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The usefulness of continuous hemodynamic monitoring to guide therapy in patients with cardiopulmonary disease

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"A single day is enough to make us a little larger or, another time, a little smaller"

Paul Klee

"Pygmies on the shoulders of giants see further than the giants themselves"

Stella Didacus

Contents

Abstract

Introduction: Cardiovascular disease, whether secondary to myocardial injury, pulmonary hypertension or renal failure, have high morbidity and mortality. New treatments have improved quality of life and survival, but hospitalization rates remain high. Continuous hemodynamic monitoring allows for a new perspective in cardiovascular disease management allowing for treatment strategies based on measurements performed while the patient tends to normal daily activities.

Feasibility: Hemodynamic monitoring by the means of an implanted pressure sensor has been shown earlier to be accurate in pressure measurement, safe to implant and stable in measurements over long-term. This thesis looked at acute and long-term stability of an oxygen sensor measuring mixed venous oxygen saturation from the right ventricle (Study I). The oxygen sensor was implanted in nine patients with a conventional pacemaker indication and showed a good correlation compared to invasive methods over the first year and a stable response to non-invasive, submaximal exercise levels over six years. Study II established that one data point, the night-time minimum, from the 24-hour hemodynamic trend replicated hemodynamic values collected during a controlled rest in the clinician's office. This value is used as a "quick look" value to look for hemodynamic changes over time. In addition to the fully implanted lead and memory device, the hemodynamic monitoring system includes remote monitoring, e.g. sending the data stored in the implantable hemodynamic monitor to a secured website for review by the treating clinician. Study III described this telemonitoring system and demonstrated that the transmission rate was acceptable and apparently independent of age and disease stage.

Applicability: In patients with heart failure, peak VO2 has been shown to be a good predictor of outcome. However, maximal exercise tests are cumbersome to perform and involve risk for the patients. Submaximal tests, e.g. 6-minute walk tests are routinely used to evaluate patient status in the hospital clinic. Study IV compared hemodynamic response during maximal and submaximal exercise in 30 patients with heart failure. During submaximal exercise the pressures increased 70-80% and heart rate 90% of the change achieved during maximal exercise. Thus, submaximal exercise hemodynamic response could be a tool in patient assessment in patients with heart failure. Study V looked at five patients with pulmonary hypertension, treated with an inhaled prostacyclin analog, iloprost. The effect of the drug lasted shorter when the patients used the treatment at home than under supervision in the hospital. The treatment effect in both setting was shorter than previously demonstrated in other studies. The most probable explanation for this is that hemodynamic measurements occurred during normal, daily activities in Study V, while earlier measurements have been performed in stationary patients during invasive studies. Study VI found progressively increasing cardiac pressures between hemodialysis treatments in 16 patients with end stage renal disease. The pressure increase, especially after a weekend when hemodialysis treatment was withheld for an extra day, was in the same magnitude as seen in patients with heart failure before a volume overload event leading to hospitalization. These recurrent changes in cardiac pressures might result in myocardial damage. More frequent dialysis treatment might be beneficial and might prolong the time to develope a reduced ventricular function.

Conclusion: The hemodynamic monitoring system and its components are feasible and mixed venous oxygen might add value to the system. One single data point could be extracted from the continuous 24-hour measurements that mimic a controlled rest allowing for a "quick look" that can advise the clinician of possible changes in the hemodynamic trends. This thesis supports the use of implantable hemodynamic monitoring in patients with cardiovascular disease of different origin associated with compromised hemodynamics. These observations may help to evaluate disease progress and to make therapeutic decisions.

List of original papers

I Kjellstrom B, Linde C, Bennett T, Ohlsson Å, Ryden L. Six years follow-up of an implanted SvO2 sensor in the right ventricle. Eur J Heart Fail 2004; 6:627-34

II Adamson PB, Kjellstrom B, Braunschweig F, Magalski A, Linde C, Kolodiezj A, Cremers B, Bennett T. Ambulatory hemodynamic monitoring from an implanted device: components of continuous 24-hour pressures that correlate to supine resting conditions and acute right heart catheterization. Congest Heart Fail 2006;12:14-19

III Kjellstrom B, Igel D, Abraham J, Bennett T, Bourge R. Trans-telephonic monitoring of continuous heamodynamic measurements in heart failure patients. J Telemed Telecare 2005; 11:240-44

IV Ohlsson A, Steinhaus D, Kjellstrom B, Ryden L, Bennett T. Central hemodynamic responses during serial exercise tests in heart failure patients using implantable hemodynamic monitors. Eur J Heart Fail 2003; 5:253-59

V Fruhwald FM, Kjellstrom B, Perthold W, Watzinger N, Maier R, Grandjean PA, Klein W. Continuous hemodynamic monitoring in pulmonary hypertensive patients treated with inhaled iloprost. Chest 2003; 124:351-59

VI Kjellstrom B, Braunschweig F, Löfberg E, Fux T, Grandjean P, Linde C. Progressive increments in right ventricular pressures between hemodialysis sessions recorded by an implantable hemodynamic monitor. Submitted Nephrol Dial Transplant 2007

Abbreviations

ESC	European Society of Cardiology
AHA	American Heart Association
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
NYHA	New York Heart Association
HIV	Human Immunodeficiency Virus
USA	United States of America
ADHERE	Acute Decompensated Heart Failure National Registry
IHM	Implantable Hemodynamic Monitor
COMPASS-HF	Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure
FDA	Food and Drug Administration
ICD	Implantable Cardioverter Defibrillator
REDUCE-HF	Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients with Chronic Heart Failure
RVSP	Right Ventricular Systolic Pressure
RVDP	Right Ventricular Diastolic Pressure
ePAD	estimated Pulmonary Artery Diastolic Pressure
EPR	External Pressure Reference
IRM	Interactive Remote Monitor
ISP	Internet Service Provider
LVEF	Left Ventricular Ejection Fraction
USRD registry	United States Renal Disease Registry

Introduction

Hemodynamics – a history

The movement of blood, hemodynamics (hemo = blood, dynamics = movement) has intrigued people for centuries. In the early teachings (1) it was believed that the ingested food supported the formation of blood in the liver and from there it was transported through the body. The main function of the right ventricle was thought to be the cleaning of the blood so that impurities could be disposed of by the lungs during exhalation. The cleaned blood was then moved from the right to the left by pores in the wall separating the ventricles. Variations of this belief lasted well into the 16th and 17th centuries and it was William Harvey (1578-1657) in the 17th century that realized that the venous valves directed the blood in only one direction. Thereby, the cardiopulmonary system was defined as a one-directed, closed circuit where the right heart pumped the blood to the lungs and the left heart to the rest of the body (2).

The development of the cardiac catheterization techniques, as used today, was started in the mid 19th century with animal studies, initially using glass tubes that were inserted in the vessels and advanced to the heart (1). The first documented human catheterization was performed by Werner Forssmann (1904-1979) who published his results in 1929 (3,4). He introduced a urologic catheter in a vein in his left arm about 30 cm, walked to the x-ray lab and there advanced the catheter all the way to the right ventricle. This achievement led to a dismissal from his hospital position (5) and that he received the Nobel Prize in Medicine 30 years later (1956). The Nobel prize was shared with Andre Cournand (1895-1988) and Dickinson Richards (1895-1973). They utilized right heart and pulmonary artery catheterization in patient care and worked to achieve a better understanding of the cardiac function. Their pioneering work was followed by further refinements of the techniques and in the 1950s, Sven-Ivar Seldinger (1921-1998) developed the percutaneous approach for the introduction of cardiac catheters, a technique widely used today (6). Almost 20 years later (7), Harold James Swan (1922-2005) developed the balloon-tipped catheter for easier advancement into the heart and pulmonary artery and William Ganz (1919-) incorporated the thermodilution method of measuring cardiac output. Their work resulted in the Swan-Ganz catheter, still used in millions of catheterizations every year.

"The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the venous artery to the lungs, spread through its substances, be mingled there with air, pass through the arterial vein to reach the left chamber of the heart and there form the vital spirit"

ibn al-Nafis, ca. 1240

"in cases of shock…it may be desirable to deliver medications directly to the heart in a less dangerous fashion, namely the catheterization of the right heart from the venous system. Experiments on cadaver were productive. I was able to catheterize any vein in the anticubital fossa and…reach the right ventricle…I next undertook experiments on a living subject, namely myself"…

Werner Forssmann

"Novelties should not be rejected precipitously…dissent should be tentative rather that unyielding"

Andre' Cournand

Hemodynamics – the present

Today, invasive hemodynamic measurements, such as right heart or pulmonary artery catheterizations, are mostly used in the intensive care setting, peri- and post-operatively and in the management of pulmonary hypertension and candidates for heart transplant. However the number of catheterizations performed every year is declining (8). Non-invasive methods such as Echo-Doppler cardiography have simplified hemodynamic measurements and provide non-invasive information, similar enough to be used in the routine care. Also, several non-invasive techniques to measure flow, volume or cardiac output have been developed and are used to evaluate patients in the clinical setting. Taking into account a higher cost for the health care system and increased risks for the patient that invasive measurements might incur, the decline of use is not surprising.

This change is also reflected in the current heart failure guidelines. The ESC guidelines (9) for treatment of chronic heart failure suggest that *"Routine right heart catheterizations should not be used to tailor chronic therapy"*. The AHA heart failure guidelines (10) are also stringent in the use of hemodynamic measurements. They write *"There has been no established role for periodic invasive or noninvasive hemodynamic measurements in the management of heart failure"*. This comment relates to that drug treatment is generally prescribed based on symptoms and that most clinical trials did not use hemodynamics as end points. However, the AHA guidelines continue with *"Nevertheless, invasive hemodynamic measurements may assist in determination of volume status and in distinguishing heart failure from other disorders that may cause circulatory instability, such as pulmonary diseases and sepsis"*.

The evidence from nonrandomized studies regarding the value of tailoring therapy by right heart or pulmonary catheterizations to predict long term benefits for heart failure patients is conflicting (11-18). Only one randomized study, the ESCAPE trial, has evaluated the usefulness of catheterizations in patients admitted to a hospital with acute heart failure (19). In this study 433 patients with acute heart failure were assigned to receive therapy guided by clinical assessment plus right atrial and pulmonary capillary wedge pressure or to therapy guided by clinical signs alone. In the pulmonary catheter group, the target was a pulmonary capillary wedge pressure ≤15 mmHg and an atrial pressure of ≤8 mmHg. During the hospitalization, significant improvement in signs and symptoms of volume overload was achieved in both groups. In the 6-months following discharge there was no additional mortality or morbidity benefit from pulmonary artery catheterizations.

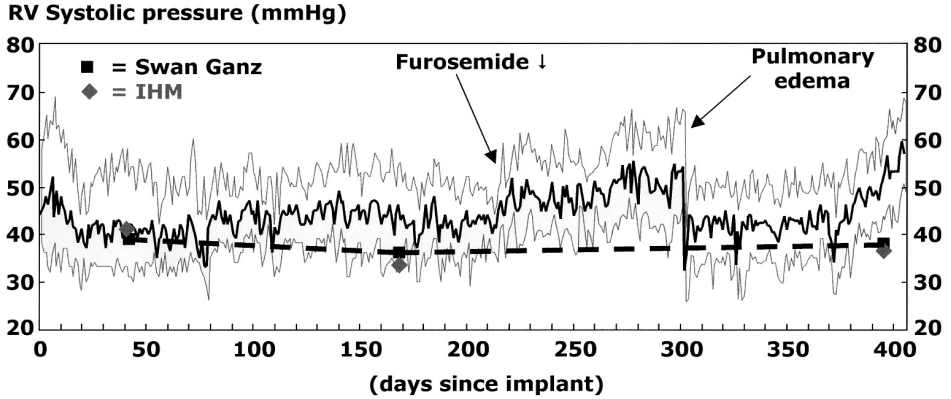

Figure 1. Illustrates the relation between intermittent right heart catheterizations and continuous hemodynamic monitoring. The graph shows a one year trend of continuous right ventricular systolic pressure. The solid black line represents the daily medians and the gray lines are the daily range (6th and 94th percentile of daily value). The black squares shows values from a Swan Ganz catheter and the gray diamonds from the implantable hemodynamic monitor, both measured simultaneously during a right heart catheterization. The dotted line shows the trend according to the "spot checks", performed with invasive tests.

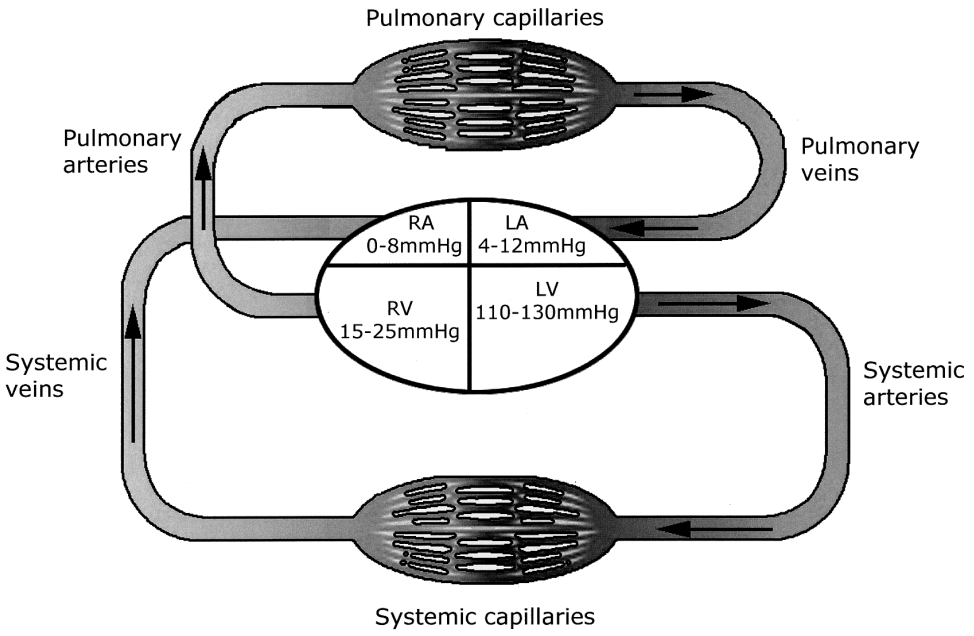

Figure 2. The cardiovascular system, see text for more details.

Although acute hemodynamic data does not seem to predict clinical outcome, long term hemodynamic data over months or years might positively impact patient care or prognosis (20). The difference may lie in the relationship between acute and chronic hemodynamic patterns (Figure 1). Multiple variables such as discomfort from the invasive procedure, drug compliance, diet, exercise or changes in sympathetic tone may unduly influence single, acute measurements. Long-term non-invasive measurements on the other hand may remove inaccuracies found in acute determinations.

Hemodynamic Measurements – what is normal?

The cardiovascular system is a closed circuit with the heart as a central pump that moves the blood into the pulmonary and systemic vascular beds (Figure 2). Included in the cardiovascular system, in addition to the heart and the blood, are the arteries that regulate the blood flow and deliver oxygenated blood to individual organs dependent on metabolic need. It also includes the capillaries, where the exchange of nutrients, respiratory gases and metabolites takes place and the veins that return the deoxygenated

Table 1. General hemodynamic premises and normal pressure values (21)

Variable	Pressure (normals at rest)
CVP ≈ RAP ≈ RVDP	0-8 mmHg
RVSP ≈ PASP	15-25 mmHg
LVDP ≈ LAP ≈ PCWP	4-12 mmHg
LVSP ≈ ASP	110-130 mmHg
PCWP related with PADP	8-15 mmHg

ASP = aortic systolic pressure, CVP=central venous pressure, LAP=left atrial pressure, LVDP=left ventricular end diastolic pressure, LVSP=left ventricular systolic pressure, PADP=pulmonary artery diastolic pressure, PASP=pulmonary artery systolic pressure, PCWP=pulmonary capillary wedge pressure, RAP=right atrial pressure, RVDP=right ventricular end diastolic pressure, RVSP=right ventricular systolic pressure.

blood to the heart. The veins also function as a reservoir and during resting conditions, approximately 70% of the blood volume resides there. Redistribution of blood volume to other parts of the vascular system is achieved by venoconstriction upon need and can occur instantly or over hours or days.

Normal cardiac pressure values at rest and the general premise of their relationship are presented in Table 1.

Cardiac output defines the amount of blood leaving the heart during one minute. It is calculated as the product of stroke volume and heart rate. In a healthy heart the resting cardiac output is 4-6 L/min, thus at a heart rate of 70 bpm, the stroke volume is 55-80 ml. However, the total volume in the left ventricle is 120-140 ml which means that only 50-75% is ejected with each beat. This is measured as the ejection fraction. The blood remaining in the ventricle is the reserve volume that can be utilized during increased flow demand.

Stroke volume is determined by the preload (stretch of the myocardial fibers, myocytes), the afterload (vascular resistance), the contractility (volume and contractile force) and the synchrony of the ventricles. This is illustrated by the Frank Starling law that shows the relationship between the ventricular end-diastolic myocardial fiber length and the ventricular performance. As these measurements are not available outside the experimental lab, the myocardial fibers length is measured as the ventricular end-diastolic pressure and the performance as the stroke volume (Figure 3A). According to the Frank Starling law, an increase in venous return will increase the ventricular end-diastolic pressure and thereby stretch the cardiac myocytes prior to contraction (Figure 3C). The stretch increases the sarcomere length, which results in an increased generation of force. This enables the heart to eject the additional venous return and thereby increase the stroke volume. One can think of it as a slingshot, the harder you pull

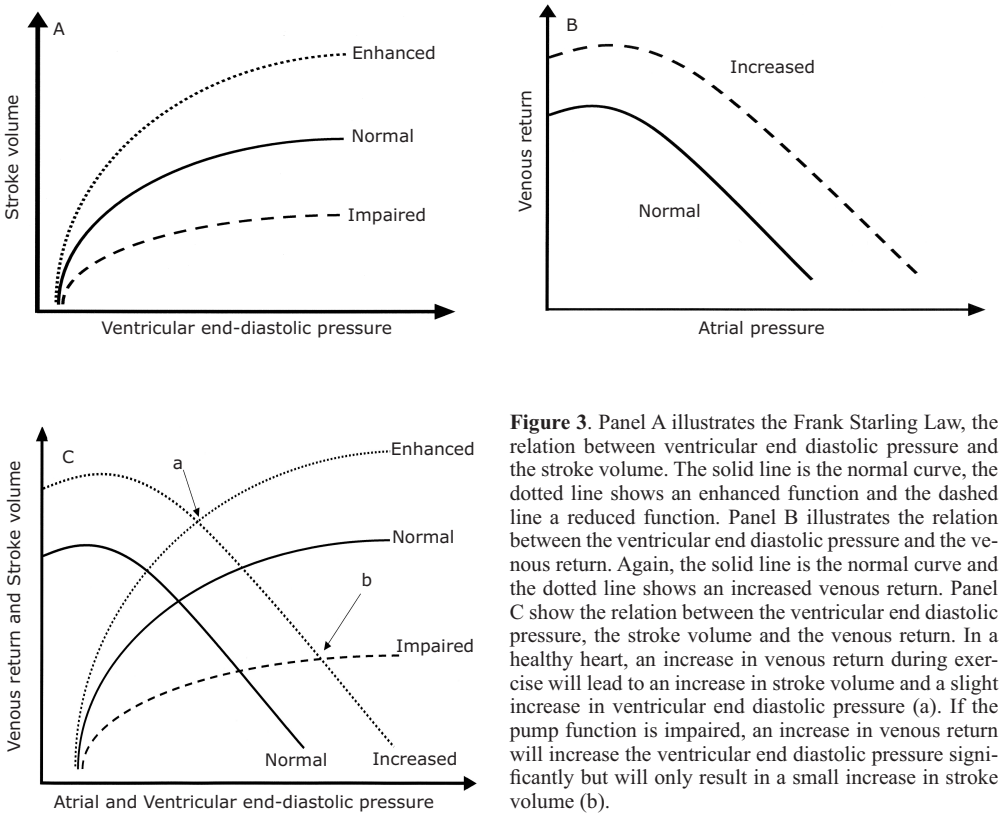

Figure 3. Panel A illustrates the Frank Starling Law, the relation between ventricular end diastolic pressure and the stroke volume. The solid line is the normal curve, the dotted line shows an enhanced function and the dashed line a reduced function. Panel B illustrates the relation between the ventricular end diastolic pressure and the venous return. Again, the solid line is the normal curve and the dotted line shows an increased venous return. Panel C show the relation between the ventricular end diastolic pressure, the stroke volume and the venous return. In a healthy heart, an increase in venous return during exercise will lead to an increase in stroke volume and a slight increase in ventricular end diastolic pressure (a). If the pump function is impaired, an increase in venous return will increase the ventricular end diastolic pressure significantly but will only result in a small increase in stroke volume (b).

the rubber band, the more force is accumulated and the longer the shot will be.

During exercise the cardiac output can increase 3-4 times compared to rest. However, the stroke volume can only increase 40-60%, thus the ability to increase heart rate is of key importance to increase blood flow to meet the metabolic demand during exercise. At low levels of exercise the increase in heart rate and contractility are mostly a result of a reduction in vagal tone while at higher levels of exercise, after the anaerobic threshold has been reached, the sympathetic nervous system becomes dominant. This results in activation of catecholamines, that increases the heart rate and cardiac contractility. Catecholamines will also cause vasoconstriction and increased systemic vascular resistance and thus an elevation in arterial blood pressure.

Another important factor in the regulation of cardiac pressures and flow is the renin-angiotensin-aldestorone system. Renin is produced mainly in the kidneys in response to decreased kidney perfusion and plays an important role in the production of angiotensin II and aldestorone release. Angiotensin II is a potent vasoconstrictor while aldestorone enhances sodium and water reabsorption and reduces potassium reabsorption. The renin-angiotensin-aldestorone system is activated by changes in volume, like blood loss or decreased cardiac output. This will trigger vasoconstriction in peripheral vessels aimed to preserve the perfusion pressure to vital organs.

Measurements of intra-cardiac pressures are most commonly measured with fluid filled catheter techniques on the low pressure, right side of the heart. The catheter is introduced through a vein (femoral, brachial or subclavian dependent of clinician's preference) and advanced through the right atrium to the right ventricle and then commonly into a small branch of the pulmonary artery. By occluding the artery with an inflated balloon at the tip of the catheter, the pulmonary vascular system in front of the catheter will function as an extension of the catheter lumen. This will give an estimate of the left atrial pressure (≈left ventricular end diastolic pressure).
The techniques to monitor cardiac output are several, however, the Fick principle is believed to be the most exact method, often referred to as the "gold standard". The principle states that the total uptake of a substance by an organ is the product of the blood flow through that organ and the arteriovenous difference of the substance. In other words, cardiac output is measured as the relation between the oxygen consumption (difference in oxygen content in inspired vs expired air) and the arteriovenous difference (difference in oxygen content in the arterial vs venous blood):

$$\text{Cardiac output} = \frac{\text{Oxygen consumption}}{\text{Arteriovenous oxygen difference}}$$

This method needs access to venous and arterial blood sampling and analysis of the blood gases (oxygen content) as well as collection and analysis of the respiration gases. As this requires advanced equipment and results are not readily available, other, simpler techniques have been developed. Additional invasive techniques include thermodilution and dye dilution. Non-invasive techniques such as Doppler-ultrasonography, thoracic bioimpedance, pulse contour and helium re-breathing are readily available, though in general less accurate. Moreover, it is most often in the presence of low cardiac output that these methods are less reliable than the Fick principle. Hence the Fick principle is the preferred method in low cardiac output, especially in clinical research.

Heart failure

Heart failure has been defined as "a clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses" (22). It has also been described as "a clinical syndrome in which the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirement of the body" (23). Both definitions are fitting for this thesis that has a focus on hemodynamics. However, it is important to keep in mind that a change in hemodynamic measurements is only one of several aspects used to diagnose heart failure. According to the ESC guidelines

for treatment of chronic heart failure (9) the clinical diagnosis of heart failure therefore requires all three of the following criteria to be met: 1) symptoms of heart failure (dyspnea and fatigue) at rest or during exercise, 2) evidence of cardiac dysfunction and 3) response to heart failure treatment.

The prevalence of heart failure in Europe is approx 1-2% of the population (24). It is associated with frequent hospital admissions (25) and constitutes approximately 5% of all acute medical admissions (26) every year. In Sweden it is the most common discharge diagnosis within internal medicine and the prevalence of heart failure has been estimated to 220 000 persons or 2.5% of the Swedish population (27). Despite improved treatments, the 5-year survival-rate is less than 50% and in patients with severe heart failure, mortality approaches 50% annually (28,29).

The most common type of heart failure is impaired left ventricular function due to ischemia, myocardial infarction or hypertension leading to systolic or diastolic heart failure, or a combination of both. Right ventricular failure occurs more often secondary to left ventricular failure but also due to precapillary pulmonary vascular damage, right ventricular ischemia/ infarction or congenital heart disease.

In systolic heart failure, an increased ventricular volume leads to a stretch of the myocardial fibers (myocytes) and thereby contractile dysfunction and impaired emptying of the ventricle. Initially, despite the reduced ejection fraction, the increased ventricular volume might maintain a normal stroke volume or at least sufficient to satisfy the body's metabolic need at rest. Though, during exercise or at increased metabolic demand, the contractile force will not increase enough to maintain a sufficient cardiac output (Frank Starling law, Figure 3 A och B). Symptoms in mild to medium systolic heart failure are therefore often connected to fatigue and dyspnea at light to moderate exercise (forward failure). If impaired contractile dysfunction affecting the filling of the ventricle is predominant, the pressure will "back up" in the lungs and pulmonary congestion or edema might occur (backward failure).

Diastolic heart failure is characterized by impaired filling of the ventricle due to a thickening of the heart muscle. The ejection fraction is often normal or even increased, though the stroke volume might be decreased even at rest due to the decreased ventricular volume. Symptoms are similar to that of systolic dysfunction but dominated by dyspnea and pulmonary congestion.

Despite the different presentation of structural changes in the ventricle both systolic and diastolic heart failure are characterized by increased filling pressure. The myocardial strain will cause increased levels of catecholamines even at rest or low levels of stress. Therefore, during exercise the increase in catecholamine levels might be smaller than in a healthy heart and compensatory factors like increased heart rate and blood pressure might be dimished. The exercise capacity will be limited primarily by symptoms of dyspnea and fatigue and exercise may be terminated early, even before the anaerobic threshold is reached.

Hemodynamically, medical heart failure treatment aims to normalize the Frank Starling

"for when the phlegm descends cold to the lungs and heart, the blood is chilled; and the veins being forcibly chilled, beat against the lungs and heart, and the heart palpitates, so that under this compulsion difficulty of breathing and orthopnoea result"

"[The patient] appears yellow; the whole body is edematous; the face is red; the mouth dry; he is thirsty; and when he eats, respiratory quickens. In the same day at some times he may appear better while at others he is suffering acutely and seems on the verge of dying"

Hippocrates

Table 2. Comparison of hemodynamic values (night time minimum as defined in Study II), measured by the implantable hemodynamic monitor in three different patient populations.

	Heart failure (Study II, n=30)	Pulmonary artery hypertension (ref 34, n=22)	End stage renal disease (Study VI, n=16)
Right ventricular systolic pressure (mmHg)	41±15	73±24	29±7
Right ventricular diastolic pressure (mmHg)	10±6	13±7	5±5
Pulmonary artery diastolic pressure* (mmHg)	21±7	29±10	15±6

*ePAD, see description of the implantable hemodynamic monitor for details (page 21).

curve by changing the end-diastolic filling pressure and stroke volume relationship, e.g. by moving the curve up and to the left. Diuretics and venous vasodilators decrease the ventricular filling but do not change the stroke volume. On the other hand, arterial vasodilators and inotropes cause an increase in stroke volume but with only a small effect on the ventricular filling pressures. Treatment is therefore often designed to give a combination of these effects. The ESC and AHA heart failure guidelines recommend diuretics, angiotensin converting enzyme inhibitors, beta-blockers and aldestorone antagonists or angiotensin receptor blockers in patients with NYHA II-III heart failure and symptoms of volume overload (9,10).

Pulmonary arterial hypertension

Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure ≥25 mmHg with a capillary wedge pressure ≤15 mmHg, measured at rest by right-heart catheterization (30). The classification of pulmonary arterial hypertension include idiopathic pulmonary arterial hypertension (previous called primary pulmonary hypertension; cause unknown), familial pulmonary hypertension (an inherited genetic disorder) and pulmonary hypertension associated with other diseases or conditions, such as collagen vascular disease, congenital left-to-right shunt, portal hypertension, HIV infection, drugs and toxins. It is unclear whether the various types of pulmonary arterial hypertension share one common pathogenesis, but mechanisms such as impaired production of vasodilators (nitric oxide and prostacyclin) along with overexpression of vasoconstrictors such as endothelin-1 are generally affected (30). Treatment has therefore been focused on these pharmacologic targets to improve symptoms and slow the disease progress for patients with pulmonary arterial hypertension.

As the name implies, the disease affects the pulmonary arteries, and in particular the small arteries. It is characterized by vascular remodeling that result in a progressive increase in pulmonary vascular resistance. To move the blood through the non-compliant pulmonary circulation, the force of the right ventricular ejection has to be increased which results in increment of the right ventricular systolic pressure (Table 2). The pulmonary artery diastolic pressure is also increased due to the resistance to the diastolic blood flow. The increased workload of the right ventricle will lead to changes in the right ventricle such as hypertrophy and/or dilatation and ultimately to right ventricular failure. On the other hand, the left ventricular end diastolic pressure will not be increased as the post capillary vessels, the pulmonary veins, are not affected by the disease.

The prevalence of pulmonary arterial hypertension is low and the patient population in Europe and USA has been estimated to 130 000 (31). The mortality is high, median survival without treatment has been reported as low as 2.8 years after diagnosis (32). However, new treatments have improved these numbers and a recent report on long term treatment with an endothelin receptor antagonist (bosentan) showed survival rates of 85 and 70% after 12 and 24 months respectively (33).

In a literature search performed by *McLaughlin and colleagues* (30) it was shown that a worsening hemodynamic status is correlated to an increased mortality in patients with idiopathic pulmonary arterial hypertension, independent of therapy. The hemodynamic variables that best predicted survival were right atrial pressure, mixed venous oxygen saturation and cardiac output/cardiac index. Arterial oxygen saturation, mean pulmonary pressures, heart rate and cuff systolic pressure did not predict survival in a consistent fashion in these patients.

End stage renal disease

End stage renal disease is defined as complete or near complete failure of the kidney function to excrete wastes, concentrate urine, and regulate electrolytes. This usually occurs as chronic renal failure progresses and the function of the kidney is below 10% of normal. At this stage the kidneys are no longer able to maintain a functional level necessary for day-to-day life and dialysis or transplant is necessary to sustain life.

The kidneys main functions are 1) regulation of volume, 2) extraction of waste products, 3) regulation of the acid-base balance and 4) regulation of the electrolyte balance. They also play an important role in production and secretion of hormones such as renin, aldestorone and erythropoietin. These functions all aim to regulate the volume and composition of the body fluids, despite huge fluctuations created by variations in fluid and food intake.

Dialysis means transfer of solute (dissolved solids) across a semi permeable membrane and hemodialysis means “cleaning the blood”. In a simplified explanation; the blood is circulated through a dialyzer (artificial kidney) with two spaces separated by a thin membrane. Blood passes on one side of the membrane and dialysis fluid passes on the other. Waste products and excess fluid pass from the blood through the membrane into the dialysis fluid that is discarded. The cleaned blood is then returned to the vascular system. A hemodialysis procedure normally takes four to five hours, and commonly three treatments per week are prescribed (35,36).

In Sweden, approximately 6800 patients are on chronic hemodialysis treatment (37) and around 1200 new patients are added every year. Cardiovascular disease is a common complication to end stage renal disease and accounts for 40-50% of the deaths (38). Progressive increase in systemic vascular resistance due to vascular stiffening and loss of compliance is seen in patients on hemodialysis treatment (39). This contributes to ventricular failure and thereby volume overload and increased filling pressure. Co-morbidities such as hypertension, diabetes mellitus and anemia also add to the risk (37). In Europe the 5-year survival among hemodialysis patients is 50-60% (39,40) and in USA it is 30% (38). The reason for the lower survival rates in USA than Europe is not clear, though it has been speculated that shorter dialysis time (41), frequency and timing of dialysis e.g. night and weekend dialysis (42), cultural/race dependence, less involvement of nephrologists in the USA dialysis clinics (43) and less compliant patients (44) might increase the mortality.

Volume management – a challenge

In the ADHERE registry including 65 000 patients in the USA hospitalized for acute decompensated heart failure (45), symptoms of volume overload was the major reason for heart failure hospitalizations. Interestingly, 50% of the patients had preserved left ventricular ejection fraction. Similar data was reported in the EuroHeart Failure Survey (46). Despite effective volume management during the hospitalization, as indicated by significant weight loss, decrease in edema and jugular venous pressure (19), about 20% were readmitted for heart failure within 3 months (45,46) and a fourth of those were readmitted already within the first week after discharge (46). One possible explanation is premature hospital discharge, in fact 30% of heart failure patients still have symptoms of heart failure at the time of discharge (45). Furthermore, a study from a heart failure program (47) found that the majority of the medication changes in the first 3 months after discharge were adjustments of diuretics, indicating that the patients were not in a stable optivolumic state when they left the hospital.

Physical signs of congestion such as pulmonary rales, jugular venous distension or a third heart sound correlate only moderately with measurements of ventricular function (48,49). Therefore, early stages of volume overload might be missed during a routine clinical examination. For the patient at home, measuring changes in body weight by a scale is a simple method for volume monitoring and often the only one available. Patients are generally recommended to call their clinic when their weight has increased more than 2-3 kg over 2-3 days (9). However, few data exists to support these weight criteria and two recent studies even question its validity, either as an indication of clinical deterioration (50) or to prevent hospitalizations (51).

Patient compliance is another factor that impacts hospitalizations and when to seek care. In a literature study (52) it was shown that on average only 40% of the patients reported that they weighed themselves regularly (range 12-75%). The same review also reported on the delay in seeking care from the first awareness of symptoms. Dyspnea warranted contact after a median duration of 3 days while symptoms of edema, cough and fatigue was tolerated for a median of 7 days (52). Volume management in patients with ventricular dysfunction thus remains a challenge. Patient symptoms and clinical signs are inconclusive and additional tools are therefore desired to assess fluid status and validate accurate treatment response.

Ambulatory hemodynamic monitoring - past, present and future

Past

Ambulatory, continuous hemodynamic monitoring was first attempted by using fluid filled (53) or micromanometer tipped catheters connected to a Holter recorder (54-57). These recordings where performed with the patient in the hospital but allowed the patient to move freely within that environment. The length of the reported recordings varied from hours up to 4 days. The results from these studies were the first to describe cardiac pressure levels and diurnal variations in an ambulatory heart failure patient. In a study of eight patients with chronic heart failure (54) the mean daytime pulmonary artery systolic pressure was 30±5 mmHg and pulmonary artery diastolic pressure was 14±6 mmHg, indicating a mild to moderate heart failure. At night the pulmonary artery systolic pressure increased an additional 5±3 mmHg and the pulmonary artery diastolic pressure 4±2 mmHg. These early studies laid the foundation for today's fully implantable systems that measure cardiac pressures and gave an early insight to what continuous cardiac pressure monitoring might reveal.

Present

A series of studies have been performed to verify the feasibility of continuous implantable hemodynamic monitoring (IHM) in patients with heart failure and devices for remote transfer and use of the data. The first acute studies supported the ability to reliably estimate pulmonary artery diastolic pressures from the right ventricular pressure signal (58-60). This was followed by studies of permanently implanted pressure sensors aimed to show accuracy in right ventricle pressure measurements and that the performance was stable over time (Figure 4). The results of these studies support the technical feasibility and the long-term accuracy and stability of these systems (61-65). More over, in 32 patients implanted with an IHM, changes in right ventricular pressures preceded patient symptoms in mild decompensation (not hospitalized) with at least 24 hours and in severe decompensation (hospitalized) with 4±2 days (66). The authors concluded that if the changes had been detected at an early stage and medication regiments changed, periods of decompensation and subsequent hospitalization might have been avoided.

In addition to the feasibility studies, several small research studies have been performed (67-69) reflecting the utility of the IHM as a research tool. Also, the enthusiasm to show how the IHM can be used to provide informed care in individual patients led to a number of case studies being published (70-74). However, these studies were based on retrospective analysis of the IHM data and it become clear that an important part of the ambulatory hemodynamic monitoring concept was easy and instant access to the information

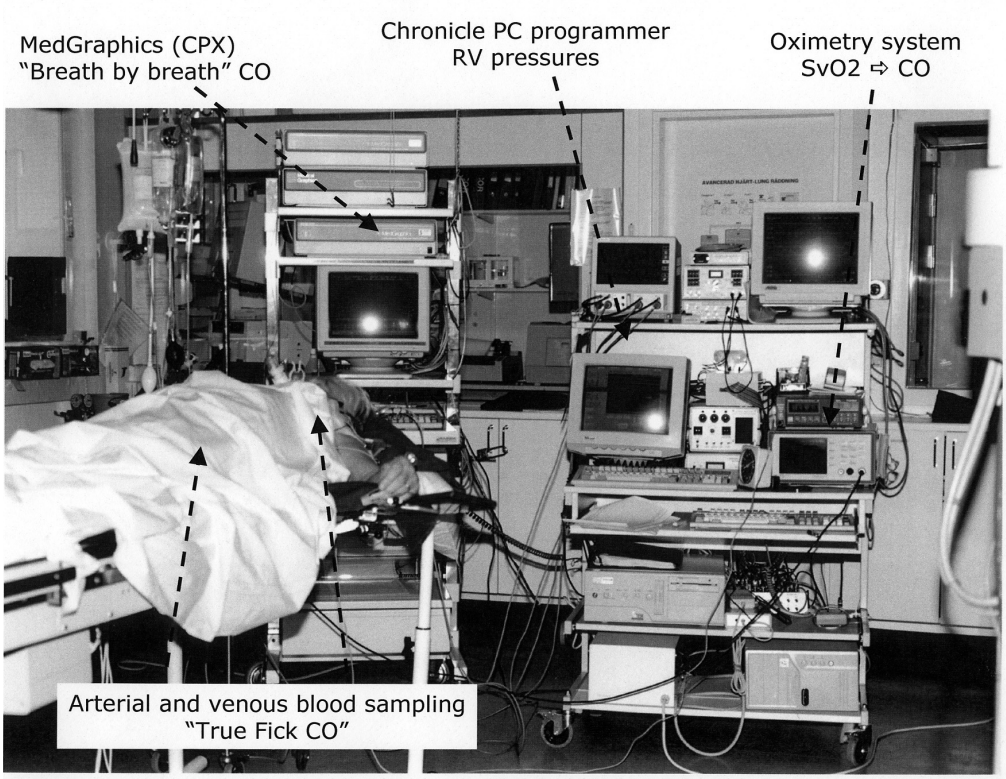

Figure 4. Photo from a cath lab examination in the IHM-1 study. The aim of the IHM-1 study was to study accuracy and long term (1 year) stability of a pressure and an oxygen sensor permanently implanted in the right ventricle. The patients underwent catheterizations at the day of implant and 1, 3 and 12 month after implant. The picture shows the patient to the left and all the equipment that was needed to test sensor accuracy surrounding him.

on a regular basis. The Chronicle information network (Carelink) is a web based system that allows the patient to send data stored in the IHM via a regular telephone line to the internet. The clinician has access the hemodynamic data from any computer or similar device with an internet connection and can thereby detect changes in the hemodynamic trends without the patient having to visit the clinic.

A randomized study to establish the efficacy of Chronicle Guided Care in heart failure patients has been conducted (COMPASS-HF) and the results were presented at an FDA review meeting March 1, 2007. The trial enrolled 274 NYHA class III-IV patients who were followed for 6-months (75). All patients received an IHM and were randomized to either a treatment group where clinicians had continuous, remote access to the IHM data or a control group where clinicians were blinded to the IHM data. After the 6-month randomization period, the data were un-blinded for all patients. The study showed a 38% reduction in the relative risk of HF hospitalization between control and treatment groups. However, the study turned out to have over-estimated the primary endpoint event rate and was underpowered to achieve statistical significance. It was also reported that the hospitalization event rate remained low in the treatment group in the 6-months following the un-blinding, and that the control group's HF hospitalization event rate decreased to match the rate achieved in treatment group.

Future

Ongoing research is directed towards simplifying the use of the IHM system, to combine the IHM with other device therapies and to better understand disease pathophysiology and the discrimination of underlying co-morbidities in patients implanted with an IHM.

Today the review of the IHM trends is done by the clinical staff on a regular basis. This is time consuming and in addition, identifying meaningful changes requires training and experience. To provide easy access to the data, improved techniques such as wireless telemetry and automated detection of hemodynamic changes (76) have been reported. The latter could provide early warning of potential cardiac decompensation and assist data reviews. Future algorithms might include, among other, estimation of cardiac output by pulse contour analysis (77,78) and detection and discrimination of ventricular arrhythmias (79).

The possible combination with other technologies and devices includes impedance measurements (80), cardiac pacing (in particular cardiac resynchronization therapy) and automatic drug delivery systems. A combination device, the Chronicle-ICD is currently being implanted in the REDUCE-HF trial. The IHM part of the device utilizes the same technology as previously described and is not used for ICD arrhythmia detection. Similar to COMPASS-HF, all patients receive an IHM and are randomized to either a treatment arm where clinicians have access to the IHM data or a control arm where clinicians are blinded to the IHM data. The primary endpoints are safety and a 30% reduction of all HF related events in the treatment group compared to the control group (81).

Dr Pickering, a pioneer in ambulatory blood pressure monitoring wrote "Ambulatory monitoring provides a unique opportunity for studying the temporal relationships between lifestyle factors and blood pressure. These include physical activity, mental activity, environmental stressors substances ingested for pleasure such as smoking, alcohol and caffeine, and nutrition (82)". Though his comment was meant for cuff blood pressure monitoring, it is definitely applicable for implantable hemodynamic monitoring too and there is still much to be learned.

Aims of the study

The general aim of this thesis was to show the feasibility and applicability of continuous hemodynamic monitoring in patients with overt or imminent heart failure.

Specific aims were to:

I demonstrate accuracy and long term stability of an implanted venous oxygen sensor

II identify which components of 24-hour data from an implantable hemodynamic monitor best estimate resting conditions

III demonstrate feasibility and usability of a trans-telephonic system with internet based display of continuous hemodynamic data

IV study right ventricular hemodynamics, including mixed venous oxygen, during different types of exercise and levels of exertion

V assess applicability of continuous hemodynamic monitoring in patients with pulmonary hypertension and if optimization of therapy (inhaled iloprost) was feasible

VI assess applicability of continuous hemodynamic monitoring between dialysis sessions in patients with end stage renal disease

Material and Methods

Technical components - sensors

The oxygen sensing lead (Model 4327A, Medtronic, Inc., Minneapolis, USA) was a polyurethane permanent pacing lead with a porous platinum steroid tip carrying an oxygen sensor. The oxygen sensor (Figure 5) consisted of a sealed capsule containing red and infrared emitting diodes, a photo detector and an integrated circuit, located 2.8 cm from the lead tip. It used tines for passive fixation. Oxygen saturation was detected as a ratio of red/infrared reflection as the sensor emitted red and infra-red light into the blood. The reflectance of the red light depended on the proportion of oxygenated hemoglobin which also indicated "changes in the color of the blood" (e.g., arterial blood with high oxygen saturation = light red; venous blood with low oxygen saturation = dark red). The reflection of infrared light was relatively independent of oxygenated hemoglobin and therefore served as a reference. A photodiode detected the reflected light and measured the time required for fixed amount of light energy to be collected. That time related to the oxygen saturation level. An electrical signal was transmitted to the pulse generator using the outer coil connector of the lead.

The pressure sensing lead (Model 4328A, Medtronic, Inc., Minneapolis, USA) was a unipolar, 58cm lead with polyurethane insulation. The pressure sensor capsule was placed 3 cm proximal to the tip and had a maximum diameter of 3.7 mm. It used tines for passive fixation. A nickel alloy was utilized as conductor while the sensor capsule was constructed of titanium and titanium alloys, which were covered in polyurethane and medical adhesive. The pressure sensor capsule (Figure 6) was hermetically sealed and included a deflectable titanium diaphragm. Motion of the diaphragm changed the capacitance and thereby reflected pressure change. Digital sampling was used to construct continuous pressure waveforms for storing hemodynamic information. From each cardiac cycle, right ventricular systolic (RVSP) and diastolic (RVDP) pressure, maximum positive and negative change in pressure over time (dP/dt), pre-ejection and systolic time interval, central venous temperature and heart rate were measured. Pulmonary artery diastolic pressure (ePAD) was estimated as the right ventricular pressure at the time of dP/dt_{max} (Figure 7, 58-60).

It has been suggested that with the sensor placed in the apex, there might be an increased risk of

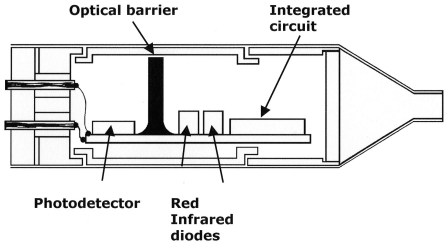

Figure 5. *Mixed venous oxygen sensor* Oxygen saturation was detected as a ratio of red/infrared reflection as the sensor emitted red and infra-red light into the blood. Red light was dependent on the proportion of oxygenated hemoglobin while the infrared light was independent and served as a reference. A photodiode detected the reflected light and measured the time until a fixed amount of light energy has been collected. That time correlated to the oxygen saturation level.

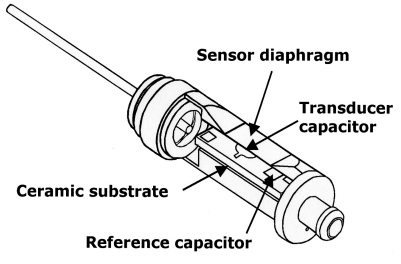

Figure 6. *Pressure sensor* Motion of the titanium diaphragm in response to the cardiac contraction changed the capacitance and thereby reflected changes in cardiac pressure. Digital sampling was used to construct continuous pressure waveforms for storing hemodynamic information. The diaphragm was connected to the internal circuitry that transmitted the pressure data up the lead to the IHM for measurement and storage.

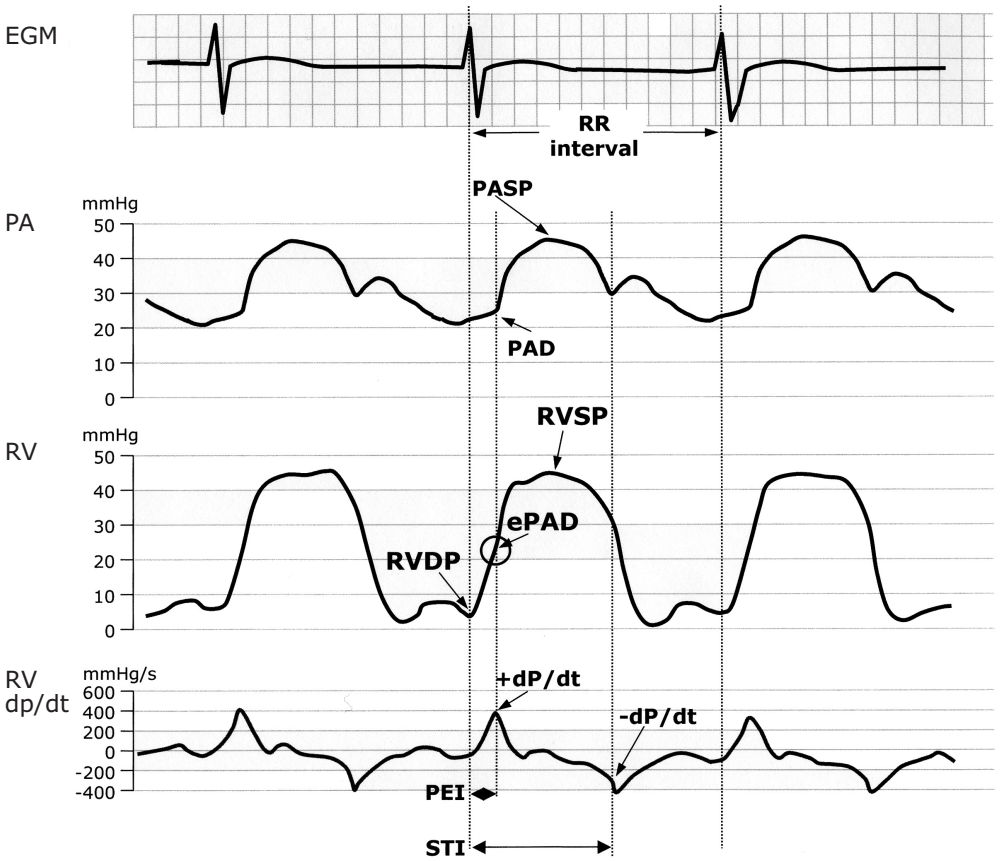

Figure 7. Schematic illustration of how the hemodynamic variables are derived from the intracardiac signal and the pressure waveform. The pulmonary artery diastolic pressure (ePAD) is derived from the right ventricular pressure waveform at the time of maximum dP/dt when the pulmonary valve opens and the pressure in the right ventricle (RV) and the pulmonary artery (PA) are assumed to be equal. Right ventricular diastolic pressure (RVDP) is measured at the time of R-wave detection and the right ventricular systolic pressure (RVSP) is measured as the maximal pressure in a 500 ms window, starting at time of r-wave detection. Pre ejection interval (PEI), systolic time interval (STI) and heart rate (RR-interval) is also measured.

tissue overgrowth (62, 64). Therefore, the tip of the lead was placed in the right ventricular outflow tract or high on the right ventricular septum in the belief that a placement in areas of high flow would reduce tissue encapsulation.

Technical components - devices

The OxyElite (Model 8007, Medtronic, Inc., Minneapolis, USA) was a dual chamber, unipolar, rate response pacemaker. Rate-response was provided by an activity sensor, a piezoelectric crystal mounted on the inside of the pacemaker can. The algorithms for the activity sensor as well as the pacemaker functions were the same as in the Elite (Model 7075, Medtronic, Inc., Minneapolis, USA) pacemaker. Pacemaker parameters and mixed venous oxygen saturation histograms stored in the device memory were interrogated by use of the pacemaker programmer (Model 9760, Medtronic, Inc., Minneapolis, USA). The oxygen saturation histogram feature in the OxyElite continuously measured and stored mixed venous oxygen saturation in 4-second intervals during ambulatory conditions and sorted the measurements into eight histogram bins ranging from <49% up to >77% in steps of 4%. When the programmer telemetry head was placed over the pacemaker, real time mixed

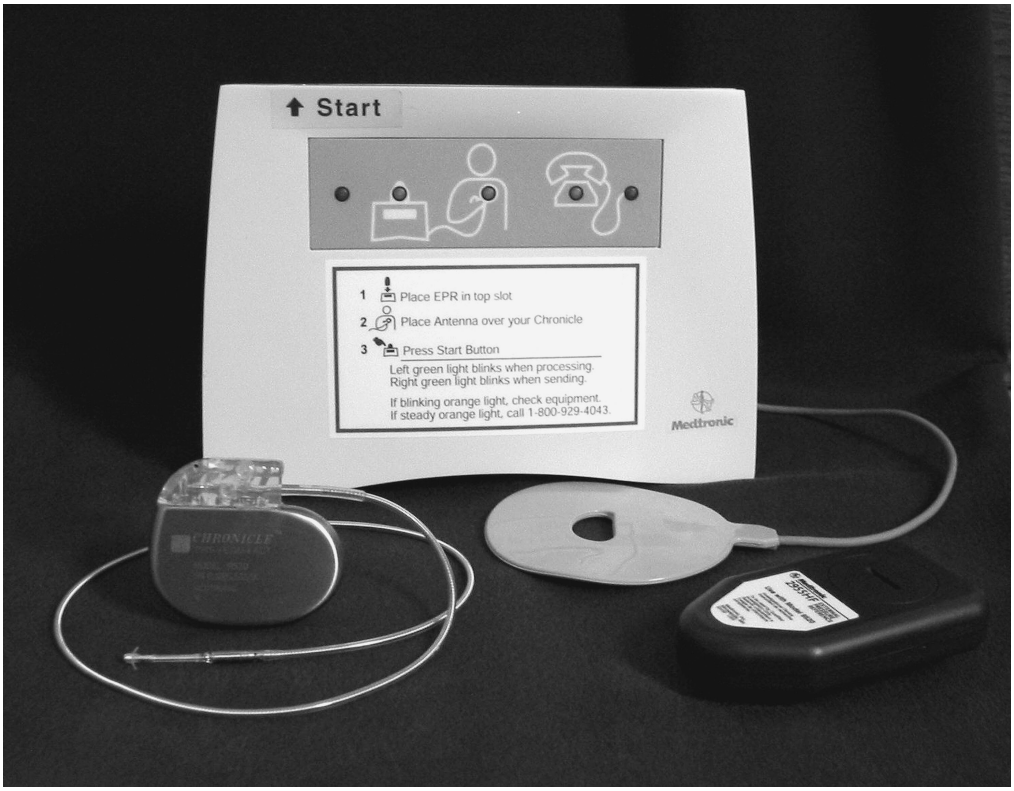

Figure 8. The interactive remote monitor with the flat radio frequency antenna is shown behind the implantable hemodynamic monitoring system consisting of the Chronicle IHM and pressure sensor lead to the left and the external pressure reference to the right.

venous oxygen saturation could be read on the programmer screen and/or stored on a diskette for future analysis.

The implantable hemodynamic monitor (IHM; Models 10440; IHM-1 and 9520; Chronicle®, Medtronic, Inc., Minneapolis, USA) was a memory device that stored values from a sensor or sensors placed in the right ventricle. The IHM-1 was equipped with two sensor leads, one oxygen sensor and one pressure sensor while the Chronicle only had the pressure sensor (Figure 8). The other major difference between the two devices was the memory capacity. The IHM-1 had a 32 kilobytes random access memory and the Chronicle 128 kilobytes. This affected the resolution of the stored data and allowed the Chronicle to store values at a higher resolution for longer periods than the IMH-1. In most other aspects both IHM's were similar. Beat-by-beat values from the pressure sensor were stored as the median and range (6th and 94th percentiles) over each storage interval. The IHM-1 also stored mixed venous oxygen saturation. The storage interval was programmable, ranging from 3 hours to 3 months, and could be adjusted to fit the patient's follow-up schedule. With a storage interval of 3 hours one data point represents 2 seconds. This storage interval was used when the patient was in the clinic for an acute test such as catheterization, exercise test or drug intervention. A longer storage interval was used when the patient was at home. In the early studies, longer storage intervals (1-3 months) were used as the patient had to come to the clinic for data retrieval. After the Chronicle information network (see next paragraph) was introduced, a storage interval of 1-2 weeks where each data point represents 4-8 minutes became the standard.

The right ventricular pressure sensor measured absolute pressure, requiring correction for continuously varying ambient atmospheric pressures by a time-synchronized external pres-

sure reference (EPR) device (Figure 8). Through the use of custom software, the absolute sensor data was then corrected for changes in barometric pressure. Activity counts were determined by a piezoelectric crystal mounted inside the monitor can.

The interactive remote monitor (IRM; Model 9521, Medtronic, Inc., Minneapolis, USA) was used to send the data stored in the IHM from any remote site having a standard phone line, e.g. the patient's home, to a central server. The IRM had a flat radio frequency antenna, which was placed over the implanted device and the patient's EPR was placed in a separate slot in the IRM for transmission of the collected barometric pressure (Figure 8). The IRM was operated by a one-button maneuver that started the download of the IHM and EPR data and the transmission by a built in modem that dialed an Internet Service Provider (ISP) to transfer the data to the central server. Patients followed the transmission procedure by observing indicator lights on the IRM. When the process was completed the IRM modem automatically disconnected from the ISP. If a file transfer failed, an email message was sent to the treating clinic requesting that the clinic staff contact the patient to request a repeat file transfer.

The Chronicle information network (Figure 9) provided the health care staff with easy access to the patient's hemodynamic information. The user logged on to a Web site using a personal ID and password to gain access to data from patients registered at their clinic. A quick-look screen displayed a summary table of night time rest values (midnight to 04:00, at zero activity counts) during the last data-collection period alongside data from any one previous data-collection period. Differences between the periods were shown as actual values (real change) and as percentage change (Figure 10). Based on individualized, expected ranges for each variable, out of range data and/or changes in individual variables were highlighted. Data were also displayed as trends of all hemodynamic variables, with resolution depending on the length of the displayed period (Figure 11). Separate trends were also provided of the last 6 months of night time rest data. A list of triggered events with the option to review events in high resolution and samples of pressure waveforms were also available. Additionally, the user could enter notes describing changes in treatment, interventions, hospitalizations or other information.

The distribution of the technical components in Study I-VI can be found in Table 3.

Study I

OxyElite, long term follow-up of an implantable Sv02 sensor

Nine consecutive patients with an indication for a DDD pacemaker were implanted with an OxyElite, a dual chamber pacemaker modified to utilize a right ventricular oxygen saturation lead.

Table 3. Use of the technical components in the studies included in this thesis

	Study I (n=9)	Study II* (n=32)	Study III* (n=134)	Study IV (n=21)	Study V (n=5)	Study VI (n=16)
Oxygen sensing lead	X			X		
Pressure sensing lead		X	X	X	X	X
OxyElite	X					
IHM-1				X		
Chronicle IHM		X	X		X	X
Interactive remote monitor		X	X			
Chronicle information network		X	X			

*The patients in Study II who received an IHM in USA and were still being in follow-up when remote monitoring was introduced are also included in Study III. Except for these studies there was no overlap in study populations between the studies.

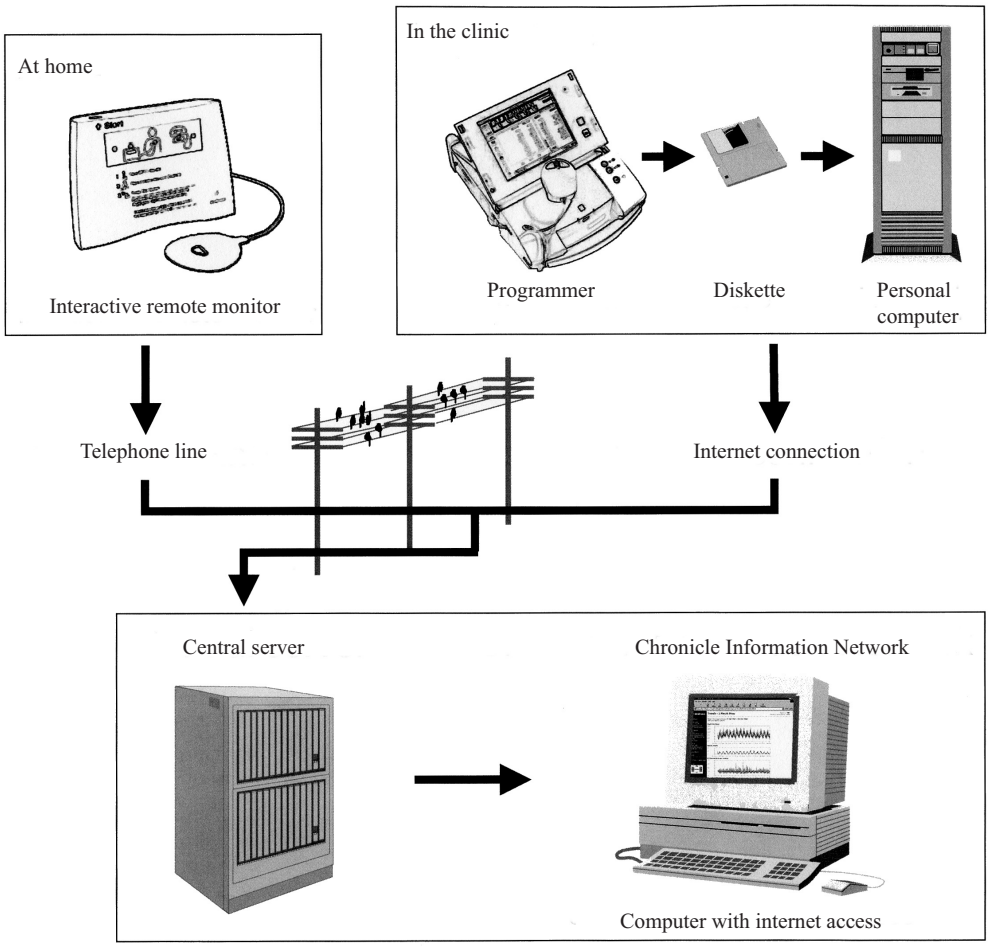

Figure 9. Chronicle information network architecture. Stored hemodynamic data is transmitted from the implantable hemodynamic monitor via an interactive remote monitor or a programmer/personal computer to a central server. Data can be viewed from any web-enabled computer.

The average age was 69±14 years, two patients were in NYHA class I and seven in NYHA class II. The indications for a pacemaker were; AV-block II-III (n=5), AV-block I with syncope (n=1), bradycardia (n=2) and sick sinus syndrome (n=1). Six patients had a history of ischemic heart disease. All patients except one were treated with aspirin during the course of the study.

Invasive studies comparing the mixed venous oxygen saturation from the implanted sensor to reference (Opticath, Oximetrix system, Abbot Laboratories, Chicago, USA) was performed at 0, 3 and 9 months. Symptom limited, bicycle exercise tests were performed 1-7 days, 3.5 and 9.5 months post-implant. Metabolic assessment (CPX, MedGraphics, St Paul, USA), venous oxygen saturation from the implanted sensor and arterial oxygen saturation (Ohmeda, Louisville, USA) measurements during the exercise test allowed for cardiac output calculations using the Fick principle.

Sub-maximal bicycle exercise tests (5 minutes at 60% of the previously determined maximal workload) were performed every 2-4 weeks during the first year of follow up and subsequently every 6 months. After 3-3.5 years of follow up, the bike test was replaced by an uncontrolled exercise that included mixed venous oxygen saturation measurements at supine rest and after 30-60 seconds of light exercise. This walk-in-place test was performed at each 6-

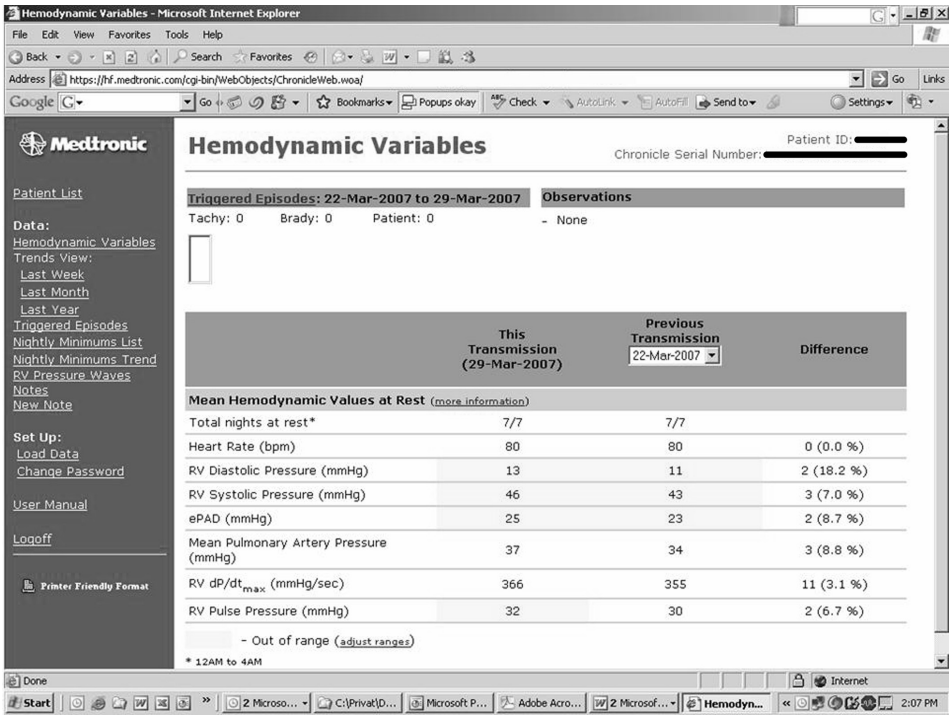

Figure 10. An example from the quick look screen used on the Chronicle information network. The screen shows the night time minimum values from the last transmission (column to the left), a previous transmission (column in the middle) and changes between the two selected transmissions (column to the right).

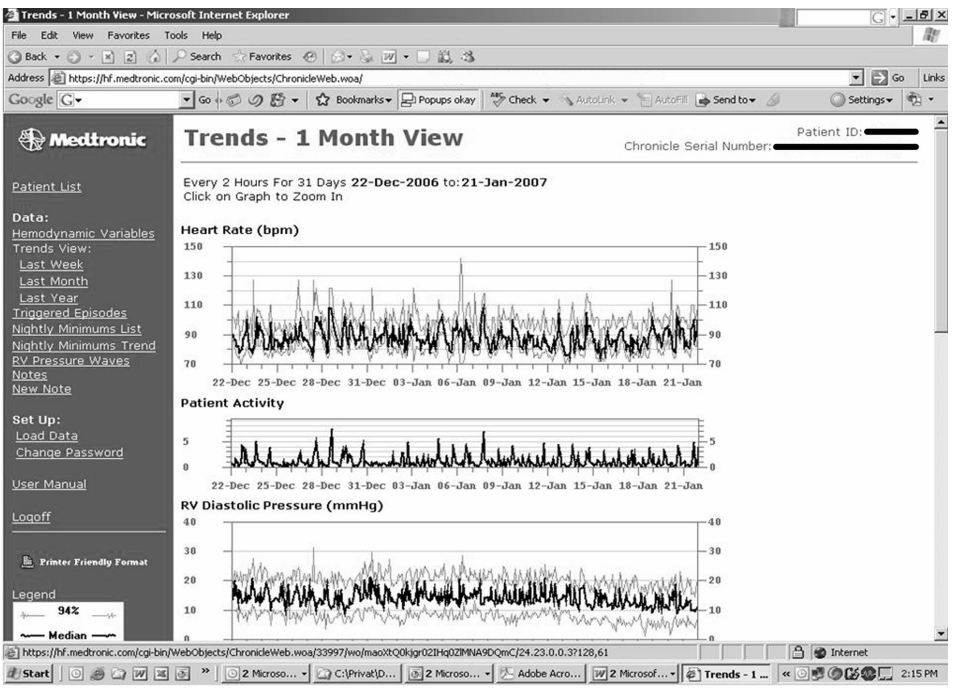

Figure 11. An example from the Chronicle information network showing a 1-month, continuous hemodynamic trend. Each data point represents a 2 hour median.

month follow-up visit for the remaining time of follow-up. Mixed venous oxygen saturation was recorded at supine rest before exercise, at peak exercise and following recovery after exercise.

Study II

Components of continuous 24-hour pressures that correlate to supine resting conditions and acute right heart catheterization

Thirty-two patients diagnosed with chronic heart failure received an IHM. The average age was 59±10 years, one patient was in NYHA class I, 14 in NYHA class II and 17 in NYHA class III. Nineteen patients had heart failure of ischemic origin, and the average LVEF was 29±11%. All patients except one were treated with angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers while beta-blockers were used in 78% and diuretics in 88%. At time of implant the average right ventricular systolic pressure was 48.3 ±16.2 mmHg, right ventricular diastolic pressure 9.4 ± 5.3 mmHg, estimated pulmonary artery diastolic pressure 23.3 ± 8.9 mmHg and heart rate 76.5 ± 15.1 bpm.

During the first year after implant the patients participated in monthly clinic visits for the first 6 months and bimonthly thereafter. At each clinic visit the IHM data was collected in a high- resolution mode (storage interval of 2 seconds) during a controlled, supine rest period of at least 5 minutes. Data from the last minute of the resting period were averaged and defined as "controlled rest". Between clinic visits the IHM was programmed to continuously store hemodynamic values and heart rate. Data were stored as medians and the 6th and 94th percentiles for each storage interval. The recommended follow-up interval programming was 1 month (storage interval 24 minutes) for the first 6 months and 2 months (storage interval 48 minutes) thereafter, although other resolutions were allowed depending on the patients or the investigators schedules. Values from the week before and the week after each clinic visit were averaged and represent the ambulatory data. The ambulatory hemodynamic values were divided into 7 components of a 24-hour recording (Figure 12) and compared to the controlled rest values.

All patients also underwent right heart catheterizations at the time of IHM implant and at 3, 6 and 12 months after IHM implant to verify system performance. This included independent measures of pulmonary artery and right ventricular pressures using fluid filled catheters. The method found to be the best estimate of controlled rest was compared to acute invasive catheterization values.

Study III

Trans-telephonic monitoring of continuous hemodynamic measurements

Over a 3-year period, from September 1998 through October 2001, 148 patients had an IHM implanted worldwide. The mean age was 56±13 years, 89 were male and average LVEF was 28±14. The distribution in NYHA classes was 1, 22, 70 and 7 patients for class I, II, III and IV respectively. Mean follow-up time was 23±14 months (range 0.5-53). Of the total implants, 12 were done in Europe and 4 in Canada where the patients did not have IRM access. Thus 134 patients were included in the study.

Transtelephonic transfer of hemodynamic data from the IHM's to the Chronicle information network was analyzed on a monthly and yearly basis from August 2000 to November 2003. Success rate of data transfer, reason for transfer failure and amount of data lost due to transfer failure were analyzed and reported upon.

In addition, a usability study concerning the patient's ability to transmit IHM data was performed in the first 20 patients provided with an IRM. The mean age of these 20 patients was 59±13 years (range 20-75) and 8 were male. Before using the IRM for the first time, the patients underwent a training session including a video film and a hands-on-demonstration on how to setup and use the IRM in their homes. The patients were then asked to call the Medtronic Patient Services directly the three first times they used the IRM in their homes. The Patient Services asked standardized questions about the usability of the system.

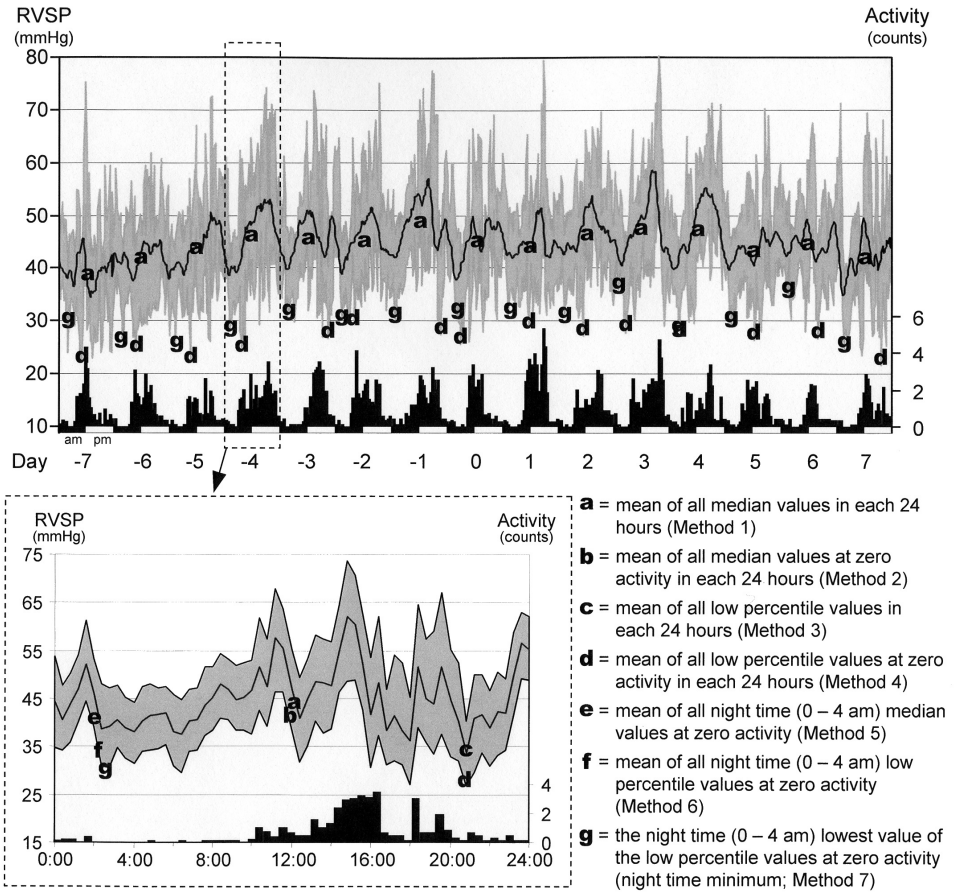

Figure 12. Seven different derived estimates from the chronic ambulatory data that seemed the most likely estimators of the controlled supine rest values were identified. A single value was calculated from the 24-hour, ambulatory data for each of the methods listed in the figure.

Study IV

Hemodynamic observations during exercise measured by implantable pressure and oxygen saturation sensors

Twenty-one patients at three centers had an IHM implanted. The mean age was 61 years (range 26-79), 17 were males and the mean LVEF was 24% (range 10-40). Six patients were in NYHA Class II and the remaining 15 in NYHA class III. Fifteen patients had ischemic origin to their heart failure. The patients were followed for a mean of 25±14 (range: 1-39) months.

Standardized, serial exercise tests were performed to evaluate the right ventricular and pulmonary pressures and the mixed venous oxygen saturation responses during hemodynamic stress.

Three types of exercise was performed; 1) a maximal, symptom limited bicycle exercise test, 2) a submaximal bicycle exercise test, using 30-40% of the patient's maximal load during the baseline symptom limited exercise test and 3) a six-minute walk test. The symptom limited bicycle exercise test was performed just after implant and repeated after two, six and 12 months of follow-up while the submaximal tests on bike or walking was performed approximately every four to six weeks after implant. During all three types of exercise tests, hemodynamic data from the IHM system were stored in the high resolution setting (beat-by-beat measurements averaged over 2-8 second data storage intervals).

Study V

Hemodynamic observations in patients with pulmonary hypertension treated with inhaled Iloprost

Five female patients with pulmonary hypertension received an IHM. Four patients were diagnosed with pulmonary artery hypertension and one with pulmonary venous hypertension. The mean age was 45±16 years, the average right ventricular systolic pressure was 68±13 mmHg. All patients were treated chronically with aerosolized iloprost, a prostacyclin aimed to reduce pulmonary vascular resistance and thereby increase cardiac output and reduce right ventricular pressures.

A 20% reduction in pulmonary artery systolic pressure after inhalation is considered a positive response (83) and is expected to last 60-120 minutes (84) before returning to pre inhalation levels. This necessitates repeated inhalations six to nine times a day to obtain a sustained clinical benefit.

The effect of iloprost inhalation was studied in a supervised ("short") and in a non-supervised ("long term") protocol. The supervised protocol included high resolution hemodynamic data collection (storage interval 2 seconds) for 20 minutes before the start of inhalation, 2 inhalations and 30 minutes after the second inhalation while the patient was at the clinic. This allowed analysis of one full inhalation-cycle (four hours) for analysis. The supervised protocol was performed one day after IHM implantation and after one, two, and three months during regular outpatient check-ups.

The non-supervised protocol documented the pulmonary artery systolic pressure (=right ventricular systolic pressure) response of inhaled iloprost in an ambulatory setting with the IHM programmed to a storage interval of 52 seconds. This allowed for four to six inhalations in a 24-hour period. The non-supervised protocol was performed one day after the IHM implantation and after two and five months in coordination with regular outpatient check-ups.

The effective period of inhaled iloprost was defined as the time until a 50% loss of the initial, acute pulmonary artery systolic pressure response.

Study VI

Hemodynamic observations in patients with end stage renal failure treated with hemodialysis

Sixteen patients with end-stage renal disease and on chronic hemodialysis were implanted with an IHM. The mean age was 68±9 years, LVEF 45±9% and LVEDD 49±7 mm. All patients underwent hemodialysis 3 times per week. Two patients had normal urine production. All patients had a peripheral arteriovenous fistula. Hemodynamic measurements from 12 consecutive weeks of observations were analyzed. One value representative of the daytime period, when the patient was assumed to be active, was calculated as an average of all stored median values between 8:00 and 20:00. A value representing rest was analyzed as the night-time minimum (see study II, Figure 12). Averages of the hemodynamic data from the day of dialysis (1st day), the day after dialysis (2nd day) and the day after a weekend (extra day) and data from first, second and third night after dialysis were calculated.

Before and after each dialysis session routine body weight and blood pressure (cuff manometer) was measured at the dialysis ward and symptoms such as leg cramps, headache and nausea during the dialysis were noted.

Statistical methods

The hemodynamic monitor stored all measured data as a median together with the 6^{th} and 94^{th} percentile over a certain, programmable, time period. Conventional statistical methods were used for calculations of means and standard deviation. For paired comparisons between measurements a two sided Student's t-test was used (Study I, II, IV and VI). Analysis of variance (ANOVA) was used to verify hemodynamic changes during exercise in study IV. Statistical differences were considered significant if $p<0.05$. Descriptive statistics were used in Study III and V. Changes in hemodynamics (Study IV and VI) are presented as percent change for all variables except RVDP where actual values were used. Small changes of RVDP might be proportionally large if expressed as percent change. In Study I the correlations between

mixed venous oxygen values obtained with different methods were evaluated according to a simple linear regression model. The resting hemodynamic data in Study II and IV was calculated from the last 60 seconds of the resting period. Peak exercise values (Study IV) was calculated from the last 15-30 seconds before the exercise was terminated. The ambulatory hemodynamic values in Study II were averaged over 7 days before and/or 7 days after the controlled rest. Ambulatory values in Study VI was measured as mean of a daytime (8:00 – 20:00) medians or a night-time minimum (0:00 – 4:00) value from the day/night before each dialysis treatment.

Ethical consideration

The study protocol was approved by local the ethics committees at the Karolinska Institute (Study I, II, III, IV, VI) and the University of Graz (Study V). All patients gave their informed consent to participate after receiving verbal and written information.

Results

Study I

OxyElite, long term follow-up of an implantable mixed venous oxygen sensor

A total of 24 serial invasive tests were performed in the nine patients during the first year of follow-up. Mixed venous oxygen saturation measured by the implanted oxygen sensor showed high correlations to blood samples and Opticath values collected simultaneously in the pulmonary artery (Figure 13). During the same period, the patients performed 23 cardiopulmonary exercise tests with breath-to-breath cardiac output measurements. The oxygen sensor as well as the cardiac output measurements at rest were stable over time and showed a reproducible response to posture changes and exercise.

Long-term follow-up of the oxygen sensor performance was evaluated by the sub-maximal exercise tests and "walking-in-place" tests. Eighty-eight submaximal bicycle tests and 23 walking-in-place tests were performed during the study. The resting mixed venous oxygen saturation values were stable over the six years of follow-up (NS vs. the 1 year follow-up) and the response to the exercise showed a good reproducibility.

Study II

Components of continuous 24-hour pressures that correlate to supine resting conditions and acute right heart catheterization

Resting hemodynamic values was available in 30 patients from a total of 145 clinic visits. Ambulatory data from the week before and after the visit was used as comparison. The average right ventricular and pulmonary artery pressures at rest were elevated. All hemodynamic methods derived from the 24 hour IHM data, except the night-time minimum with zero activity method, overestimated resting values of right ventricular systolic and diastolic pressures and ePAD (estimated pulmonary artery diastolic pressure). There was no difference between resting pressure values and the night-time

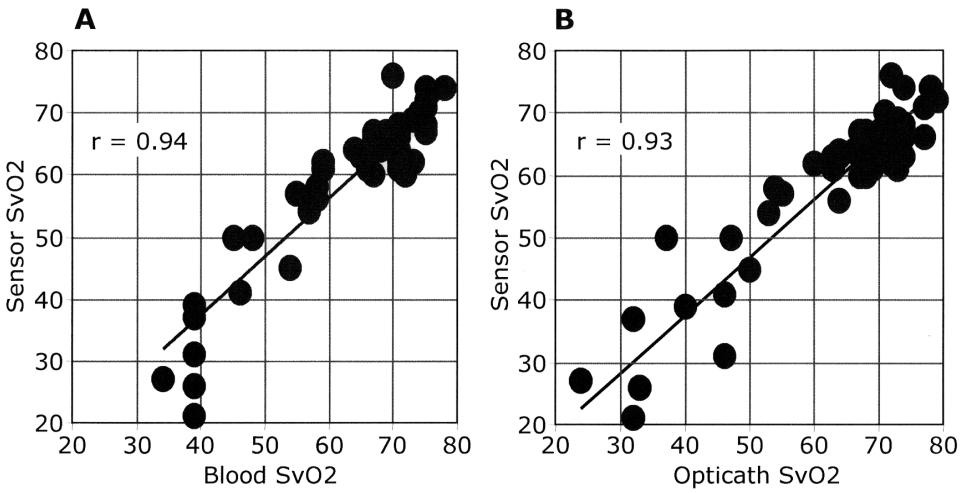

Figure 13. Panel A: the correlation between SvO2 measurements by the implanted SvO2 sensor and pulmonary artery blood SvO2. Panel B: the correlation between SvO2 measurements by the implanted SvO2 sensor and the Swan-Ganz opticath. Values are from rest and exercise performed at implant (only rest), 3 and 9 months after implant. Both methods demonstrate a good correlation, although a greater variability was observed during exercise (lower SvO2 values).

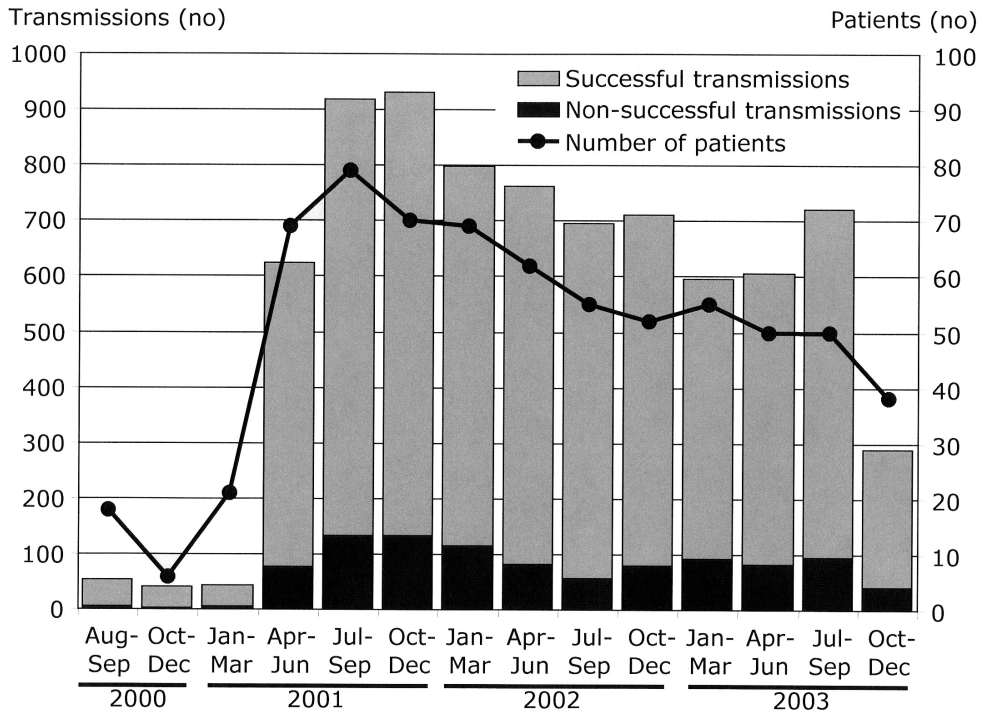

Figure 14. Number of patients that sent data via the interactive remote monitor to the Chronicle information network and total number of transmitted files are shown on a quarterly basis. The bars are divided into successful and non-successful transmissions.

minimum pressure values (<0.05 mmHg, NS). Therefore, the night-time minimum pressure was chosen as the component of the 24-hour continuous hemodynamic recording that best approximated rest. Resting heart rate was significantly different from all of the seven methods applied on the ambulatory data and interestingly, the night-time minimum heart rate was the poorest estimate.

The values from the right heart catheter (right ventricular systolic pressure 45±17 mmHg, right ventricular diastolic pressure 12±6 mmHg, estimated pulmonary artery diastolic pressure 24±8 mmHg) were higher than the night-time minimum, although for right ventricular diastolic pressure the difference was not statistically significant. None of the other IHM parameters from the 7 methods in this study consistently approximated values derived from right heart catheterizations.

Study III

Trans-telephonic monitoring of continuous haemodynamic measurements

During the study period, 7791 data transmissions were performed and of those 6778 were successfully transmitted. Ten percent had to be retransmitted at least once and 1.5% at least twice. Success rate was stable over time and independent of number of transmitted files or number of active patients (Figure 14). One year after the first transmission, an average of 244 files was transmitted each month with a mean frequency of 6.5 days between transmissions. Variations in the number of file transmissions related to fluctuations in number of active patients and upgrades to the technology seen over the course of the study. Failed transfers were most commonly related to interrupted telephone transmission or errors related to the external pressure reference.

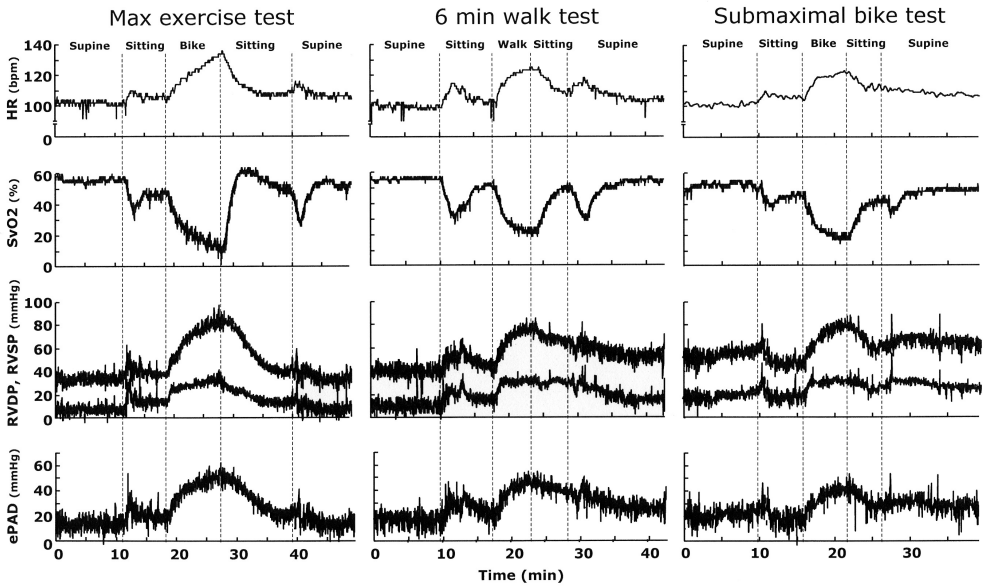

Figure 15. Continuous, high resolution (2 second) hemodynamic data collected and stored by the implantable hemodynamic monitor during three different types of exercise (maximal exercise test, 6 minute walk test and submaximal bike test). All three trends are from the same patient. The trends show heart rate (HR), mixed venous oxygen saturation (SvO2) measured in the right ventricle, right ventricular systolic and diastolic pressure (RVSP, RVDP) and estimated pulmonary artery diastolic pressure (ePAD).

Patients included in the usability study performed 109 successful data transmissions within the first 3-48 days after receiving the IRM. In reply to the usability questions, patients ranked the IRM as "very easy to use" 93% of the time and as "somewhat easy to use" for the rest. Age or gender did not appear to make a difference in the responses. Nine calls from six patients requested technical support. Four calls were due to an incorrect password in the IRM. Reconnecting the telephone plug or repositioning the external pressure reference in its slot solved the remaining five problems.

Study IV

Hemodynamic observations during exercise measured by implantable pressure and oxygen saturation sensors

During the course of follow-up the patients performed 70 maximal exercise tests on bike, 196 submaximal bike tests and 172 6-min walk tests. Hemodynamic values at rest were similar for all tests, heart rate 78±15 bpm, mixed venous oxygen saturation 65±9%, right ventricular systolic pressure 41±13 mmHg, right ventricular diastolic pressure 6±4 mmHg and estimated pulmonary artery diastolic pressure 20±6 mmHg. During the maximal exercise test heart rate increased by 52±19 bpm while mixed venous oxygen saturation decreased by 35±10 saturation units (%). Right ventricular systolic and diastolic pressure increased 29±11 and 11±6 mmHg, respectively, while estimated pulmonary artery diastolic pressure increased 21±8 mmHg (Figure 15).

Compared to the hemodynamic response during maximal exercise test, submaximal bike and walk tests resulted in mixed venous oxygen saturation changes of 80 and 91% of the maximal test values, while changes in right ventricular and pulmonary artery pressures ranged from 70 to 79% of maximal test responses. This indicates that the hemodynamic response during submaximal exercise tests reflects changes achieved during maximal exercise in patients with heart failure.

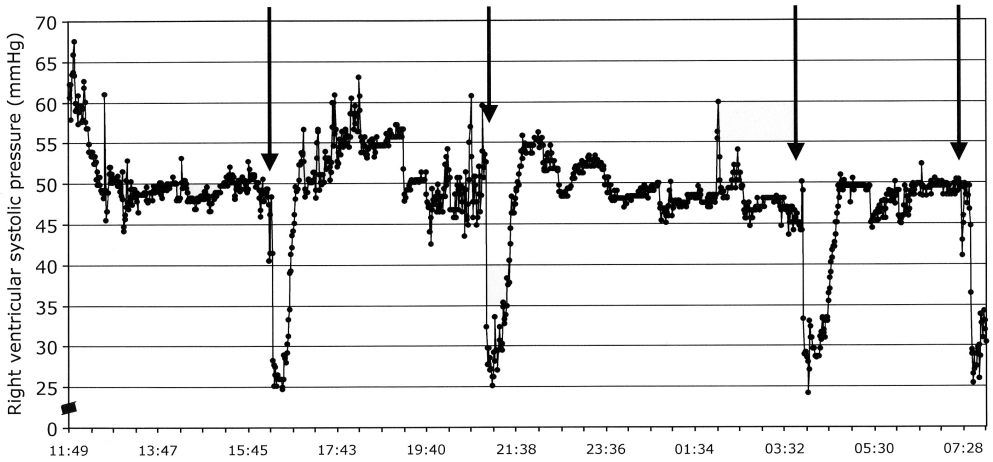

Figure 16. Right ventricular systolic pressure tracing during 20-hours in a patient with pulmonary hypertension, treated with inhaled iloprost. The arrows mark the beginning of each iloprost inhalation.

Study V

Hemodynamic observations in patients with pulmonary hypertension treated with inhaled iloprost

Patients included in the study had various degrees of pulmonary hypertension as indicated from their right ventricular systolic pressure measured before starting the inhalation. The average pressure was 68±13 mmHg, varying from mild (45mmHg) to severe (119mmHg) in the five patients. All patients had a positive acute response to inhaled iloprost, expressed as a reduction of pulmonary artery systolic pressure of 20% or more. In the supervised protocol, the inhalations were performed in the hospital under a clinician's supervision. The time at effective pressure response levels was rather short, varying from 29 to 80 minutes per inhalation. Average time for all patients was 49±8 minutes.

In the non-supervised protocol, performed while the patients were at home, the pulmonary artery systolic pressure levels before inhalations as well as the maximal response to inhalations (Figure 16) were comparable to the values in the short-term protocol. However, the time at the lower pressure levels were 19 minutes in the long-term protocol compared to 31 minutes in the short-term protocol. As a consequence of this, the total effective treatment time was shorter in the non-supervised protocol (33±3 minutes) than in the supervised protocol. During the total recorded time, 265 hours, the time at effective vasodilatation lasted only 13% of the whole time span.

Study VI

Hemodynamic observations in patients with end stage renal failure treated with hemodialysis

Fifteen patients had continuous hemodynamic recordings for 12 weeks after the IHM implant. One patient had only 5 weeks of hemodynamic data recorded. During the study period a total of 555 hemodialysis treatments were performed in these 16 patients (Figure 17).

Progressive increments in daytime cardiac pressures were observed in all patients when the 1st day was compared to the 2nd and the extra day. On the 2nd day the right ventricular systolic pressure and estimated pulmonary artery diastolic pressures had increased 8-9%. On the extra day, the pressures had increased an additional 5-7% compared to the 1st day. Significantly higher right ventricular and pulmonary pressures were reached on the extra night after dialysis in 14 of 16 patients. Two patients with preserved diuresis did not show any change in cardiac pressures.

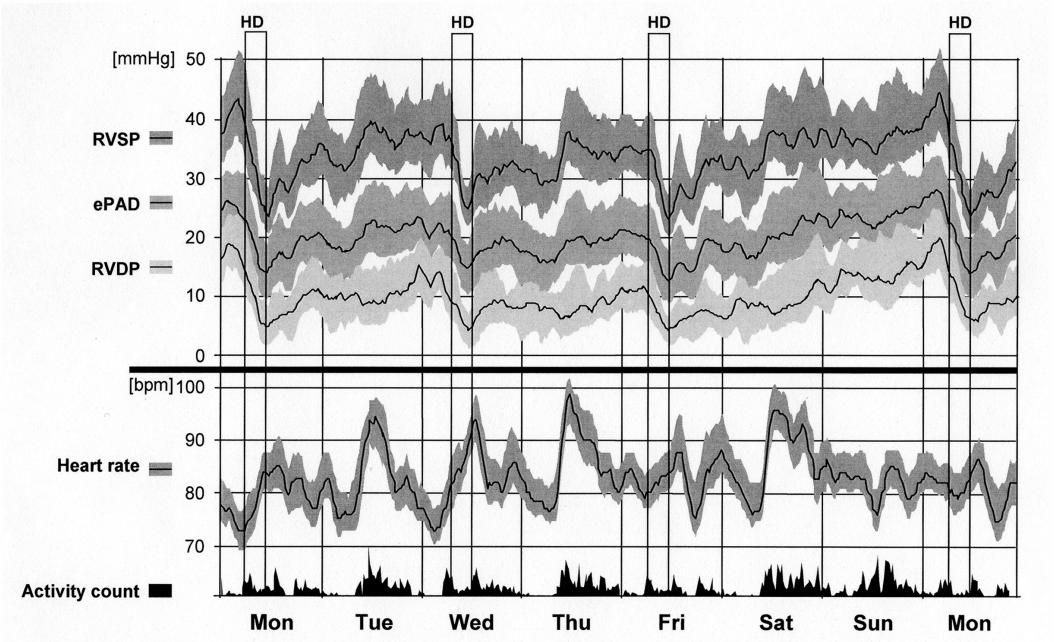

Figure 17. Patient example illustrating an eight day trend with right ventricular systolic (RVSP) and diastolic (RVDP) pressures, estimated pulmonary artery pressure (ePAD) and heart rate. Hemodialysis procedures (HD) are indicated at the top of the graph. Activity count shows the time spent physically active. The solid line shows the median value and the shaded areas are the range (6 and 94 percentile).

The patient's weight increased 2.3±1.1 kg before the second and third dialysis in the week. After a weekend, the patient's weight had increased 3.1±1.7 kg. There was no significant difference in cuff blood pressure before and after dialysis or between dialysis sessions.

General discussion

The implantable hemodynamic monitor provides an opportunity to observe continuous heart rate and right ventricular and pulmonary artery pressures in the ambulant patient. This information can be a valuable complement to traditional patient assessment and support the clinician in establishing an optimal range of hemodynamic values in the individual patient. The result may be better quality of life and a reduced need for in-hospital care.

The three first papers in this thesis aim to establish a platform showing that implantable biosensors and the technology surrounding them are feasible and how to handle the huge amount of data that is collected and stored by the implantable hemodynamic monitor 24-hours, every day and all year long. The three latter papers aim to demonstrate clinical usefulness of the implantable hemodynamic monitor in cardiovascular diseases associated with compromised hemodynamics. The commonality between the papers is that clinically relevant hemodynamic values can be measured from the right ventricle and that these observations may help make therapeutic decisions and evaluate disease progression.

Mixed venous oxygen saturation - what does it mean?

The importance of mixed venous oxygen saturation is not always recognized. Cardiac output alone or together with other diagnostic information e.g. cardiac or systemic pressures, heart rate and arterial oxygen saturation does not reflect the tissues metabolic demand or if this demand is met. To assess this, values from both oxygenated (arterial) as well as deoxygenated (venous) blood is needed. While arterial oxygen saturation can be accurately measured with non-invasive methods (63,64), measurement of mixed venous oxygen saturation require invasive techniques, or with an implantable sensor, a “semi-invasive” technique (Study I and IV).

Long term stability of the oxygen sensor

The oxygen sensor used in Studies I and IV was initially developed for rate adaptive pacing but long term stability in oxygen measurements could not be proven (85-87) and the sensor was abandoned for this purpose. After changes in sensor design had been made to improve function, the oxygen sensor was implanted for monitoring purposes, attached to a pacemaker lead in Study I and as a sensor lead in an IHM system (64, Study IV). The oxygen sensor in Study I demonstrated a reliable long term performance over six years. This was in contrast to Study IV where 40% of the oxygen sensors showed intermittent responses or stopped responding within the first year (64) without any apparent technical explanation. Tissue overgrowth might have been augmented due to the presence of two sensors in the ventricle, but this hypothesis was never proven and the real cause remains unknown. As a consequence the oxygen sensor was removed from the next generation IHM system, the Chronicle®. However, the research to develop an oxygen sensor with improved long-term stability has continued and could possibly be reintegrated in a future IHM system.

Utility of continuous mixed venous oxygen saturation

When the patients in Study I received the pacemaker with mixed venous oxygen measurement capabilities, they either had no or only mild symptoms of heart failure (NYHA class I-II). However, during the follow-up period of more than 6 years some patients developed symptoms of other cardiovascular diseases. The ambulatory oxygen saturations showed interesting changes in the trend patterns that were consistent with changes in the patients’ medical conditions. As this was a pilot study, this observation will need to be confirmed in a larger patient group. The findings, however, are to some extent supported in Study IV where patients with symptomatic heart failure and an IHM with both pressure and oxygen saturation sensors were studied.

During exercise, even at low levels of exertion such as moving from supine to sitting, a rapid decrease in mixed venous oxygen saturation was observed (Figure 15). This indicates that during daily life activities, one could expect to see more time spent at lower mixed venous oxygen saturation in patients with a more severe disease status.

Due to the need for invasive procedure, the use of mixed venous oxygen saturation is underutilized. Nevertheless, if this measurement could be integrated in the IHM it would have potential to alert the clinician on early changes in the patient's condition and to support diagnostic and therapeutic decisions in patients receiving an IHM.

Making sense of continuous hemodynamic data

"The best thing with the IHM is that it gives us a lot of data. The worst thing with the IHM is that it gives us a lot of data" (88). This quote, from a clinician who has been working with the IHM for many years, is very true. The IHM measures every waveform and stores a median value of those measurements every 4-8 minutes. With an expected battery life of 3.5-4 years, this means 250000 ~ 500000 values from each variable are collected during the IHM's lifetime. All these values have to be processed and displayed in a manner that makes it possible for the user to interpret the data and then act accurately to the gained information. In other words, it is important to find the variable or varaibles that together with the best analysis method can provide the most relevant data for clinical management in individual patients, with a variety of diagnoses and with different clinical questions to be answered. The discussion below will focus on analysis methods and presentation of data.

Night time minimum values

The analysis performed in Study II was an attempt to find one data point from the 24-hour continuous hemodynamic data that would reflect measurements typically acquired during supine rest in the clinicians office. This value would then be used to get a "quick look" or a "snap shot" of the changes going on in the patients hemodynamic trend over time (Figure 10). The method applied to the ambulatory data that was found to best mimic a controlled, supine rest value was the lowest value collected by the IHM between midnight and 4 am when the patient was at rest as indicated by zero activity counts. This method is referred to as the *night-time minimum value*. Changes in the night time minimum values will likely reflect changes in volume status and provide an easy mean for the user to decide when to look in more detail at the full hemodynamic trends or not.

Median and range values

The Chronicle information network (Study III) is the web based application where the IHM data is displayed and it utilizes the night time minimum from Study II on its first page. With this "quick look" the user can get a first impression if changes have occurred since the last transmission of hemodynamic data. Next, the hemodynamic trend data are displayed with four different time scales (Figure 18). All trends show median, maximum and minimum values. The one year view shows daily medians and ranges (daily maximum and minimum) that provide an image reflecting long-term disease progress or treatment effects. This type of general hemodynamic changes might be hard to visualize in trends covering a shorter time period. However, one-month or one-week trends, showing 2-hour median and range values, allow for more detailed observations of short term hemodynamic changes in association with acute hyper or hypovolemia, response to drug interventions or arrhythmias. The detailed trends over one-day (6-minute median and range), together with a description of symptoms or activities can support findings associated with alternations in the circadian patterns (89). For example, sudden pressure changes during night might indicate sleep apnea (90) or if they occur in the morning hours they could be effects linked to medication intake (89).

Today, when evaluating a patient's hemodynamic trend on the Chronicle information network all the aspects above have to be taken into account. Though this is less time consuming than it might sound, it is very much dependent on the users

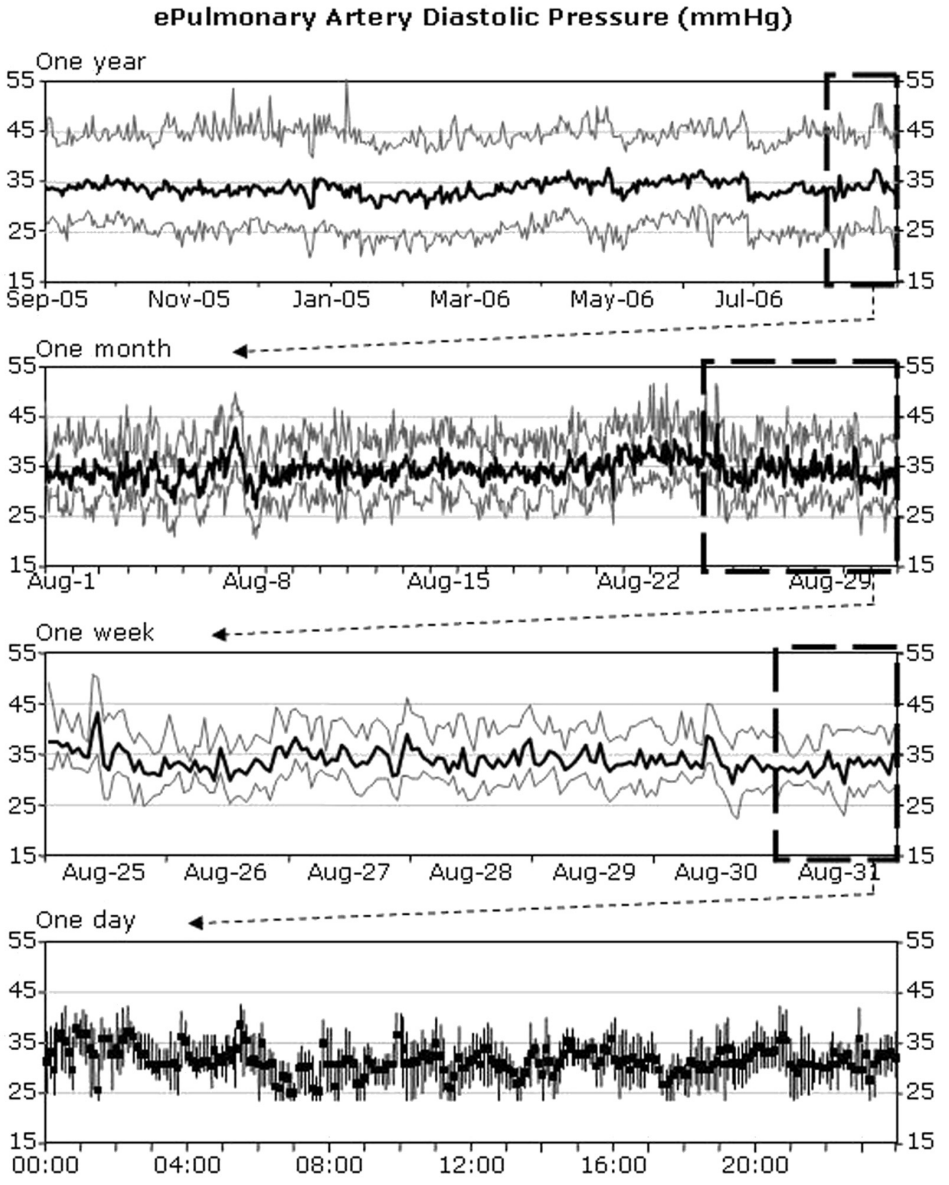

Figure 18. Illustration of the four timescales used on the Chronicle information network to display continuous hemodynamic trends. All trends show a median value (black line) and 94th and 6th percentiles (gray lines).

experience, knowledge and skills. To manage the patients in the daily care, algorithms that automatically detect changes from the patient individual "optimal" are a necessity. Such methods have been reported (76) and could be implemented in future generations of the IHM system.

High resolution values

The IHM can also store hemodynamic data in a 2 second resolution for 3 hours. Using an IHM designated programmer, high resolution data can be printed for immediate review or saved to disc for later processing. Thus, this resolution

is restricted to use in the clinic and the most common use today is hemodynamic observations during exercise testing (Study IV) or drug interventions (Study V). However, it might be speculated that broader uses of this high resolution data could be helpful in remote monitoring. Standardized home exercise could be followed closely and improvements or declines in patient status might be detected early. Drug titrations could be performed with a greater base of knowledge of hemodynamic effects. Acute treatments could be given at the patients local hospital or clinic and supervised by the primary treating center (or a specialist treating center) located somewhere else. The list of possibilities is endless.

In summary, each of the hemodynamic trends and resolutions has the potential to add value in its own way. The high resolution display of the data offers new insights and better understanding of the underlying pathophysiology and co-morbidities of diseases while averaging and calculations of medians give an opportunity to observe long-term changes of the disease state. Various resolutions may all affect the patient treatment and might be essential to provide a better care of patients with cardiopulmonary disease.

Alternative hemodynamic monitoring possibilities

Development of implantable pressure monitoring systems is also being attempted by others. Examples of these systems include the use of pressure sensors placed in the pulmonary artery (HeartSensor™; CardioMEMs and Remon Implant; Remon Technologies), in the left atrium (HeartPod™; Savacor, St Jude) or in the left ventricle (LVP-1000; Transoma Medical). These sensors are positioned by means of invasive techniques but do not have a permanently implanted transvenous lead or memory device. Thus, the sensors provide only "snap-shot" on-demand readings, retrieved with an external activation source held outside the body. In Study II we showed that cardiac pressures measured with the IHM at rest either in the patient's home environment (night, no activity) or during a clinic visit were very similar to each other. This "snap shot" value extracted from the continuous trend was intended to give the user guidance for further exploration of the stored hemodynamic trends. Ongoing and future studies will show if the "snap shot" approach, when measured recurrently and in the ambulatory setting, provides enough information to improve the patient's quality of life and outcome or if more comprehensive data that includes ambulatory information will add incremental benefits.

Telemonitoring – a future perspective in patient care

Telemonitoring, the use of information technology to remotely monitor health status, fits well with modern demands for patient care. Improved communication systems allow for rapid and safe transfer of information from one location to another. Today a broad spectrum of applications e.g. weight, ECG, arterial oximetry, blood pressure, heart rate and symptoms can be transferred from patients via telephone lines, cell phones or internet to their clinicians (91-93). Most studies have shown high levels of acceptance by the users and good compliance with these systems.

The Chronicle information network has been available since the autumn of 2000. Study III describes the early phases and the first versions of the system. Since then hundreds of additional patients in USA and Europe have transmitted IHM data to the Chronicle information network. The findings in Study III demonstrated that patients, independent of age and disease severity, seemed to be able to handle the technology in a satisfying way. Results from the COMPASS-HF trial (75) that included 274 patients diagnosed with heart failure in a wide range of ages and with some patients in a severe disease stage (NYHA class III-IV, age range 21 to 91 years) showed 99% transmission compliance to the Chronicle information network. These results support the conclusion in Study III, that use of telemonitoring for the IHM system is feasible. And, it should only get easier as future technology implementations like wireless transmissions (94) make the technical skills of the user superfluous.

Today's modern society is working in an environ-

ment were technology is becoming an integrated part of daily life. Next generations of patients will probably require less travel, less time off from work or activities and lower costs for health care. At the same time they will also expect the quality and accessibility of care to be higher than today. Telemonitoring could provide the patient easy access and feedback of information that might help self-adjusting of medications and support drug and diet compliance. In addition, the feeling of security patients might sense by being monitored should not be underestimated.

From the care givers perspective it is important that the telemonitoring system can be integrated in the clinic setting. This will necessitate reorganization of the outpatient clinic to accommodate interpretation of new data and to be able give proper patient advice based on the received information. Also, it is important that the new technology contributes to the sentiment of giving satisfactory care without increasing the economic or time burden for the staff at the clinic. After reviewing the literature about available telemonitoring systems, interestingly, no systematic evaluation of the staff's satisfaction with telemonitoring was found. To make telemonitoring an integrated part of the health care system all aspects should be taken into consideration and studies in this field are warranted.

Continuous hemodynamic monitoring – a cardiovascular disease management tool

Access to continuous hemodynamic trends means that administration of treatments aimed to improve cardiovascular function can be made based on an improved platform of knowledge. Treatment choice and drug dosage can be founded on individual patient response at the present stage of the disease. Figure 19 illustrates difficulties in finding the correct dosage of beta-blockers in a patient with heart failure (95). Recommendations for treatments and target dosage are usually based on large study materials. Over and/or under treatment is probably more common than currently known and might lead to inadequate response as well as intolerance or unnecessary side effects. Optimizing and individualizing treatments by the use of the hemodynamic information provided by an IHM might homogenize therapy response and thereby further improve the patient's quality of life during daily living. Dietary and drug compliance are other important factors in the patient care and the IHM can also be used to educate the patient by showing what salty snacks (Figure 20) or skipping diuretics (Figure 21) do to their cardiac pressures.

Heart Failure

Peak VO2, reached during maximal exercise is considered a good predictor of mortality (96-98) and is commonly used as an endpoint in heart failure trials and in the evaluation of patients for heart transplantation. However, submaximal tests are generally easier to perform and more convenient for the patient. Six-minute walk tests are highly reproducible (99,100) and have become the standard in large, multi center trials to show improvement and serve as an indicator of disease progress.

Study IV evaluated the hemodynamic response to maximal and submaximal levels of exercise. Two types of submaximal exercise were performed, a 6-minute walk test and a 6-minute upright bike test where the patients peddled at a steady rate of 40% of their maximal workload. There was no difference in pressure or heart rate response between the two submaximal tests. Those changes, achieved during submaximal exercise were 70-90% of the responses reached at the peak of the maximal exercise tests.

Another study (101) in a similar heart failure population (Study III population) investigated the correlation of submaximal exercise response to daily hemodynamic ranges. The results showed that the peak pressure values reached during a 6-minute walk test were 80-90% of those during the daily measurements (Figure 22). Therefore we believe that the hemodynamic response to exercise reflects the hemodynamic response in daily activities in heart failure patients. Submaximal exercise tests could thus replace maximal test in the assessment of the heart failure patient's functional status during daily activities.

Moreover, patients with an IHM could perform scheduled, predefined activities on a regular basis at home, mimicking those carried out

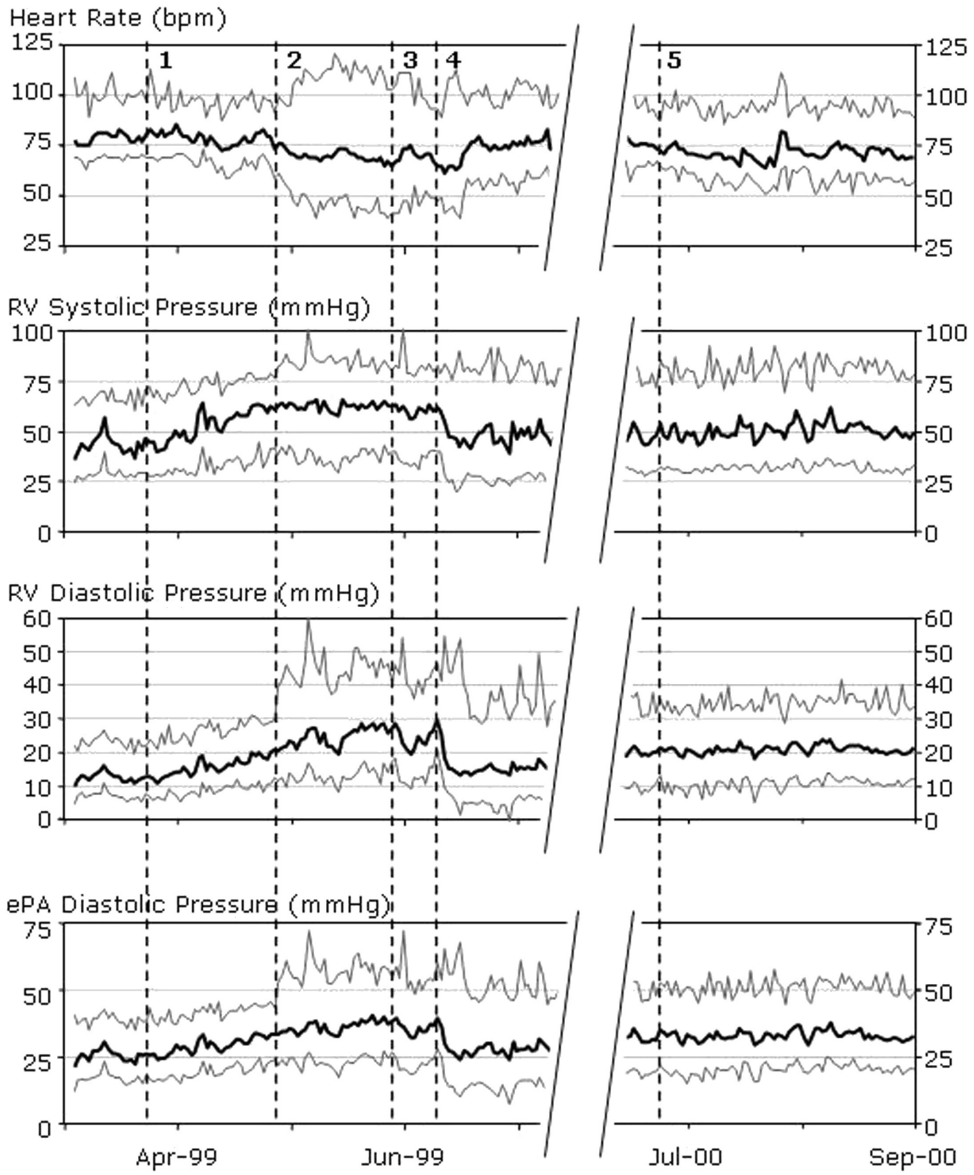

Figure 19. Sixty-two year old man with ischemic cardiomyopathy, NYHA class III. The trends show the daily median (black line) and the daily ranges (gray lines). At the IHM implant in February 1999 the patient had just started treatment with carvedilol and uptitration to 25 and 50 mg/day (note 1 and 2) continued. In May, 1999 the patient had gained 8 kg over the last month and was admitted to the hospital (note 3). I.v. diuretics were started and the patient diuresed 4 kg in 24-hours. After five more days on i.v. diuretics, no further weight loss was achieved. Carvedilol was then lowered to 38 mg/day (note 4) and the patient lost another 4 kg within the next 2 days and could be discharged to home. One year later carvedilol was increased to 50 mg/day (note 5) without any further consequences.

during daily life such as walking around the block, up and down stairs or carrying grocery bags or a load of laundry. The hemodynamic response would be available for the clinician to review on the Chronicle information network and might at occasions be able to replace the clinical assessment at the hospital. The response to this type of exercises would give a good

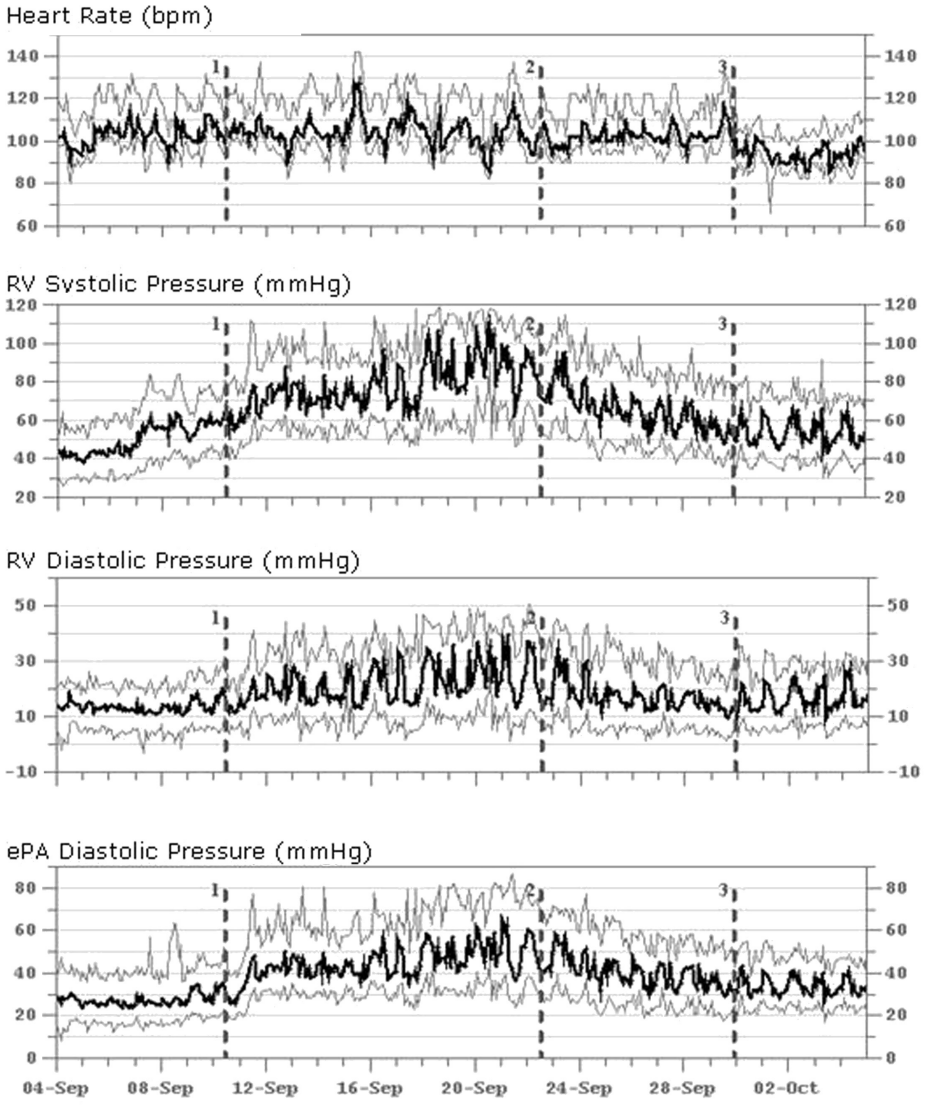

Figure 20. Sixty-two year old woman diagnosed with hypertrophic cardiomyopathy in 2002. At time of implant in December 2004 the patient is in NYHA class III. The trends show the daily median (black line) and the daily ranges (gray lines) over one month when the patient was non-compliant to dietary restrictions and ate salted popcorns. Note 1 - an increase in right ventricular systolic pressure is noted and the patient was contacted by phone. The patient stated she was feeling OK. Note 2 - reinitiated phone contact with the patient who continued to be dietary non-compliant. The patient's weight increased 4 kg and metolazone 2.5 mg/day was initiated. Note 3 - the patients weight have decreased and the patient considered optivolumic. Carvedilol 6.25 mg/day was initiated.

estimate on how heavy daily activity in fact is for a patient and comparisons over time could serve as an indicator on deterioration or improvement.

An additional finding in Study IV was that mixed venous oxygen saturation decreased more during the 6-minute walk test than during the 6-minute bike test. One explanation might be that the 6-minute walk test exposes patients to a higher workload compared with the limited bicycle test.

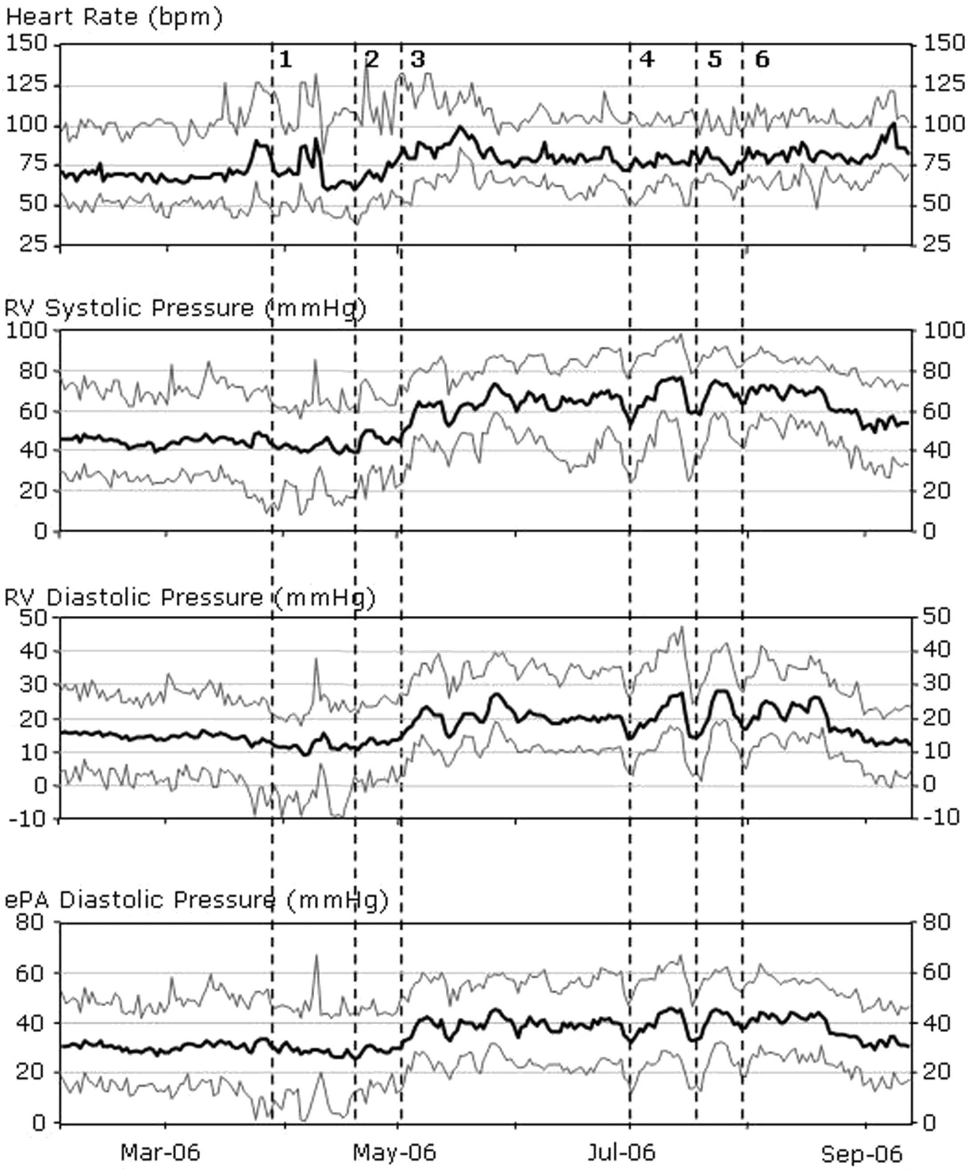

Figure 21. Seventy-eight year old man with dilated cardiomyopathy, NYHA class II who developed general eczema and was admitted to the dermatology department (note 1). Due to suspected drug allergy, carvedilol was terminated and bisoprolol started before hospital discharge (note 2). Three weeks later the patient was seen at the ER for hypoglycemia and by mistake, diuretic treatment was stopped (note 3). The mistake was discovered the next time the patient sent IHM data to the IN website and after phone contact, diuretic treatment was restarted. Due to deteriorating health the patient was non-compliant with drug intake and in June and July the patient was admitted 3 times to the cardiology clinic for volume overload and treatment with i.v. diuretics. During each hospitalization the cardiac pressures decreased but immediately increased when the patient returned home (notes 4-6). In August, 2006 the patient moved to an assisted living facility and with support from the staff, drug compliance improved and cardiac pressures decreased. The trends show the daily median (black line) and the daily ranges (gray lines).

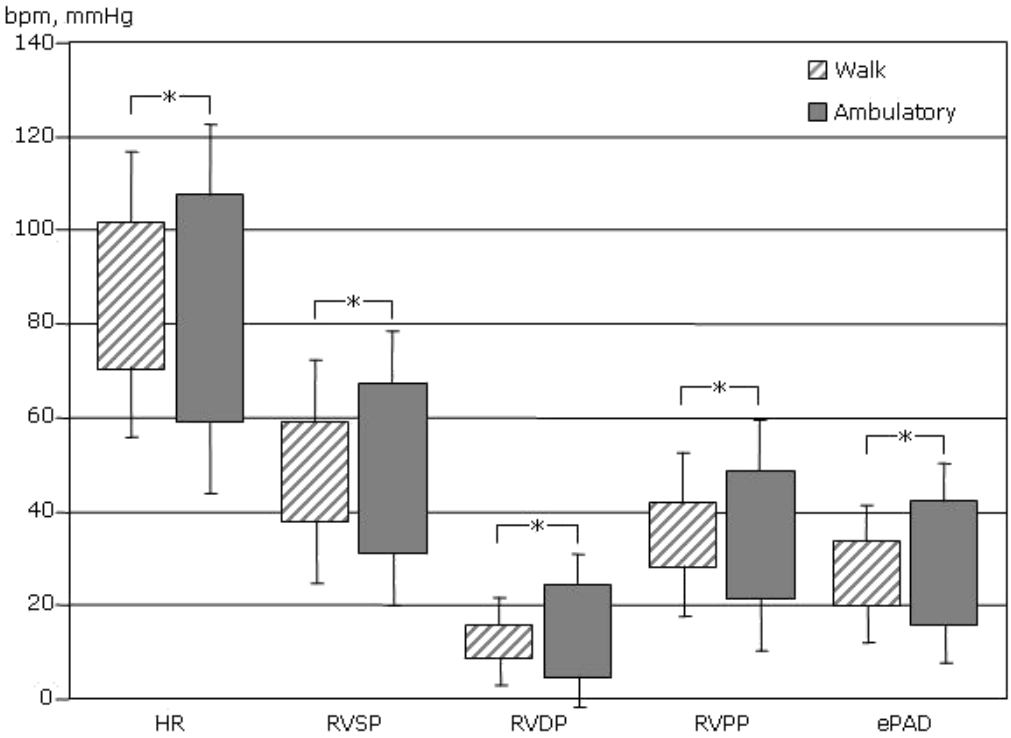

Figure 22. Hemodynamic ranges during a 6 min walk tests (striped bars) and during ambulatory measurements (solid gray bar). The bottom of the bar is the resting value, e.g. for the exercise tests it is the rest before exercise and for ambulatory data it is the daily minimum. The top of the solid bar is the maximum value, e.g. for the exercise tests it is the peak values of the test and for ambulatory data it is the daily maximum. The error bars are the SD of the ranges.

During the walk test, patients were asked to walk as fast as they could while during the bike-test they paddled at a fixed rate and workload which might be less strenuous for some patients. Also, walking does engage the whole body which might increase the total tissue oxygen demand compared to biking which at least at submaximal levels engages mostly the lower body. This type of information might impact daily living recommendations or help deciding type of exercise and level of workload in exercise programs for patients with cardiovascular disease.

Pulmonary hypertension

Medical therapy for patients diagnosed with pulmonary arterial hypertension is targeted directly towards the increased pulmonary vascular resistance and elevated pulmonary artery pressures. Prostacyclins, receptor antagonists and phosphodiesterase inhibitors are treatments available today, most of them approved for use in this patient population in the last decade. The optimal dose of the drug is determined by close monitoring of symptom relief and of hemodynamics where an optimal treatment response is a significant decrease in pulmonary vascular resistance without lowering the systemic pressure to a symptomatic level. This is typically measured as an increase in cardiac output and decrease of pulmonary artery pressures.

Study V looked at hemodynamic response to inhaled iloprost in five patients with pulmonary hypertension. All patients were already on chronic iloprost treatment at the time of IHM implantation. Therefore the hemodynamic treatment effect over time was not evaluated.

The protocols included supervised iloprost inhalations during a hospital visit followed by

a one day period at home with non-supervised inhalations. The same drug dosage and the same nebulizer were used in both settings. The acute effect of iloprost inhalation was a rapid decrease in pulmonary pressures (Figure 16). When the patient was supervised, the time at the low pressure level lasted longer then after a non-supervised inhalation. In contrast, the time to a 50% return of pre-inhalation pressures was similar between the two protocols. So what could have made the difference in the treatment response? Hemodynamic data collection was performed with the IHM programmed to different resolutions (median of 2 vs. 52 seconds) in the two protocols. Although the lower resolution (52 seconds), used when the patients were at home, filtered out the lowest and highest values during the data collection period this would only have impacted a few minutes of the data collection and is unlikely to have caused the difference. Therefore, the most plausible cause is compliance with inhalation techniques and the environment. In the clinic, the patients were observed during the inhalation which implies higher compliance with inhalation recommendations. While at home, the patient might make the inhalation shorter rather than longer and be more prone to return to daily activities immediately when the inhalation is finished. Moreover, the effective treatment time varied between patients. Thus, the IHM might support decisions about inhalation frequency in individual patients and if and when additional treatment is required.

Treatment of patients with pulmonary arterial hypertension has used symptom relief as a sign of decreased pulmonary vascular resistance and increased cardiac output. However, more recently improved right ventricular and pulmonary artery pressures have been suggested as a treatment goal that might lead to improved survival (30). While pressures at rest might show improvement to treatment (34), even a small amount of exertion will increase the right sided cardiac pressures significantly (68,102) due to the non-compliant pulmonary arteries seen in these patients. These increased pressures might cause additional damage to the vasculature if not reversed (30) and thereby accelerate the progression to right heart failure. The IHM, with the pressure sensor placed in the right ventricle, appears as a promising and exciting new tool in these patients and might support therapy decisions in the setting where multiple drug treatment is common.

Renal failure

In Study VI, patients with end stage renal disease on hemodialysis treatment and with an IHM implanted were investigated. The study focused on evaluation of hemodynamic trends between the dialysis sessions and put extra emphasis on the extended time without dialysis that occur after the weekend, on a Monday or Tuesday. The study population as a whole had cardiac pressure values in the normal to upper ranges of normal values (Table 2). The recurring volume overloads seen in patients on hemodialysis treatment are in the same magnitude that might cause symptoms and even hospitalization in patients with heart failure (66). In heart failure patients, increased cardiac pressures were seen over a week before the hospitalizations, though about half of the pressure increase tended to occur during the last 24-hours before the event (66).

It could be hypothesized that the recurrent alternations in filling pressures, related to fluid status in patients on dialysis treatment, might incur activation of neurohormones and the sympathetic nervous systems resulting in myocardial damage. This might be the start of a viscous cycle where a worsening of the ability of the cardiovascular system to compensate for changes in volume load leads to acceleration in the development of left ventricular dysfunction (103,104). Though, this might not be preventable in the long term, improved treatment strategies may prolong the time to symptomatic ventricular dysfunction in patients on hemodialysis treatment. The results in Study VI suggests that three dialysis treatments a week might not be optimal for these patients and that more frequent dialysis sessions may decrease the burden of pulmonary congestion and possibly the development of alterations in cardiac function.

In dialysis patients venous access is essential and there might be hesitations to implanting a purely monitoring device. Retrospective studies from the USRD registry of patients on dialysis treatment receiving an ICD for secondary

prophylaxis of malignant arrhythmia showed an improved survival (105). Although the effectiveness of primary prophylactic ICDs has not been addressed in the dialysis population it is conceivable that this treatment may be helpful to improve survival since sudden cardiac death is the single largest cause of mortality in end stage renal failure. Therefore, the combination of an ICD with hemodynamic monitoring capabilities would probably be more accepted by clinicians for use in this patient population.

Summary

Hemodynamic data from the IHM is valuable when data is 1) acquired reliably, 2) readily interpreted and 3) integrated effectively into patient care.

The IHM systems reported here were either investigational devices or first generation systems and previous work (64,65), including these systems and Study I in this thesis, have shown that hemodynamic data can be acquired accurately by biosensors both acutely and over long term. To support interpretation of continuous hemodynamic data, developments of effective methods for information management are underway and will provide improvements in the effectiveness of future systems.

At present, the incorporation of IHM data into routine patient care requires the user to obtain necessary knowledge and allocate the time needed for data review. An appealing future application would be if an integration of ambulatory hemodynamic information into the diagnostic assessment of patients was possible. The IHM data could be pooled into a database with other clinical information from the same patient. Advanced algorithms would then perform a cross-analysis and provide accurate, reliable status reports and treatment suggestions. While this is not available yet, continuous hemodynamic monitoring, as evidenced in this thesis, has great potential for guiding therapy and observation of disease progress in patients with cardiovascular diseases associated with compromised hemodynamics.

Lessons learned from my research. Despite all advances in technology and the benefit they can give in the care of a patient, technology will not be able to replace the human factor. The patients will always need that we take the time to listen to them. Technology is wonderful, it is the future and we will be there with it.

Conclusions

I Accuracy and long term stability of an implanted venous oxygen sensor was demonstrated

II Night-time minimum accurately reflected hemodynamic measurements during controlled, supine rest

III Access to patient hemodynamic data trans-telephonically and via the internet was feasible and usable, independent of patient age and disease severity

IV Hemodynamic response during submaximal exercise tests in heart failure patients was similar to that during maximal exercise

V Continuous right ventricular and pulmonary artery pressures provided information on treatment response to inhaled iloprost in patients with pulmonary hypertension

VI Progressive right ventricular and pulmonary artery pressure increments, related to volume load, was seen between dialysis sessions

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