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Left ventricular function's relation to load, experimental studies in a porcine model.

Roman A'roch

Fakultetsopponent:
Professor Lars-Åke Brodin
Medicinsk teknik, Skolan för hälsa,
Kungliga Tekniska Högskolan, Stockholm

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perseverare autem diabolicum”
Seneca the younger

Dedicated to
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ABSTRACT

Background: Loading conditions are recognized to influence ventricular function according to the Starling relationship for length/stretch and force. Many modern echocardiographic parameters which have been announced as describing ventricular function and contractile status, may be confounded by uncontrolled and unmeasured load. These studies aimed to measure the relation between four different types of assessments of ventricular dysfunction and degrees of load. Study I examined the 'myocardial performance index' (MPI). Study II examined long axis segmental mechanical dyssynchrony. Study III examined tissue velocities, and Study IV examined ventricular twist. All studies aimed to describe the relation of these parameters both to load and to inotropic changes.

Methods: In anesthetized juvenile pigs, left ventricular (LV) pressure and volume were measured continuously and their relationship (LVPVR) was analysed. Preload alterations were brought about by inflation of a balloon tipped catheter in the inferior vena cava (IVCBO). Inotropic interventions were brought about by either an overdose of anesthetic (combine intravenous pentobarbital and inhaled isoflurane, Study I), or beta blocker and calcium channel blocker given in combination (Studies III and IV). In one study (II), global myocardial injury and dysfunction was induced by endotoxin infusion. MPI measurements were derived from LVPVR heart cycle intervals for isovolumic contraction and relaxation as well as ejection time. Long axis segmental dyssynchrony was derived by analysis for internal flow and time with segmental dyssynchronous segment volume change during systole, hourly before and during 3 hours of endotoxin infusion. Myocardial tissue velocities were measured during IVCBO at control, during positive and then later negative inotropic interventions. The same for apical and base circumferential rotational velocities by speckle tracking. Load markers (including end-diastolic volume) were identified for each beat, and the test parameters were analysed together with load for a relation. The test parameters were also tested during single apneic beats for a relation to inotropic interventions.

Results: MPI demonstrated a strong and linear relationship to both preload and after-load, and this was due to changes in ejection time, and not the isovolumic intervals. Long axis segmental dyssynchrony increased during each hour of endotoxin infusion and global myocardial injury. This dysynchrony parameter was independent of load when tested by IVCBO. Peak systolic velocities were strongly load-independent, though not in all the inotropic situations and by all measurement axes. Peak systolic strain was load-dependent, and not strongly related to inotropic conditions. Peak systolic LV twist and untwist were strongly load-dependent.

Conclusions: MPI is strongly load-dependent, and can vary widely in value for the same contractile status if myocardial load is varied. Mechanical dyssynchrony measures are load-independent in health and also in early global endotoxin myocardial injury and dysfunction. Peak systole velocities are a clinically robust parameter of LV regional and global performance under changing load, though peak systolic strain seems to be load-dependent. Left ventricular twist and untwist are load-dependent in this pig model.

Key words: heart function, preload, afterload, contractility, myocardial tissue velocity, speckle tracking

ORIGINAL PAPERS

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

I Michael Haney, Roman A'Roch, Göran Johansson, Jan Poelaert, Björn Biber
Beat-to-beat change in 'myocardial performance index' related to load.
Acta Anaesthesiol Scand 2007; 51: 545–552

II Roman A'roch, Paul Steendijk, Anders Oldner, Eddie Weitzberg, David Konrad, Göran Johansson and Michael Haney.
Left ventricular mechanical dyssynchrony is load independent at rest and during endotoxaemia in a porcine model.
Acta Physiol (Oxf). 2009 Aug;196(4):375-83.

III Roman A´roch, Ulf Gustafsson, Göran Johansson, Jan Poelaert, Michael Haney.
Strain and peak systolic velocities: relation to load in a porcine model.
Manuscript.

IV Roman A´roch, Ulf Gustafsson, Jan Poelaert, Göran Johansson, Michael Haney.
Left Ventricular Twist is load-dependent.
Manuscript.

CONTENTS

Abbreviations

2D Two dimensional
3D Three dimensional
ANOVA Analysis of variance
AS Aortic valve stenosis
AV Atriovenricular
CT Computer tomography
CO Cardiac output
CVP Central venous pressure
ECG Electrocardiogram
EDPVR End-diastolic pressure-volume relationship
EF Ejection fraction
ESPVR End-systolic pressure-volume relationship
IVCT Isovolumic contraction time
IVCBO Inferior vena cava balloon occlusion
IVRT Isovolumic relaxation time
LV Left ventricle
LVEDP Left ventricle end-diastolic pressure
LVESP Left ventricle end-systolic pressure
LVPVR Left ventricle pressure-volume relation
M-mode Motion mode
MAP Mean arterial pressure
MHz Mega Hertz
MPI Myocardial performance index (Tei index)
MR Mitral regurgitation
MRI Magnetic resonance imaging
ms millisecond
PRSW Preload recruitable stroke work
PSS Peak systolic strain
PSV Peak systolic velocities
RV Right ventricle
TDI Tissue Doppler imaging
TTE Transthoracic echocardiography
TVE Tissue velocity imaging echocardiography
SV Stroke volume
SW Stroke work
US Ultrasound
ε strain

Preface

One can wonder…. Why would I, an anesthesiologist/intensivist, get interested in heart function, and then that this interest would result in this thesis? Being from the start a "clinician", I approached cardiovascular instability/insufficiency with the tools commonly available at the bedside, including arterial pressure, central venous pressure, pulmonary artery catheter, and other signs of hypo perfusion. With advances in technology and widespread use of echocardiography outside the cardiology and clinical physiology suites in late 1980's and early 1990's, I also was introduced to examination and quantification of heart function with ultrasound by my friend and tutor Michael Haney. And, as a clinician, one was sincerely happy to "see" changes in heart function using these methods, which showed things that one could only infer before. I started enthusiastically using echocardiography to try to provide better care for my patients.

After encountering patients with valvular disease, including aortic stenosis (AS) or mitral insufficiency (MR) or as well septic patients, I realised that not all that one sees is easy to interpret. How good is ejection fraction (EF), the most commonly used echocardiographic index of heart function, for quantifying myocardial function? The heart seems to be depressed in patients with AS, using the EF as a measure of contractile status, but after a valve replacement operation the EF is markedly improving without any inotropic stimulation. Or, in severe septic shock, heart function assessed with EF is seemingly within normal limits at the same time that the arterial blood pressure is very low. One raises the blood pressure to normal levels to preserve perfusion in vital organs, and suddenly EF is showing very low values. These are examples of load-mismatching. Did contractile status change or is EF just a relatively nonspecific index of ventricular contractile status? To find out how changing load mirrors ventricular performance and contractile status, I turned to experimental conditions.

Umeå, the 15th of April, 2011

Vålådalen, 2005: a research conference and an impressive spring-summer storm, at the start of my research education

INTRODUCTION

The Clinical Issue

When patient has an acute illness which leads to circulatory insufficiency, clinicians will intervene quickly, and support the inadequate circulation. A common problem is that it is often not clear, from just simple measures of heart rate and blood pressure (and general clinical status), which parts of the circulation are not functioning adequately. It may be difficult, using just general circulatory parameters, to understand if the heart is functioning adequately or not.

Since a rapid and sure assessment of heart function (or vascular function) is not always readily available at the bedside for patients with acute circulatory insufficiency, clinicians are sometimes forced to make an 'educated guess' about where the problem lies, and treat/support the circulation aggressively, sometimes even with potent drug therapy. Possible treatments of acute circulatory insufficiency could be diuretics or intravascular fluids, or vasopressor or vasodilators, inotropes or beta-blockers. Since the choices are often completely opposed to each other in effect, it is paramount to have as much good information about the pathophysiology of the patient as possible, when instituting therapy. A well-meaning but wrong guess could be detrimental to patient's well-being.

The ideal bedside diagnostic test for heart function would be relatively or completely non-invasive, very reproducible, applicable in all patients regardless of patient age or body configuration, specific and sensitive in detecting changes in heart effects concerning the circulation, etc.

The circulatory system includes the heart, but also all the blood vessels. It is unlikely that a diagnostic system will be soon available which can simultaneously evaluate the function of the heart and all blood vessels at the same time. In this thesis, I have focused on assessment of heart function. I have tried to evaluate some promising bedside methods for assessing heart function, and have combined different methods (reference methods) to help to assess several common echocardiographic parameters that have recently been introduced to clinical practice. I wanted to test some aspects of the validity of these methods, since I hope that they will become more commonplace and readily accessible in clinical practice.

The practical question that is the basis for this whole thesis is the following: if I get 2 different values from 2 different measurements of a certain echocardiographic measure of heart function in the same patient, a measure that supposedly reflects ventricular function, does this mean that ventricular function has changed?

Clinical settings

While my clinical background and interest in acute circulatory insufficiency has to do with critical care or perioperative patients, this is also an issue in for other patient groups, and in particular patients with acute or chronic heart disease. The clinical setting for the acute and serial assessment of heart function whenever there is consideration for treating the patient with inotropic or vasoactive agents, whether this is acute or chronic. In the perioperative setting, where patients are systematically exposed to fasting, and sometimes large amounts of perioperative blood loss or tissue edema related to their surgical illness, there is a common pattern of threatened circulatory insufficiency if the patient is subjected to rapid reduction in their blood volume (or 'fluid shifts', in perioperative slang). This means that perioperative physicians are alert and prepared to provide aggressive intravascular volume expansion if hypovolemic or hemorrhagic shock is threatened. The situation in the ICU is commonly more multifaceted, as far as the different factors which contribute to circulatory insufficiency. While hypovolemic shock occurs, a more common patient scenario is where there is a critical illness-related impairment of vascular function which leads to a relatively inadequate venous return to the heart. Heart function can be negatively affected by the same systemic critical illness, but the heart has reserves which also can be awakened to increase heart function. A patient can be very hypotensive, in shock, though with extremely good heart function. Another patient can have normal blood pressure, but have dangerously impaired heart function. Therefore, clinicians need a readily available and rapid means to evaluate heart function at the bedside. And, if potent medications which affect the heart are contemplated, then there needs to be a quantitative assessment of heart function to confirm the need, and serial measures of heart function to confirm effects of the drug intervention. We need to limit exposure of patients to potent drug therapy and possible harmful side effects where the drugs are not indicated or likely to provide benefit. Too often, this type of vasoactive or inotropic intervention is performed empirically, that is, without the support of any quantitative assessment of heart function. This practice needs to be improved in the future, I hope by systematic introduction of echocardiographic parameters which are strongly indicative of myocardial function.

This type of reliable serial assessment of ventricular function is needed as well for some patient groups with chronic diagnoses, including chronic heart failure. Heart failure, where the heart becomes dilated, or has significant regional dysfunction, has an aspect of ventricular dyssynchrony. A portion of this thesis concerns quantification of local or regional dyssynchrony.

Heart anatomy and pump function

Simplistically, the heart is a muscular servo pump connected to pulmonary and systemic vascular systems. The principal job of the heart and vasculature is to

maintain an adequate flow of blood, oxygen and metabolic substrates to all of the tissues of entire body, under a wide range of conditions. From an operational point of view, adequate cardiac function can be defined as the ability of the heart to be filled (from venous return) at a low enough pressure not to cause pulmonary congestion, and then deliver a sufficient quantity of blood to the vasculature at a high enough pressure to perfuse the tissue. The heart needs to have sufficient performance reserves to be able to increase its work and effect during exercise and higher demand (1).

The heart as a muscular pump consists of two functionally separate, but at the same time intimately interwoven halves, the left and right sides. The right heart ejects blood into a low pressure system (the pulmonary vasculature, low pressure in health), and the left heart pumps into a high pressure system (2). Though my research questions are relevant for the right heart as well, I have focused my experiments first on the left ventricle.

The human left ventricle is a truncated ellipsoid with a normal wall thickness in adults of approximately 10 mm. The structure is constructed from billions of cardiomyocytes (cardiac muscle cells) which are connected to each other in a highly organized manner. It is well known that transmural distribution of muscle fibres of the left ventricle vary in orientation, and this is with a purpose. The left ventricular (LV) twist, or the wringing motion of the heart, is a key element for regulating LV systolic and diastolic heart mechanics (3,4). Geometry of the myofibres changes smoothly from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium. The complex spiral orientation of myofibres finally produces ventricular deformation in three dimensions. LV twist generates positive torsional deformation forces developing in the subepicardium, added to the negative torsional deformation forces originating in the subendocardium. As the forces in subepicardium act on larger lever arms, the resulting motion is counter-clockwise LV twist viewed from the apex toward the base developing during ejection.

The systolic torsional deformation is also important for the accumulation of potential energy in titin and collagen matrix. Near the end of systole, largely during the period of isovolumic relaxation, the rapid reversal of twist motion leads to clockwise recoil of twist or untwisting. This release of restoring forces accumulated during systole, is thought to contribute to diastolic suction, which probably facilitates early diastolic filling (5). This issue of the relevance of ventricular suction has been the subject of much debate:

> "*Whatever role cardiac suction of venous blood may play in determining circulatory dynamics, no one can deny that mention of this term (diastolic suction) has proven a most effective method of raising blood pressure in several generations of cardiovascular physiologists*" (6) (Figure 1).

This sophisticated structure can translate 10-14% decrease in myocyte length to 40% thickening of the LV wall (7) finally resulting in chamber performance of 50-60% in ejection fraction.

The right ventricle (RV) is an approximately crescent shaped structure formed by a roughly 4 mm thick sheet of myocardial fibres which collectively are referred to as the right ventricle free wall. This right ventricular free wall interdigitates anteriorly and posteriorly with LV muscle fibres. The right ventricle is "wrapped around" the LV, and so the LV and RV share a common wall, the interventricular septum. Left ventricular function, through its own force generation during systole, supports RV contraction via "belt action" (8). A pair of valves between atria and ventricular chambers (tricuspid and mitral), and then the ventricular chambers and vascular systems (pulmonic and aortic), prevent backflow.

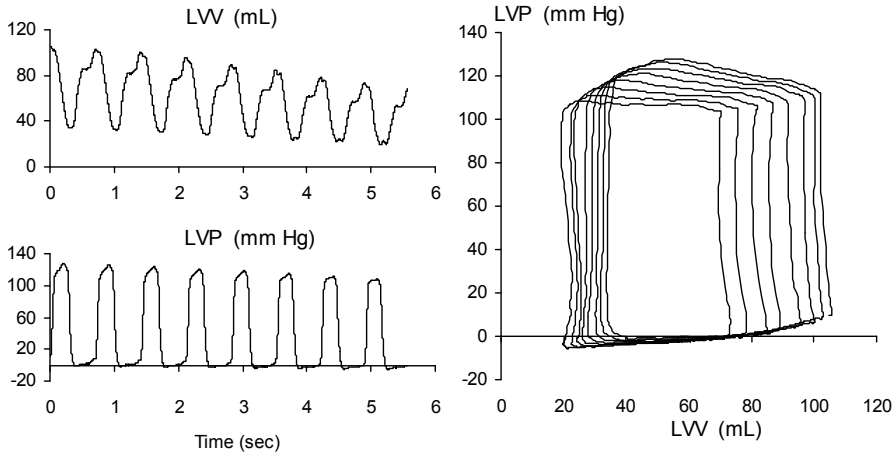


Figure 1. Preload reduction under vena cava occlusion with generation of negative early diastolic pressure is depicted. Eight beats are shown, with progressive load reduction and progressively more negative early diastolic pressure.

Physiological background (heart function)

Historical

The concept of the heart as a muscular pump evolved from physiological experiments with muscle bands from as early as the 18th century. Transition from these rather simplistic, but very illustrative ideas led to the concepts of the independent role of preload, contractility and afterload in muscle bands. This in turn developed into a paradigm of complex overlapping effects of load and contractile function in left ventricle chamber. Beyond this, there became recognition of ventricular interactions and interactions with vascular and

respiratory systems. This complexity makes determination of heart pump function challenging. Nevertheless the concepts are necessary in order to isolate the heart's role in the circulation, and the relation of the status of the cardiomyocytes internally in general in relation to what is measured externally as mechanical pump function.

Preload

Preload, as a term in clinical context for the whole heart, is the stretch on the myocardial wall of the LV or RV at the end of diastole, just before contraction begins. The term preload was created from studies on isolated muscle strips while putting a certain weight on the muscle before it started its contraction, and the "translation" of this concept to a heart chamber can be done in several ways. The length of the sarcomere at end-diastole (which is the fundament of Frank-Starling 'Law') is probably the most meaningful measure of preload of a myocardial strip, but at present time we do not have any techniques to measure this in intact heart chamber.

Often, the heart chamber condition at end-diastole is described in mechanical terms of stiffness ($\delta P/\delta V$) or compliance ($\delta V/\delta P$). Wall stress at end-diastole would be a strong surrogate, but it necessitates intracavitary pressure measurement and measurement of internal radius and wall thickness (this is simplified to wall thickness in the model of thin-walled spheres, which includes heart chambers). Wall stress [σ] is defined as the force per unit cross-sectional area of muscle. Using Laplace´s law simplistically, we can calculate $\sigma = \mathbf{LVP * r/h}$, where LVP is left ventricular pressure, r is the internal radius of curvature of the chamber, and h is the wall thickness). The end-diastolic volume (EDV) is another strong surrogate, but the main limitation with EDV is that present clinical methods do not measure volumes reliably, outside of the invasive experimental setting (Figure 2). This probably will soon change, perhaps with 3D echocardiography. In clinical practice, the end-diastolic pressure (EDP) provides an alternative measure of preload. Although EDP is commonly not measured directly by means of left sided catheterization, it can be indirectly assessed by measuring the pulmonary artery occlusive pressure (PAOP) using a Swan-Ganz catheter, which is placed via right heart in the pulmonary artery.

Preload in the practical patient context is changing on a beat-to beat basis. It is a function of venous return as well as heart rate, or diastolic filling time. Venous return (and cardiac output) is responsive to demand from vital organs and whole body need for substrates to keep up with their metabolic demand. While preload typically remains within a range consistent with effective ventricular ejection, heart rate can be adjusted so that when the body's metabolic needs are very high (in illness or during physical activity in high degree), the cardiovascular system performance (venous return and cardiac output) can increase manifold even though preload for each beat will remain within a relative narrow range. Preload is a

strong determinant of contractile force, which has been called the length-dependent contractile activation, or the 'Starling' relationship.

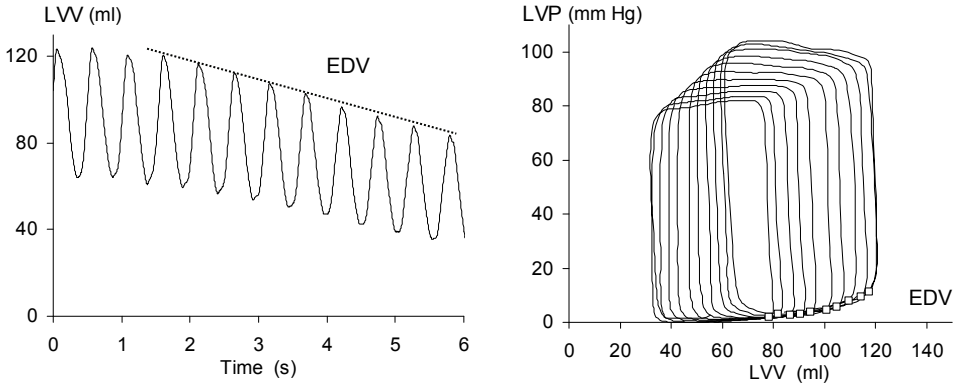


Figure 2. Preload reduction under a vena cava occlusion with LV end-diastolic volume (LVEDV) marked. Reduction in LVEDV results in reduced end-diastolic pressures and stroke volumes. One can see that stroke volumes are very little changed during this sequence.

Contractility

Contractility is the inherent capacity of the myocardium to generate force during systole or contraction, or the muscle cell's own physiochemical internal status that interacts with external conditions of muscle cell stretch (preload) or resistance to contraction (afterload). Contractility is difficult to measure clinically. It is influenced by many processes and local factors which are also difficult to measure (ions, hormones, other things), which are also difficult to measure clinically. Clinicians want to quantify it, and to do this it is necessary to separate measure and control factors which influence ventricular performance from the effects of load (9).

The ability of the ventricles to generate pressure (and hence blood flow) is derived from individual cardiomyocyte shortening and force generation. This cell shortening and force comes from regulated interactions between contractile proteins, which are found in an organized and repeating structure called the sarcomere. The sarcomere is a 3 dimensional structure, where each heavy chain of myosin filament is surrounded by 6 thin actin filaments in a honeycomb-like arrangement. The thin filaments are composed of linearly arranged globular actin molecules. The thick filaments are composed of bundles of myosin strands with each strand having a tail, a hinge, and a head region. Force is produced when myosin binds to actin and, with the hydrolysis of ATP, the head rotates and extends the hinge region. Relaxation requires uncoupling of the actin-myosin bond, and this occurs when a new ATP molecule binds to the ATP-ase site on the myosin

head. If no ATP-energy is available, a state of ”rigor” or increased stiffness can be observed.

Actin-myosin interactions are regulated by troponin and tropomyosin (10). Troponin is a macromolecule with three subunits: troponin T binds the troponin complex to tropomyosin, troponin C has binding sites for calcium, and troponin I binds to actin. When intracellular calcium concentrations are low, the troponin complex pulls the tropomyosin from its resting state so that it will block the actin-myosin binding sites. When calcium concentrations rise, and calcium binds to troponin C, troponin I releases from actin allowing the tropomyosin molecule to be pulled away from the actin-myosin binding site. This eliminates inhibition of actin-myosin interaction and allows force to be produced. This arrangement of proteins provides a means by which variations in intracellular calcium can readily modify instantaneous force production. Calcium rises and falls during each beat, and this underlies the cyclic rise and fall of muscle force. This rise of local calcium concentration causes release of a larger pool of calcium stored in the sarcoplasmic reticulum (SR), through calcium release channels called ryanodine receptors. This process whereby local calcium regulates SR-calcium release is referred to as ‘calcium-induced calcium release’. Calcium concentration rises transiently from 0.1 to 10 μmol/L in the cytosol. Calcium release is rapid and does not require energy because of the large calcium gradient between the SR and the cytosol during diastole. In contrast, removal of calcium from the cytosol and from troponin occurs against a concentration gradient and is an energy requiring process. In addition to calcium, cardiac muscle fiber length (as mentioned earlier) exerts a major influence on force production. Understanding of influence of sarcomere length on generated force is aided by understanding some details of sarcomere geometry. The actin filaments are approximately 1μm in length and myosin filaments approximately 1,5μm.

When the myofilaments are activated by calcium during contraction (systole), optimal force generation is achieved when sarcomere length is about 2.2-2.3μm, a length which allows maximal myosin head interactions with actin, with no interactions between the thin filaments on the opposite sides of the sarcomeres. At a sarcomere length of ~1.5 μm, the ends of the thick filaments hit the Z discs and force is largely eliminated. In cardiac muscle, constraints imposed by the sarcolemma prevent myocardial sarcomeres from being stretched beyond ~2.3 μm, at least acutely even under conditions of severe heart failure when very high distending pressures are imposed on the heart. Cardiac muscle is therefore constrained to operate on the so called ascending limb of the force-length relationship. This fundamental property of cardiac muscle is referred to as the Frank-Starling ‘Law’, which means that increased pre-contractile/systolic fibre length (preload) will generate increased force within physiological range (10). This is not, however, to be confused with the clinical phenomenon of where a dilated left ventricle, dilated due to disease and long term pressure-overload, does not have an efficient

mechanical ejection despite very high wall tension during systole (where reduction of ventricular volume is a therapeutic goal to achieve better ventricular efficiency). Once the ventricle dilates past a certain point (in disease), the wall tensions required to generate ejection increase exponentially, according to the Law of Laplace (mentioned earlier).

The force-frequency relationship (Bowditch or treppe effect) is the name for the phenomenon where higher heart rates lead to enhanced force generation, probably due to increased intracellular Ca^{2+} concentration (11). The force-afterload effect (Anrep effect) describes the increase in contractile force in response to a sudden increase in afterload. The Gregg phenomenon (the garden hose effect) is increased force generation in experimentally increased intracoronary pressure. βeta-adrenergic receptor activation via second messenger, which is intracellular cAMP, leads to complex cell function changes involving inotropic, chronotropic, dromotropic, batmotropic and lusitropic effects.

In the clinical setting, ventricular performance can change from beat to beat related to changes in external constraint on the muscle (preload and afterload), even with unchanged intrinsic contractile conditions in the cardiomyocytes. Thus altered loading conditions by themselves have the potential to result in reduced or limited LV performance at a time when the heart's intrinsic contractile state may be normal, depressed or perhaps supranormal (12). Just consider the case of haemorrhagic shock: the LV performance is very low, but there is nothing intrinsically wrong with the heart, and reflex responses probably have led to maximal heart contractile conditions.

Afterload and ventricular-vascular interactions

The transformation of muscle force into intra-ventricular pressure is modified by factors including the function of cardiac valves and the pressure in the arterial system against which the ventricles contract. Afterload is the hydraulic load imposed on the LV or RV during ejection. In absence of significant valvular pathology (mitral regurgitation or aortic stenosis), the load is mainly generated by the arterial system. Afterload is basically the force in the ventricular wall which would try to pull it apart during systole or contraction. There are several aspects and practical approximations of afterload. Clinically, the most commonly applied simplification for afterload is aortic blood pressure, which is the pressure that the ventricle must overcome to eject blood into the arterial tree. Clearly, there is interplay between the heart and the vascular system. The heart generates force leading to blood ejection into the aorta and vascular tree during systole. How much pressure results from this ventricular contraction is dependent on a complex set of factors in the arterial tree and blood, though details in these vascular factors are beyond the scope of my study here (13).

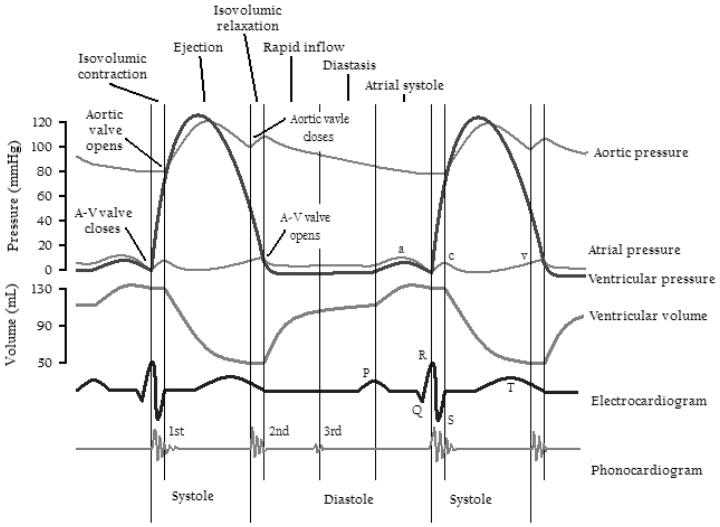


Figure 3. Stylised waveforms are superimposed to show their relation during a cardiac cycle (a so-called 'Wiggers' diagram), in the left ventricle. *With permission from DestinyQX*

Global ejection parameters

While the cardiomyocyte and ventricle contracts, the result or output of the contraction leads to a specific amount of work or performance. Normally, most of ejected volume flows out of the ventricle in first third or first half of the ejection period, generating peak flows and peak power for ejection during this same period. The ventricular pressure curve during systole is very rapidly rising (during isovolumetric contraction), (Figure 3-5), has a relatively narrow peak, and then a rapid pressure decline. The arterial pressure pressure curve during ejection is more broad-based, can increase or decrease during the ejection period (or both), depending on and related to the complex compliance of the vascular system (14).

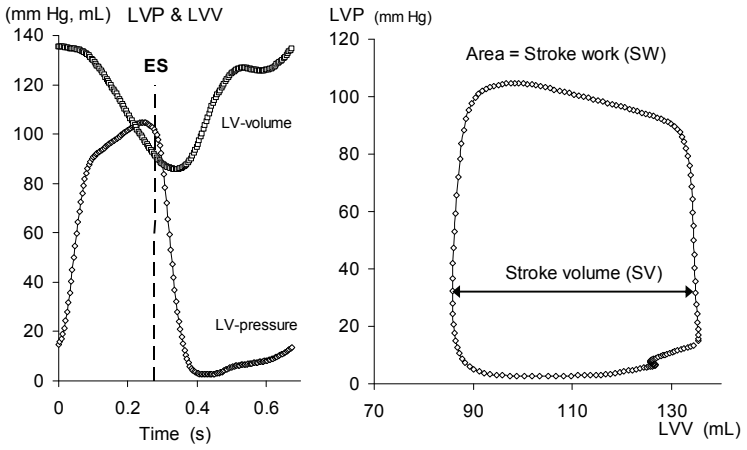


Figure 4. In this typical heart cycle, ventricular pressures increase steadily during ejection. Derivation of stroke volume and stroke work is shown.

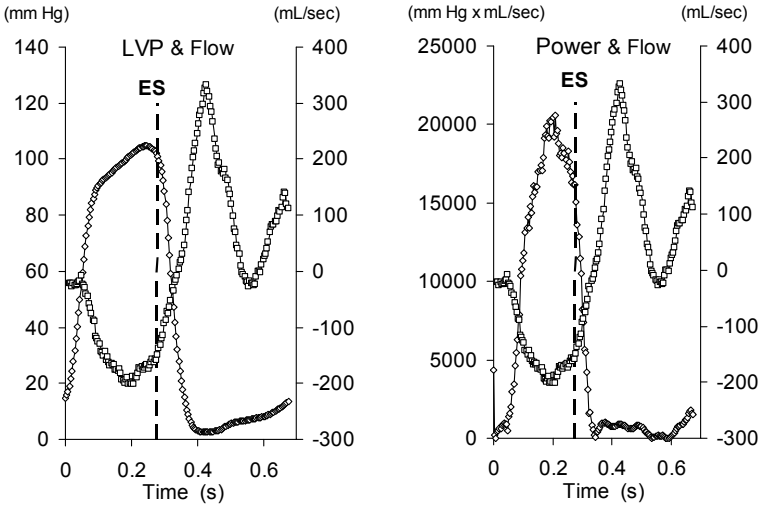


Figure 5. Left ventricular pressure (LVP, diamonds) and flow (squares) in one heart cycle are illustrated (left panel) and Power (ABS(pressure x volume)) and flow on right panel. End-systole is marked ES. Note that maximal power occurs during mid-ejection and not (typically) at peak ejection pressure.

Ventricular performance can be measured and described in many different ways (15). One traditional way to describe ejection is to present the absolute volume (stroke volume) or relative amount of ventricular emptying during systole (ejection fraction), a product of stroke volume and pressure during ejection (stroke work) (Figure 4), or even the time that is required for ejection to be completed (ejection time). If one considers the hypothetical situation where the heart's contractile status is steady, normal and unchanging, then we can imagine what happens with ejection when one increases the hydraulic load against which the ventricle must contract. Same intrinsic force generation, but more afterload. The ejection indices mentioned above will all change (presumably, and this is part of the study questions here).

Ejection fraction has been widely used as an index of ventricular function (16). It is easy to measure, but highly load-dependent. The ejection fraction has wide clinical popularity for evaluating systolic function in part because it provides a number that is easily interpreted in some ranges: when collected from a patient with normal loading conditions, the farther below 50% the EF is, the more abnormal the systolic function (17). Ejection fraction can be estimated using a number of different techniques, including ventriculography, MRI and echocardiography (18).

The obvious shortcoming of ejection fraction as an index of ventricular function status is that preload (only at low EDV), afterload and LV contractile status all presumably influence the EF values. Ventricular configuration is probably important. Furthermore, in the presence of left ventricular hypertrophy with preserved external cardiac dimensions, a reduction in LV long-axis shortening would presumably not be accompanied by a concomitant reduction in ejection fraction, despite a fall in stroke volume (19). One editorial (16) calls "*Ejection*

fraction: a measure of desperation?" and the desperation is that while one recognises the severe limitations in applying EF results to heart dysfunction grade, there are few readily accessible clinical alternatives at the current time.

Myocardial performance index (Tei index) and load

One parameter that tries to incorporate ejection with pre- and post-systole has been used widely to try to quantify changes in heart function in serial measures, and this was called the myocardial performance index (MPI), which was introduced in 1995 (20-27) This is a calculated parameter based on relation of specific time intervals for parts of the heart cycle (Figure 6). The MPI is calculated as the sum of the time for the isovolumic relaxation time and the isovolumic contraction time, divided by ejection time, MPI=(IVRT+IVCT)/ET. Mathematically, one can see before testing this that the shorter the ejection time, the higher the MPI index. However, although studies have presented associations of MPI levels over time with clinical events (28), its direct correlation to contractility status, especially when there are load changes is challenged (29-32, 34, 35). The strength of MPI, when it was introduced, was that it was then perceived to be strongly resistant to changes in heart rate or load. This question was the basis for Study I.

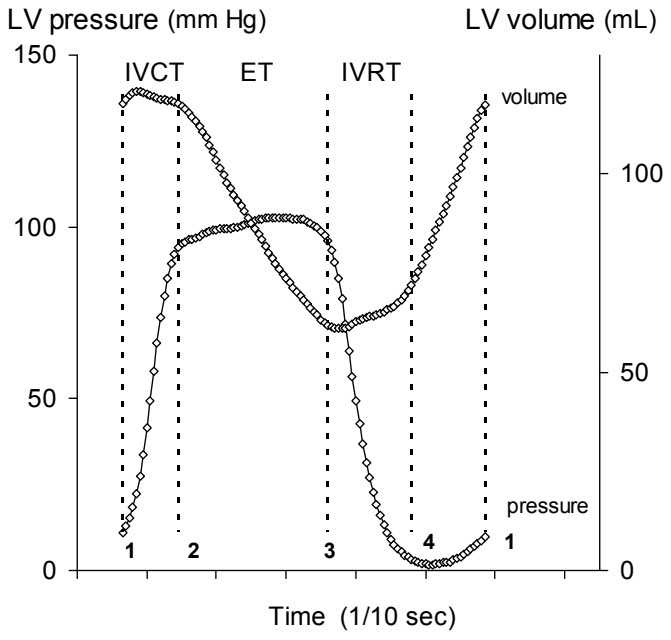


Figure 6. A representative single heart cycle with separate pressure and volume curves vs. time and there were 4 milliseconds between measurements. Specific points in the cardiac cycle are marked: 1=end-diastole, 2=start ejection, 3=end-systole, 4=end-isovolumic relaxation. The intervals used to derive MPI are depicted: IVCT=isovolumic contraction time, ET=ejection time, IVRT=isovolumic relaxation time, LVV=left ventricular volume, LVP=left ventricular pressure.

Dyssynchrony, dysynchrony and load

Left ventricular dyssynchrony is the term for ventricular motion during systole which does not contribute to ejection (Figure 7). Normally, there is a pattern of activation of the left ventricle which is complex and leads to mechanical efficiency: contraction occurs in an advanced sequence, from apex to base, and from endocardium to epicardium (3). Dyssynchrony (36-43), can be a regional phenomenon when there is a local injury and that region of the ventricle no longer contracts, or may even passively distend (accepts volume, like a balloon, when other parts of the ventricle are contracting/shortening). Dyssynchrony can also occur when there is a disturbance in the carefully timed activation of ventricular muscle, related to an injury in the electrical conducting system of the heart.

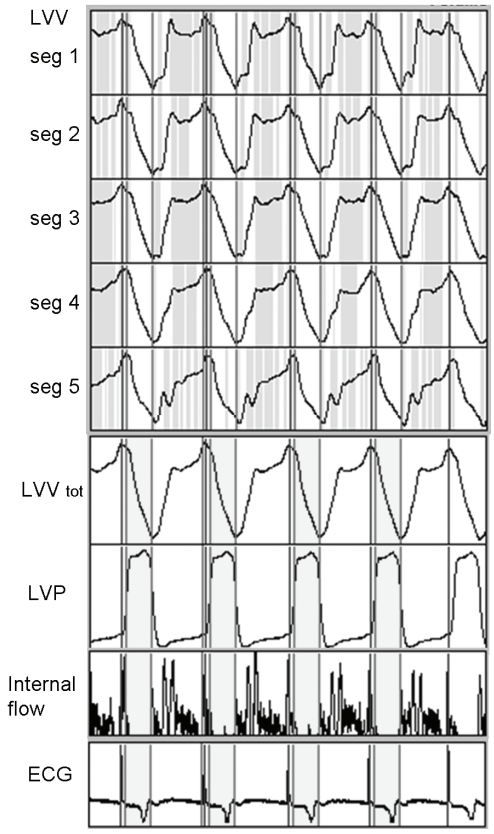


Figure 7. Dyssynchrony derived from conductance catheter signals. Dyssynchrony can be analysed in 5 segments along the long axis as changes in volume and flow between 5 segments (Internal flow). Systole is marked with vertical lines and shaded areas in the lower 4 panels. Internal flow (dyssynchronous volume change between segments) occurs in this example mostly at the start of ejection.

If one or more parts of the heart contract late, then this will impair the efficiency of ventricular ejection, an efficiency which is very high in health, but, when impaired by mechanical dyssynchrony, can contribute very much to heart failure. This type of dyssynchrony is the object of treatment with multi-lead sequential pacemakers for treatment of heart failure. (Figure 8) A third type of dyssynchrony can be noted when there is a regional dysfunction, as in Tako-tsubo cardiomyopathy (44,45). A fourth type can be observed with a global injury to the ventricle, where small regional variations in systolic volume changes can become exaggerated, and it is this type of regional dyssynchrony in an acute global ventricular injury model that I have chosen to examine in the thesis. Finally, mechanical interactions between the ventricles can affect the efficiency of left ventricular ejection, and while right ventricular overload is generally recognised to

pose a diastolic or filling impairment to an otherwise healthy left ventricle, this also can negatively affect left ventricular ejection.

Ventricular dyssynchrony can be measured locally, in the heart wall by comparing multiple points, or regionally, by comparing regions. I have examined regional dyssynchrony in this thesis, though local tissue velocities are commonly used for this purpose in the clinical setting (Figure 8).

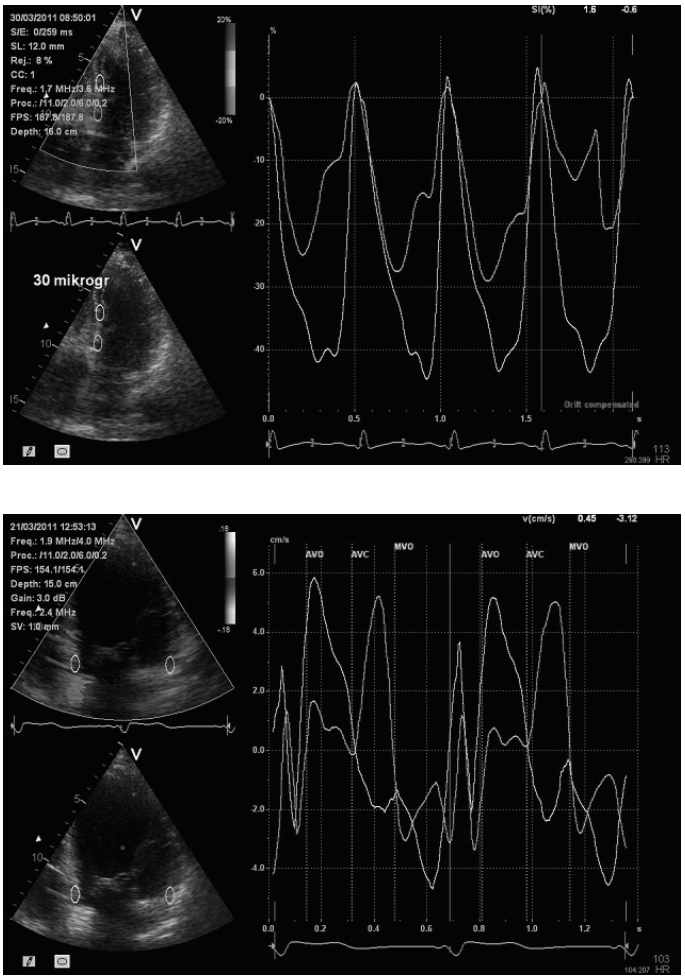


Figure 8. Tissue velocities recordings from a healthy patient (upper panel) and from a patient with clear dyssynchrony (lower panel). Analysis of peak systolic strain in septum (apical 4 chamber view, above) as well as basal septum and lateral wall in the perianular region (below). Peak systolic velocities are well timed in health (above) and regionally much delayed actually in diastole in the lateral wall.

It is unclear if load differences for different beats affect dyssynchrony parameters, though it is reasonable to suspect that since regional volume changes during systole might be effected by load alterations, that measures of dyssynchrony might likewise be affected. This was the background for the study question for Study II.

Localised ejection parameters

Traditionally, we have used global parameters to describe the action of the heart in general. This is probably mostly because until recently there were no tools or instruments to allow high resolution signal acquisition of the mechanical activity of very localised parts of the heart,. There have been models that suggest that the heart muscle can be viewed in some way in a unified model, as a single muscle band (46-48).

If this is so, then a localised measurement of ventricular wall mechanical activity would provide a good indication of the activity of the whole ventricle. If the wall was very heterogeneous, as far as different muscle bands, fibres, and directions, the forces could be relatively well distributed, but it is not clear that a localised tissue velocity that was sensitive for direction would be highly reproducible as one moved from point to point, and region to region. The different bands are strongly coupled to each other, so they draw each other towards each other when they shorten. On the other hand, if there were regions or bands that were injured, dysfunctional, or uncoordinated in their activation times, then it is hard to imagine that the ventricle wall can be uniform or homogeneous in its force generation or distribution, or motion. To date, these issues are unclear.

When assessing localised myocardial tissue velocity (Figure 9), 49-74 one can also further analyse these signals to generate local tissue strain or deformation during contraction. Deformation rate or strain rate can also be calculated. It is not clear if these parameters are directly influenced by loading conditions, and this was the basis for my Study III.

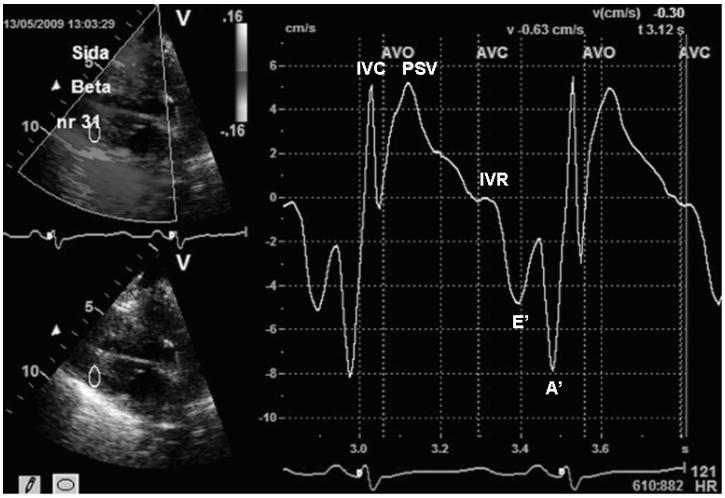
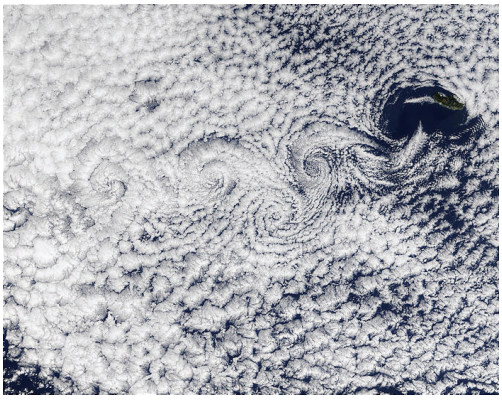


Figure 9. Typical example of tissue velocities in parasternal long axis for radial velocity analysis. Positive and negative wave of isovolumic contraction (IVC-marking),peak systolic velocities (PSV-marking), isovolumic relaxation (IVR-marking), early diastolic velocities (E´-marking), and atrial

Complex myocardial contraction: twist/systole and untwist/relaxation

Circumferential motion of the left ventricle during the heart cycle is a modern way to assess heart motion and function, and this is thought to have clear implications for even perioperative and intensive care patients (75). Circumferential motion is measured directly in specific planes of the heart, and the pattern of circumferential motion is different for different orthogonal planes. In health, for the apical short axis plane, circumferential motion is general and counter-clockwise. In the heart base, circumferential motion has a much smaller magnitude, and it occurs generally in a clock-wise direction. At the mid-ventricular level, there is a complex circumferential motion, and the summary of the multiple regions at that level is that there is little net mid-ventricular circumferential motion as a result. The convention for quantification of twist is to add the relative motion of the apical and base planes together. Torsion is the term for twist when the long-axis length of the ventricle is also taken into consideration. Torsion is thought to contribute to effectiveness and efficiency of ejection, possibly by helping to aim a force vector from the ventricular contraction towards the outflow tract (8). Magnetic resonance assessment of blood flow eddies during ventricular ejection suggest that there is a vortex involved in normal systolic ejection, and presumably torsion contributes to this (76). Regional pressure differences in the ventricle are perhaps generated with help, in part, from regional differences in twist, and this has been demonstrated particularly for diastole, filling, and untwist (77). In the pressure-volume plane, negative pressures during the transition from isovolumic relaxation to early diastole are not uncommon in healthy hearts, and we have observed this frequently in our experimental models.

With hardware and software developments in recent years, circumferential velocity assessment (speckle) is readily available in commercial echocardiographic machines, though many aspects of these parameters have been little studied so far concerning relation to load (Figure 10). It could be the case that circumferential velocities and twist are highly dependent on loading conditions, which is the basis for my Study IV.



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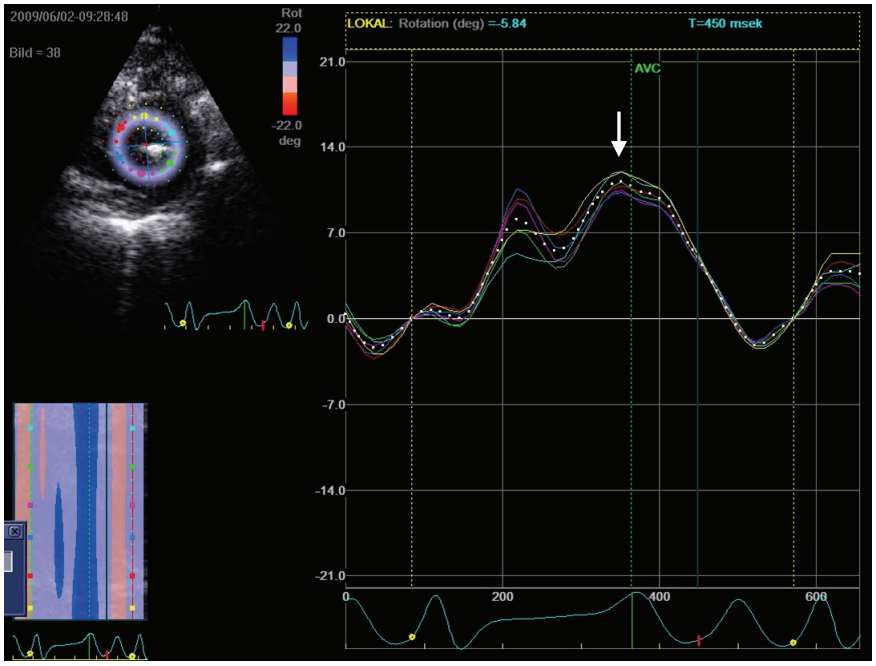

Figure 10. Representative images of counter-clockwise apical rotation for the first beat in a vena cava occlusion sequence by speckle tracking imaging. Rotation in individual segments and mean values are presented. Maximal apical rotation (arrow)

Heart ultrasound, history

At the University Hospital in Lund, Sweden, in 1953, Inge Edler and Helmuth Herz brought a non-medical ultrasound scanner which they had borrowed a from Kockum´s shipyard in Malmö, in order to generate images of the heart. For the first time, there was a non-invasive record of the heart from the precordial window, the signal from movements of left atria and ventricular walls clear in the image (78). The reflected sound signal from boundaries of cardiac structures was detected by the same crystal which generated the sound waves. These mechanical signals were transformed to electrical signal and displayed on a cathode-ray-tube as a series of vertical spikes. The amplitude of each spike was dependent on strength of the signal, and this type of presentation of ultrasound signal was later named "A-mode". The A-mode was quite impractical for clinical use; the interpretation of moving spikes with different amplitudes was rather confusing. By replacing the signal amplitude to different shade of gray-scale, a new type of presentation, the "B-mode" (brightness), was introduced soon after. This is still a single line (single amplitude) interrogation technique. This was further developed to allow both the "M-mode" and "real-time 2-dimensional" echocardiography, which are still today the foundations of the comprehensive echocardiographic exam. M-mode received

its name from its function, with continuously moving multiple B-mode dots at multiple depth locations relative to the transducer/receiver along the time axis producing continuous linear waves (motion). Initially, the ultrasound data was acquired at 2-5000 frames per seconds. In order to avoid excessive heat production, samplings rates have been reduced to around 200-250 samples/second. This excellent time resolution is a strength of the echocardiographic method. And fine time resolution of heart structure motion is invaluable for diagnosis of heart disease. Hardware and software developments in the 1980's led to the introduction of real-time 2-dimensional echocardiography into clinical practice.

Based on the idea of frequency shift based on motion, described by Christian Doppler in 1842 (79), another important technique of ultrasound was introduced by Satomura and Yoshida in the 1960's, Doppler echocardiography. This method is used to obtain high resolution for velocities of blood or tissue.

Our eye is not as good a judge of motion as we think. Virtually every individual will detect rapid motion if occurs over a period longer than 80 milliseconds. Military pilots with long training and using colorization of the image can be taught to identify motion with temporal resolution approaching 20 milliseconds, and this approaches the temporal replenishment rate of the optical rods and cone in our retinas (80). This experience is confirmed in heart imaging, where even experienced echocardiographers can only reliably identify computed regional delays larger than 89 milliseconds within a 2-D echo image. How fast do we acquire data to resolve all myocardial motion? One group has reported (81) using spectral analysis to determine the frequency components of the integrated backscatter curves acquired at a heart rate of 70/minute from normally contracting myocardium. They concluded that for any cardiac imaging technique, data must be acquired and processed at > 100 samples/second to resolve myocardial motion.

Since its introduction in 1989 by Isaaz, tissue velocity echocardiography (TVE) has been widely used for non-invasive quantification of the complex myocardial function (62). Tissue velocities have been studied as far as their relation to load, but no conclusive findings have been reported to resolve this question.

AIMS

Hypotheses

- The 'myocardial performance index' is dependent on loading conditions.
- Long-axis segmental dyssynchrony is dependent on loading conditions.
- Myocardial systolic velocities and strain are dependent on loading conditions.
- Myocardial twist is dependent on loading conditions

Specific aims

- to analyse the relationship between 'myocardial performance index' and loading conditions during controlled load alteration, and then also during load alterations performed together with an inotropic intervention.
- to analyse the relationship between long-axis segmental dyssynchrony and loading conditions during controlled load alteration, and then also during load alterations performed in a model of global ventricular injury/dysfunction.
- to analyse the relationship between peak systolic myocardial velocities and strain vs. loading conditions during controlled load alteration, and then also during load alterations performed together with an inotropic intervention.
- to analyse the relationship between myocardial twist and loading conditions during controlled load alteration, and then also during load alterations performed together with an inotropic intervention.

REVIEW OF THE METHODS

Material

All of the studies in this thesis were conducted in a large animal model at Umeå University, and all had approval from the Umeå Regional Ethical Animal Use Board (MH- A21-04, A09-07, A37-09). An anesthetised pig model was chosen first because these studies were highly invasive, and they could not be conducted in human material, at least with regards to the reference methodology for left ventricular load and function assessment. A pig model was chosen because the anatomy and function of the pig heart is very close to the human heart. Juvenile pigs were chosen because of their size, to allow human catheters and methods to be used for data collection. The pigs were raised at the local agricultural gymnasium, and were without exception healthy. The model of a healthy heart was chosen so that different inotropic (negative and positive) interventions were freely available. These experiments were all acute, that is, that the animal was anesthetised, instrumented and studied, and then euthanized on the same day. There was no chronic injury model aspect here. These animals were not sexually mature, and they were mixed female and male siblings for each week's experiments.

Preparation

The animals were brought to the large animal experimental facility at least one day before the experiment. They were sedated first in their pen with intramuscular ketamine together with either azoperone (and when this was no longer available commercially) or xylazine. An intravenous catheter was placed in the sedated animal, and then they were anesthetized using traditional intravenous anaesthetic agents and no muscle relaxants. They were intubated through a tracheostomy and then managed for the experiments with the goal of normal ventilation and normovolemia, with the details indicated in the Studies.

We placed venous and arterial catheters through open access to neck vessels by cut-down. The animals for the most part lay on their back (supine), though if the echocardiographic window was judged to be suboptimal, the animals were laid on their sides. Animals were maintained in a normothermic state using active external warming.

Measurement methods

Measurements included multilead ECG and fluid filled pressure measurement systems for venous, arterial, and pulmonary arterial pressures. All continuous data was recorded by a digital signal acquisition software (AcqKnowledge, Biopac, Santa Barbara, California, USA). Thermodilution flow measurement for cardiac output were acquired using a pulmonary artery catheter. Left ventricular tip manometry is used for the high fidelity ventricular pressures that are needed for high resolution of pressure changes, particularly during the isovolumic phases of

the heart cycle. There are essentially continuous signals available for both tip manometry (LV pressure) and conductance volumetry (LV volume), and these were recorded at 250 Hz. This frequency (4 milleseconds between measurements) is a compromise between enough time resolution to be sensitive for the physiological phenomena we aimed to study (rapid pressure, and to a lesser extent volume change during a heart cycle), and on the other hand not generating unnecessarily large or ungainly data files. We have in the past used either 400 Hz or 250 Hz where there is a particular interest in resolution of ventricular pressure change, and both have been adequate.

Left ventricular conductance volumetry signal was gathered from a combined tip manometer and conductance catheter using a specific signal processor and amplifier (5DF, CD Leycom, Leiden, The Netherlands). This catheter was guided fluoroscopically into the heart through an introducer placed in the carotid artery. The catheter's a pig-tail end was placed into the LV apex, for optimal catheter stability. The best position for LV volume signal was achieved through a combination of catheter position, evaluated fluoroscopically, and volume signal-appropriate physiological volume reduction during systole and volume increase during diastole, with strongly isovolumic phases in between. When the isovolumic phases, or rapid pressure rise and fall, demonstrated decreasing or increasing volumes, fluoroscopy was initiated to try to identify catheter movement or instability in the central LV long axis during systole, and catheter repositioning was performed to eliminate this potential source of volume artefact. Ventricular pressure and volume signals were gathered using commercial software (Conduct 2000, CD Leycom, Leiden, The Netherlands).

Left ventricular volumes were measured using signals derived from the electrical conductance of blood surrounding multiple catheter electrode inside the LV (82, 83) (Figure 11).

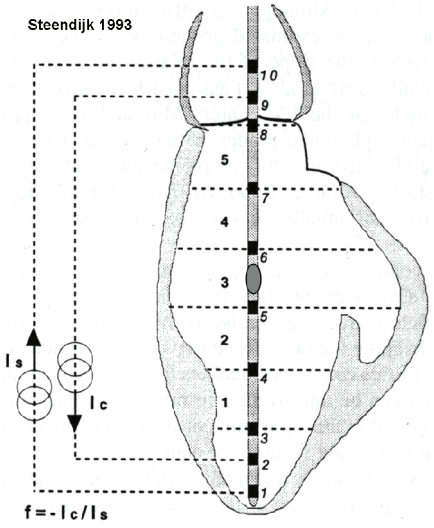

Figure 11. A stylised long axis view of a stylised left ventricle shows the position of a multi-electrode conductance catheter, with 5 volume segments.

The catheter generates two fields of electrical potential, and then measures the interaction of all the tissue with those potentials. This provides signals from multiple spherical fields which are aligned up and down along the long axis of the left ventricle. This multi-segment conductance has been designed this way so that individual spheroid segments, if they are not sensing corresponding ventricular blood

volume (as would happen if a segment was lying across the aortic valve, and was in the ventricle for part of the heart cycle and outside for part), then that segment can be left out of the total ventricular volume measurement in the off-line ventricular volume processing work.

There is a software step for signal averaging, since very sensitive electrical sensing of this kind can often demonstrate a bit of variation. We have systematically averaged (5 point averaging), once, and this is the minimal number of beats in one smoothing iteration.

These multiple long-axis segments were later assessed off-line and then included for calibration. The calibration steps include a second method stroke volume measurement, to calibrate the conductance maximal and minimal volume signal differences to a known stroke volume. We have used thermodilution cardiac output measurements divided by heart rate. Then, the zero offset, which is the amount of conductance signal which is generated by tissues other than intraventricular blood, is measured by a routine which involves injection of salt solution that leads to conductance signal change but no volume change. This allows a calculation of the amount of zero offset for the conductance signal. A third calibration step is included that concerns blood conductivity (which can change over the course of and experiment, if something significant changes in the blood), and this is measured directly from a blood sample from the animal.

Myocardial tissue velocity was measured using a standard commercial echocardiography machine (Vivid 7 dimension, General Electric, Horten, Norway). These measurements are usually based on detection of the low velocities and high amplitude motion of myocardial tissue, by application of low-pass filtering to the received Doppler signal. This helps to distinguish tissue signal from the high velocities and low amplitude motion of blood (84).

Myocardial tissue velocity is based on the principle of Doppler shift which occurs in reflected sound waves bouncing off of tissue in motion, though there is a difference in processing which allows better appreciation of tissue velocities for a whole plane. This assessment of a whole plane allows an estimation of tissue deformation or strain as well as strain rate. Tissue velocity imaging used to assess myocardial contractility has a number of limitations: 1) as with all Doppler-based methods, the most accurate velocity measurement comes from reflections of tissue motion that is closest to the line of the ultrasound beam; 2) velocity may reflect local tissue passive motion rather than actual local active contraction where even akinetic segments may show motion due to tethering of adjacent normally or even compensatorily enhanced contracting segments. To overcome these tethering issues, strain rate and strain can be derived, which reflect local tissue deformation. Deformation is the linear compression or expansion along the x-, y-, or z-axes. Mathematically, there are several ways to represent strain. The most commonly used in cardiology is Lagrangian strain (ε), a change of dimension divided by the initial dimension: $\varepsilon=\Delta L / Lo$ where Lo is the end-diastolic dimension of a

myocardial segment. In this case, **ε** is negative for long-axis strain (myocardium shortens) and positive for radial strain (wall thickening).

Speckle tracking

The emitted ultrasound pulse is not only reflected and detected, but it is also scattered. If the size of the interrogated object is approximately similar to the transmitted wavelength, or the surface of the object is not smooth, a new echo will be produced and they are the basis for 'speckle' pattern formation. This is a type of acoustic 'noise' in the image, and this signal can be used for tracking. As most structures which cause scattering of sound are stationary within the uncompressible tissue, the speckles are fairly stable and strongly related to myocardial motion (85,86). In speckle tracking analysis, regions of speckles (kernels =blocks of approximately 20 to 40 pixels) in myocardium are identified and are traced frame-by-frame to allow calculation of tissue deformation in 2 or 3 dimensions, using a sum-of-absolute differences algorithm. Speckle tracking echocardiography is independent of transducer orientation, and this allows accurate display of tissue velocity, strain rate, strain, rotation, and other derived parameters in orthogonal planes. Speckle tracking was validated as a means of analysis of tissue motion and deformation (87,88).

These impressive new methods have moved quickly into clinical practice. One observer has reflected over this process (89):

> *"Echocardiography is in the midst of revolution. Its cause is the emergence of the new techniques to quantify segmental systolic and diastolic function. However, as in all revolutions, "old" ways may be held in low esteem, whereas "new" ways are held in awe, although frequently with insufficient information to support these views".*

Left ventricular wall circumferential motion has been recognised as an important aspect of ventricular contraction and relaxation (90-121). This circumferential motion, which is interpreted globally for the ventricle in the long axis as twist or torsion, began to be analysed using 'speckle' methods (88) during the last few years.

Experimental protocols

All four studies included a protocol based measurement sequence for resting status, for a controlled preload alteration, and for inotropic alterations, both negative and positive. The specific inotropic alterations where not the same for all 4 studies.

Resting measures

Resting measures were those where parameters were taken during apnoea. Blood pressure, flows, and chamber volumes vary typically from beat to beat in awake subjects or animals, and this is due to a combination of the effects of active breathing on the circulation, and also autonomic nerve system reflexes. The resting measures that are gathered here are heart cycles where the respirator is disconnected and the animals lay still, so that the beats in the sequence were at a form of circulatory equilibrium for venous return and heart performance.

Controlled load alterations

Controlled load alterations can be brought about by a number of means, either by restricting inflow to the heart, or by restricting outflow. We have used the method of transient balloon catheter occlusion of the inferior vena cava (IVCBO), which is a relative gentle intervention. The goal was to achieve a series of beats (following the resting measure at apnoea) which had a measurable but limited change in load and heart performance. Restriction of outflow, for example by aortic balloon occlusion, has been tried in our lab in other experiments, but is not at all gentle, and leads to violent circulatory reflex activation. The controlled load alteration with transient vena cava occlusion (Figure 12) leads to decremented changes in both pre-systolic and systolic load (122-125) without generating a prominent immediate baroreceptor response. The same type of transient vena cava occlusion can be performed in an open preparation, using vena cava slings or snares. In studies where it is a clear advantage to have and undisturbed thorax, pleura and pericardium, then it is routine to perform these load alterations with a balloon-tipped catheter. The same load alterations were performed during the inotropic interventions.

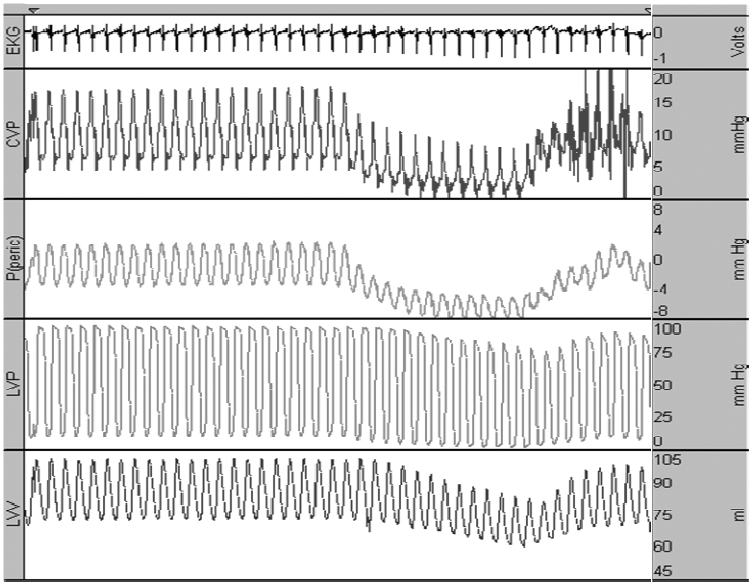

Figure 12. Example of a preload reduction with a inferior vena cava balloon occlusion (IVCBO) resulting in a drop in both left ventricular pressure (LVP) and volume (LVV).

The idea in performing a progressive load alteration over a series of beats is to analyse the relation of the beats to each other, both for load and for heart performance. It is the way that the heart performance change, in the given load context, which is the means for quantitatively assessing contractile status (126,127,123).

One can also extrapolate from a single beat concerning the volume and pressure level to which a ventricle ejects (128) to a presumed extreme measure. One ventricular performance measure which is readily available is the volume to which the ventricle ejects at a particular end-systolic pressure level (129). Another typical and reliable measure of ventricular performance during load variation is preload-recruitable stroke work (130-132) (Figure 13). These pressure-volume assessments for load were used for comparisons to known ventricular performance measures as well as test measures, in Study I- MPI, in Study II- segmental dyssynchrony, in Study III- myocardial tissue velocities and strain, and in Study IV- ventricular twist.

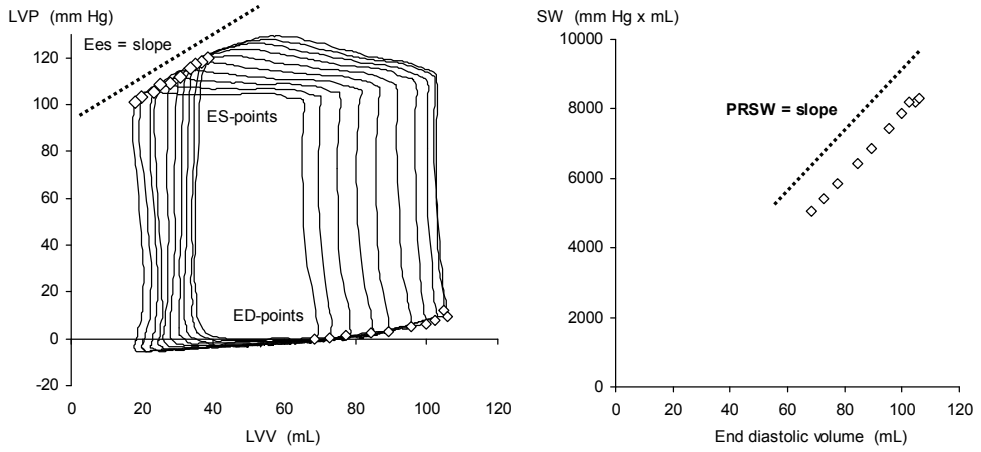

Figure 13. End systolic elastance (Ees) is the slope of the regression line for the end systolic points of each loop (left panel). Stroke work is the area of each loop. Preload recruitable stroke work (PRSW) is the slope of the regression line between stroke work and end-diastolic volume of each loop (right panel). The x intercept of these regression lines is also important.

Inotropic interventions

Inotropic interventions were included in order to test the relation of the chosen heart function parameter to a clear distinct change in inotropic status. Positive inotropic intervention is relatively easy to produce in the experimental model (pig), just by titrating in a strong positive inotrope, adrenaline. Negative inotropic interventions are included in order to mimic the clinical problem of impaired heart

function. In the first study, a large dose of inhalational anesthetic agent (isoflurane) in combination with barbiturate intravenous anesthesia, was a reproducible means to depress myocardial function. In the second study, endotoxin infusion was used to generate a global myocardial dysfunction (133-135) related to a toxic and inflammatory myocardial process. This was a global injury model, and specific inotropic drugs were not given. In the third and fourth studies, a combination of betablocker and calcium channel antagonist were used to achieve a decrease in heart function based on a target dose. Since these drugs, and particularly verapamil, led to decreases in blood pressure, phenylephrine was also given to the animals to maintain a minimum adekvat myocardial perfusion pressure (mean arterial pressure 70 mm Hb).

Analysis

Analysis of ventricular contractile status (pressure-volume plane)

We used well described routines to analyse pressure-volume relations. First, the data for selected measurement sequences were identified, and the pressure-volume data calibrated. Then, using non-commercial software that employs the same calculation routines as in Conduct 2000 (CD Leycom, Leiden, The Netherlands), matched performance measures, including stroke work, were calculated together with load indices (end-diastolic and end-systolic pressures and volumes) for all beats. These were further analysed with linear regression for the relation between the ventricular performance measure and the load measure (130,131).

'Myocardial performance index'

In Study I, the 'myocardial performance index' (20) was calculated using the sum of the time for the isovolumic relaxation time and the isovolumic contraction time, divided by ejection time, MPI=(IVRT+IVCT)/ET. These intervals were measured from pressure-volume data. End-systole was defined as maximal elastance at the end of ejection, or, when (rarely) there was no clear point maximal elastance, end-systole was determined manually in a point by point examination of the late systolic and early isovolumetric relaxation period, so that it was placed before rapid pressure decay.

Long-axis segmental mechanical dyssynchrony

In Study II, dyssynchrony was calculated for the 4 or 5 individual segments together with the simultaneous global volumes. This was done using non-commercial software which identified when a segmental volume change during ejection was increasing, rather than decreasing (136,137). The relative time during systole that there was segmental dyssynchrony was reported, as well as a measurement of 'internal flow', which was volume change in segments which did not contribute to ejection.

Resolution of myocardial tissue velocities, ventricular wall strain, strain rate

In Study III, the regions of interest were the periannular base (septal and posterior aspects), which were chosen to maximise reproducibility. The echocardiographic software's (EchoPac 6, General Electric Healthcare, Horten, Norway) region of interest (ROI) was set to a default of 6 x 6 millemeters. Tissue velocity and strain measures were calculated for selected beats (beats in the vena cava occlusion sequence), and peak systolic velocities and strain were manually measured for each beat. This measurement was performed once for each measurement sequence, and all measurements were performed by me. Once the first beat was measured and the ROI was set, there was 'anchoring' of the ROI for the rest of the beats in the sequence. There was frame by frame control (10 millesecond between frames) by myself to confirm that the ROI was in the correct chosen position, and if it was not, then the ROI position was adjusted. In the same sequence for strain analysis, there was a default selection of strain length: 12 mm. Drift compensation was activated-meaning that strain started automatically at zero at pre-systole. E' and A', as well as the positive and negative phases of isovolumic contraction velocity and isovolumic relaxation velocity were measured, but were not analysed further since they typically were not measurable throughout the whole vena cava occlusion sequence. They merged at the lower loads to a fused signal, and were no longer distinguishable from each other.

Left ventricular twist

From short axis speckle images of the base and apical regions, circumferential velocities for 6 regions were determined (EchoPac 8, General Electric Healthcare, Horten, Norway). From these segmental measurements, a rotation was determined for each segment, based on averaging of segmental values. Then, twist was calculated as the net maximal difference between apical and basal rotation.

Statistics

In Studies I and II, descriptive statistics for hemodynamic measures were described with means ± standard error of the mean. In Studies III and IV, descriptive statistics for hemodynamic measures were presented with means and 95% confidence intervals. For sequences with multiple beats, repeated measures ANOVA was used to identify a change during the course of the sequence. For paired comparisons where the pre-intervention measurement was compared to the post-intervention measurement (each animal was its own control), either a paired t-test (Studies I, II, and III) or a Wilcoxon sign rank test (Study IV)was used to identify differences. For comparison of a control value to 3 different points in a sequence, a Dunnett's multiple comparison test was used (Study III).

RESULTS

Load characterisation, inotropy and ventricular performance

In Study I, the load alteration sequence produced very clear beat-by-beat decreases in end-diastolic volume, as well as in a typical ventricular performance parameter (Figure 14). This relation between EDV and SW was very linear, and also clearly related to inotropic status, where the lower inotropic status had generally lower performance values, but at higher preload. The positive inotropic condition showed generally higher performance measures at lower preloads. The same absolute performance levels occurred in all 3 conditions for this example, though with lower load for the positive inotropic condition.

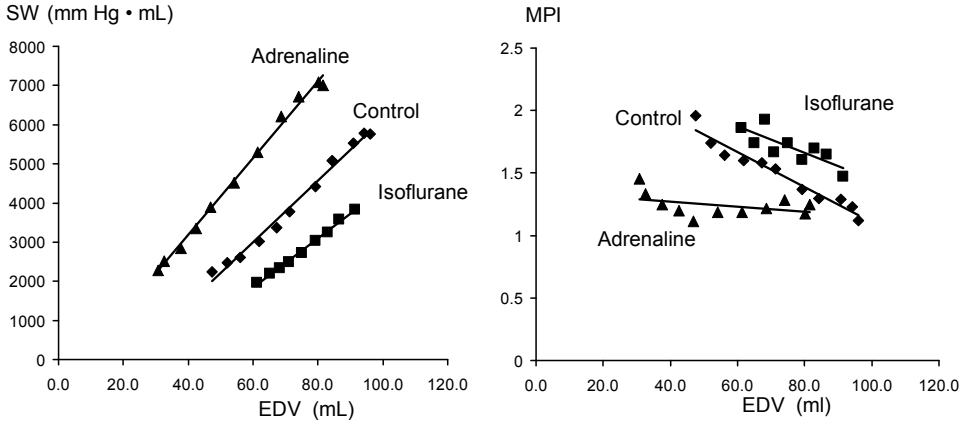

Figure 14. Typical pattern of myocardial performance index (MPI) increase during the pre-load reduction manoeuvre from measurement sequences in a single representative animal during control and two inotropic interventions. The absolute values of MPI (right) and stroke work (SW) (left) are derived from the same left ventricular pressure–volume points (including the same end-diastolic volumes, EDVs) and reflect changes in myocardial contractile status. The relative positions of the MPI measurement sequences show higher values for the negative inotropic intervention and lower values for the positive inotropic intervention at a common pre-load level.

Myocardial performance index (MPI)

A relation for MPI to load is shown in the MPI vs. EDV plot (same figure, right panel). There is a relation between MPI and inotropic state, though this is not simple to characterise. The regions for MPI/EDV relations were typåically distinct for the 3 different inotropic conditions in each animal (Figure 14), though the same MPI (1.5, for example in same Figure) could be observed for all 3 inotropic states, though at different preloads. Furthermore in a beat by beat analysis, grouped for all measurement sequences, all inotropic conditions, MPI rose during decreasing EDV (Figure 15-16). The component intervals of MPI, when analysed separately,

also showed a consistent performance related to load change. The isovolumic intervals were steady and unaffected by load change. The ejection times decreased with decreasing load.

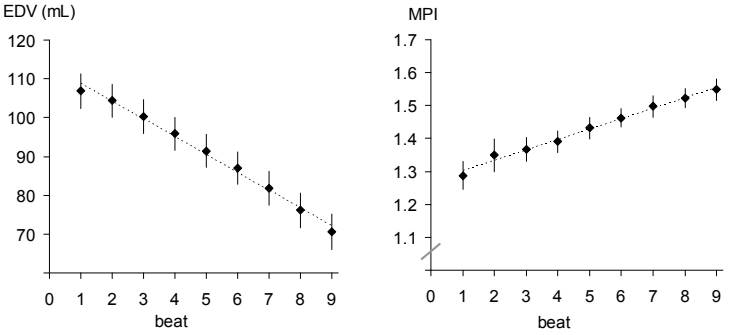

Figure 15. First nine beats for all pre-load reduction sequences in all animals. Left: mean end-diastolic volume (EDV) is grouped for each of the sequential points in all 40 pre-load reduction measurement sequences. Mean ± SEM is shown. The pre-load reduction sequences demonstrate a progressive decrease which is also strongly linear. Right: the myocardial performance index (MPI) shows a strong relation to EDV, increasing from beat to beat during a progressive preload reduction.

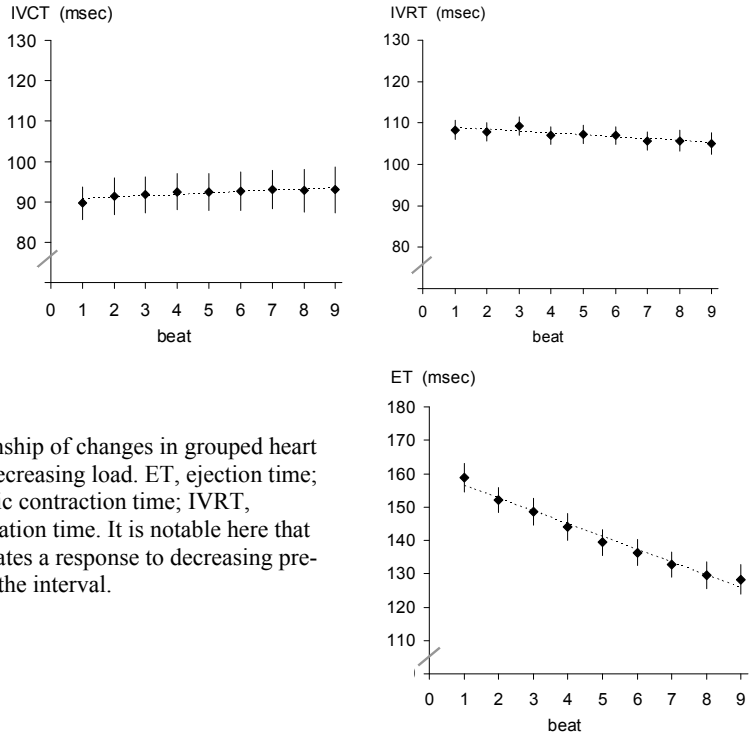

Figure 16. Relationship of changes in grouped heart cycle intervals to decreasing load. ET, ejection time; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time. It is notable here that ET alone demonstrates a response to decreasing pre-load by shortening the interval.

Segmental dyssynchrony

In Study II, segmental dyssynchrony during resting measurements increased progressively during each hour of endotoxin infusion (Figure 17). This was also demonstrated by individual segments, general increase in dyssynchrony during the 3 hours of endotoxin infusion, though there was no indication that a specific segment in the long axis was more affected than another. (Figure 18) For each hourly measurement, there was a load alteration sequenced measurement as well, and these are shown in the figure in terms of change in EDV. The same results are clear when presented for absolute EDV, though in a figure the results are very much on top of each other, which is why we chose this alternative for presentation. Analysis of the sequence showed that there was not change in mechanical dyssynchrony related to load reduction throughout the 3 hours of endotoxin infusion.

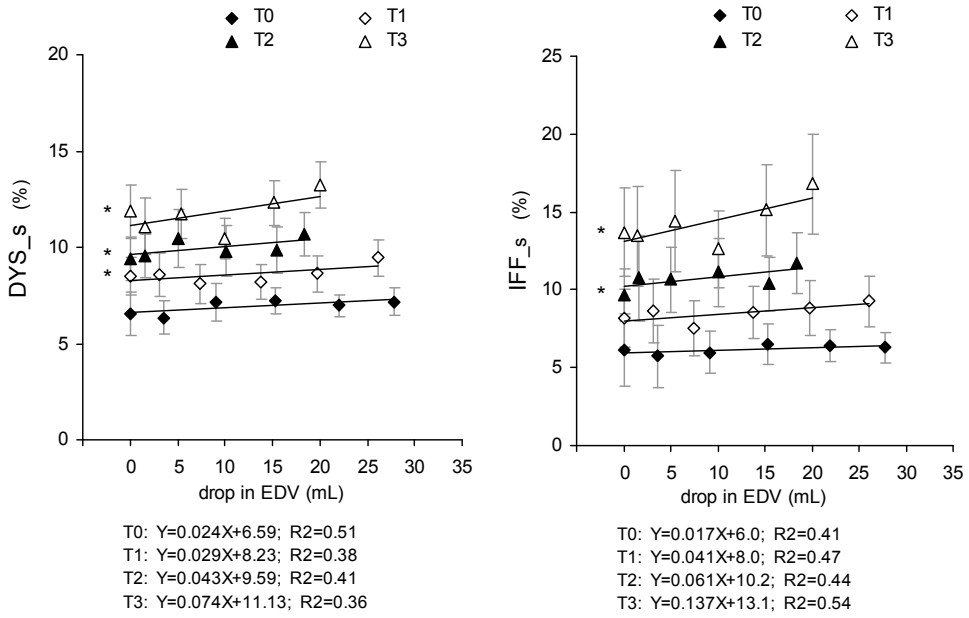

Figure 17. Figure 1 Systolic dyssynchrony (DYS_S) and internal flow (IFF_S) during transient and progressive controlled pre-load alteration by inferior vena cava occlusion are shown. No differences were demonstrated for either parameter during the course of the preload reduction sequence as presented for six consecutive beats with progressive pre-load reduction. Differences in the starting (resting) levels of dyssynchrony related to endotoxin infusion are demonstrated by contrasting the first beats in the sequence, before load reduction from resting levels occurred, for absolute levels of dyssynchrony during hours of endotoxin infusion (T1, T2 and T3), compared to resting, healthy (T0). Data are presented as mean ±SEM, n = 11. One-way repeated-measures ANOVA was used to test for changes over the six consecutive beats at each time point.

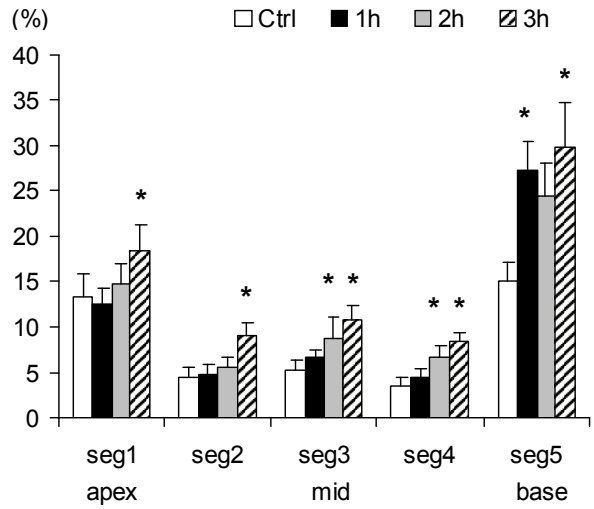

Figure 18. Systolic dyssynchrony by segment during endotoxin infusion. There was no significant difference in systolic dyssynchrony by segment during the course of 3 h of endotoxin infusion. This supports the interpretation that endotoxin's negative effect on ventricular function in this early phase is global. There is no sign of apical 'ballooning' as part of the process. Data are presented as mean ±SEM, n = 11. *P < 0.05 vs. control using one-way repeated-measures ANOVA followed by Dunnett's multiple comparisons test.

Tissue velocities

Peak systolic velocities showed no response to the vena cava occlusion sequence in control and positive inotropy conditions, and then also a small decrease in the negative inotropic group for the longitudinal axis measurement. (Figure 19,20). This was a observed at the end of a 9 beat sequence where there was approximately 20 ml higher ventricular volume throughout the heart cycle in the beta blocked group compared to control. (Figure 21). For peak strain, there seemed to be an increase with decreasing load, and particular for the negative inotropic group, where there seems to be a clear dependence of peak strain on load (strain increases when load decreases (Figure 22).

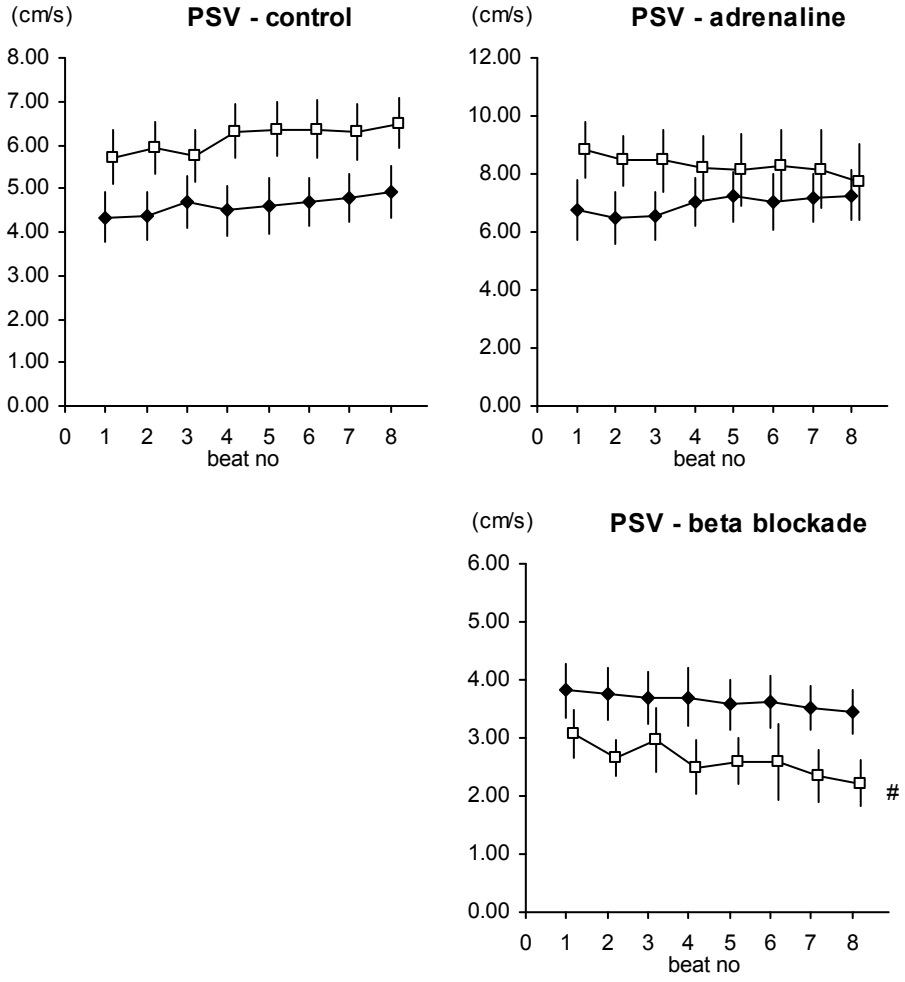

Figure 19. Peak systolic velocity (PSV). PSV showed a no change in PSV value during progressive load reduction for 5 of these 6 groups, and the decrease in PSV for the longitudinal axis measurement in the negative inotropy group was small.
Data are presented as mean ±SEM, n=13. Filled diamond = Radial projection; Open square = Longitudinal projection. # $p < 0.05$ with Repeated Measures ANOVA.

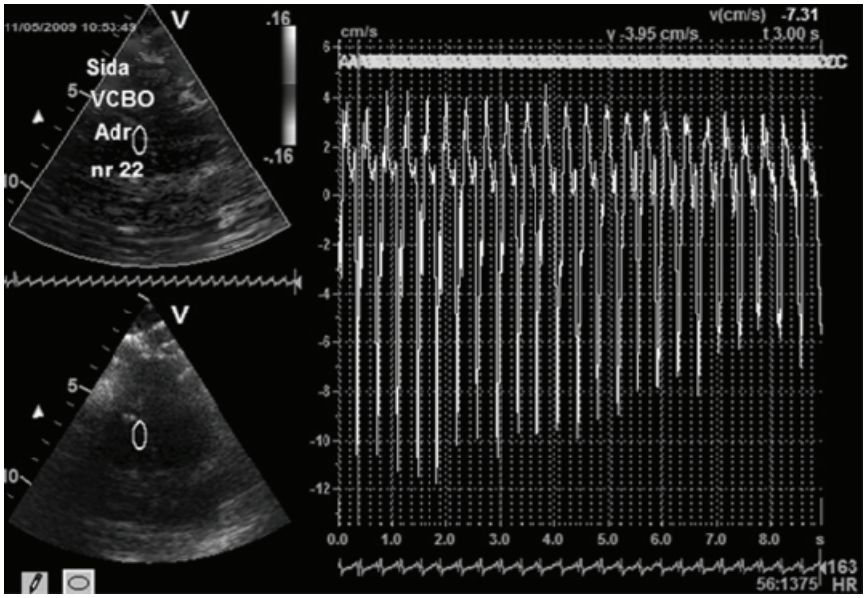

Figure 20. Tissue velocities from 4 chamber image, septal base region, signal from multiple beats during vena cava occlusion and adrenaline intervention. PSV coincides with the maximal velocities, which remain relative constant throughout the load reduction (see also progressively changing E' and A', which move to a fusion curve during the last beats in the sequence. (paper III)

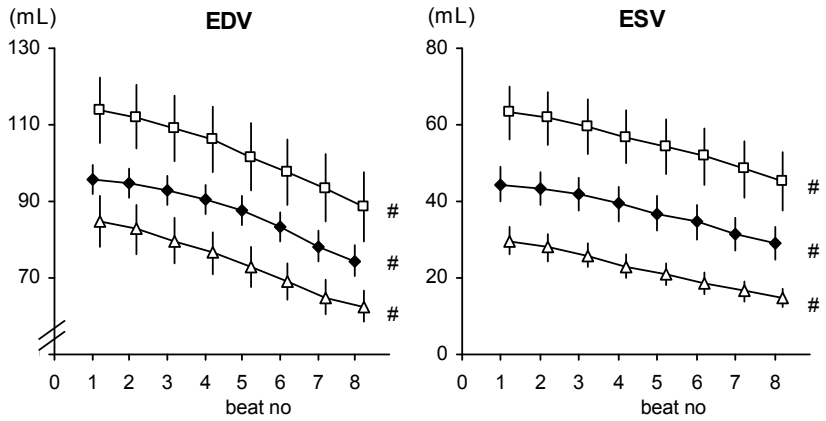

Figure 21. Data are presented as mean ±SEM, n=13. Filled diamond = Control; Open triangle = Adrenaline; Open square = Beta-blockade. EDV = end diastolic volume; ESV = end systolic volume. # $p < 0.05$ with repeated measures ANOVA. End-diastolic and end-systolic volumes for the load alteration sequences are shown here, grouped by beat in the sequence. All the first beats are grouped together, all the second beats, etc. The change in load, as demonstrated by volumes for the sequences and then also for the same sequences collected during experimental alteration in inotropic status, is clearly shown. These load ranges correspond to the grouped tissue velocity and strain measures in later figures.

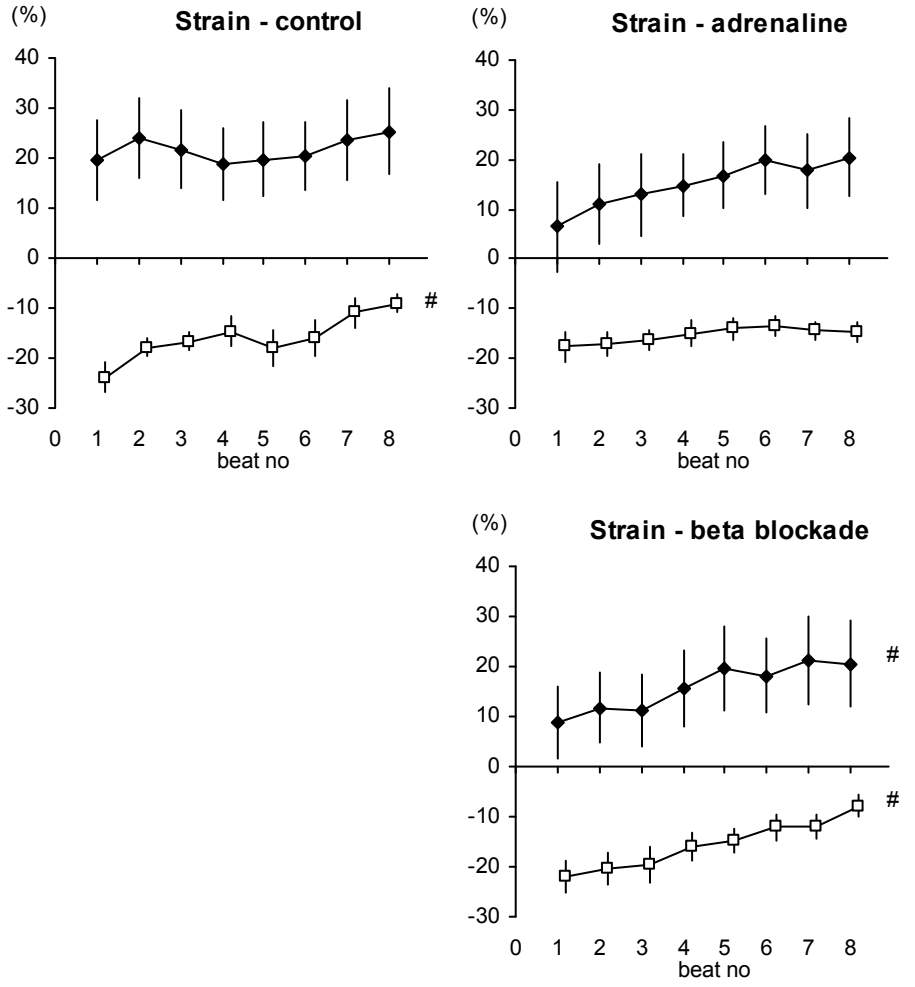

Figure 22. Systolic Strain. Data are presented as mean ±SEM, n=13. Filled diamond = radial projection; Open square = longitudinal projection. # $p < 0.05$ with repeated measures ANOVA. Systolic strain increased during load reduction in half the group, and notably for the negative inotropy groups.

Twist, circumferential rotation

For twist, the first and last beats in the load alteration sequence (8 beats) were compared, and there was a clear increase in maximal twist related to the load decrease (vena cava occlusion sequence) in the control group. The same was observed for the positive inotrope group, though not for the negative inotrope group. (Figure 23).

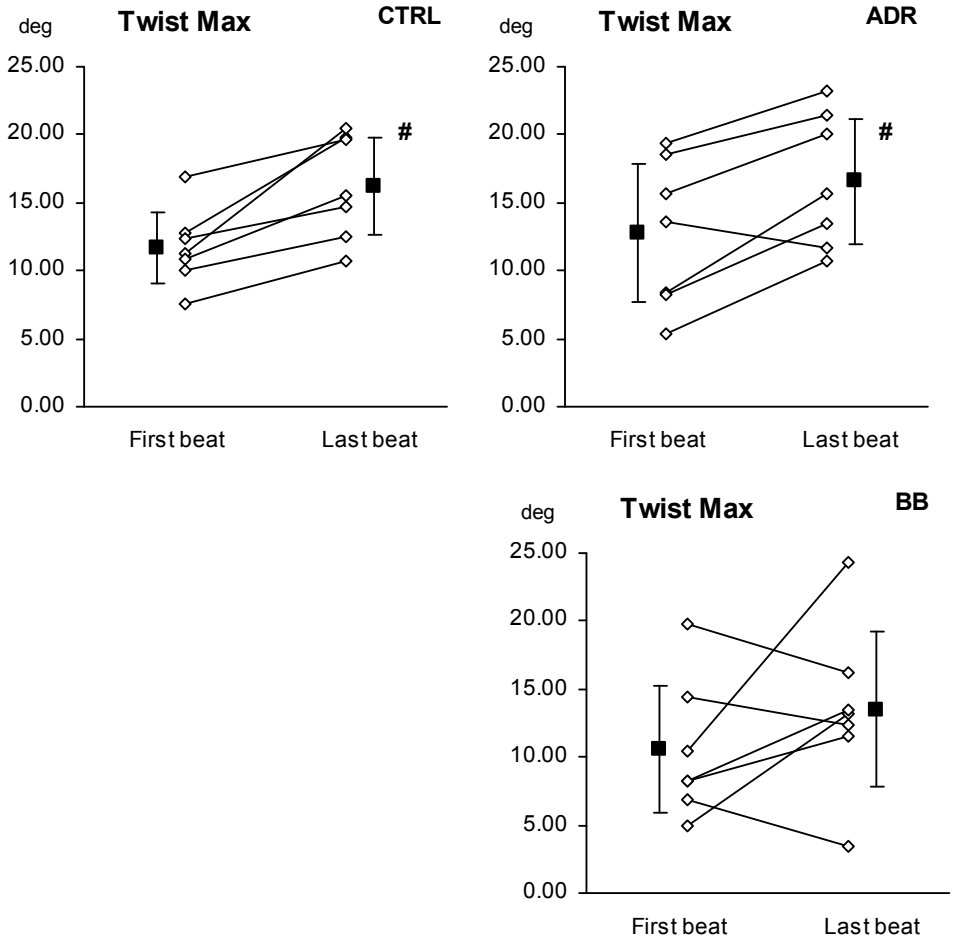

Figure 23. LV twist changes for the first and last beat in a sequence of eight consecutive beats in a vena cava occlusion manoeuver were analysed by speckle tracking imaging. Left ventricular twist increased significantly in control group and in positive inotropic condition. There was a trend to increase but no significance was reached in negative inotropic condition. Both individual and grouped values are presented. CTRL=control group, ADR=adrenaline group, BB=beta-blockade group. # = $p < 0.05$ using Wilcoxon's signed rank test vs. first beat

DISCUSSION

Physiological implications

Study I

In Study I, the model of controlled load alteration over a family of heart beats is demonstrated. There is a progressive and highly linear relation between beat number and EDV, or preload. This very highly controlled progressive unloading occurs in a load-'region' that is in the normal working range for the heart. This is the same for Studies I, III, IV, and is important because the load intervention does not demonstrably awaken the baroreflex, and therefore is highly reproducible. Over this sequence, myocardial contractility is unchanged from beat to beat. It is possible to also read in the load increase sequence after the vena cava balloon is deflated. We have chosen the first beats rather than a more prolonged apnoeic sequence in order to avoid significant carbon dioxide retention, reflex stimulation and possible confounding factors related to that. This is relevant when there are many measurement sequences.

The physiology behind the MPI, or the relation between different intervals in the heart cycle is complex. The idea of contrasting the isovolumic interval times with the ejection time is thought to help make the parameter more independent of heart rate, since presumably all the cycle intervals change in some relative proportion to each other when heart rate changes. It is less intuitive how the parameter would be resistant to changes in load. It is widely thought that with marked systolic dysfunction, the ECG QRS interval is prolonged. In theory, increasing degree of dyssynchrony and diminished force generation (hydraulic power) in systolic dysfunction should lead to less ejection and smaller stroke volume. By ejecting against less hydraulic resistance the ejection time can be longer and consequently the MPI higher. This is not consequently so, as the effect on the isovolumic phases is more complicated. Our ejection time results, analysed for inotropic conditions, supported this somewhat (Study I, Table 1), though there were not large differences in all group. The negative inotrope (isoflurane) group showed a tendency to support this, though this test was confounded by the fact that the negative inotrope group had lower systolic pressures and hence lower systolic loads. Also, isoflurane was a mild negative inotrope in this setting, in combination with high dose barbiturate. These negative inotropic results might have been more distinct if we had chosen an stronger negative inotrope with unchanged systolic pressure.

Study II

The pathophysiological effects of endotoxin on myocardium were used here as an acute global injury model to generate a mild or moderate amount of dyssynchrony. One clear early effect of endotoxin on the heart is early right ventricular pressure overload from pulmonary hypertension. It was unclear how much effect

this right heart pressure overload and alterations in ventricular interactions would have on left ventricular dyssynchrony. In the septic state, which the endotoxin infusion approximates, there are direct toxic effects on myocardial cells, which are well recognised to lead to effects on both diastolic and systolic function (138), namely acutely increased diastolic compliance and decreased systolic function. The subject (or animal) responds to this toxic insult in the model with an increased sympathetic nerve system expression, often compensating for the toxic injury-related systolic dysfunction, since myocardial cells at rest have quite a bit of contractile reserve. This was the case for our experiments. There was no net change in the load-independent parameters of contractile function.

Still, there was a progressive increase in segmental mechanical dyssynchrony. The mechanism is unclear, but I can speculate that something about the toxic effects disturbed the uniformity of contraction. The pulmonary hypertension and right heart overload appeared to be a bit progressive, and we know from other experiments in our lab that for many hours of high dose endotoxin infusion leads to progressive circulatory decompensation in the pig model. It is possible that this progressive right heart mechanical overloading lead to progressive effects on left heart filling and regional systolic motion. It is also possible that progressive myocardial injury from endotoxin infusion lead to cellular oedema, and this could lead to disturbances in electrical impulse spread or in local force distribution.

One might expect that at higher loads, the likelihood for more mechanical dyssynchrony would be higher. The degree of load and amount of dyssynchrony have a logical connection when the heart is over distended. Dyssynchrony should be less when overdistention is eliminated. This model presented no left ventricular overdistension. If anything, with maximal pulmonary hypertension, the left ventricle was underloaded (as shown in the LV volumes, Study II, Table 1). Since the LV was never highly loaded, this gives more strength to the finding that more time with endotoxin infusion was associated with more dyssynchrony. On the other hand, in this normally loaded LV model, dyssynchrony did not change during the vena cava occlusion sequence. This also supports the finding that dyssynchrony correctly identifies the global toxic injury with endotoxin infusion. Since the dyssynchrony parameters are load-independent, they are more specific for changes in ventricular function.

Study III

Tissue velocities are now relatively simple to measure. It is another matter how much one a local tissue velocity represents local conditions during systole and how much it represents a global aspect of the ventricle. The study design included measurement of tissue velocities close to the atrioventricular plane, in order to maximise the reproducibility of the measures, as well as to make a measurement which reflected as much as possible a global systolic function. One aspect of tissue velocities is that if the heart was dramatically underloaded (as in bleeding and shock), then there would be less intraventricular or hydraulic force generated in the

ventricle, and presumable higher peak velocities, since there would be no opposing hydraulic forces. We have not studied this extreme case in this model, but based on an extrapolation from this thought, we would expect that systematic reduction in intraventricular hydraulic force would lead to increases in peak systolic tissue velocities. The model here was set up to test this issue where the myocardial contractile status would not change from the start to the end of the vena cava occlusion sequence, though there would be a ventricular volume reduction of at least 25%. This was a rigorous setting to test tissue velocities for load dependence. The response that we observed was not repeated in every group and every inotropic condition, but a pattern of load independence for peak systolic velocity was clear.

Peak strain behaved differently compared to peak tissue velocities. Strain has an indirect relation to velocity, since it is force in the muscle fibre that determines both: the more force, the higher the velocity and the more the displacement or deformation of muscle during systole. There has been much work to try to correlate isovolumic acceleration at the start of systole with LV contractility, though a clear relation has not been resolved. One issue is that tissue velocities and strain rate are so sensitive to many factors, that the signals are often difficult to reproducibly acquire in settings where there are physiological challenges to heart function. We initially tried to include isovolumic acceleration and strain rate in our study here, but with the dimension of the load alteration, we were not able to acquire reproducible results.

Study IV

Ventricular twist is a fascinating phenomenon when first observed in a 'living' setting, though it is not at all surprising once one appreciates the architecture of the multiple and complex 'bands' which encircle the ventricles, and which make up a significant part of the ventricular wall. It is not clear how much or how little ventricular twist contributes to mechanic function of ejection. We can presume that it is there for a reason, and that there is some relation between the normal architecture/function of the heart and optimal heart performance in ejection. There is a complex relation between these different fibre bundles and bundle directions which also seems to contribute to optimal 'compression' and wall deformation.

In Study IV, we used our stable model of controlled load alteration as well as inotropic intervention. The load ranges were normal, so that twist was tested in the normal resting operating range of the heart. Untwist was also tested. If we consider the extreme case of the very unloaded ventricle, we might presume that elastic forces in the heart would lead to untwist after systole, and that the twisting forces would be very prominent in the setting where there was very low intraventricular hydraulic force. With more ventricular overloading, if the twist forces are relatively weak, in relation to the intra-ventricular hydraulic forces during systole (overloaded and high afterload), then we would presume that twist effect would be reduced compared to normal. We have tested twist in the setting of normal load (controlled). Our findings for untwist were as expected, that this event

became relatively more prominent with less load and with more inotrope. Twist behaved the same way, in response to load reduction. There was a more marked increase in twist during this 20% ventricular volume decrease than there was from strong positive or negative inotrope. From this we might deduce that twist in the normally contractile heart is relatively maximal. In this study, there were relatively few experiments, and more would be needed to clearly establish a relationship of these inotropic interventions to twist change.

Clinical implications

Study I

Our results establish beyond a doubt that MPI is load-dependent, and that if MPI is to indicate anything clearly about a change in heart function, that it needs to be presented together with an index of load. Alternatively, MPI can be presented from serial measures where load has been maintained unchanged, if it is going to reflect any change in myocardial function. This later case is not clinically practical. The MPI has been used to assess heart function. When we combined all groups, the ejection time was very strongly related to load, while the isovolumic intervals were not at all responsive. On the day that I write this text, MPI (or myocardial performance index) gives between 2000 and 3000 results for a Medline search for publications in peer reviewed scientific journals, and almost none of them have reported MPI together with a reliable index of load. It is rare that blood pressure is reported in these publications, and it is not common that blood pressure is measured during echocardiographic examinations (though this, I hope, is changing).

Study I presents convincing evidence that the same MPI level can be observed in the same subject/animal with 3 widely different inotropic conditions. This does not mean that all previous studies employing MPI need to be discarded, though many of them probably should be re-evaluated at least a bit. Rather, in the future, when MPI is going to be used for serial measurements of heart function, that it needs to be interpreted together with chamber size and arterial blood pressure.

We did observe some kind of relation of MPI to contractile state, and this was discerned when coupling MPI to an index of chamber size (EDV). There might have been a difference sometimes in the character of MPI change in relation to load decrease for each of the inotropic conditions (more steep relation with negative inotropic conditions, or tendency for higher MPI with the negative inotropic state compared to the others, if measured at exactly the same EDV, see Figure 14), though this relation appears to be quite complex, and further analysis of this was beyond the scope of the study. To paraphrase Karl Marx, '*…one test of truth is the length of time that is believed*.' Since MPI has been employed in clinical studies for soon 20 years, it may be that people now are less likely to approach MPI with a critical viewpoint.

Study II

The clinical applications of ventricular long axis segmental dyssynchrony in this form is limited by the high degree of invasiveness for acquiring signal, though this probably would change if the same signals could be acquired non-invasively. The segments that are analysed here are not equal in size. There is a larger mid-ventricular segment which dominates. More importantly, the long-axis segments do not directly conform to functional regions of the heart. Not by coronary circulation and not necessarily by function segments. To follow a blood cell along its path in the heart, it flows in during diastole, and then is ejected in a swirl or vortex (76). This segmental model breaks down the ventricular ejection moment into static sections, though the actual blood flow may appear to be quite different. In the setting of diseased myocardium, the segments may conform poorly the diseased aspect of the ventricle.

In our study, we examined an global toxic inflammatory heart injury, which is not uncommon in the clinical setting. To the extent that this dyssynchrony measure can be sensitive in detecting global cardiomyocyte or ventricular dysfunction which is not shown by pressure or other global performance indicators, it might be useful to help identify if a patient is getting sicker (more toxic/inflammatory effect on the heart muscle) or better (less effect/less dyssynchrony in the ventricle).

Study III

At the beside, where patients demonstrate general circulatory insufficiency in an acute critical illness, but where it is not clear to what extent the heart is involve in the circulatory insufficiency, it would be ideal to have a readily available, easily applied, non-invasive, user-independent, means to resolve the therapeutic question of need for/or effect of a cardiotonic or vasoactive intervention (pharmacological). Most of the clinical measurements of the central circulation that are used in clinical practice at the bedside involve some aspect of what happens inside the ventricular chamber. They are not directly assessing what happens in the ventricular wall. It may be that what happens in the ventricular wall is at least as important when considering treatment aimed at the heart specifically.

The general clinical application of routine collection and analysis of myocardial tissue velocities is soon coming. The reports on the strength of the relation of peak systolic velocity to contractile function have been quite mixed in the literature, but I believe that our study has demonstrated convincingly that when all the relevant factors are controlled experimentally, peak systolic velocity is load-independent, and has a strong relation to contractile status changes during serial measures. This supports the routine use of this parameter for serial measurement in individual patient where quantification of myocardial function is of interest for clinical decision-making. To the extent that there is regional disease or injury in the myocardium, then the echocardiographic examination must also catalogue this in order to be able to find the tissue velocity to be representative for a widespread myocardial condition.

Tissue velocity is used most commonly today for identification of timing of systole for different regions of the ventricular contraction, during for example stress echocardiography for diagnosis of ischemic heart disease or myocardial viability, and also for pacemaker resynchronisation optimalisation. Still, I believe that measurement of peak systolic velocities will also become established as a means of serial study of heart function in both the acute and chronic settings.

Study IV

Twist during systole, and untwist during diastole, are mechanical aspects of heart function that are impossible to ignore once one is aware of them. While these parameters are not widely available and implemented in clinical practice today, there is reason to believe that twist and untwist are strong markers for systolic and diastolic performance. In our study, they were demonstrated to be load-dependent, just as many other ventricular performance indicators such as cardiac output, dP/dt or ejection fraction. Circumferential velocities are the subject of intense study today, and it is reasonable to expect that they will be noted in the future in routine echocardiographic examinations as one indicator of healthy or impaired ventricular performance.

Methodological considerations

Echocardiographic applications have some degree of variation in reproducibility for measurements like tissue velocity (139). Factors which contribute to this variability include the quality of echo signal acquisition, chosen frame rate and resolution of images/signals, chosen filtering of ultrasound signal, the complexity of the structure which is being interrogated (in relation to the amount of structure which is being combined into a measurement), operator skill and attention, and perhaps other things. For tissue velocity measurements, tracking of the same area of the heart while it moves within the frame is a source of variability. Also for tissue velocity measurements, the size of the region of interest (the operator-identified area to be quantified) is the area where the mean velocity is measured, though there can be wide variations in local tissue velocities, and these are averaged. Then, there is the matter of interpreting complex waveforms and matching these to heart cycle phases. For strain, the strain length adds an element of variability, and strain length is the distance over which deformation is measured and reported.

Possibly the largest contribution to variability of some echocardiographic measurements is the difference that is reported when two different observers try to measure the same thing (139). Differences can be observed when the same observer tries to measure the same aspect or event in the heart at different points in time. Offline measurement routines also can contain some degree of variability, when it involves placing a curser manually. We did not try to address this form of variability in the study design, since this project was more hypothesis generating. The measurement sequences were standardised, but there were 2 echo operators

working together during recording, and the offline measurements were performed by myself. I have been very ambitious with the technical aspects of optimal measures, but there still is a chance that there was variability and potential observer bias that has slipped into these results since there was a single echo operator and basically single measurement.

Speckle tracking in the left ventricular is a method which is sensitive to artefact, in part because the 'speckles' themselves might be considered a type of artefact (something generating a scatter signal), and therefore other artefacts can be readily included in the rather advanced segmental calculations. In our series with speckle tracking, there was a 7.5F left ventricular catheter with the pigtail in the apex. This did disturb some of the data collection, at least as far as the automatic ROI setting. This ROI in these cases needed to be manually set. All measurements were controlled for correct ROI position.

There was not a reproducibility issue with the reference measurements for load and contractile status, left ventricular pressure volume. There are issues concerning accuracy of the volume measurements derived from conductance volumetry. The analysis of ventricular pressure and volume to derive load-independent parameters of contractile function, or even just simple volume, are quantitative and highly reproducible, though it is difficult to corroborate exact ventricular volumes by other methods. Perhaps this will change as 3D echocardiography techniques continue to develop. There are very reproducible conductance volumetry calibration steps (and zero offset measurements), which I have described earlier, and these steps are combined to optimise the volume calibration, though still there is some degree of uncertainty since there is no other readily available method to measure LV volume throughout the heart cycle with high resolution, with which to compare to the conductance method. Still, the most important thing for assessment of function and function change is a reliable relative volumetric assessment. This is judged to be reliable.

The controlled load alteration in this balloon vena cava occlusion model is highly reproducible, though there can be problems with assessments of sequences if there were dysrhythmias. The inotropic intervention was based on doses from earlier lab experience. The ideal test groups would have been different grades of negative inotropic effect. In these juvenile pigs, the relatively large doses of beta blocker and calcium channel antagonist produced relatively more blood pressure drop than negative inotropic. This may have to do with the circulatory physiology of the pig. It was, however, not easy to produce a moderate, severe, or clearly graded degree of negative inotropic effect. The echo parameters have their main clinical value for evaluating patients with heart dysfunction. With respect to this, positive inotropic experimental interventions in the model have less clinical relevance, and much of our focus in interpretation of our results focused on the control and negative inotropic (or cardiac injury) groups.

Future directions

Other promising echocardiographic parameters are of interest in this research line, as far as validation for load-independence and relation to contractile status changes. We have a stable and reliable experimental platform to test new parameters, with a very strong reference methodology to assess preload and ventricular performance in many aspects. With this platform, I am to continue to evaluate echocardiographic parameters which show clinical promise.

These same non-invasive assessments of the heart need to be well validated and implemented in clinical practice. After this lab experimental series, it is reasonable to move, with at least some of the parameters that we have examined here, to the bedside for assessment of patients whose myocardial performance is dynamic. I hope to work steadily to help to establish many of these principles of assessment of ventricular performance and load relations into my own and our own local practice in the intensive care unit. I hope to expend the same type of research activities into the perioperative and intensive care setting where the best possible rapid assessment of myocardial dysfunction and response to therapy is needed every day.

CONCLUSIONS

- The 'myocardial performance index (MPI) is strongly load dependent, and can vary widely in value for the same contractile status if the load is varied.

- Further work is needed to establish the relationship of MPI to contractile status.

- The mechanical dyssynchrony measures that I studied were not affected by load alteration in health, and they are load-independent even in the setting of increased mechanical systolic dyssynchrony resulting from acute endotoxin infusion.

- Left ventricular systolic dyssynchrony measures do not appear to be greatly affected by the early acute pulmonary hypertension as tested in our pig model.

- More study is needed to validate the range of parameters of mechanical dyssynchrony in health and disease.

- Peak systolic myocardial tissue velocity (PSV) is a clinically robust parameter of LV regional and global performance under changing load.

- Peak systolic myocardial strain seems to be load-dependent, and has no clear relation to inotropic changes in serial measures.

- These findings support a broader use of PSV in serial measures in patients to assess changes in ventricular function.

- Left ventricular twist and untwist are load-dependent in this pig model.

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Populärvetenskaplig sammanfattning på svenska

Med teknikens utveckling har sjukvården nu många nya metoder (inklusive ekokardiografiska) för att undersöka hjärtats funktion. Pålitligheten hos dessa nya metoder att spåra och med exakthet mäta hjärtas förmåga att pumpa blod behöver granskas. För att behandla patienter med cirkulationssvikt, där hjärtat kan vara inblandat, behöver man validerade mätmoment för att identifiera patienter som behöver hjärtstöd och validerade mätmoment även för att följa effekten av terapeutiska interventioner.

Vi har testat 4 olika moderna metoder i en stordjurs experimentell modell. Detta för att se hur mycket metoderna påverkas av ändringar i hjärtats kontraktilförmåga och hur mycket de påverkas av mängden blod som fyller hjärtat innan det slår. Vi har studerat relationen mellan de olika intervallerna i hjärtats slagcykel. Vi har studerat om olika segment längs hjärtats vänsterkammare slår olika under kontraktionsfas, när det uppstår en global skada. Vi har studerat fokala vävnadshastigheter och hur starkt de spårar kontraktilförmågan under systole och hur starkt de påverkas av hjärtats laddning eller mängden blod i kammaren innan kontraktionen. Vi har studerat hjärtats ”twist aspekt”, där hjärtspetsen och hjärtbasen vrider sig under kontraktionen samtidigt som hjärtats yttre väggar drar in och upp mot hjärtats centrum.

Vi har funnit att hjärtats fyllnadsgrad har en stark påverkan på de flesta parametrarna av hjärtprestationen , inklusive ’myocardial performance index’, men inte på ’long-axis segmental dyssynchrony’. Vi har funnit att maximal vävnadshastighet verkar vara oberoende av hjärtats fyllnadsgrad, men stämmer väl med kammarens interna kontraktilförmåga. Vi har funnit att vänsterkammarens twiströrelse påverkas av kammarens fyllnadsgrad. Vi planerar att fortsätta studera de mest lovande av dessa parametrar i patienter där hjärtfunktionsnedsättning är misstänkt.

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