low. The filtering is accompanied by delimitation of the reflections originating from the blood having relatively low amplitudes. Longitudinal velocities are more often measured, since they are uniform in direction (towards the base or the apex during diastole and systole, respectively), and easily obtained in the 4-chamber view.

The velocity in different discrete locations as, for example, in basal septum, can be determined for each frame. Hence, a velocity-time curve for the complete heart cycle can be obtained. It has been shown that post- and pre-ejectional as well as systolic velocities change in a predictable pattern during myocardial ischemia (Edvardsen et al. 2000, Jensen et al. 2001, Edvardsen et al. 2002). Disturbed relaxation has been shown to alter isovolumic relaxation velocities (Thomas et al. 1992). Longitudinal movement, i.e. the time integral of longitudinal velocity of the mitral annulus correlates (although non-linearly) to ejection fraction (Emilsson et al. 2000). Implications to VI.
- Frame rate requirement for TVE -

For the conductance catheter and modern pressure sensors, bandwidth and thus possible sampling rate is not an issue in physiological measurements.

However, in order to calculate a contractility index (Vogel et al. 2002, Vogel et al. 2003), the peak velocity during the isovolumic contraction phase (IVC) is required, and, given its short duration in time, it is necessary to use quite high sampling rates (frame rates).

To estimate the necessary frame rate, the first positive wave of IVC may be considered to increase and decrease linearly with maximum velocity in mid-IVC. The duration is set to 50 ms (Lind et al. 2004). In order to measure peak IVC velocities not less than 90% of true velocity, i.e. measured with very high frame rate, sampling must occur at least every 50 x 0.10 ms. That corresponds to a frame rate of 200 frames/s. Maximal error of 20 % thus corresponds to a frame rate of 100 frames/s. An empirically determined value of at least 100 frames/s has been suggested, with appreciation to noise inherent with high frame rates (Lind et al. 2002).
Methods

Ethical approval

I-VII All the animals received humane care in compliance with the European Convention on Animal Care. The studies were approved by the Ethics Committee for Animal Research at Karolinska Institutet, Stockholm, Sweden (I-II, VI), and the Ethics Committee for Animal Research, Uppsala (III, IV, V, VII).

VI, VII, VIII The studies were approved by the ethics committee at Karolinska Institutet - Huddinge University Hospital (VI, VIII), and Uppsala University (VII), and all the study subjects gave their informed consent to participate.

Experimental set-up (I-VII)
- Anaesthesia and surgical procedures -

Main characteristics are presented. For full details, see manuscripts.

Pigs with a body weight of I: 38-42 kg, n = 6; II: 38 to 43 kg, n=18, III: 30-33 kg, n=4; IV: 30-34 kg, n=5; V: 33-37 kg, n=7 kg, VI: 38-43 kg, n=6, VII: 30-40 kg, n=8, were premedicated with intramuscular ketamine hydrochloride (20 mg/kg) and atropine sulphate (0.5 mg). Anaesthesia was induced with intravenous sodium pentobarbital (15 mg/kg) and maintained with a cocktail (0.35 ml/kg/h) containing 2 mg fentanyl citrate, 25 mg midazolam and 24 mg pancuronium bromide in a volume of 57 ml. The infusion was preceded by a bolus of 0.15 ml/kg. (I, II, VI), or after an overnight fast, the pigs were premedicated with intramuscular azaperon 2-4 mg/kg. Anaesthesia was induced by intramuscular bolus of tiletamin/zolazepam 6 mg/kg, xylazin 2.2 mg/kg and atropin 0.04 mg/kg, and was maintained by a continuous infusion of clomethiazol 16 mg/kg/h (VII, ketamine 30 mg/kg/h), fentanyl 4µg/kg/h and pancuronium bromide 0.08 mg/kg/h (III, IV, V, VII: 0.3 mg/kg/h).

After meticulous hemostasis, 10000 IU of heparin sodium was given. Heparin infusion was repeated with 5000 IU every hour. (III, IV, V, VII).

The pigs were intubated and ventilated with a volume cycled ventilator (Engström 300, Datex-Engström AB, Bromma, Sweden). Blood gases were analysed and kept within normal limits. An electrocardiogram was recorded using surface electrodes.

At least 1 l Ringer’s acetate solution was given for fluid substitution during the experiment, more if signs of hypovolaemia were observed by visual inspection of the heart, or if arterial pressure fell. Catheters were inserted into the right femoral artery and vein for drug and fluid administration, blood sampling, and pressure monitoring. A Swan-Ganz catheter (Baxter Healthcare Corp., Santa Ana, CA, I, II, VI CritiCath SP5107-H, BD, Franklin Lakes, NJ, U.S.A.,
was placed in the pulmonary artery through the right external jugular vein for cardiac output measurements (I-VII) and injections of hypertonic saline solution for parallel conductance calibrations (I, II, VI, VII), or by EF measurements (III, IV, V, VII).

After a median sternotomy, the pericardium was opened (I, II, VI) or kept intact (III, IV, V, VII). A 5F transducer-tipped pressure catheter (Mikro-Tip, Millar Instruments Inc., Houston, TX, I, II, VI), or a guidewire-mounted pressure sensor, diameter 0.36 mm (Pressure Wire, Radi Medical Systems AB, Uppsala, Sweden) was inserted and was connected to a PWI-10 pressure wire interface (Radi Medical Systems AB, Uppsala, Sweden) (III see below, IV, V, VII). A 7F, 12-pole apex conductance catheter (Cordis Webster, Baldwin Park, CA) (I, II, IV, VI, VII) with 7 mm spacing between the electrodes was introduced into the left ventricle through a stab wound in the apex (I, II, VI), or introduced into the left carotid artery and advanced into the left ventricle (III see below, IV, V, VII). The tip of the conductance catheter was brought through the aortic valve (I, II, VI), but in IV and VII, the proximal electrode was kept outside the ventricle. Before taking each set of measurements, the exact position of the catheter was confirmed by inspecting the pressure and volume signals (I-VII), or by using ultrasound (III, IV, VII), see below.

In V, only a pressure catheter (Radi Medical, described above) was inserted from apex through the intact pericardium, into the left ventricle through a 1.0 mm peripheral venous catheter.

- Other equipment -

III - An intravascular ultrasonic probe (Acuson AcuNav), linked to Acuson Sequoia 512, was advanced through the right external jugular vein into the right ventricle for measurement of ejection fraction. EF was determined throughout the experiment. In addition, in collaboration with Radi Medical Systems, Uppsala Sweden, we designed a thin and soft conductance catheter. The diameter of the catheter was 0.36 mm, the same as that of an ordinary guide wire. The catheter has four electrodes placed accordingly to II. It was also equipped with a high bandwidth pressure sensor manufactured with Radi Medical’s Pressure Wire technology. An 8.5 F vascular introducer was advanced from the right carotid artery into the LV over a J-tipped guide wire. Passage into the LV was verified with pressure measurement in the vascular introducer. The 0.36 mm pressure-conductance catheter was placed through the introducer in the LV. The introducer was then withdrawn to the ascending aorta.

IV, VII - Ultrasound imaging was performed using the commercially available Vivid 7 (General Electrics Vingmed Sound, Horten, Norway) with a standard 2.5 MHz phased array transducer with a frame rate of 175±46 Hz. The transducer was placed directly onto the pericardium in an
apical position giving a 4-chamber view. Mitral and aortic valves were examined with doppler technique (IV). EF was determined throughout the experiments employing modified Simpson’s method.

- **Haemodynamic data** -
Haemodynamic data were acquired during disconnection of the ventilation in end-expiration to minimize the effects of intrathoracic pressure variations (I-VII). To decrease preload, the inferior vena cava was occluded (I-VII, not IV). To increase afterload, the descending thoracic aorta was clamped during a few beats (I, II, VI), or by infusion of phenylephrine (0.05-0.3 mg) (III, V, VII). Contractility was increased by infusion of adrenalin (10-20 µg) (V, VII).

- **Data acquisition** -
Sampling frequency was 200 to 250 Hz using an AD converting board (DAS-1601, Keithley Data Acquisition, Taunton, MA) (I, II, VI), or 400-1000 Hz using a data acquisition card inserted into a PC (NI DAQCard-6036E/1200 for PCMCIA, National Instruments, Austin, Tx) (III, IV, V, VII). The digitized signals were later treated with a low-pass filter with cut-off frequency of 100–125 Hz, depending on sampling frequency (I, II, VI).

- **Use of conductance catheter** -
The conductance catheter was connected to a Leycom Sigma-5-DF signalconditioner processor (CardioDynamics BV, Zoetermeer, The Netherlands) (I, II, IV, VI, VII). The volume signal was processed and stored (Conductance-PC software, CardioDynamics BV) (I, II, VI), or directly stored on the computer hard disk for later analysis (III, V, VII). The absolute total LV volume was reached by calibrating the signal for blood resistivity, for parallel conductance and for cardiac output measured by thermodilution. The cardiac output was measured by thermodilution 3–5 times for each determination.

- **Ischemia** -
An apical myocardial infarction was induced by ligating the left anterior descending coronary artery (LAD) immediately distal to the second diagonal branch (I).
Experimental protocol

After preparation, the animals were stabilized for 20-30 minutes (I-VII). Following calibrating procedures, haemodynamic data were acquired at baseline, or during changes in loading conditions or contractility, respectively. After 60 min of apical ischaemia, haemodynamic data were again acquired (I). Finally, the pig was given a lethal injection of pentobarbital and potassium (I-VII).

Measurements in humans

VI - Using ultrasound tissue doppler, 18 healthy men were studied. Longitudinal velocities were measured in the LV septum and lateral wall. Velocities were integrated to displacement, i.e. movement in LV wall.

VII - Measurements were done in a 60-year old man undergoing coronary bypass surgery shortly after acute myocardial infarction. After sternotomy, but before establishment of cardiopulmonary bypass circuit, a guide-wire mounted pressure sensor (Radi Medical as described above) was introduced into the left ventricle through one of the pulmonary veins and left atrium. The measurements were then performed during repeated gentle compressions of vena cava, during one measurement even accompanied by lowering of the legs (reduction of preload), and during repeated gentle compressions of the ascending part of the aorta (afterload increase).

VIII - The study population consisted of nine individuals (5 men and 4 women, 39±23 years old) without any signs of coronary artery disease and normal left ventricular function, and 3 patients (2 men, 84 and 50 years old, and 1 woman, 75 years old) with severe valvular abnormalities (aorta stenosis, aorta insufficiency, and mitral stenosis, respectively) for demonstration of potential pathological flow-volume loop morphology. All the study participants were subject to resting echocardiography. Individuals with poor image quality, complex atrial or ventricular arrhythmias, or previous revascularisation were excluded from the study.

Echocardiographic imaging was performed with the subjects in left lateral position using a commercially available system (Aloka PhD Prosound SSD 5500, Aloka, Tokyo, Japan). Images were obtained in the three standard apical views (four chamber, long axis, two chamber) using a standard 3MHz transducer. Two-dimensional gray scale images with real-time left ventricular endocardial detection were stored digitally for subsequent off-line analysis.

Using commercially available software (ASMA, Aloka, Tokyo, Japan), an ellipsoid region of interest (ROI) was defined so that the left ventricular endocardium could be encapsulated for the whole cardiac cycle while taking care to avoid inclusion of data external to the left ventricular cavity. The left ventricular endocardium was then automatically detected in real time for each
frame throughout the cardiac cycle (100 frames/s). The left ventricular cavity thus delineated was subsequently displayed 'filled in' with orange pixels. Using the quantitative features of the ASMA software the cardiac cycle volume characteristics based on this area of orange pixels was then obtained in graphical form for the whole of the left ventricle as well as for six regional segments of the ROI. These segments of ROI varied from the accepted standard of segmentation of the left ventricle (Henry et al. 1980) and, in particular, the regions of interest of the basal segments crossed the mitral valve plane in the apical views. The six segments did however allow separations of data into basal, mid-level, and apical regions. All images were stored as digital cineloops in DICOM format for reference of segment location while global and regional data characteristics were also exported in a hexadecimal numerical format to a standard PC for off-line data analysis.

Data analysis and calculations
All calculations, except in I and all statistical analysis, were made using Matlab (The MathWorks Inc, Natick, MA, U.S.A.) software.

In III, IV, and partly in VII, stroke volume (SV) was calculated from cardiac output divided by heart rate for which the volume signal was calibrated. The maximum of the volume curve was given by end-diastolic volume, calculated as stroke volume divided by ejection fraction. Ejection fraction was derived from ultrasound measurements.

-The respective studies -
I - End-diastole was defined as maximum global volume and end-systole as the point of maximum elastance, i.e. the maximal value of LV pressure/ LV global volume. Global stroke volume (SV) was calculated as end-diastolic minus end-systolic volume. A computer algorithm was constructed to compare the curve shape of segmental volumes with the curve shape of global volume. Global volume was obtained by summarizing the segmental volumes. In order to analyse the absolute difference between curve shapes of segmental versus global volume, segmental volumes were normalized to equalize the corresponding global volume 1:1 at global end-diastole and end-systole. For the calculation at baseline and during apical ischaemia, the mean of 10 beats was used. During vena cava and aortic occlusion the first beat in each acquisition was used as reference. Both the mean and peak differences are presented as percentages of global stroke volume.

II - A global volume curve was obtained by summing the inverted segmental voltages, as described. A potential profile was calculated for every sample of each measurement (figure 8),
giving a 3-dimensional matrix with time, position of the potential, and potential. The interpolation of the potential profile along the catheter length was done in 50 steps, i.e. each segment was divided into ten equidistant steps, which gave 50 intervals defined by 51 positions. The first virtual electrode (on the single-segmental catheter) was positioned at position 1, and the second at, for example position 11. Volume was then calculated at each sample using these positions of the electrodes, rendering a volume curve. The same was then made for each possible position of the virtual electrodes for that particular measurement. All volume curves calculated were then scaled twice, giving them the same mean, maximum and minimum value as the global volume curve, and were then compared to the global volume curve using a mean square error algorithm.

Figure 8. Interpolation of the electric field along the catheter at one single time sample position of the potential, and potential.

Each deviation calculation was summed and divided with the number of measurements, rendering a three-dimensional matrix with position of (virtual) electrode one, electrode two, and a mean volume deviation in percent for each pair of electrode positions. At the minimum volume deviation, the best electrode positions were found.

III - All data were analysed off-line, and each measurement was inspected visually. The conductance signals were upsampled with Lagrangian interpolation to 1 kHz and synchronised with the pressure and ECG signals. All signals were low pass filtered with a digital IIR 3-pole Butterworth low pass filter having a cut off frequency of 33 Hz.

IV - All conductance-derived volume derivatives were set to zero during IVCT and IVRT, with care taken to let volume changes be equal in both IVCT and IVRT. Volume derivatives were then integrated back to volume. The area of the pressure-volume loop was calculated, both with and without manipulated volume.

V - Maximum pressure, for all measurements, was determined with software instructions. This was controlled on a plot.
To determine the width of the systolic pressure complex, we chose a model where the pressure complex starts at \((\text{maximum pressure} - \text{minimum pressure})/2\), i.e. half of maximum pressure. This model has its advantages: it is easy to measure, no fluctuations of the pressure in the beginning of systole will interfere, and most important - it is otherwise very difficult to determine end-systole.

Time to reach maximum pressure was then calculated, and divided by the width of the systolic pressure complex, to obtain a relative value (presented as percent).

VI - The displacement curves were compared with the volume curves, measured with the Biometrics conductance catheter on pigs undergoing open-chest surgery with intact pericardium.

VII - Maximum \((P_{\text{max}})\) and minimum pressures \((P_{\text{min}})\) were determined automatically for every analyzed heartbeat. The minimum pressure \((P_{\text{min}})\) was defined as the lowest pressure value occurring during the diastole preceding the measured systolic complex. By subtracting \(P_{\text{min}}\) from \(P_{\text{max}}\) amplitude of maximal systolic pressure increase was obtained and, for each analysed systolic pressure complex, the algorithm then defined a time point corresponding to 0.7 of \(P_{\text{max}}\) amplitude corrected for the 0 mm Hg pressure level on the ascending and descending limb of the systolic pressure curve according to the formula \(\Delta P = 0.7(P_{\text{max}}-P_{\text{min}})+P_{\text{min}}\). A straight line was subsequently fitted to the part of the systolic pressure complex between these time points minimizing the mean square error.

**Figure 9.** Calculation of \(\Delta P/\Delta T\). A straight line is fitted to the systolic pressure complex during \(\Delta T\), i.e. the time period between the cut-off point corresponding to \(P_{\text{max}}\) amplitude scaled by the factor of 0.7 and corrected for 0 mm Hg pressure level at the ascending and descending limb of the systolic pressure curve. In this example, the fitted line has negative slope of magnitude \(\Delta P/\Delta T\). For comparison, the fitted lines corresponding to \(\Delta T\) defined by factors other than 0.7 \(P_{\text{max}}\) are also given.
The factor 0.7 was chosen empirically after analysis of several different types of systolic pressure curves in order to: a) maximize the inclusion of aortic valve opening time in the analysis, minimizing at the same time the influence of isovolumic contraction and relaxation (figure 9), and b) to make the algorithm robust and to render the greatest possible amplitudes of $\Delta P/\Delta T$.

Following the data analysis, the slope of the fitted line ($\Delta P/\Delta T$, mm Hg/s) was plotted versus $\Delta P_{\text{max}}$ using Matlab software with $\Delta P/\Delta T$ on the y-axis, and $\Delta P_{\text{max}}$ on the x-axis. The slope was designated negative when $P_{\text{max}}$ occurred early in systole whereas late systolic $P_{\text{max}}$ resulted in a positive slope. All the $\Delta P/\Delta T$ and $P_{\text{max}}$ values were normalized by subtraction of the respective baseline values and hence, the plots originated always at zero. For each baseline analysis including measurements on 5 – 10 heartbeats prior to each provocation only a single pair of $\Delta P/\Delta T$ and $P_{\text{max}}$ values representative of one heartbeat was utilized for normalization procedure. All heartbeats at baseline and during changes in loading conditions and contractility normalized in this way were graphically presented.

VIII - Hexadecimal numerical data (figure 10A) were converted to decimal format and imported to Matlab (Version 6.5, TheMathWorks Inc., Natick, MA, U.S.A.). The values were then adjusted by a calibrating factor exported from the ASMA acquisition software and expressed in cm$^2$. After low grade temporal filtering using polynomial fitting (Savitzky and Golay 1964), graphs of both global and segmental area versus time were established in each cardiac view (figure 10B). The area (estimate of left ventricular volume) was then plotted against its first derivative (area change - indicative of ventricular flow) to create loop plots for the whole ventricle and for each segment.

**Figure 10.** Derivation of the flow-volume estimates loop. (A) Hexadecimal area information are exported. (B) All values converted to decimal format are plotted as area (estimate of left ventricular volume) versus time. (C) The area ("volume") is the plotted against its first derivative (indicative of ventricular flow) to form the final flow-volume estimates loop.
called global and segmental (regional) estimates of flow-volume loops, respectively (figure 10C). The loops created in this way lack time scale and, instead, have the estimate of left ventricular volume (left ventricular 2-D area) as x-axis. Consequently, expressions pointing to early/late diastolic/systolic maximum flows mean in reality maximum flows at small/large left ventricular volumes, respectively.

**Statistical analysis**

I - Data are presented as medians (range) unless otherwise stated. The haemodynamic data at baseline and during ischaemia were compared using the Wilcoxon matched pairs test.

VII - Pairwise comparisons were performed using Student’s test for paired samples (two-tailed). The significance level was set at $p<0.05$.

VIII - All statistical analyses was performed using standard statistical software (SPSS version 11.01). Continuous data are presented as mean and standard deviation while categorical data are presented as frequency. Mean values for each variable were compared by independent t-test and ANOVA. Frequency analysis between categories was achieved with the $\chi^2$ test.
Results

Study I

Baseline stroke volume for segment 3 constituted 34 (14–39)% of global stroke volume, and for segment 4 29 (20–44)%. The baseline differences in curve shape between normalized segmental and global volume are presented in figure 11.

The mean absolute difference for segment 3 over a cardiac cycle was 4 (1–8)%. For this segment the peak difference in four of the six subjects never exceeded 9% of global stroke volume. However, in subjects 5 and 6 the peak differences for short periods in mid-systole were approximately 10% and 18%, respectively, and almost 30% in mid-early diastole.

- Apical myocardial ischaemia -

After 60 min of apical ischaemia, a marked dyskinesia appeared in the two most apical segments (1 and 2) represented by a greater difference between segmental and global volume (figure 11). However, this lack of agreement was not seen in the adjacent segment 3 where the mean absolute difference was in the range of 2–3% with no peak over 7%.

- Preload reduction -

With an end-systolic LV pressure declining to 60% of “preload”-baseline during occlusion of the vena cava, the mean absolute volume difference for segment number 3 was 3–7% in five of the six subjects. In subject 5 a mean difference of 39% was seen in early diastole, probably a result of dyskinesia caused by the decreasing LV volume.

- Afterload increase -

During occlusion of the descending aorta, only the “afterload”-baseline and two additional beats were analysed since LV end-systolic pressure had reached its maximum already within a few beats. The mean difference increased from 3 (2–10)% at “afterload”- baseline to 7 (3–12)% at the third beat. The peak difference, located to the “isovolumic relaxation period” was temporarily high in subjects 3–5.

- General observations -

During the heart cycle, short episodes of increased difference between segmental and global volume occurred. In two of the six subjects the difference occasionally peaked over 10% at baseline, in the same two subjects over 15% during vena cava occlusion and in three subjects the difference peaked over 20% during aortic occlusion.
Figure 11. The maximal absolute difference in curve shape between normalized segmental and global volume as a percentage of global stroke volume, calculated in individual subjects at baseline (n = 6) and after 60 min of apical ischemia (n = 5), at 5 time points in systole and 10 in diastole. Segment 5 is located at the heartbase, segment 3 at midventricular level and segment 1 at the apex. Subject no. 6 is marked (+), no. 5 (x), and nos. 1–4 (□).
Study II

Figure 12 shows a three-dimensional plot of the total mean deviation in percent per time sample per measurement, including all measurements (i.e. steady state, preload reduction, afterload increase, infarction), with position of the virtual electrodes on the x- and y-axis. As can be seen, half of the data is zero. This is due to the fact that in the calculations, electrode one was not allowed to be more proximal than electrode two. Had this been allowed, the calculations would have been made twice, resulting in a mirror of the existing plot.

![3D-plot of the deviation](image)

**Figure 12.** 3D-plot of the deviation. x1 and x2 are positions of electrode 1 and 2, respectively.

The 3D-plot has one minimum (deviation 0.05% per sample). This suggests that the best way to position the electrodes, in order to obtain a volume curve as similar as possible to one obtained with the 5-segmental catheter, is position 11 for (virtual) electrode 1, and position 51 for electrode 2. Thus, 4/5 of the whole length of the catheter should be used, disregarding the apical region.

Study III

The ultrasound images (figure 13, left) shows that the catheter was positioned along the myocardium. Movements in the myocardium may contribute to the notches in the volume curve, figure 14, right.

However, the method seems to be stable and delivers consistent and reproducible volume and pressure data from the individual animal.
Figure 13. To the left, an ultrasound image of the left ventricle with electrodes of the catheter marked with arrows. To the right, measured volume and ECG as functions of time.

Study IV

All P - dV/dt plots (figure 14, left) showed a non-zero flow signal during IVC and IVR. No pig had any but small physiological mitral regurgitation. There were small signs of aortic regurgitation due to the conductance catheter position through the aortic valve.

The area of the pressure-volume loop, using the calculated volume (figure 14, right), increased with on average 22% ranging from 12 to 43%.

Figure 14. To the left, a plot of left ventricular pressure and the first derivative of the volume (flow). Flow into the left ventricle is defined as positive. To the right: pressure plotted against volume with and without manipulated volume. The original data forms the smaller loop.
Study V
As shown in figure 15, the pressure curves originating from a single pig have different appearance, with early, mid-, or late peak values depending on loading state.
In figure 16, data from all subjects are shown in the (time-to-max/maximum pressure)-diagram. The different loading conditions and contractility are grouped in the plot. The reduced preload measurements have a tendency downwards to the left, and increased afterload a tendency upwards and to the right. The adrenalin infusion gives values down to the right. Three beats (a, b, c) are considered to be outliers. They originate from the same animal.

Figure 15. Baseline (top left), preload reduction (top right), afterload increase (bottom left), contractility increase (bottom right).

Figure 16. Relative time to maximum pressure vs. maximum pressure. Beats from the provocations are presented as reduced preload (▽), increased contractility(◊), increased afterload(□).
Study VI

The curves from the two types of measurements were similar, with almost identical appearance during IVC and IVR. In figure 17, four plots are shown - two originating from conductance measurements, and the other two from tissue doppler measurements. The left two plots show conductance (i.e. volume) and displacement versus time, respectively. In figure 17, to the right, conductance and displacement are plotted against their own first derivatives. The isovolumic phases are marked in all plots. Displacement in the septum was more pronounced than that in the lateral wall.

**Figure 17.** To the left: displacement from tissue doppler, and volume from conductance. Displacement towards apex is defined as negative. To the right: Displacement vs velocity (top), and conductance (volume) vs flow (dvolume/dt). Flow into the left ventricle is defined as positive.

Furthermore, figure 18 shows the same kind of plots from unpublished data. In the top frame, volume from conductance is plotted against flow, and in the bottom frame tissue displacement is plotted against velocity. In these measurements in pigs (same as in VII) conductance and tissue velocities were obtained simultaneously. All data points within the isovolumic phases are marked with black squares. As can be seen, isovolumic phases indicate opposite directions. Data are being evaluated.

**Figure 18.** See text for details.
Study VII

Typical beat-to-beat plots of end-diastolic and end-systolic volumes (EDV, ESV) for each intervention type are shown in figure 19. As can be seen, the respective left ventricular volumes changed significantly in a way that could be expected from the performed interventions, thus being indicative of expected changes in loading and contractility states. Examples of typical systolic pressure complexes are shown in figure 15, in Study V, above.

Figure 19. Typical end-diastolic (EDV) and end-systolic volumes (ESV) from conductance catheter measurements presented in a beat-to-beat plot for each intervention type (left to right): vena cava occlusion, phenylephrine injection, and adrenalin injection.

A slight decrease in heart rate occurred during preload reduction and afterload increase. On the other hand, administration of adrenalin caused, as expected, a substantial increase ($p<0.001$) in heart rate.

During vena cava occlusion (reduced preload), the lower peak systolic pressure occurring early in systole and followed by rapid pressure decrease produced negative $\Delta P/\Delta T$ values and their shift to the left lower square of the plot area (figure 20/a). On the other hand, the increased peak systolic pressure occurring during late systole after administration of phenylephrine (increased afterload) resulted in positive $\Delta P/\Delta T$ values that shifted to the right upper square of the plot (figure 20/b). The administration of adrenalin produced most often biphasic response. Initially, the increased early systolic peak pressure resulted in negative $\Delta P/\Delta T$ values at increasing $P_{\text{max}}$ values and hence shifted the plot to the right lower square (figure 20/c).

Subsequently, the form of the systolic curve changed and the $\Delta P/\Delta T$ values became increasingly less negative moving toward the right upper square of the plot as the peak systolic left ventricular pressure continued to increase (figure 20/c). In three of the animals (animals 3, 7, and 8), this biphasic response to adrenalin was preceded by increasing $\Delta P/\Delta T$ and $P_{\text{max}}$ for a brief period of time (3 to 11 heartbeats, i.e. not exceeding 7 seconds). This resulted in triphasic response pattern
with the first phase mimicking the pattern obtained during the phenylephrine-induced increase in afterload, i.e. the shift of the plot toward right upper square.

Figure 20. Individual $\Delta P/\Delta T$ versus $P_{max}$ plots for all the 8 experimental animals during different provocations. In response to preload reduction, the $\Delta P/\Delta T$ values shift to the left lower square of the plot (a) whereas during afterload increase the values shift to the right upper (b) and during increased contractility to the right lower square (c) of the plot.

The changes in $\Delta P/\Delta T$ and $P_{max}$ values during the very gentle manipulations of preload and afterload in the patient undergoing coronary bypass grafting were, accordingly, smaller than those observed in animals. However, the reaction pattern, as reflected by $\Delta P/\Delta T$ vs. $P_{max}$ plot, was fully consistent with the pattern found in animal experiments. The plot is shown in appendix VII.
Study VIII

- Echocardiographic data and feasibility -

All individuals in the normal group had normal resting ventricular wall motion. Of the 36 echocardiographic images available for acquisition in this group, 28 (75%) provided sufficient resolution to allow adequate automated endocardial border detection. The 4-chamber view was most favorable in this respect with all the images obtained in this view allowing adequate delineation of the left ventricular cavity whereas the percentage of qualitatively satisfactory images in the two other views was lesser (67% of the images in apical 2-chamber view and 55% of the images in apical long axis view, p=0.001). There were several reasons for exclusion of images from analysis, sub-optimal image quality being the most prominent factor. Another important reason was inability to obtain the region of interest closely enough to the shape of the left ventricular endocardium throughout the cardiac cycle which fact would result in underestimation of global and regional data and their contamination with extraneous signal components from outside the left ventricular cavity. An irregular RR-interval of the cardiac cycle and poor breath holding resulted in poor reproducibility of the flow-volume loops and the corresponding images were therefore excluded from the analysis as well.

- Estimated global and regional flow-volume curves -

Figure 21 provides a schematic diagram of an estimated global left ventricular flow-volume loop whereas typical estimated regional curves and a typical global flow-volume loop from a healthy individual are shown in figure 22.

As illustrated in figure 22A, the loop proceeds in clockwise direction with positive values for flow into the left ventricle during diastole and negative flow values for flow out of the ventricle during the systolic ejection. As could be expected, the loop indicates maximum left ventricular volume at end-diastole and minimum volume at end-systole. Besides the main systolic and diastolic cardiac events (systolic ejection, diastolic E- and A-waves) that are clearly identifiable within the estimated flow-volume loop, the systolic and diastolic isovolumic events can be identified as well. Estimated regional flow-volume loops were more complex in their forms in comparison to the global ones and there occurred differences in curve morphology between the loops from different left ventricular cavity segments (figure 22). As can be seen from figure 22, the regional loops tend to display, in general, somewhat more pronounced isovolumic changes in the septal segments (segments 4-6) then in the free wall segments (segments 1-3). In turn, estimated volume changes during rapid diastolic filling and systolic ejection appear to be more pronounced in the free wall segments.
Normal ranges of estimated global and regional flow-volume loop variables were determined, as well as examples of loops from patients with severe valvular abnormalities, see VIII.

**Figure 21.** (A) A schematic diagram of a left ventricular global flow-volume estimates loop. The flow-volume estimates loop proceeds in a clockwise direction. Minimum and maximum volumes are readily identified as well as maximum systolic and maximum diastolic flow. Isovolumic systolic and diastolic events are also identifiable. Integrals of the flow-volume estimates loop are also shown representing the (B) diastolic, (C) systolic, (D) early diastolic, and (E) early systolic volume changes.

**Figure 22.** Global and segmental left ventricular flow-volume estimates loops derived from image obtained in 4-chamber view obtained in four chamber view. Note the variation in the forms of segmental flow-volume estimates loops depending on segment location.
Summary of the results

The question addressed in I was how well a single mid-ventricular segment of the conductance catheter describes the curve shape of global left ventricular volume. Given certain assumptions and limitations, the conclusion was that it is possible to use a single-segment conductance catheter, or to echocardiographically measure the short-axis area at mid-ventricular level, in order to describe the dynamics of global left ventricular volume.

In II, calculations were presented how to position electrodes on a single-segment catheter, using conductance data from the five segment catheter. The conclusion was that the measuring segment should include most part of the left ventricle, except for the apical region.

As presented in III, a thin and flexible pressure-conductance catheter was constructed, with electrode positions as described in II, and was used in animal experiments. Both left ventricular volume and pressure could be measured with good reproducibility. Isovolumic events were more pronounced than was usually seen using the rigid five segmental catheter.

Left ventricular isovolumic events were investigated in IV and VI. Study VI presents the observation that the myocardial displacement and conductance signal have similar appearance, especially during the isovolumic phases, thus indicating a relation between geometry and conductance. Furthermore, as presented in IV, the first derivative of conductance, that can be seen as an estimate of flow, revealed non-zero values during the isovolumic phases, despite the fact that no regurgitation was present. It was suggested to use these findings to adjust the conductance signal during the isovolumic phases.

In V and VII, the systolic left ventricular pressure waveform was described. The first attempt, made in V, was to determine the part of systolic time to reach maximum pressure. Systole was defined as the width of the systolic pressure complex, at half of maximum pressure level. The results indicated that discrimination between different loading conditions and contractility could be achieved by analysis of the systolic pressure waveform, even if baseline values showed considerable variation.

This methodology was modified in VII, in which only the systolic pressure complex above 70% of the amplitude of the pressure signal was used in order to include most of the ejection phase and exclude most of all other phases. Through interpolation, a straight line was used to represent
that pressure interval. Using this approach, discrimination between the induced changes in contractility and loading conditions was possible, and baseline variation was considerably decreased.

In VIII, continuous left ventricular area was measured using automated border detection. The obtained area was subsequently employed as an estimate of left ventricular volume (as in I). The first derivative of the area, representing area change, was suggested to relate to blood flow. The measured area was plotted against its first derivative to form flow-volume estimates loops, and loops from three patients with valve abnormalities exemplified the possible applicability of such an approach.
Discussion

The most important starting point for this thesis has been the pressure-volume relationship in the left ventricle. From there, attempts have been made not only to measure but also to evaluate these variables in order to translate pressure-volume data into non-invasive equivalents. Hence, the presented work contains both technical and physiological contributions.

Conductance and volume (I, II, III)

Measurements of left ventricular volume are important in the evaluation of left ventricular function (Chuang et al. 2000). If true volume could be measured with high enough sampling frequency, variables such as, for example, ejection fraction, or end-diastolic volume or rate of filling could be easily calculated.

However, many methods used for measurements of left ventricular volume, such as contrast ventriculography (Vine et al. 1976), radioisotope imaging, magnetic resonance, 3D echocardiography (Aakhus et al. 1994) and computed tomography have disadvantages of being invasive, lacking of on-line data presentation facilities or demanding gated data sampling during several heart beats. Depending on the diagnostic requirements, each technique may however be sufficiently good.

As far as on-line, long-term measurements of left ventricular volume are concerned, some techniques have been presented and explored. The use of radiopaque metallic markers (Vine et al. 1976), sonomicrometry (Rankin et al. 1976), or the conductance catheter (Baan et al. 1981) will deliver on-line volume data, but unfortunately, they are all invasive and, in most cases, not suitable for clinical use.

Hence, the technical development should be focused on making the methods mentioned above less invasive, and on designing better on-line estimates of left ventricular volume. For example, left ventricular cross sectional area can be measured on-line, with high sampling frequency, using echocardiography.

In I, the aim was to evaluate the respective segments of the five segmental conductance catheter, in order to investigate the possibility to construct and use a single segment conductance catheter. It was shown that a mid-ventricular segment of the conductance catheter reflected global volume changes most accurately, even during induced apical ischemia.
Provided that the electrical field is homogeneous and parallel to the catheter, the measured conductance will reflect exactly the blood volume of the ventricle between the electrodes, excluding blood above and below these electrodes. Indeed, at mid-ventricular level, this has been shown to be the case (Steendijk et al. 1992). Furthermore, since in most cases the distance between the measuring electrodes is small, it is reasonable to assume that left ventricular short axis cross-sectional area measured echocardiographically at mid-ventricular level will reflect global volume much to the same extent as mid-ventricular conductance. This is in accordance with studies performed by Gorcsan, Moynihan and others (Parisi et al. 1979, Moynihan et al. 1980, Gorcsan et al. 1993).

It was also shown in I that the end-systolic and end-diastolic mid-ventricular segmental conductance changed proportionally to global conductance during the induced changes in loading conditions, although the difference between global and segmental curve shape during the heart cycle were not negligible.

The mid-segmental volume constituted as much as 30% of the global volume. It is therefore reasonable to assume that the single segmental conductance catheter can be used to estimate global left ventricular volume. However, the comparison between mid-ventricular segmental conductance and global conductance was consequently biased by a margin of 30 %, since no independent reference method was used. In addition, the assumption that segmental volume is comparable to short axis area is conditioned by the fact that this area represents only a thin mid-ventricular disc of considerably smaller volume.

For the reasons mentioned above, mid-ventricular segmental conductance could constitute an estimate of global volume dynamics, with the estimating strengths somewhere in between the strengths of total conductance derived from the five segmental conductance catheter, and echocardiographic short axis area measured at mid-ventricular level. Each method seems to have strengths and weaknesses, but all of them may be useful depending on experimental and diagnostic purpose.

Since the segments on the five segmental catheter are discrete and not changeable, an effort was made in II to optimise the positions of the measuring electrodes of a single segment catheter. Data from measurements using the the five segmental catheter during steady state as well as
during changes in loading conditions were included in the calculations, and as many measurements from as many different animals as possible were used. It was assumed that the obtained result would then be generally applicable to left ventricular conductance measurements. However, since every induced change in loading condition is preceded by a steady state phase, included in the measurement, a majority of steady state beats were included in the calculations. This might have slightly affected the result of the calculations.

On the other hand, the calculated electrode positions were used to ‘re-run’ the experiments. During these ‘re-runs’, no significant differences in curve shape, or any proportional differences in end-diastolic or end-systolic volume during provocations were found. This, together with the fact that the number of measurements and animals included in the calculations were considerable, supports our belief that our initial approach to the problem was sufficiently appropriate, even if it would be of advantage to validate the calculated positions of the electrodes on independent data.

The electrical field was calculated from segmental data using cubic interpolation, which approach simply seemed to be reasonable. Cubic interpolation is very smooth in space and this should also be the case for the electrical field in the left ventricle and surrounding tissue.

Since data from the commercially available five segmental catheter were used in this study, the calculations are valid for a single segment catheter having the same dimensions and mechanical properties as the catheter used. Furthermore, the calculations were made on data from a dual-field catheter. In order to experimentally verify the validity of the calculations, such a dual-field single segmental catheter should be constructed. However, this would be pointless, since the goal of constructing a single segment catheter would be both to maintain the quality of the volume measurements, and to reduce the number of electrodes and thus cables inside (and consequently the diameter), allowing the catheter to be soft and flexible and thus avoiding risk of damaging the valves or inducing arrhythmias. The calculated positions of the measuring electrodes may thus be seen as a starting point of further development.

As presented in III, a single segment conductance catheter, including a pressure transducer, was constructed inspired by calculations performed in II. The catheter was aimed to be very soft and thin, minimising thereby a possible interference with cardiac electrophysiology.
As discussed above, calculations from II are perhaps not quite valid for this type of flexible catheter. During the animal experiments, the catheter could only be positioned, as expected, along the myocardial septum and not in the center of the ventricle. Thus, it is likely that the electrical field induced in the intraventricular blood volume was considerably inhomogeneous. Furthermore, due to its flexible properties, the catheter probably moved or was bent during the cardiac cycle, which could have induced a heart cycle-varying electrical field and thus measurement artefacts.

For such a small diameter of a catheter (below 0.5 mm), the distance between the cables or leads become very small. Since currents of several kHz are used, there is capacitive coupling between the cables (i.e. microphony). During the construction phase, the level of microphony was tested, and was found to be acceptable in the frequency range of use (<50kHz). However, some noise would be inavoidable.

The problems discussed above were anticipated to occur. And yet, due to the difficulties and complexity of the conductance technique, a series of animal experiments had to be performed to test the properties of the catheter in reality. It must be stressed that not only the quality of the measurements were evaluated, but also the practical usefulness of the catheter from the surgeon’s point of view (user perspective), and in terms of interference with the cardiac electrophysiology (patient perspective).

The obtained results showed, as was expected, pronounced changes in conductance during the isovolumic phases, especially during the isovolumic contraction. This may have been caused by movement or bending of the catheter. However, the measurements were consistent within each animal in terms of curve shape and volume change during provocations, and very few arrhythmias were induced. The practical use of the catheter was also evaluated, revealing that the small diameter and flexibility of the catheter can make it somewhat difficult to handle before the insertion. However, this is of minor importance.

In III, no reference method was used. It would have been desirable to compare the results from the single segmental catheter with simultaneously measured data from commercially available five segmental conductance catheter. It is, however, not possible to measure conductance simultaneously, since the respective electrical fields will interfere with each other and the measurements would have to be performed anyway one at a time. Comparisons that may be of
interest are for example comparisons of curve shapes during the cardiac cycle, proportional changes during different provocations, parallel conductances, and estimated noise level.

The comparison between data obtained simultaneously with the commercially available five segmental catheter and the single segment catheter as suggested above has been performed subsequently in animal experiments by our group (Carlsson 2002). In terms of data quality (noise) and expected behaviour during provocations, the five segmental catheter may be preferable. On the other hand, data from the single segmental catheter showed that it delivers an expected volume curve appearance, regarding percentage of atrial contribution, and decreasing or increasing total volume during provocations. Cardiac function may thus be evaluated using a single segment catheter. Furthermore, the small diameter and flexibility of the single segmental catheter constitute properties that are clinically preferable.

**Area as volume estimate (VIII)**

In **VIII**, the feasibility of a non-invasive assessment of left ventricular flow-volume relationship throughout the cardiac cycle was explored using transthoracic echocardiography technique. Flow-volume measurement is well established as a clinical measure of lung function through its ability to demonstrate the dynamic nature of an underlying obstructive or restrictive process (Petty 1981). Although there are differences in the underlying dynamics, potentially, the same measure may be applied to the function of the left ventricle.

A flow-volume loop does not represent any known physical property as energy or such. Its advantage lies in its visual appearance. If cardiac flow-volume presentation of data shares the same features as for the respiratory case, obstructive and restrictive flow patterns will be revealed in the plot. A glance will be sufficient to differentiate healthy from diseased.

Flow will be greater in big than in small hearts and will also change along with the heart rate. This puts forward the need of normalising the data with respect to heart rate, body area, age, etc. On the other hand we do not know at this moment whether loops from big and small ventricles generally have the same features or not. It is therefore perhaps too early to normalise data, given the small amount of research in this field.

The reliability of presented methodology is based on certain assumptions. The assessment of changes of global left ventricular volume, described in **VIII**, was obtained by measuring left
ventricular 2-D areas in echocardiographic images and the measured 2-D areas were the same as those used for calculation of left ventricular volumes and ejection fraction with Simpson’s rule algorithm (Folland et al. 1979, Parisi et al. 1979, Moynihan et al. 1980). The Simpson's algorithm has been shown to perform sufficiently robustly in the clinical setting (Chuang et al. 2000) and the left ventricular area measurements have been shown to accurately reflect changes in the left ventricular volume measured with conductance volumetry (Gorcsan et al. 1993). Hence, the currently measured left ventricular area would constitute a reasonably good estimate of left ventricular volume dynamics.

It has to be emphasized that, in VIII, left ventricular volume was not calculated but, instead, time-dependent left ventricular area was measured and then employed to calculate its first derivative in order to obtain an estimate of time-dependent volume, i.e. flow. It has to be remembered, however, that area so measured may differ in its dynamic behavior (and then amplified in its first derivative) from corresponding volume data, although both data sets still reflecting the same underlying (patho-) physiological processes, as discussed in connection with I. Consequently, the area-based measures in this study are called flow-volume estimates.

A study in which employment of the concept of flow-volume loops onto 3D echocardiographic data is presently ongoing at our department.

**Volume curve artefacts (IV, VI)**

Estimates of left ventricular volume, either by the conductance catheter method or by echocardiographic area measurements, seem to reflect not only volume, but also changes in geometry. This can be seen with both methods during the isovolumic phases (Salisbury et al. 1965). As for the conductance catheter method, the measured conductance most often decreases during isovolumic contraction (although volume should be constant) and increases during isovolumic relaxation. It has been argued that these changes reflect true volume changes, caused by mitral and aortic valve insufficiencies. However, in IV, no insufficiencies were detected, at least not during the isovolumic contraction phase, since no mitral regurgitation was found by performing simultaneous ultrasound doppler measurements. Nevertheless, the conductance signal decreased during isovolumic contraction and, whatever the cause for this, the decrease must be seen as erroneous if interpreted as volume. In this case as well as for the conductance increase during isovolumic relaxation, an adjustment should be made independently of type of
measurement or provocation, and type of patient or animal, if an adjustment of the conductance signal is desirable.

In IV, we used the left ventricular pressure measured simultaneously with conductance, in order to determine the duration of the isovolumic phases. Subsequently, during these phases, conductance change (i.e. first derivative of conductance) was forced to zero. This type of modification is probably not accurate in the case of mitral or aortic regurgitation.

By performing such an adjustment, the curve shapes during systole and diastole are maintained. The obtained volume curve are thus very suitable to use in a flow-volume plot, as was discussed above, since only the conductance changes reflecting volume changes will be used.

On the other hand, when plotting the first derivative of conductance (~flow) against pressure (figure 14, Results), the isovolumic events are made clearly visible. If there is no isovolumic volume change, it must be another physiological process influencing the conductance measurement. Our guess is that conductance to some extent reflects the geometry of the left ventricle and the obtained data may be possibly used to quantify these events. This could be of clinical importance, for example in order to detect ischemia (Edvardsen et al. 2000, Jensen et al. 2001, Edvardsen et al. 2002).

During calculations, two major problems were encountered. Firstly, changes during the respective isovolumic changes were not equal. This resulted in a disturbed balance in estimated flow, i.e. for each heart beat, the flow into the ventricle was greater than the flow out from the ventricle and into the aorta. This was adjusted manually, but it needs to be handled if this type of adjustment is to be made automatically. Secondly, subsequent to this adjustment, all transitions, as for example the transition from isovolumic contraction phase to ejection phase, were somewhat abrupt, and thus not physiological. A softer transition can be achieved using some form of polynomial to interpolate the transition, with end slope values of zero for the isovolumic ‘side’ and the end-point derivative of the conductance signal at onset of ejection.

However, the isovolumic changes in conductance apparently result in the decrease of the area of the pressure volume loop and, consequently, also in the decrease of the estimated energy imparted to the blood. Our study also revealed that the extent of loop area decrease differs from animal to animal. The pressure-volume loop area may thus hypothetically depend on the position
of the catheter, the geometrical shape of the ventricle, the loading condition of the ventricle, or the contractility. Without any adjustment in order to account for isovolumic conductance changes, the loop area may be inaccurate.

If, and only if, the end-diastolic and the end-systolic volumes measured with the conductance catheter are correct, perhaps a simplified loop should be used for monitoring purposes (figure 23). Volumes previously mentioned should be used, together with minimum and mean ejection pressure.

In VI, which was mainly presented as an observation and an idea, the same kind of pattern in curve shape as in the conductance signal was seen in myocardial longitudinal displacement, echocardiographically measured using doppler velocity imaging. Displacement was calculated from the velocity signal. From this observation, it is natural to hypothesize that the geometry of the left ventricle is related to the conductance signal.

A limitation is that, apart from the different species (pigs-humans), measurements were performed in an open chest model (pigs), and in a normal clinical setting for the humans (apparently with closed chest).

Hence, considering Laplace’s law, an isovolumic increase in pressure should result in a more spheric shape of the ventricle (minimising energy). Consequently, conductance should increase. As presented in VI, longitudinal displacement towards the apex (increasing sphericity) and a simultaneous decrease in conductance are contradictory, in respect of geometry vs. displacement. Unpublished data reveals, however (figure 18, Results), that in an open chest animal model the directions of change in simultaneously measured myocardial longitudinal displacement and conductance are opposite and thus coherent regarding geometry assumptions.

**Systolic pressure wave form (V, VII)**

Given the impracticability of intraventricular simultaneous pressure and volume measurements, alternative ways to obtain the information about alterations in cardiac function have been explored, mostly by analyzing the influence of varying hemodynamics on central arterial pressure
wave form (Murgo et al. 1980) and by reconstruction of central arterial pressure curves from those recorded more peripherally (Adji and O'Rourke 2004, Gallagher et al. 2004). However, the approach is not optimal since central arterial and left ventricular pressure wave forms during systole are not identical due to different compliance compartments, Venturi effect and the occurrence of the reflected pulse waves (Noble 1979, Nichols and Pepine 1982). The influence of load and contractility on the left ventricular pressure wave form has, to our knowledge, not yet been studied systematically.

In a number of studies, however, changes in left ventricular curve shape accompanying load changes have been presented, even if not explicitly analysed (Elzinga and Westerhof 1973, Ishide et al. 1980, Piene and Myhre 1984, Ishide et al. 1985, Yaginuma et al. 1985, Myhre et al. 1986, Yaginuma et al. 1986). Pressure recordings from the right ventricle (Vogel 2003) also showed the same kind of changes in systolic pressure wave form induced by changes in loading conditions.

In the course of the animal experiments, performed to evaluate the conductance catheter, we noticed that the systolic pressure curve shape changed during changes both in loading conditions and in contractility. It was even so that during the measurements, the engineers behind the PC and thus having access to the continuous left ventricular pressure curve had better control over tendencies of subject hypovolemia than the surgeon. However, this observation needed to be quantified in some way.

In $V$, our first attempt in that direction was presented. The systolic pressure complex used was defined between time points corresponding to 50% of the pressure amplitude. Hence the data used in each beat covered an interval from about mid-isovolumic contraction phase to mid-isovolumic relaxation phase. The choice of 50% was made ad hoc, using intuitive sense of reasonable compromise between including as much of systole as possible, and always excluding diastolic events.

Since the choice of quantification of the systolic pressure complex was time to maximum pressure related to the width of the systolic complex (as defined above), at least baseline heart beats showed great variability in respect of the time-to-max parameter. This comes out of the fact that at baseline, the pressure is approximately constant during the ejection phase. In the worst cases, maximum pressure varied between early and late systole from beat to beat.
In VII, the approach was different. In order to decrease baseline variability and still discriminate between changed loading conditions and contractility, some other variable than time to maximum pressure, used in V, had to be considered. $P_{\text{max}}$ decreases with decreasing preload, but increases both with increasing contractility and afterload. Another variable used together with $P_{\text{max}}$ should then have some other behaviour, during inotropic and loading changes.

The well documented variables $(dP/dt)_{\text{max}}$ and $(dP/dt/P)_{\text{max}}$ are usually used as measures of contractility, but are more or less loading dependent (Kass et al. 1987). Furthermore, these variables do not reflect the curve shape.

As far as $(dP/dt)_{\text{max}}$ is concerned, the absolute maximal values for this variable are obtained during the isovolumic phases. Hence, both $(dP/dt)_{\text{max}}$ and $(dP/dt/P)_{\text{max}}$ are coupled to aortic impedance only in an indirect manner. Furthermore, $(dP/dt)_{\text{max}}$ values during provocations are to a considerable extent proportional to those of $P_{\text{max}}$ and, consequently, cannot be expected to provide any substantial additional information.

During ejection phase, the pressure waveform will in most (if not all) cases have its maximum and minimum $(dP/dt)$ values at the opening and closing of the aortic valve, respectively. These values are also proportional to $P_{\text{max}}$ as above.

If $dP/dt$ were measured, for example in the middle of the ejection phase, in order to evaluate the slope of the pressure curve during ejection, it might be sensitive to transient events that in some cases would be included in the measurements as, for example, the initial overshoot during adrenalin provocation. However, in many cases, the value of $dP/dt$ may be close to zero, although some transient early or late events still may take place during the ejection phase. More smoothing of the data will inevitably result in considerable loss of information.

Taking together, in order to account for early as well as for middle and late events during the ejection phase, a mean $dP/dt$ of the ejection phase should be calculated (using mean square error linear interpolation). This variable $(\Delta P/\Delta T)$ appears to be a good compromise between stability, acceptable signal-to-noise ratio, and sensitivity.

The present results may have several clinical implications since during various surgical procedures and especially during cardiac surgery, early detection and management of alterations in loading
conditions and contractility are of a great importance. The method described in VII may provide, for example, a sensitive tool for monitoring of intravascular volume since hypo- and hypervolemia will cause changes in pre- and afterload that will be reflected by clear-cut and opposite changes in $\Delta P/\Delta T$ versus $P_{\text{max}}$ plot. Consequently, an early detection of intra-operative bleeding or fluid retention would be made and the effects of appropriate action could be immediately evaluated.

Furthermore, adrenalin, owing to its positive chronotropic/inotropic effect and dose-dependent vasodilatation or vasoconstriction, is frequently used to counteract low-output state and shock that may occur in connection with various surgical procedures. The primary aim of such a pharmacological intervention is increased cardiac output. Since modern infusion devices allow precise titration of adrenalin doses adjusted to obtain a desirable effect, an enhancement of cardiac output without too strong energy consuming inotropic effect would thus be possible. With the use of the presented monitoring method, a negative shift of $\Delta P/\Delta T$ values accompanied by increased left ventricular pressure, i.e. the descending limb of the currently observed adrenalin-induced $\Delta P/\Delta T$ loop, would clearly indicate the occurrence of such an effect.

As can be seen in the results of VII, baseline values of $\Delta P/\Delta T$ were different from animal to animal, although all animals were young and healthy. This is likely due to inter-individual differences in baseline hemodynamics in terms of for example blood volume, combined with differences in contractility.

Thus, preload and afterload can be regarded as relative to the contractility of the myocardium. The straight line formed by the interventions of increased afterload and decreased preload (figure 24), may change in position (x-axis intercept). The slope could be interpreted as dynamic range and the intercept as a contractility measure. That means that a steeper slope will be due to a greater increase in $\Delta P/\Delta T$ (than is usually seen) for a given increase in maximum

![Figure 24. A parallel shift of data reflects contractility changes, and a change in the angle $\phi$ probably reflects the dynamic range (probably compliance) of the circulatory system.](image-url)
pressure. This example probably partly reflects an arterial tree with low compliance. An increased contractility will show as a parallel shift downwards and towards the right, thus moving the x-axis intercept to the right.

**Sampling frequency and bandwidth of the pressure signal**

It is probably always better to use a transducer and a measuring system with broad bandwidth, compared to one with a narrow one. However, the challenge is most often not to construct a new system, but to choose one that is sufficiently good for the measurement. It is also important to choose high enough sampling frequency for the measurement. Given that the pressure signal contains only low-frequency components, not exceeding 30 Hz (Nichols and O'Rourke 2005), and that the sampling frequency should be 3-4 times higher than bandwidth of the signal to be measured (Sigwart 1978), a sampling frequency of 120 Hz should be sufficient.

A system using a fluid-filled catheter for pressure measurement could in theory be used to measure the systolic curve shape. Such a system has high enough bandwidth, given that the catheter is accurately flushed, in order to decrease the number of micro-bubbles.

However, damping might be a big problem. If the system is under-damped, considerable oscillations will occur after the isovolumic contraction phase (at the onset of ejection) thus distorting the pressure signal. It is likely that these oscillations will increase with increased contractility. The $\Delta P/\Delta T$ value will then be more negative than otherwise. An over-damped system will show a too low pressure value at the onset of ejection. $\Delta P/\Delta T$ will thus be more positive than otherwise. Hence, it is recommended not to use such a system when monitoring left ventricular pressure curve shape.

**Monitoring of pressure and volume**

As a conclusion from experimental experiences gathered during the performed measurements preceding and leading to this thesis, the use of a simplified pressure-volume loop may be an applicable alternative for pressure and volume monitoring, as described in figure 25. Discrete pressure values from the end of the isovolumic relaxation phase and from end-diastole should

![Figure 25. A PV-loop using only using discrete values. Suggested for monitoring purposes.](image-url)
be used together with calculated pressure values at onset of ejection and at end-ejection, obtained from the interpolation of $\Delta P/\Delta T$ (in respect of time). The volumes or their estimates used to construct the simplified loop should only be end-systolic and end-diastolic.

On the other hand, the curve shape will then be hidden. As has been discussed, the volume curve shape, whatever the measuring method, reflects some known or unknown physiological events. Isovolumic changes may be quantified, and flow-volume loops may be constructed.

**Power in a pressure-volume context**

It has been shown, that velocity of contraction may be increased without any change in force, e.g. with heart rate (Sonnenblick 1962b). In this respect, pressure-volume loops hide the velocity component, since work per beat and thus area of the loop remain the same regardless of heart rate.

Calculations done for a MSc thesis at Division of Medical Engineering in collaboration with the author (Elmgren 2005), aimed to plot pressure and volume data divided by the square root of heart cycle time ($T$), respectively (figure 26 below). The area of the loop would then reflect the power of the heart cycle: $(P \times V)/\sqrt{\langle T \rangle}$, and change position and size with heart rate. Further, the loop would not change in shape compared to its pressure-volume equivalent. An evident drawback is that instant power is not measured, and that data itself does not reflect power. This concept could easily be combined with the suggestion given in the previous paragraph.

![Figure 26. To the left, PV-loops during infusion of adrenalin. To the right, the same measurement, but with axes scaled with $1/\sqrt{T}$, respectively. The area of the loops to the right thus reflecting mean developed power.](image-url)
Conclusions

A number of measurement techniques and data analyses and display modes have been evaluated. Results suggest that cardiac monitoring could be improved by the use of a thin, flexible single segmental conductance catheter and by automatically applying some of the results to standard measurement equipment.

- Mid-ventricular segmental conductance seems to be a good estimate of left ventricular volume, even during induced apical ischemia.

- With strategically positioned electrodes on a single segment conductance catheter it is theoretically possible to achieve the same performance as from the five segmental conductance catheter.

- A thin and flexible single segmental pressure-volume catheter produces reproducible data. The conductance changes as expected during changes in loading conditions.

- The conductance signal changes during the isovolumic phases, despite that left ventricular volume is constant. This observation can be applied to adjustment of the conductance curve shape.

- The curve shape of left ventricular pressure reflects changes in loading conditions and contractility. The curve shape can be described using a simple computerized algorithm and changes can be discriminated and categorized.

- Left ventricular area, continuously measured during the entire cardiac cycle using echocardiography with automated boundary detection, and its first derivative can be presented as a flow-volume estimates loop in order to potentially detect and visualize abnormalities of left ventricular function.
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