Acoustic and Afterload evaluation of Left Ventricular Assist Devices

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Acoustic and afterload evaluation of left ventricular assist devices

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Cover/picture/Illustration/Design: Soundwave from a HeartMate II.

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To Melker and Ellen, the light of my life!

It always seems impossible until it's done

-Nelson Mandela

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Abstract

Background: Heart Failure is a serious condition with consequences not only for the individual patient but also for the society with a 5-year mortality rate of 45-60%, and a substantial economic burden. The estimated prevalence in Sweden is 2.2% and the age adjusted prevalence increases with higher age. The etiology of heart failure varies although with somewhat similar pathogenic mechanisms. The fundamental treatment for heart failure is pharmaceutical in combination with life-style changes, and physiotherapy. For some patients the implantation of cardioverter defibrillator, or resynchronization therapy might be an option.

For patients with advanced heart failure, the use of long-term circulatory support can be an option as a bridge to transplantation, or as destination therapy. However, this treatment entails a risk of multiple adverse events. The incidence of pump thrombosis increased as a clinical problem in 2012 and the need for diagnostic methods were desired. The aim of this thesis was to develop and to evaluate the use of a mock loop circuit to study the acoustics of left ventricular assist devices, to evaluate different recording devices and to study the effect of afterload on pump function.

Methods: Two different mock loops, with the possibility to insert artificial thrombus and to adjust preload and afterload were created to facilitate recording of the left ventricular assist devices. An iPhone/iPod™ was used as recording device since remote monitoring is desirable. The sounds from HeartMate II™ during different conditions were studied. The iPhone/iPod was evaluated in comparison to dedicated recording equipment, and the mock loop recordings to clinical situation.

The sound from HeartMate 3™ was studied, compared between in vivo and in vitro recordings, and the use of an electronic stethoscope was evaluated. The impact of afterload on left ventricular assist devices was studied in a mock loop circuit with different changes in preload and afterload.

Results: Mock loop circuit is a promising method to safely change the surrounding conditions as the pump is working. The sound from both HeartMate II™ and HeartMate 3™ can be recorded and analyzed in frequency and time domain. When inserting artificial thrombus in a HeartMate II™ the frequency spectrum is altered. The use of dedicated recording devices is superior to both electronic stethoscope and iPhone/iPod™, but these handheld devices can be used in clinical settings. The recordings from mock loop circuit and patients appear similar for both HeartMate II™ and HeartMate 3™. The flow of the devices is affected by the afterload. The HeartMate 3™ is more resistant to increased clot analogs within the pump. For both pumps, best efficacy is seen for clean circuits. The flow rate from the monitor might

be misleading since the measured flow rate and the flow rate from monitor can differ due to surrounding conditions. The estimated flow might be adjusted by fitting a parabolic curve.

Conclusion: The use of mock loop circuit to study both flow and sound under different conditions is valid. It is possible to record and study the sound from both HeartMate IITM and HeartMate 3TM. The sound holds information of pump function and appears similar in vivo and in vitro. All recording devices can be used, but dedicated equipment is superior to the more handheld devices, although these might have a function as a screening device. The flow measurement on the monitor might not be valid and optimization of fluid status and afterload can further increase pump efficiency.

Keywords: Afterload, Electronic stethoscope, Flow, HeartMate II, HeartMate 3, iOS-devices, Sound Analysis

List of original papers

This thesis consists of 4 papers. Three of them are published in International, peer-reviewed scientific journals. In the text, the studies are referred to by Roman numerals. Studies I-III are reprinted with the permission of the publisher. Study IV have been submitted for publication.

- I. Hubbert L, Sundbom P, Loebe M, Peterzen B, Granfeldt H, Ahn H. Acoustic analysis of a mechanical circulatory support. *Artificial organs*. 2014;38:593-8.
- II. Sundbom P, Roth M, Granfeldt H, Karlsson DM, Ahn H, Gustafsson F, et al. Sound analysis of a left ventricular assist device: A technical evaluation of iOS devices. *The International journal of artificial organs*. 2018;41:254-60
- III. Sundbom P, Roth M, Granfeldt H, Karlsson D.M, Ahn H, Gustafsson F, et al. Sound analysis of the magnetically levitated left ventricular assist device HeartMate 3™. *The International journal of artificial organs*. 2019, doi: 10.1177/0391398819857443.
- IV. Fuchs G, Sundbom P, Broman L.M, Hubbert L, Prahl Wittberg L. In-vitro study of the impact of LVAD loading on mechanical performance.

Abbreviations

ACC/AHA	American College of Cardiology/ American Heart Association
ACE	Angiotensin converter enzyme
ACEI	Angiotensin converting enzyme inhibitor
AIDS	Acquired immunodeficiency syndrome
ANP	Atrial natriuretic peptides
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor Neprilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BB	Beta blockers
BNP	B-type natriuretic peptides
BP	Blood pressure
BPM	Beats per minute
BTT	Bridge to transplantation
Ca ²⁺	Calcium
CMR	Cardiac magnetic resonance imaging
CO	Cardiac output
CRT	Cardiac resynchronization therapy
DCM	Dilated cardiomyopathy
DFT	Discrete Fourier transform
DT	Destination therapy
DTFT	Discrete-time Fourier transform
EC	Excitation-contraction
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
ESC	European Society of Cardiology
ET ₁	Endothelin 1
FDA	Federal drug agency
FFT	Fast Fourier transform
GH	Growth hormone
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HM3	HeartMate 3
HMII	HeartMate II

Htx	Heart transplantation
HVAD	HeartWare ventricular assist device
Hz	Hertz
IABP	Intra-aortic balloon pump
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
INTERMACS	Interagency Registry for Mechanically assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
L	Liter
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LV	Left ventricular
LVAD	Left ventricular assist device
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MI	Myocardial infarction
Min	Minute
MRA	Mineralocorticoid /aldosterone receptor antagonist
MRI	Magnetic resonance tomography
NEP	Natriuretic peptide c-receptor
NP	Natriuretic peptides
NT-Pro-BNP	N-terminal of brain natriuretic peptide
NYHA	New York Heart Association
PSD	Power spectral density
PWM	Pulse width modulation
RAAS	Renin-Angiotensin Aldosterone system
ROS	Reactive oxygen species
RPM	Revolutions per minute
RV	Right ventricular
TGF- β	Transforming growth factor- β
vWf	Von Willebrand factor

Introduction

Heart failure (HF) is a clinical condition characterized by symptoms caused by reduced cardiac output (CO) and/ or elevated intra-cardiac pressures at rest, or during exercise.¹ The classical symptoms include peripheral edema, shortness of breath, and fatigue. These symptoms can be accompanied by other signs such as elevated jugular venous pressure and pulmonary crackles. The reduction of CO is caused by a functional, or structural, cardiac abnormality with neurohormonal activation, and complex pathophysiology.¹ The diagnosis of HF carries substantial risk of mortality and morbidity. For patients that deteriorate in their disease, despite optimal medication, heart transplantation (Htx) or mechanical circulatory support (MCS) might be an option. For patients treated with a left ventricle assist device (LVAD), adverse events can occur with devastating effects. One of these events is pump thrombosis. The relatively high incidence of pump thrombosis implies the need for non-invasive methods to assess the presence of pump thrombosis. This resulted in the start of this thesis.

To understand the concept of LVAD-treatment, an understanding on the basic epidemiology, physiology, pathophysiology, and treatment of HF is necessary. The proportion of patients eligible for advanced treatment is small but might be higher if patients were referred to HF-centers to a larger extent. Most of the patients that are treated with LVAD are amongst the sickest of the HF-population and are, despite LVAD treatment, in need for adequate pharmacological treatment.

The first four chapters within this thesis summarize the current knowledge of HF and HF-treatment. This alone can help to minimize mortality and morbidity, if used in every-day clinical practice. The remaining chapters focus on the acoustic and afterload evaluation of LVAD.

Heart failure

Epidemiology of heart failure

It is estimated that 23 million humans worldwide suffer from HF. From 1970-1990 the prevalence of HF increased due to ageing population, to some extent increased incidence and improvements in the treatments of acute cardiovascular disease resulting in more patients surviving the initial event.² In 2010, the estimated prevalence of HF within Sweden was 2.2%, and the mean age of 77 ± 13 years. The prevalence has lightly increased for women whilst overall prevalence has plateaued.³ The prevalence and incidence increase with age and constitute a substantial financial burden, consuming approximately 1-2% of total health care expenditure.⁴ The total annual cost for HF in Sweden has increased from the estimation of 2.6 billion in 1996 to 5.0-6.7 billion in 1999, of which hospital admissions accounted for the main proportion (47%) of total cost.^{5, 6}

The diagnosis of HF carries substantial risk of mortality and morbidity. The 30-day mortality is around 10%, 1-year mortality is 20-30%, and 5-year mortality is 45-60%.² HF is mainly categorized according to different aspects depending on left ventricular (LV) or right ventricular (RV) function calculated by objective means, or symptoms addressed by the patient.¹ HF is a multi-organ disease where advanced HF with inadequate end-organ perfusion results in physiological derangements, neurological complications, metabolic wasting and subsequently death.

Pressure-volume loop

The maintenance of cardiovascular homeostasis requires ability to adapt cardiac function to different hemodynamic conditions.⁷ The basis for this adaptation is the Frank-Starling mechanism named after the work of Starling in 1914 and Frank in 1959.^{8, 9} The mechanism state that an increase in arterial resistance or venous return lead to increased end-diastolic volume and subsequently increased contractility/stroke volume.⁷ The end-diastolic volume, also known as preload, generates an increased pressure in the LV. When the pressure exceeds the intra-aortic pressure, also known as afterload, the mitral valve closes and the aortic valve opens. This process can be measured and plotted as a pressure-volume loop. See figure 1. The increased contractility is mainly attributed to the response of Calcium (Ca^{2+}) released on the sarcomere. Elongated sarcomere results in increased sensitivity for Ca^{2+} stimulus. Phosphorylation of multiple cardiomyocyte proteins and receptors participate in the

myocardial response to stretch of which many affect Ca^{2+} levels (see Pathophysiology; Calcium signaling dysfunction).⁷

Figure 1. The figure shows a pressure volume loop of the left ventricle. Ventricular filling (phase a, diastole), isovolumetric contraction (phase b, systole), ejection phase (phase c, systole), isovolumetric relaxation (phase d, diastole) EDPVR: End-diastolic pressure-volume relationship, ESPVR: End-systolic pressure volume relationship, LVP: Left ventricular pressure, LV Vol; Left ventricular volume, SV; Stroke volume. (Reprinted with permission from Richard E. Klabunde, www.cvphysiology.com)

Classification of heart failure

HF can be predominantly affecting left or right ventricle or both (biventricular). Historically, the classification is based on LV function measured by ejection fraction (EF), $((\text{Systolic volume} - \text{Diastolic volume}) / \text{Diastolic volume})$. Due to the multifactorial etiology, HF can occur without impact on EF. Consequently, and in lack of studies of patients with $\text{EF} > 40\%$, HF is now described in three categories. This categorization is: heart failure with reduced ejection fraction (HFrEF) with an EF below 40%, heart failure with mid-range ejection fraction (HFmrEF) with an EF between 40 and 50% and heart failure with preserved ejection fraction (HFpEF) with an EF above 50%.¹

Most clinical studies are performed on patients with HFrEF whilst patients with HFpEF acquired scientific interest during recent years.¹ However, there is low evidence of effective therapies yet available for HFpEF, but further research is ongoing. Previously patients with HFmrEF was classified HFrEF, but the European society of cardiology (ESC) states in their latest guidelines from 2016 that these patients represent an entity of its own that needs further scientific investigation. In order to classify patients to the correct group, an objective assessment is necessary. This assessment could be by either echocardiography or and cardiac magnetic resonance imaging (CMR).¹

Another approach in classification of HF is based upon functional status and severity of symptoms. The New York Heart Association (NYHA) classification has been used for a long time, and it categorizes patients in one of four groups based upon self-reported physical limitations. See Table 1. The NYHA-classification is often used when communicating the severity of HF, and can also be used as a prognostic marker in which patients in NYHA class IV have the highest mortality.¹⁰ The American college of cardiology / American heart association (ACC/AHA) classifies HF in four stages depending on risk factors and abnormalities that are associated with HF. The scale constitutes of four progressive stages, A-D, and once a patient reaches a higher stage there is no moving backwards to previous stages. Progression in stages is associated with reduced 5-year survival and increased biomarker.¹¹ The Interagency Registry for Mechanically Circulatory Support (INTERMACS) classify patients with advanced HF in 7 clinical categories depending on symptoms and the use of inotropic treatment. This classification further divides patients in functional classes, NYHA IIIb-IV.¹² See Table 1. A portion of patients with HF will progress to advanced HF. Advanced HF is defined as patients that, despite optimal treatment fulfil the criteria below¹³

1. Severe and persistent symptoms. (NYHA III-IV)
2. Severe cardiac dysfunction defined by a reduced LVEF $\leq 30\%$, isolated RV failure, or non-operable severe valvular abnormalities or congenital abnormalities or persistently high (or rising) Brain natriuretic peptides (BNP) or N-terminal of brain natriuretic peptide (NT-proBNP) values and diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.

4. Severe impairment of exercise capacity with inability to exercise or low 6-minute walk distance (<300m) or peak exercise oxygen consumption (<12-14mL/kg/min) estimated to be of cardiac origin.

Table 1. Comparison of ACC/AHA stages of HF, NYHA functional classification and INTERMACS-classification

ACC/AHA Stages of HF		NYHA Functional Classification	INTERMACS- Classification
A	Patients at risk for heart failure who have no structural heart changes	None	
B	Patients with structural heart disease who have not yet developed symptoms of HF	I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF	
C	Patients who have developed clinical HF	I No limitation of physical activity. Ordinary physical activity without symptoms II Slight limitation of physical capacity. Comfortable at rest. Ordinary physical activity results in symptoms of HF III Marked limitation of physical capacity. Comfortable at rest but less than ordinary activity causes symptoms of HF	7 Advanced NYHA III 6 Exertion limited 5 Exertion intolerant 4 Resting symptoms 3 Stable on inotropes 2 Progressive decline 1 Critical cardiogenic shock
D	Patients with refractory HF requiring advanced intervention	IV Unable to carry on any physical activity without symptoms of HF, or symptoms of heart failure at rest	Symptoms with minimal capacity ADL possible but meaningful activity limited Comfortable at rest, symptoms with minimum activity On oral therapy at home Continuous inotrope dependent Worsening on inotropes Cardiogenic shock

ACC : American College of Cardiology. AHA: American Heart Association. HF: Heart Failure. INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

NYHA: New York Heart Association

Pathophysiology of heart failure

Introduction to pathophysiology

The aim for the healthy heart is to deliver nutrients and oxygen to the multiple organs within the human body. To be able to perform this important task the heart contract in both longitudinal and circumferential way with a rhythm of 50-70 beats per minute (bpm). A numerous of diseases can affect the normal physiology of the heart and cause an impairment of the possibility to maintain normal hemodynamics. These diseases result in impairment of the ejection or of the ventricular filling. The initial disease affects the myocytes that will lead to subsequent structural changes leading to HF. A summary of etiologies of HF is presented in table 2. The major pathogenic mechanism is ischemic dysfunction within myocytes, ventricular remodeling, increased hemodynamic overload, excessive neuro hormonal stimulation, abnormal myocyte calcium cycling, accelerated apoptosis, excessive or inadequate proliferation of the extracellular matrix and genetic mutations. Occasionally patients may suffer from HF that resolves completely, examples of these etiologies are viral myocarditis, Takutsubo cardiomyopathy, and peripartum cardiomyopathy.¹⁴⁻¹⁶

Ventricular remodeling

In the presence of myocardial infarction (MI) which is the predominant etiology of HF, often 1 billion or more cardiomyocytes die within 20 minutes. The inner layer of myocardium is affected first, and the wave of cell death moves towards the outer layer reaching all affected cells (including nerves, fibroblasts and vascular cells) within 3-6h.¹⁷ Consequently, since the cardiomyocytes are not able to regenerate, this generates a massive inflammatory response, recruiting neutrophils and macrophages that subsequently results in a fibrotic scar.^{18, 19} Thereafter, early and late remodelling occur, including hypertrophy and fibrosis of the surrounding myocardium eventually leading to impaired cardiac function.¹⁹ The fibrosis is mediated by fibroblasts and myofibroblasts, and causes both the pivotal scar formation (to prevent rupture of cardiac wall) and the reactive fibrosis in the surrounding tissue.²⁰

The healing after heart-damage is complex and involves numerous hormonal and paracrine mediators that can induce increased remodeling in the remote uninjured myocardium.¹⁸ The remodeled myocardium, and mainly the scar, will act as a non-excitabile area that can cause re-entrant arrhythmia and sustained ventricular arrhythmia.²¹ The equilibrium of immune response to infarction has a deleterious effect on adverse remodeling but is also important for proper infarction healing.²¹ The reactive fibrosis is accompanied by hypertrophic growth of cardiomyocytes as they try to compensate the increased workload. They do so by expand in size, which will

decrease wall tension and increase cardiac function. However, the increased mechanical stress will sustain fibroblast activation and continued collagen deposits, leading to interstitial fibrosis that influence the diastolic function and increase wall tension.¹⁸ A route to HF has emerged.

The model of fibroblast activation by induced mechanical stress can be applied to other etiologies as well. Multiple pro-fibrotic cytokines are involved in control of fibrosis. The best characterized pro-fibrotic cytokine is Transforming growth factor- β (TGF- β) that can rapidly be released and activated in the response to reactive oxygen species (ROS).¹⁸

For dilated cardiomyopathy (DCM) the etiology is multifactorial with familial transmission in 20-35% of the cases with a wide variety of genetic disorders. Alcohol abuse accounts for a substantial number of patients with LV-dilatation in high-income countries. These are often referred to as alcoholic cardiomyopathy.²²⁻²⁴ Most of the genetic disorders, or acquired etiologies, affect one or more genes that encode the sarcomere, cytoskeleton, nuclear envelope, transcriptional pathways, or mitochondrial proteins.²⁵ For example, one commonly affected gene is the TTN gene that encodes the protein Titin, a component of the sarcomere structure.²⁶ As DCM progress, the LV will dilate and assume a spherical shape. This results in a decreased stroke volume and CO, impaired ventricular filling and increased end-diastolic pressure. See figure 2. The compensatory effects in the vascular system includes a decreased arterial compliance, increased systemic vascular resistance, increased venous pressure, and increased circulating blood volume.²⁷ DCM is often accompanied by diastolic dysfunction in both the active and passive compliance phase that leads to rapid ventricular filling. The increased preload and afterload affect the wall stress and results in activation of secondary neuro-hormonal systems, see section of neuro-hormonal stimulation.²⁵

Hypertension is another common etiology of HF. Hypertension cause a structural effect on the myocardium that starts with hyperplasia of fibroblasts and hypertrophy of vascular smooth muscle layer which in turn results in expansion of interstitial collagen.²⁸ All combined, the changes contribute to ischemia at the micro and macrovascular level. The ischemia and the remodeling events result in up-regulation of hypertrophic genes and a LV hypertrophy. The LV hypertrophy leads to concentric remodeling (increased wall thickness to cavity diameter) or concentric hypertrophy (increase in absolute LV thickness).²⁹ The hypertrophy results in increased distance between epicardial and endocardial layers, inadequate coronary growth, increased perivascular fibrosis, and medial thickening.^{27, 28, 30} All these mechanisms impair the myocardial perfusion and result in ischemia and increased LV-pressure that in turn result in secondary neuro-hormonal activation, see section of neuro-hormonal stimulation.³¹

Figure 2. In Heart Failure the impaired ventricular contraction (inotropy) cause a decreased stroke volume that generates a downward shift (a to b) in the Frank-Starling curve which results in a compensatory rise in preload, shown as end diastolic pressure, to maintain stroke volume. (Reprinted with permission from Richard E. Klabunde, www.cvphysiology.com)

Table 2. Etiologies to heart failure

Etiology	Sub-group	Specific diseases
Ischemic heart disease		Myocardial scar after infarction Endothelial dysfunction Epicardial coronary artery disease Myocardial hibernation/stunning Defect coronary microcirculation
Inflammatory and immune-mediated	Infections	Bacterias, HIV/AIDS, fungi, protozoa, spirochaetes, Rickettsia, parasites etc
	Inflammatory	Autoimmune diseases, Systemic lupus erythematosos, Churg-Strauss vasculitis
Metabolic	Nutritional	Obesity, Deficiencies in thiamine, selenium, phosphates, calcium, iron, L-carnitine.
	Hormonal	Addisons disease, thyroid diseases, parathyroid diseases, metabolic syndrome, Phaeochromocytoma, diabetes, GH deficiency States related to pregnancy and peripartum
Infiltrations	Malignancy	Infiltrations and metastases
	Not related to malignancy	Amyloidosis, lysosomal storage disease, sarcoidosis, haemochromatosis
Toxic	Substance abuse	Alcohol, amphetamine, anabolic steroids, cocaine
	Medications	Cytostatic drugs, immunomodulating drugs, antidepressants, anti-inflammatory drugs,
	Radiation Heavy metals	Copper, iron, lead, cobalt
Genetic abnormalities	Diverse forms	DCM, Left ventricular non compaction, ARVC,HCM, Muscular dystrophies and laminopathies, restrictive cardiomyopathy
Hypertension		
Arrhythmias	Tachyarrhythmias	Atrial and ventricular arrhythmias
	Bradyarrhythmias	Sinus node dysfunction, conduction disorders
Valve disease	Congential	Atrial and ventricular septum defects
	Acquired	Aortic, mitral, pulmonary and tricuspid valve disease
High output		Anemia, pregnancy, thyrotoxicosis, sepsis
Volume overload		Renal failure, iatrogen volume overload
Others	Pericardial	Constrictive pericarditis, pericardial effusion
	Endomyocardial	hypereosinophilic syndrome, endocardial fibroelastosis, endomyocardial fibrosis

HIV: Human immuno deficiency virus. AIDS: Aquired immunodeficiency syndrome. GH: Groeth hormone. DCM: Dilated cardiomyopathy. ARVC: Arrhythmogenic right ventricular cardiomyopathy. HCM: Hypertrophic cardiomyopathy

Neuro-hormonal stimulation

Angiotensin II (Ang II) is expressed and activated by fibroblasts within the initial infarction scar and have multiple effects on the cardiac remodeling.³² Ang II is also the central signal molecule of the Renin-Angiotensin Aldosterone System (RAAS) that is a central part of the excessive neuro hormonal response. When the CO decreases, the renal perfusion will be affected, and Renin will be produced to induce sodium retention and increase blood pressure (BP). Renin will cleave angiotensinogen, produced by the liver, to angiotensin that will be converted to Ang II by Angiotensin converting enzyme (ACE). Ang II will then bind to one of its 2 receptors, primarily AT1R, that results in secretion of aldosterone, vasopressin secretion, and vasoconstriction within small vessels resulting in increased BP. It is suggested that stimulation of AT2R counteract the effect of AT1R.³³ Ang II also promotes fibroblast proliferation, myofibroblasts differentiation, secretion of pro-inflammatory cytokines, Extracellular matrix turnover, and up regulation of TGF- β within the myocardium.

Endothelin 1 (ET1) is also reported as a pro-fibrotic paracrine signal released downstream of Ang II and TGF- β .³² Both Ang II and ET1 affect the intracellular levels of Ca^{2+} and the inotropic effect of the heart.⁷ In the presence of low CO, arterial baroreceptors and ventricular reflexes will try to increase CO by increased heart rhythm, heart wall contraction (inotropy), vascular tone and increased sympathetic renal nerve activation leading to additional water retention. The physiological response is an intravascular increase in volume that for the patient with HF results in congestion.³⁴

To counteract the Renin induced sodium retention, primarily the heart secretes natriuretic peptides (NP) that aim to protect the heart from volume overload by induced natriuresis, vasodilatation, heart wall relaxation and, diuresis. There are two forms of NP, Atrial NP (ANP) and B-type, BNP. The ANP is dominantly produced in the atria whilst BNP mostly is produced in the ventricle. BNP is synthesized when increased wall tension occurs whilst ANP is stored in granule and released with minor triggers. BNP is cleaved from its inactive state, pro-BNP, to active state, BNP, and NT-Pro-BNP. The peptides are degraded by neutral endopeptidase and cleared by natriuretic peptide c-receptor (NEP). Both are present in kidneys, vascular wall, and lungs.³⁵ All the peptides can be measured as a biomarker for volume overload, but with different specific features depending on degradation habitus of the patient and renal function.³⁶

For patients with chronic or acute HF the level of NT-pro-BNP is a prognostic marker for morbidity and mortality.^{37, 38} However, in patients with severe HF a relative state of deficiency and resistance to NP might be present due to an overwhelmed system and downregulation of receptors as well as an increased clearance of peptides by NEP.³⁵

Calcium signaling dysfunction

Another mechanism that is central for HF is altered excitation-contraction (EC) coupling. This derives from a maladaptive redistribution of intracellular Ca^{2+} , altered expression and function of Ca^{2+} handling proteins, and changes in the architecture of the cell membrane.

Depolarization of the cardiomyocyte requires complex membrane with t-tubular network that is situated close to the sarcoplasmic reticulum and leads to rapid diffusion of Ca^{2+} . This induces Ca^{2+} release on the sarcomere and facilitate muscle contraction. Multiple channels (L-type, SERCA2a) and receptors (RyR2) facilitate this transport and reabsorption of Ca^{2+} and their function is impaired in HF. Another altered part of intracellular Ca^{2+} is the increment within mitochondria that impairs mitochondrial function and increases ROS and induces apoptotic pathways. The changes in Ca^{2+} signaling results in remodeling of t-tubule architecture, alteration in handling proteins that promotes slowed relaxation, spontaneous Ca^{2+} release, increased apoptotic pathways, reduced and delayed force of contraction. All these effects are essential parts of the pathophysiology of HF.³⁹

Heart failure with preserved ejection fraction

Approximately 50% of all patients with HF suffer from HFpEF where the primary dysfunction is within the relaxation phase.^{1, 40-42} The relaxation phase is equally important as contraction phase for normal cardiac function. Diastolic dysfunction mostly affects exercise function when cardiomyocytes cannot be elongated in response to higher demand of CO. Diastolic dysfunction can occur regardless of, or in combination with, reduced EF. The prevalence of HFpEF is rapidly rising, up to 1 in 10 elderly individuals is affected. Patients with HFpEF, in comparison with those with HFrEF, are more likely to be older, female, and have diabetes, atrial fibrillation, hypertension, and other co-morbidities.^{40, 42, 43}

The ventricular remodeling that occurs as a result of cardiac insult or inflammation worsens the diastolic dysfunction. The pathophysiology for the diastolic dysfunction is multifactorial and includes chronic pro inflammatory state, collagen deposition, oxidative stress, chronotropic incompetence, RV dysfunction, systolic abnormalities not seen in echocardiography, and hypo-phosphorylation of titin.^{40, 41, 44-48}

Titin is a large muscle filament protein that acts as a scaffold for the sarcomere, and is a major component in myocardial elasticity and passive stiffness.⁴⁹ Titin acts both as a mechanic-sensor and molecular target by modulating the active force development due to length-dependent activation.^{7, 50} The activation of titin is regulated by

phosphorylation and adapts quickly to changes in hemodynamic requirements.⁷ The phosphorylation facilitates by different kinases that are affected by stimulation by NP, nitric oxide and the sympathetic nerve system, thus linking titin to multiple pathways affected by HF. Titin is also related to numerous inherited conditions, especially DCM.⁴⁹ ESC require clinical symptoms, EF > 50% combined with exclusions of valvular and non-cardiac causes and elevated NP for diagnosis. Echocardiographic measurements are additional criteria and if uncertainty, a stress test or invasive measurement of LV filling pressure may be needed.¹

Figure 3. The PV-Loop of HFrEF. The loss of contraction (inotropy) results in increased end-systolic volume and end-diastolic volume which results in decreased stroke volume. As the heart remodels, the EDPVR shifts downwards and right due to increased ventricular compliance. In diastolic heart failure, the EDPVR shifts upwards and left. EDPVR; End-diastolic pressure-volume relationship, ESPVR: End-systolic pressure volume relationship, LV: Left ventricle. (Reprinted with permission from Richard E. Klabunde, www.cvphysiology.com)

Diagnosis of heart failure

The symptoms of HF are often non-specific, hence the clinical diagnosis might be hard.⁵¹ In patients with obesity or pulmonary disease, the symptoms might be even harder to detect.^{52, 53} For patients presenting with symptoms of HF, the probability of HF should be evaluated based on the patients clinical history and status. If something in the history or clinical status indicate HF, the concentration of BNP or NT-pro-BNP can be assessed as a first diagnostic step. Patients with normal levels are unlikely to have HF, therefor the test is used to rule-out HF, not to establish the diagnosis.¹ Multiple factors, such as age, renal failure, atrial fibrillation and obesity might affect the levels of NP.⁵³⁻⁵⁵ The diagnostic cut off values set by the ESC have excellent ability to exclude HF, when used in combination with clinical condition.^{1, 56} For patients with HF, the symptoms and signs should be assessed at each visit to monitor the response to treatment and to assess stability. Worsening of symptoms indicates progression of the disease and should result in additional treatment. Worsening also place the patient at high risk for hospital admission.

Combined with NP, the electrocardiogram (ECG) can provide information of potential etiology of HF and is recommended as routine use. In patients with normal ECG, the diagnosis of HF is unlikely but might occur.^{1, 51}

If the ECG is abnormal or the NPs are elevated, the patient should be examined by echocardiography to diagnose HF.¹ Echocardiography is the method of choice for the accuracy, availability, safety, and cost.⁵⁷ Gold standard for assessment of LV/ RV volumes, EF and cardiac mass is CMR. The CMR also provides information of tissue characterization but holds multiple contraindications and is relatively expensive.¹ In comparison, echocardiography can provide information on cardiac structure and function by using 2-dimensional, 3-dimensional, contrast, spectral, and color flow Doppler.⁵⁷ For measurement of the LVEF, the modified biplane Simpson's rule is recommended.¹ If HF is confirmed, appropriate treatment are initiated and determination of etiology assessed.

Treatment for heart failure

The fundamentals of the treatment for HF are pharmaceuticals that inhibit or affect one or more pathological pathways. The aim is to reduce mortality, improve physical capacity, physical status and quality of life whilst hospital admission is reduced.¹ For patients with HFrEF, a treatment that inhibits the excessive neuro-hormonal response is recommended whilst the treatment for HFpEF is more uncertain and mostly focuses on minimizing the effects of comorbidities. Most often, a combination of pharmaceuticals at an optimal level is required. If the patient remains symptomatic or deteriorates, despite optimal medical treatment, the use of additional compounds might be indicated. Unfortunately, an optimal dose is not always achieved and the prescription of ACE-inhibitors (ACEI) is inequitable.^{58, 59} Below, the ways to treat HF is described. For all patients, including advanced HFrEF, the first step is to assess if the current medication is appropriate and, if possible, optimize the medical treatment.

Pharmacological treatment

Angiotensin converter enzyme inhibitor

ACEI is the foundation of the treatment for HF.⁶⁰⁻⁶³ Multiple substances are known for having similar effect but variations in side effects. ACEI is recommended for HFrEF unless the substance is not tolerated by the patient or the substance is contraindicated.^{1, 63} ACEI is considered “first line” treatment. ACEI is also used for patients with asymptomatic LV dysfunction to minimize the progression to HF.⁶⁰ ACEI inhibits the conversion from angiotensin I to Ang II, which results in blockage of RAAS. This inhibits some of the sodium and water retention resulting in lowered BP, afterload, and congestion.^{64, 65} By using ACEI, the excessive fibrotic response is inhibited and the subsequent remodeling minimized.⁶⁵ ACEI significantly reduces both morbidity and mortality in HFrEF.⁶⁶⁻⁶⁹ The effect is not as clear for patients with HFpEF but ACEI might improve functional class and lower hospitalizations.^{70, 71} For patients with a high risk for cardiovascular events, ACEI reduces stroke, nonfatal MI, cardiovascular, and overall mortality.^{1, 72}

Angiotensin receptor blockers

Angiotensin receptor blockers (ARB) exerts its effect by blocking the AT1R and thereby inhibit the effect of Ang II.⁶⁵ This results in an effect similar to the one for ACEI and reduces both morbidity and mortality for patients with HFrEF.⁷³ However, the effect is only seen for AT1R and angiotensin can still bind to AT2R which might facilitate additional positive effects. ARB is used for patients with contradictions to, or

cannot tolerate ACEI.^{1, 63} In the ESC guidelines the use of ARB is equal to ACEI.¹ ARB is associated with lower adverse events than ACEI, but this does not effect mortality or morbidity in head to head comparison to ACEI.⁷⁴⁻⁷⁶ The addition of ARB might be considered in symptomatic patients that can't tolerate mineralocorticoid/aldosterone receptor antagonists (MRA).¹ For patients with HFpEF, ARB treatment has been shown to have a moderate impact on hospitalization but no effect on mortality.^{71, 77, 78}

Beta blockers

Beta blockers (BB) are complementary to ACEI, and should be administered in patients with a clinical stable condition with a low dose that is slowly titrated to maximum tolerated dose.^{1, 63} BB block the β -receptor and thereby inhibit excessive sympathetic response, reduce afterload, decrease plasma renin levels, and renal-nerve signaling. The BP is lowered and the CO is enhanced due to enhancement of the diastolic filling time.^{65, 79} BB have shown to reduce mortality and morbidity for symptomatic patients with HFrEF. This effect is seen regardless of ACEI-treatment.⁸⁰⁻⁸⁴ BB should also be considered for rate control for patients with HFrEF and atrial fibrillation. Furthermore, BB should be administered for those patients with asymptomatic systolic dysfunction to prevent progression, prevent remodeling, and improve survival, especially if there is a MI in the medical history.^{1, 80} Evidence of effect of BB in HFpEF is ambiguous, but pooled analysis indicates a reduction in cardiovascular mortality. However, the reduction disappears when the studies are limited to those with low bias.⁷¹

Mineralocorticoid/ aldosterone receptor antagonists

Since evidence that ACEI does not effectively suppress the production of aldosterone in approximately 40% of the patients with HF, the studies on MRA started.⁸⁵ MRA exert its effect by inhibit the binding of aldosterone to its receptor.⁸⁶ Corticosteroid and androgen receptors might also be inhibited with variation in affinity, resulting in side effects. MRA minimizes the retention of water and sodium, decreases preload, and might suppress cardiac remodeling.⁸⁶ In addition to ACEI or ARB treatment, MRA has shown to significantly reduce mortality and hospitalization in patients with HFrEF.^{1, 63, 65, 86-88} For patients with HFpEF, treatment with MRA has shown a reduction of hospitalizations, but there is no impact on mortality or morbidity.^{71, 89} Post-Hoc analysis for the use of spironolactone shows a wide regional difference in outcome, which makes the result ambiguous.⁹⁰ Spironolactone is associated with gynecomastia whilst Eplerenone is not. Both compounds improve endothelial function in non-diabetic patients, but spironolactone might increase the levels of glycated hemoglobin and does not improve endothelial function in patients with diabetes.⁸⁶

Angiotensin receptor Neprilysin inhibitor

Angiotensin receptor Neprilysin inhibitor (ARNI) is a relatively new therapeutic agent that combines an ARB (Valsartan) and a compound (sacubitril) that inhibits degradation of NP, bradykinin, and other peptides by inhibiting NEP, Neprilysin. This results in both inhibition of RAAS, remodeling, and myocardial hypertrophy.⁹¹ ARNI has shown to be superior to ACEI in reducing overall mortality, cardiovascular mortality, and hospitalizations in patients with HFrEF with LVEF $\leq 35\%$.^{92, 93} ARNI has also shown to create a greater reduction in NT-ProBNP than an ACEI (Enalapril) with a significant difference as early as one week after initiation.⁹⁴ The effect is seen over the whole perspective of LVEF.⁹⁵ The therapy is withheld for those with severe HF. However, the risk of hypotension and angioedema is increased.¹ The use of ARNI in HFpEF has not shown any reduction in mortality or hospitalizations.^{71, 96}

Diuretics

Diuretics are recommended to reduce symptoms in patients with HF. Diuretics increase physical capacity and reduce risk of death in patients with HFrEF.¹ The aim of diuretic medication is to maintain euvolemia with the lowest achievable dose, higher doses are related to worse prognosis.⁹⁷ The dose is changed over time, and to individual needs, and preferably self-adjusted according to symptoms and weight. A good adherence to self-monitoring and adjustments results in fewer hospitalizations and emergency visits due to HF.⁹⁸ Diuretics also alleviate signs of HF in patients with HFmrEF and HFpEF.^{1, 63, 99} There are different types of diuretics (loop-diuretics, thiazides and potassium sparing) that exert effect on different receptors but the net effect is the same. Use of multiple diuretics needs careful monitoring.¹

Other medical treatments

Ivabradine exert its effect by inhibit the I_f -channel in the sinus node, reducing heart rate.¹⁰⁰ Ivabradine has shown to reduce mortality and hospitalization for patients with symptomatic HFrEF despite optimal medical treatment. The effect is seen for patients with LVEF $\leq 35\%$, heart rate ≥ 70 bpm, and prior hospitalization within 12 months.^{101, 102} Ivabradine has also shown to reverse cardiac remodeling.¹⁰³ Ivabradine should only be used in patients with sinus rhythm.¹

For patients with HF and an indication for anticoagulation should maintain on ongoing anticoagulation therapy. Addition of a low dose rivaroxaban to standard HF therapy shows no benefit in terms of mortality or morbidity.¹⁰⁴ There is no evidence that any other oral anticoagulation reduces mortality or morbidity compared to Aspirin or placebo in patients with both HFrEF and HFpEF. A small reduction in ischemic stroke can be seen but this is counteracted by the increased rate of bleeding.^{105, 106}

The combination of hydralazine and isosorbide di-nitrate, results in dilatation, both peripherally and within cardiac muscle. The treatment shows beneficial effect in small, specific groups and may only be considered for symptomatic patients with HFrEF unable to tolerate ACEI or ARB.^{1, 63, 65} The effect is inferior to that of ACEI.¹⁰⁷

Digoxin exerts its effect by elongating the conduction within AV-node, increasing contraction, and reducing heart rate. Combined, this leading to positive inotrope and negative chronotropic effect.⁶⁵ It may be considered for patients with symptomatic HFrEF and sinus rhythm, and for patients with HF and rapid rate atrial fibrillation for frequency control.¹ Digoxin does not show any reduction of mortality or morbidity in patients with HF but can improve symptoms. Some studies report increased mortality in patients using digoxin due to atrial fibrillation. This indicates that if the drug is to be used, the digoxin level must be monitored.¹⁰⁸

Renin inhibitors reduce biomarkers of HF but no effect have been seen on cardiovascular deaths or hospitalization for patients with HFrEF.¹⁰⁹⁻¹¹¹

Combination Therapy

In the current guidelines on HFrEF a combination of BB and ACEI/ARB is the first line treatment with an add-on of MRA if the patient is still symptomatic.¹ Combination therapy with BB and ACEI/ARB is well studied in large trials and has proven to reduce both mortality and morbidity.^{82, 83, 112} Combination of ACEI/ARB with BB and MRA results a further reduction in mortality and hospitalization.^{87, 88}

Combining ACEI with Carvedilol (BB and α -1 receptor blocker) shows a 65% lower risk for death in patients with moderate decreased LVEF, and for patients with severely decreased left ventricular function, addition of Carvedilol reduces the rate of death by 35%.^{82, 112} The initiation of monotherapy with BB or ACEI/ ARB shows no difference in mortality or hospitalization whilst the combination further reduces mortality and hospitalizations.¹¹³

The studies of combining ACEI, BB and ARB in patients with HFrEF shows ambiguous results. The combination has shown both increased mortality, increased adverse cardiac events, and a reduction of cardiovascular death^{76, 114, 115} The different studies cannot be compared because of non-comparable cohorts. Specific groups of patients might benefit from the combination

For patients with HFpEF, the studied effect of combination therapy is inconclusive. In one study the combination of ARB and BB shows a lower rate of all-cause death, but this finding is not supported in two other trials on the same subject.^{77, 78, 116}

In summary, combination therapy with ACEI/ARB and BB for HFrEF is widely studied and hold multiple evidence of increased survival. Addition of MRA to

previous therapy further decreases mortality in patients with HFrEF and might have an impact on mortality for HFpEF patients. Add-on of ARB to previous treatment with ACEI and BB is most likely related to increased cardiovascular death in patients with HFrEF but might be indicated for patients with HFpEF. Further studies on HFpEF treatment are necessary.

Device treatment for heart failure

Implantable cardioverter defibrillator

A major proportion of death amongst patients with HF is due to ventricular arrhythmias, bradycardia, and asystole. Pharmaceuticals decrease risk of mortality, but the risk remains high. For patients with ventricular arrhythmia that causes hemodynamic effect, the implantation of an Implantable cardioverter defibrillator (ICD) is indicated, if the patients estimated lifetime exceeds one year with good physical capacity.¹ For patients with HFrEF after MI, implantation is indicated if the reduced EF ($\leq 35\%$) is sustained, despite optimal medical treatment, 3 months after the infarction.^{117, 118} The time delay is due to the fact that, despite decrease in sudden cardiac death, the total mortality remains unchanged within the first month.^{119, 120} The mortality can also be reduced for selected patients with HFrEF of non-ischemic etiology, but the evidence is ambiguous.¹²¹⁻¹²⁴ However, current guidelines recommend implantation of an ICD since the evidence is more in favor for implantation than withholding ICD.¹ ICD is not indicated for patients with severe symptoms, such as physical status of NYHA IV that is refractory to medical therapy, not eligible for MCS or Htx.¹

Cardiac resynchronization therapy

For some patients with HFrEF the electrical conduit of the heart is affected leading to dys-synchronous contraction of the ventricles. Cardiac resynchronization therapy (CRT) is a pacemaker that corrects this delay for LV and restores synchronous contraction. The CRT holds the same features of normal pacemakers and can control heart rate (CRT-P) and can, in special cases, stop lethal arrhythmia if the CRT also holds an implantable defibrillator (CRT-D). CRT reduces mortality and morbidity whilst increasing quality of life for symptomatic patients with LVEF $\leq 35\%$ despite optimal medication.¹²⁵⁻¹²⁸ However, the effect on reversed remodeling is not seen among all patients fulfilling these criteria. Those with ischemic etiology have scar tissue that impact improvement in LV function but these patients might obtain the same prognostic benefit.¹²⁹

ECG predicts the outcome of the CRT-treatment and the most favorable effect is seen in patients with left bundle branch block (LBBB) or QRS width greater than 130ms, and especially for those over 150ms.^{1, 128, 130} Newer methods are developing and his-

bundle pacing might be an alternative in patients for whom left ventricular-lead placement is not possible.¹³¹ His-bundle pacing and CRT in combination with atrioventricular ablation can increase functional status and reduce the use of diuretics for patients with HFrEF, HFpEF and atrial fibrillation. It can also decrease the number of HF hospitalizations.^{132, 133}

Advanced treatment for heart failure

Advanced pharmacological treatment

For patients that deteriorates to INTERMACS 3-4 despite optimal medical therapy, and for patients with cardiogenic shock due to acute HF, the use of inotropic or vasoactive agents can facilitate improvement. These agents acutely increase CO but should only be used in patients with hypotension and hypoperfusion.¹ The inotropic agents all aim to increase cardiac contractility by affecting the β -adrenergic stimulation, the Frank-Starling mechanism, or the positive force-frequency relation (accumulation of intracellular Ca^{2+} at higher heart rates).¹³⁴ However, some of the inotropic agents also increase cardiac work, myocardial oxygen consumption, myocardial toxicity, myocardial hypertrophy/remodeling, renin-angiotensin-aldosterone activation, and renal sodium-water retention. These effects combined contribute to the process of HF and can explain why the use of inotropic therapy does not show any improved outcome, in some studies even worsened outcome.¹³⁵⁻¹³⁷

Vasopressors and inotropic agents, such as epinephrine, norepinephrine, dopamine, and dobutamine stimulates the β_1 receptors and to various extent also β_2 , α_1 , α_2 , and dopaminergic receptors 1 and 2 resulting in different effects on the cardiovascular system. Inodilators such as milrinone and levosimendan have a different effect on the myocardial tissue than the inotropic agents.^{138, 139} The use of inotropes generates an increase in CO and for some inotropes, increased blood pressure. For vasopressin and norepinephrine the effect is increased blood pressure whilst the inodilators increasing CO leading and act as a peripheral vasodilator which lead to lower blood-pressure.¹³⁹ Norepinephrine is preferred over dopamine sine the use of dopamine shows more arrhythmic events and increased death at 28 days.¹⁴⁰ In patients with cardiogenic shock after myocardial infarction, epinephrine shows unfavorable metabolic changes such as increased lactic acidosis and higher incidence of refractory shock than norepinephrine.¹⁴¹ Dobutamine improves cardiac contractility by being a β_1 and β_2 adrenergic agonist. Due to its effect on β_2 , the drug also induces peripheral vasodilatation. Dobutamine can be used to obtain a moderate, rapid and short-acting effect due to the short half-life.¹³⁹

Milrinone is a phosphodiesterase inhibitor that increases contractility and improves diastolic function by increasing influx of Ca^{2+} .¹³⁹ Along with the increased contractility, milrinone also generates a vasodilatation in both the peripheral and

pulmonary vasculature.¹⁴² Milrinone can be used for patients on betablockers in combination with dobutamine for synergic effect. Milrinone has a longer half-life than dobutamine.¹³⁹ Milrinone, as well as dobutamine, is however associated with higher mortality and more frequent cardiac arrhythmias when compared to placebo, and should therefore only be used in selected patients.¹⁴³

Levosimendan increases contractility by increasing the sensitivity for intracellular Ca^{2+} by binding to troponin C. Levosimendan also cause peripheral vasodilation by opening adenosin triphosphate-sensitive potassium channels in vascular smooth muscles.¹³⁹ Levosimendan has shown to cause improvement in hemodynamics and decreased HF symptoms. Levosimendan also show lower mortality compared to dobutamine and placebo.^{144, 145} However in other trials levosimendan failed to show any benefit compared to dobutamine regarding mortality and secondary outcome.¹⁴⁶ In meta-analysis in 2012 and 2016, levosimendan was associated with a reduction of mortality by 20%, but these meta-analyses had both elective and acute patients enrolled.^{147, 148} For patients undergoing surgery, the use of vasopressors 24h after surgery were lower for those treated with levosimendan but there was no difference in 30-day mortality.^{149, 150} Levosimendan has also been shown to increase diuresis and improve renal function in patients with advanced HF.¹⁵¹

Short term assist devices

Intra-aortic balloon pump

For patients with cardiogenic shock and inotrope dependence, a short-term assist device might be an alternative as bridge to recovery, bridge to Htx or bridge to LVAD. The intra-aortic balloon pump (IABP) is a short-term assist device that increases CO by approximately 20% by counter pulsation in the descending aorta. The counter pulsation results in an increase of myocardial perfusion and a reduction of the aortic, end-diastole and systolic pressures. The use of IABP may be associated with major complications such as systemic infections, stroke and major bleeding.¹⁵² In the SHOCK II trial, in which patients with cardiogenic shock caused by acute myocardial infarction were randomized to either IABP or control, the use of IABP did not increase survival at 30 days, 6 or 12 months.^{153, 154} After the presentation of this study the recommendation for IABP were lowered.¹ There might however be a place for IABP for patients with chronic HF with an acute episode, at an early phase of cardiogenic shock.¹⁵⁵

Impella

In recent years, new short-term assist devices have been presented. Another commonly used, short term assist device is the Impella (Abiomed Inc., Danvers, MA, USA) that comes in different sizes. The Impella is a catheter-mounted axial flow pump that is placed over the aortic valve and unload the LV by continuously displacing blood from

LV to the ascending aorta. The Impella 5.0 requires a surgical procedure to gain access to the femoral or the axillary artery, whilst the Impella 2.5LP and Impella CP can be placed percutaneously.¹⁵⁶ Compared to the IABP the Impella reduces LV pressure and causes a reduction in LV stroke work, myocardial oxygen demand, as well as it provides a superior hemodynamic support.^{157, 158} However, these devices have not yet been able to show any effect on mortality compared to IABP.¹⁵⁸⁻¹⁶¹ The most common adverse events are stroke, hemolysis, device related vascular complications, and non-device-related bleeding.¹⁶²

ECMO

Extracorporeal membrane oxygenator (ECMO) system consists of a centrifugal pump, membrane oxygenator, and a heat exchanger. The ECMO is mostly positioned with the inflow cannula in the superior vena cava or the right atrium. The outflow cannula may be positioned in either the femoral or subclavian artery. The system provides gas exchange, oxygenation, circulatory support, and may be used in patients with impaired oxygenation or cardiogenic shock.¹⁵⁶ When ECMO is used in patients with cardiogenic shock, the LV afterload may be increased and can worsen the myocardial ischemia, cerebral ischemia, and cause pulmonary oedema. For these patients, a combination of ECMO and Impella or IABP might be an option.¹⁶³ Compared to ECMO alone, the combination therapy results in lower in-hospital mortality and a higher rate of successful bridging to recovery or long term treatment options.^{164, 165} The most common adverse events are bleedings, stroke, kidney failure, and limb ischemia. The development of adverse-events, preimplant serum creatinine, and hypoalbuminemia are risk factors for mortality.¹⁶⁶ In a meta-analysis in 2016, survival for patients in cardiac arrest was increased when ECMO was used. For patients with cardiogenic shock, the use of ECMO showed a greater 30 day survival compared to IABP but not compared to Impella.¹⁶⁷

Surgical treatment for heart failure

Heart transplantation

Htx, the only curative therapy of HF is a surgical replacement of a patient failing heart with a normal functioning heart from a donor.¹⁶⁸ The first orthotopic Htx was performed in 1967, but survival was limited due to ineffective immunosuppression. Development of immunotherapy since the 80-ies increased survival, and Htx is now widely accepted. In Sweden approximately 50Htx are performed every year.¹⁶⁹ The vast majority of Htx are due to DCM and coronary artery disease.¹⁶⁸ The basal principles for a successful Htx are that the heart function is so poor that no other intervention could be beneficial, the function causes the patient substantial limitations in their quality of life and that the patient otherwise is strong, healthy enough to have long-term benefits from the surgery.¹⁶⁹ There are a numerous criteria and relative

contraindications to Htx and before acceptance for transplantation, the patient must undergo thorough examination.¹⁷⁰ After Htx, the patient maintains strict immunosuppression regimes and periodically undergoes cardiac biopsy to assess graft rejection.¹⁶⁸ Survival after heart transplantation has improved; in 2002-2008 the 1 year survival rate was 84% and 2009-2014 86%.¹⁶⁸ In Sweden, the 1 year survival rate was 92% in 2011 and 10 year survival rate was 71%.¹⁶⁹

Mechanical circulatory support

The low number of donor organs available is still a major issue, and is one of the driving forces for the development of MCS. During the 20th century, the use of MCS as a bridge to transplant (BTT) has increased from 22.2% in 2002 to 43% in 2013. The most used MCS are LVAD.¹⁶⁸ Previously, the use of LVAD pre-transplant, was associated with worse post-transplant prognosis but this is not seen for the continuous flow LVAD.¹⁶⁸

History of Mechanical circulatory support

The thought of replacing the human native heart with a mechanical pump has been tempting to generations of cardiologists and cardiothoracic surgeons. The first device for temporary left-heart assist (DeBakey blood pump) was implanted in 1963 and used for adequate support for 4 days. Unfortunately, the patient died due to pre-implant injury. The pump was improved and successfully used in 1966 when a patient recovered after cardiac surgery and 10 days treatment with MCS. In the following years, driven by clinical developments and American initiatives, multiple assist devices were developed. Most of them trying to simulate pulsation and were pneumatically driven. In the 80-ies, due to deaths while awaiting Htx, the previously developed pumps were approved as investigational devices and their use as BTT hence increased.¹⁷¹ In 1994, Thermo cardiosystems got their HeartMate 1000IP, pneumatically driven, approved by the federal drug association (FDA) for clinical use.^{171, 172} The sequel, electrical driven, HeartMate 1000VE were approved in 1998, showing good clinical results with a patient surviving 604 days on support, awaiting Htx.¹⁷²

Long term assist devices

Linköping university hospital was the first center in Sweden to implant a long-term assist device in 1993. In the recent decades, multiple manufactures have presented their solution to MCS but the most successful is HeartMate II (Abbott, Lake Bluff, IL, USA)(HMII) that was the one used at Linköping University hospital prior to adaptation to HeartMate3 (Abbott, Lake Bluff, IL, USA)(HM3) and therefore most reported in this thesis.

The approval for MCS as BTT resulted in more patients receiving the pumps and numerous studies were performed. The studies showed that short term use of these devices improved end-organ dysfunction, exercise intolerance, with a reasonable quality of life. The patient can also be discharged with a relatively low rate of adverse events.^{173, 174} REMATCH trial, 2001, shows a 48% reduction of death in the group randomized to device compared to optimal therapy, therefore indicating that long-term treatment is efficient. The survival rate in this study, 52% at one year for the device group and 25% for the medical therapy.¹⁷⁵ The beneficial effect continued in extended follow up.¹⁷⁶

The first generation of LVAD, no longer used, were large and limited in construction due to the pulsatile mode involving multiple moving parts. The HMII, LVAD, uses axial flow, started evolving in 1991 and came to clinical trials in 2000.¹⁷⁷ The subsequent generation were already designed as the first clinical trials started.¹⁷⁸ Multiple other LVADs were developed during the same decade.^{179, 180} The first European study of HMII ended early due to poor outcome related to pump design, and the first implantation of the redesigned LVAD occurred in 2003 with more than 6 months without adverse events.¹⁸¹ The initial design of HMII consisted of a fully integrated system with transcutaneous energy transmission system, but this was never adopted and the use of externally placed batteries is still an issue for all available LVADs.^{181, 182}

Since the new generation of LVADs was smaller, more patients, including children could be eligible for treatment. The first clinical results of HMII showed improved end-organ function, great longevity, and reached a 1- year survival rate of 80%. Adverse events such as stroke, gastrointestinal bleeding, and arrhythmia were still noted.¹⁸³ A larger, observational trial, involving 133 patients resulted in a 6-month survival rate of 75% and 1-year survival rate of 68%. The previously noted adverse events such as stroke and bleeding were still present within this study. During the trial, 2% of the patients had a pump thrombosis that needed pump exchange.¹⁸⁴ The extended survival, longevity of the device, and superiority of pulsatile pumps, have been shown in multiple studies worldwide and are widely accepted.¹⁸⁵⁻¹⁹⁸

For those treated with LVAD as BTT the post Htx survival is equivalent to that of patients with conventional transplantation. The time with HMII does not affect outcome.¹⁹⁹ HMII improves functional capacity and HF related quality of life for both BTT and destination therapy (DT).²⁰⁰ MCS as DT is used for patients with contradiction to Htx, the patient will live as long as possible with their device. With the favorable outcome of the axial flow devices, the adverse events that occur during treatment started to consume more scientific interest.¹⁸⁷ To further increase outcome, major adverse events such as neurological, thrombo-embolism, pump thrombosis, gastro intestinal bleeding, arrhythmias, and hemodynamics were addressed.^{201, 202} The success of HMII resulted in approval as DT in 2010.²⁰³

The centrifugal, continuous flow pump, HeartWare (HVAD) received approval as BTT in 2012.²⁰³ The HVAD is a smaller centrifugal pump that is implanted in the pericardium.²⁰⁴ The outcome of HMII as DT has been improved mostly due to a decrease in adverse events.²⁰⁵

The increasing use of MCS resulted in the start of INTERMACS in 2006. Between the start and 2017, approximately 25.000 patients received an FDA-approved device. Of these, approximately 18.000 were continuous flow LVAD. The major proportion was an axial flow LVAD (HMII). The survival rate has continued to improve and has reached a 1 year survival rate of 83% and 5 year survival rate of 50%.²⁰⁶⁻²⁰⁸ It has been proven that timing of implantation LVAD is a factor for survival and risk of adverse events, with survival being best for those patients who were not inotrope dependent at implantation (INTERMACS profile 4-7).^{193, 197, 206}

The use of HMII and other MCS are related to severe costs for society, and the use is frequently challenged due to the low cost-effectiveness, of which the device is the major proportion of the cost.²⁰⁹⁻²¹¹ The overall effect is still considered a success. There are individual case reports that show the long-term benefits and life-saving ability of these devices.^{212, 213} The adverse events have triggered further improvements in minimizing moving parts that can cause pump failure and minimizing shear stress that leads to platelet activation.

The HM3 differs significantly from its precursor in achieving these features.²¹⁴ The experimental studies started in 2007 and the first implantation in man occurred in 2015.²¹⁵ HM3 takes a further leap in LVAD design as it optimizes the physiological features by simulating an artificial pulse. The first trial, to achieve CE-mark showed non-inferiority in survival at 6 months (92%) compared to HMII and no pump thrombosis was reported in 50 patients.²¹⁶ Survival rates are 98%, 92%, 81% and 74% at 1 month, 6 months, 1 year and 2 years post-implantation, respectively. The HM3 is superior to an axial flow device with respect for survival free of disabling stroke, or reoperation for removing or replacing a malfunctioning device. In the studies, most patients received the device as DT.²¹⁶⁻²²⁰

HeartMate II

The HMII (figure 4) consists of an implantable housing, control device and batteries that provide a functional time about 8-12h. The device is cradled in a surgical pump pocket, below the cardiac margin. A titanium cannula is sutured to the cuff placed in the apical left ventricle. From the titanium cannula, a Dacron graft protected by silicone sheathing, leads the blood flow to the titanium inflow curve that is directly attached to the pump. The pump weight is 290g, displacing 124ml and has a diameter of 12mm. In the titanium body of the pump, magnets are fixed radially, and consecutive charging makes the titanium impeller spin. At the inflow, a three bladed

inflow stator produces a linear flow whilst suspending the impeller with a ruby bearing. Distal to the ruby bearing, the spinning three, curved bladed impeller rotates and creates radial flow through the pump. The distal part of the impeller is suspended by mechanical bearing at the outflow stators creating the axial velocity. The outflow is connected to a Dacron graft that is sutured, end-to-side anastomosis at the ascending aorta. The material in the pump is designed to create biocompatibility.

Before placing the pump in the prepared pump pocket, a trocar is used to cannulate the driveline at the right side of the abdomen. The pump typically operates in ranges of 8600 -10000 revolutions per minute (rpm) generating a flow of 3-7Liters (L) / minute (min). The fixed speed can be read on the controller, where also the calculated flow, Pulsatility Index (PI), and power consumption is displayed.²²¹ Guidelines from the manufacturer recommend anti-coagulation with warfarin in addition to anti-platelet therapy with acetylic salicylic acid at a dose of 81mg daily. The international normalized ratio (INR) is recommended to keep between 2.0 and 3.0.²²¹

Figure 4. The HeartMate IITM LVAD. The figure to the left shows the HMII with the impeller and magnetic stators visible. The image to the right shows the position in which the HMII is placed and the attached part of the system. Reprinted with permission from Thoratec corporation.

HeartMate 3

HM3 (figure 5) was first introduced in 2001 and was continuously developed until the first implantation occurred in 2015.^{178, 214, 215} HM3 is implanted in the pericardial space and consists of a compact intra-pericardial housing, control device, and batteries. The integrated inflow cannula consists of titanium with fused titanium microspheres to enhance biocompatibility and create a new intima. The inflow cannula is inserted in the apical region of the native heart and fixed by a built-in locking mechanism in the suture apical cuff. The pump weighs 200g and displaces a volume of 80ml. The rotor is magnetically suspended and rotates centrifugally creating a flow through the gelatin-impregnated woven polyester outflow graft. The outflow graft is sutured end-to-side

anastomosis at the ascending aorta. The magnetic levitation and the controlled rotation allowing wider gaps in the blood flow than previous pumps. The increased gaps minimize shear stress, resulting in stable coagulation and less von Willebrand factor (vWf) degradation.^{215, 216, 222} The driveline is placed in the same manner as for HMII and all the outer products are similar to HMII.

The pump typically operates in ranges 4000-6000rpm generating a flow of 3-7 L/min and can deliver up to 10 L/min if the speed is increased. When pump speed is fixed above 4000rpm, the system creates an artificial pulse by a rapid decrease in speed followed by a rapid increase above fixed speed. According to the manual, the increase and decrease are 2000rpm. The artificial pulsation minimizes stasis in LV, allowing flow over the aortic cusps, and rinses out the pump housing, all factors to minimize the risk of thrombosis.²¹⁶ In an analysis of the fluid dynamics, the artificial pulse showed no additional benefit on scalar washout performance but could be relevant for removal of deposits in the pump. The viscous stress proved lower in the HM3 than in previous pumps but the artificial pulse substantially increased turbulence and total stress which could activate platelets.²²³

Figure 5. The HeartMate 3™ which is the newest of LVAD. Reprinted with permission from Thoratec Corporation/ Abbot Laboratories

Monitoring of LVAD

Continuous monitoring of LVAD parameters is of importance to detect problem at an early stage. Normally, the patient is followed by routine outpatient visits with documentation of pump parameters. The patient and caregiver should be trained to observe changes in these parameters. Between these routinely scheduled visits, frequency depending on clinical stability, the patient may have monitoring phone calls.²²⁴ The effect of a standardized telephone intervention with focus on pump parameters, blood pressure, alarms, INR, and the status of the patients is associated with reduced Mean Arterial Pressure (MAP) and also has impact on the survival. The impact on survival is due to early detection of high MAP and other upcoming problems.²²⁵ Echocardiography should be performed at regular intervals to evaluate optimal pump function and potential signs of recovery. In addition, Echocardiography should be performed to evaluate sub-optimal pump function.²²⁴ Echocardiography is a key element in assessing the hemodynamic of the LVAD patients, in which the LV should remain unloaded whilst the RV should remain loaded.²²⁶ For patients waiting heart transplantation, additional right heart catheterization could be performed to assess and document pulmonary artery pressure. Right heart catheterization can be useful to assess persistent or recurrent symptoms of HF after LVAD implantation.²²⁴

Adverse events during LVAD treatment

Despite the progress of MCS, the treatment withholds multiple risk factors that can cause the patient harm, or subsequently death. The most common adverse events of the treatment are stroke, bleeding, pump thrombosis, and infection. Stroke is becoming more and more outcome-defining, but the others still have impact on mortality. In this next section, the one most relevant for this thesis, thrombosis will be discussed.

Thrombosis

During the initial trials of HMII, the event rate of thrombosis was low. In the first clinical experiment, there were no reports of thrombosis and in the European study; there were one event of thrombosis.^{183, 184} In 2008, the first case report of thrombosis showed association between sudden increase in power consumption and thrombosis forming in HMII. The thrombus occurred after withdrawal of anticoagulation due to

gastrointestinal bleeding.²²⁷ However, thrombus formation can occur without any alarm or apparent change in power, flow, or PI.²²⁸ The rate of thrombotic events reported to be lower than the risk of bleeding which created massive morbidity, despite INR, and a lowering of recommended INR were suggested in 2009.^{229, 230} Anti-platelet therapy might be reduced without generating any increase in thromboembolic events if the INR of 2.3 can be maintained.²³¹ Pump, patient, surgery technique and management-related factors are associated with the risk of thrombosis and the frequency of this condition increased during 2011-2012, resulting in alarming studies in 2014.²³²⁻²³⁸ Compared to 2008-2009, pump thrombosis in 2011-2012 increased 6-fold with a decrease in freedom from thrombosis at 6 months at 99% in 2009 to 94% in 2012.²³⁴

The studies in 2013-2014 revealed total incidence of confirmed or suspected thrombosis in 11-13.4% of HMII recipients.^{236, 239, 240} The risk of thrombosis is highest between 1-3 months post implantation.^{234, 236, 241} One of the major contributors to the increase in pump thrombosis might be inadequate anticoagulation, in which small changes can be of great importance.²³⁴ Patient-related factors that can increase the risk for pump thrombosis are atrial fibrillation, pre-existent ventricular thrombus, infection, left sided mechanical prosthesis, low-flow, hypercoagulable state, and patient compliance to medical treatment.²³² There is also a correlation between modification (sealed inflow graft) of the pump and increase in pump thrombosis, if this is a statistical phenomenon is uncertain.²⁴² Minimization of risk factors by uniform implant techniques and consistent post-op management such as heparin bridging between implantation and adequate INR, pump speeds > 9,000rpm, may reduce the number of pump thrombosis and maintain the incidence at low levels.^{243, 244}

In a study where the flow of HMII was analyzed by computational fluid dynamics, specific regions within the pump were highly thrombogenic since the flow formed entrapped circular patterns that can activate platelets. The circular patterns were found in the same places as the thrombosis was found in pumps explanted due to pump thrombosis.²⁴⁵

For HVAD the rate of thrombosis is about 8,1% and is associated with INR < 2, INTERMACS profile 3 or higher at implant, and aspirin doses < 81mg.²⁴⁶

After responding to the alarm, the abrupt increase in thrombosis plateaued in 2014 with a freedom of pump thrombosis at 6 months of 95%.²⁴¹ The risk of death after a pump thrombosis reported as high as, 24% at 3 months after thrombosis, and the incidence of neurological events and infections are greater than those patients without pump thrombosis.^{207, 234, 247} For HM3, all publications on follow-up have shown low incidence of pump thrombosis.^{216-220, 248-252} There is one reported case of outflow graft occlusion.²⁵³

Assessment of pump thrombosis

The presence of abnormalities in the system performance data (power consumption, Flow, Speed, PI) displayed at the system monitor is indicative of pump thrombosis; however, there are reports of pump thrombosis in lack of increased power consumption or low flow.²²⁷ Suspicion of thrombosis is a composition of multiple causes, for instance, a transient or gradually increase in pump power consumption, increased lactate dehydrogenase (LDH) in conjunction with low haptoglobin and/or high free hemoglobin and worsened HF-symptoms.²³² If the increase in power consumption is above 10W, or an increase of >2W from baseline over 24h, LDH level increased 3 times over the normal upper limit, there should be a high suspicion of pump thrombosis. Chest computed tomography can be of value for finding mechanical etiology such as inflow malposition or kinked outflow graft.²³² Clinical ramp-studies of the HMII have been performed to further detect device thrombosis. During echocardiography the pump-speed is sequentially increased and measurement (amongst others) of Left Ventricular End Diastolic Diameter (LVEDD) is performed. A LVEDD slope that shows that the pump is not sufficient to unload the ventricle, is an indication of thrombosis.²⁵⁴ Most of these methods are somewhat invasive and do not fully verify or rule out thrombosis. Algorithms for the treatment of suspected thrombosis has been developed. Depending on pump power consumption, LDH, Chest Computed tomography, and ramp study, they results in increase of the anticoagulation, thrombolytic therapy, or urgent pump exchange/ Htx.²³²

Sound analysis of LVAD

The use of a method with a high sensitivity to detect malfunction or thrombosis within the LVAD is desirable, especially a non-invasive method. The non-invasive method of acoustics was tested on animals in 2006, and the results indicated that experimental design could identify and detect initial signs of deterioration in the pump function.²⁵⁵ In 2007, nine patients with HeartMate XVE were monitored for any acoustic findings indicating end of life or mechanical failure. An aquatic hydrophone was used for recordings and the sound was interpreted on a laptop. All patients had their devices exchanged due to device failure, and the acoustics could differentiate between inflow valve incompetence and bearing wear, thus indicating that monitoring of LVAD can be an alternative to waiting until symptoms appear.²⁵⁶

In 2009, the rotary blood pumps had been applied to clinical practice, and they were studied for their acoustic profile by using an electronic stethoscope. The results shows that the frequency spectrum contains information of rotation rate, device design, and LV/LVAD interaction.²⁵⁷ In an abstract presented at the meeting of International

Society of Heart and Lung Transplantation (ISHLT) in 2011, the presence of thrombus within HVAD resulted in change in spectral peaks at 125-175Hz due to unbalanced impeller motion. Normalization of the frequency spectrum was associated with resolution of the thrombus.²⁵⁸

In a patient with HMII, included in the multicenter- SoundMate study, acoustic recordings prior to a thromboembolic event showed a change in the frequency spectrum, similar to the findings in the abstract presented at ISHLT. Another patient, free from events showed little or no change in amplitude or peaks in the frequency spectrum over time. These recordings were made with an iPhone, recorded at home and transferred electronically for distance monitoring.²⁵⁹

Further studies on HVAD in small settings showed that alteration in peak amplitude was associated with outflow occlusion and changes in MAP.²⁶⁰ Acoustic spectral analysis of HVAD was analyzed in 105 patients of whom 8 had signs of pump thrombosis which also was confirmed after surgical pump exchange. In this study, they normalized the spectrum towards the fourth harmonic and thereafter compared the spectrum to the normal. The study concluded that all 8 patients had a presence of a third harmonic, that was not seen for the controls, and an increase in amplitude of first and second harmonic.²⁶¹ According to a small study, the opening of aortic cusps can also be seen in acoustic analysis.²⁶²

Except from the studies from our group, only a few others have been performed on HMII. A two-tiered approach was used when both mock loop and clinical data from 10 stable patients and 2 patients with pump thrombosis were studied to detect changes in acoustics, speed, and pressure. For sampling, an electronic stethoscope was used, however, no normalization was conducted. The change in fluid viscosity, inflow and outflow pressure affected flow rates, and power consumption, but no changes in the sound spectrum could be seen. There was no imminent structural resonance within the pump. In presence of a thrombus, the spectral energy is reduced, resulting in lower amplitudes and lower area under the curve.²⁶³

To evaluate if the location and mass of the thrombus have an impact on the acoustics, an artificial thrombus model with silicone simulating thrombosis in HVAD were developed. Both acoustics and vibration analysis were performed. The results showed that the third harmonic was visible in 62.5% of the pumps at baseline and 4 dominant spectral peaks were observed in 75%. Most spectral peaks were harmonics to the fundamental frequency. The power consumption was only significantly increased when the thrombi were located on the tilted pad, and the mass exceeded 4mg, but the numbers of spectral peaks was significantly increased when the thrombus mass was 2 and 5mg and located in the primary flow path, or located in the tilted pad (all masses). The findings of impact on the third harmonic amplitude found in Kaufmann et al. could not be confirmed, but an assessment of the total number of peaks and that an

acoustic method might find thrombosis prior to elevation of power consumption was suggested.²⁶⁴

The ECMO-system, CentriMag (Thoratec, Pleasanton, CA, USA) is somewhat like the HM3 in design. One common adverse event in CentriMag is formation of thrombosis. In a small number of patients with ECMO- treatment, and in mock loop circuit, a peak at 3Hz were significant for the build-up of thrombosis, and the amplitude being gradually increased depending on the mass of thrombus.²⁶⁵

Aims

The overall aims of this thesis were to develop and evaluate the use of a mock loop circuit to further characterize and study the acoustics of LVAD. Another aim was to evaluate different recording devices and to study the effect of afterload on pump function.

The specific aims of the four studies presented in this thesis were to:

- design an experimental in vitro model to register and analyze acoustic signals from the HMII continuous flow Mechanical circulatory support, and to detect changes in sound correlating to artificial and blood clot/thrombosis, using modern telecom techniques.
- characterize the sounds of the HMII using signal processing methods in time (waveforms) and frequency (spectra) domains. Furthermore, cheap and readily available handheld recording devices suitable for use at home (iPhone and iPod) were compared with dedicated audio equipment.
- evaluate if the sounds from HM3 can be recorded and if in vivo and in vitro acoustic analyses are comparable. Also to evaluate whether an electronic stethoscope may be used for recording audio signals from the HM3.
- investigate the effects of inflow and outflow resistance of the pump on performance and the impact on the estimated flow rate indicated by the LVAD monitor. Additionally, we consider the impact of clot-analogs on the efficiency of the HMII and HM3 ventricular assist devices, their impact on the algorithm for flow monitoring and the risk for retaining clot-analogs in the LVAD.

Methods

This thesis consists of four papers with similarities between the methods used. In this section, the fundamentals of sound and signal analysis, the patients studied, the two different mock loops, characteristics of the different recording devices, software (audacity and MATLAB) used, and statistical analysis will be presented.

Sound and signal analysis

Sound, basic principles

Sound is a product of air pressure disturbances in an elastic medium due to vibration. If an object is set into motion it will begin an upward and downward oscillation until the internal resistance causes the vibration to stop. This format of vibratory motion is called a simple harmonic motion and the pattern that it creates if we plot the motion towards the baseline (before set into motion) is a sine wave, sinusoid, a pure tone that is rarely encountered in nature. The speed of sound is depending on the medium density and compressibility. The speed of sound in air is 343 m/s whilst in the human body it is 1540 m/s. When the sound passes through different mediums, the sound might be damped and could impact analysis.

The time to perform a cycle (baseline to baseline) can be measured, and the number of cycles completed in one second is called Hertz (Hz). The normal hearing range for young humans is 20 to 20.000 Hz. Simple vibratory systems can differ in three dimensions: amplitude, frequency, and phase. Amplitude refers to the magnitude of displacement or the power within the vibration, and is normally measured between maximum positive and maximum negative peak within the signal. The phase is determined by the initial direction of the vibration, resulting in different starting points for the sinusoid. For example, if a string starts its movement from baseline with a positive sinusoid, the phase is 0°. If the string instead starts with a downward movement, the phase is 180°. The frequency is affected by the mass and stiffness of the vibrating part, a stiffer part will have a higher frequency and a larger mass will have a lower frequency. Aperiodic sound shows no repeating pattern in time domain and can be divided into transient and continuous aperiodic sounds. The continuous is also called noise and the frequency spectrum is often relatively flat.

Sound is created by a deformation of the air particles that are connected, creating a chain reaction of particle density. The deformation of air particles can also affect a membrane. The membrane starts to move due to the deformation of air particles. The membrane movement can be turned into electrical components, generating a microphone.

Sound often consists of multiple sinewaves at different frequencies, at different time, and is called complex signals. If the frequencies can be determined they can be shown in regard to their amplitude, or power within an amplitude spectrum, or power spectrum. Most complex signals have energy at the multiples of the fundamental frequency, called harmonics. To determine how the power, or amplitude of the sound, is distributed over the frequencies, multiple techniques of signal analysis can be performed. The most common is Fourier transform analysis.

Fourier transform analysis

Fourier transform analysis was developed in 19th century by the mathematician Joseph Fourier, and is based on the theory that all complex waves can be derived by adding sinusoids together. The method has widespread applications in engineering, physics, and medicine. Fourier transform analysis takes a signal in time domain and determines the amplitude of each sinusoidal component that is present within the signal, and also determines the phase of the signal, see figure 6. A major assumption for this method is that the signal is stationary over time. The Fourier transform analysis was further developed to handle discrete time signals and with an output that is continuous in time and periodic. This is called a discrete-time Fourier Transform (DTFT). Since computers only can handle a finite number of values, the Discrete Fourier Transform (DFT) was developed from the DTFT. It can be seen as the DFT is the sampled version in frequency domain of DTFT. The methods to calculate DFT, are multiple and all algorithms that can calculate the DFT in an efficient way is called a Fast Fourier Transform (FFT). This method is often integrated into different sound handling software.²⁶⁶

Figure 6. Illustration of principle underlying Fourier transforms analysis. The complex signal in panel e is derived by point for point summation of the sinusoidal signals shown in panel a-d. Thereafter the sum of amplitude is calculated at each time generating the instantaneous amplitude of the complex signal in panel e. As example, at time zero, the sum of a-d are, 0,+100, -200 and 0, producing a sum of -100 which is equal to the starting sum of panel e. Adopted from ²⁶⁷

Power Spectral Density

One essential part of determining differences between recordings is normalization. The distance from the object, and the sensitivity of the microphone, may result in different amplitude within the frequency spectrum regarding the different recordings. To ensure that all recordings analyzed with FFT can be compared to each other power within the signal is set to 1. To determine the amount of power that is in different regions within the frequency spectrum, power spectral density (PSD) can be performed. PSD refers to the spectral energy distribution that will be found per unit time and is normally used for continuous signals. By calculating PSD within a signal, the area under the segment of the curve corresponds to the power within that frequency range, and can be used for determining differences between signals.²⁶⁶

The Mock Loop Circuits

The mock loop circuit, described below, was used in the simulations (paper I-II) with modulations to be able to insert artificial thrombotic materials. The model was developed by testing inputs that might affect the recording. The development started with the HMII, described earlier in this thesis, connected to the heart and lung machine within the Thoracic Intensive Care Unit to facilitate a pulsation. Multiple recordings were performed, as well as simulations with different viscosity and pulsation. These recordings were analyzed without, to our knowledge, any effect on the sound. Thereafter a mock loop circuit without pulsations was created. The LVADs were lowered into a saline bag to facilitate a dry surface for audio recording with different devices, and to mimic the location within the human thoracic cavity. The outflow of the LVAD was connected to a container filled with water by 50 cm long plastic flexible tubing with a diameter of 1.25-1.5 cm. The container was connected to the inflow by 50-cm-long flexible vinyl tubing. The distance from the LVAD to the recording device was 3cm. In the first study, ball valves on the tubing were used to create in and outflow obstructions by 50%. A specific location on the surface of the saline bag were marked at which the recordings were to be performed. Multiple recordings were made at different speed levels and sent to a computer as file attachment in e-mail for analysis. For paper III, the mock loop circuit was modulated to fit the HM3 with 50 cm plastic tubing, 2cm in diameter connecting the water chamber (2L) to the pump inflow. The graft from HM3 connected the pump outflow and the water chamber. Forceps were applied to change inflow and outflow obstruction. See figure 7 for schematic drawings of the two mock loop settings used in paper I-III.

Figure 7. A schematic figure of the mock loop circuit. To the left; the mock loop circuit used in paper I and paper II. To the right; The mock loop circuit used in paper III

In paper IV the two different LVADs were connected in a mock loop composed of a water reservoir, 3/8" PVC tubing, valves to adjust resistance (inflow and outflow of

the pump) and the possibility to include or exclude the oxygenator from the circuit by two valves. Ultrasound flow probe (Transonic H9XL, Transonic Inc., Ithaca, NY, USA) and pressure transducers (CODAN DPT-6000 system, Codan Triplus AB, Kungsbacka, Sweden) were adapted at the inlet and outlet section of the pump. This setup conveys the possibility to change the pre and afterload by different means, constrictions, circuit of different lengths, and by inserting clot analogs. See figure 8.

Figure 8. A sketch of the circuit, with possibility to adjust the pump operating conditions. The pressure gauges (P1 and P2) were placed at the inflow and outflow of the pump (LVAD). The valves V1 and V2 regulate the down-and up-stream resistance, respectively. The flow meter (Q) was placed further downstream from the oxygenator. The oxygenator could be by-passed altogether by using the valve V4. The blue arrow shows the flow direction.

Patient Characteristics

In paper II and III we included patients to be able to compare the sounds from implantable LVADs and LVADs in mock loop circuit. In paper II a male 52 years old, with dilated cardiomyopathy had the sound recorded. He received his HMII as a bridge to transplantation. No alterations in settings of the patients HMII were performed. The patient was sitting down, and by placing all audio recording devices over the lower left chest the sound was recorded. Participation of the patient was approved by the local ethics committee (2014/14-32). In paper III, the recordings from 4 patients (3 males and 1 female) with different etiologies (dilated cardiomyopathy, acute ischemic cardiomyopathy, and congenital aortic stenosis) to heart failure, were performed. Their ages varied between 24-64 years old. The patients had received their HM3 as BTT. The recordings were performed with the patients lying down with an electronic stethoscope, and microphones placed over the pump for sound recording. No changes

in any of the patients pump settings were performed. The study was approved by the local ethics committee (2019-00415).

Audio recordings and analysis

iPhone/iPod

In paper I and II, iPhone 4TM and iPodTM (Apple, Inc., Cupertino, CA, USA) with the commercially available stethoscope application iStethPro (Dr. Peter J Bentley, London, UK) was used for audio recordings, and the recordings were then transferred via telecommunication to a laptop for analysis. For the iPhone, the built-in microphone was used and lightly pressed towards the surface of the saline bag. The iPod was equipped with an external microphone, ThumbtackTM (SwitchEasy, Tracy, CA, USA) since the built-in microphone is located on the back of the device, making it impossible to handle the application without generating disturbances while positioning the device towards the underlying surface. The decision to use iPhone and iPod as recording devices was to facilitate a method for home monitoring. The sampling frequency was set to 44.1kHz for all devices, and all recordings were 8s long.

Shure microphones

In paper II and III, dedicated recording equipment as a reference device was used. Two identical microphones were used and the recordings were made at the same time with both devices to exclude impact of the specific device. The microphones used were a Shure PG58 (Shure Inc., Niles, IL, USA). The microphone provides a relatively linear frequency response over the frequencies 60-15.000Hz.²⁶⁸ This means that above or under these frequencies attenuation or amplification might occur, and the results are then not completely valid. The microphones were connected to a commercial laptop by an external sound card, Behringer FCA1616 (Behringer, Germany).²⁶⁹ The sampling frequency for the microphones was set at 44.1kHz and the recordings were performed with MATLAB (MathWorks, Natick, MA, USA).²⁷⁰

Electronic stethoscope

In paper III, evaluation of the electronic stethoscope, LittmanTM 3200 (3M, St. Paul, MN, USA) as a recording device was performed. The electronic stethoscope is a clinical tool and can be used for both routine auscultation and for audio recordings. The electronic stethoscope is capable of recording sounds in the frequency range 20-2000Hz, with 30 second clips. Three filters may be applied to amplify different regions within the frequency range. The recordings were transferred by Bluetooth to a laptop with the Littmann Stethassist (3M, St. Paul, MN, USA) software and converted to .WAV files within the software. The sampling rate for the electronic stethoscope was set to 4 kHz.

Audacity

In paper I, the frequency analysis software program, Audacity 1.3.13-beta (Unicode, Ash, Chinen and Crook, Pittsburgh, PA, USA) was used for analysis of the recordings. The software has a built-in function that calculates FFT of the signal. The software presents the frequency spectrum in a Hanning-window that can be exported. When exported, the frequency amplitudes at different, pre-specified levels are numerically presented. In our study, these values were exported to Microsoft Excel and in that software, comparisons between different spectrums could be created

MATLAB

MATLAB (Mathworks, Natick, MA, USA) is software that is developed for mathematical and technical variables. It is built of matrixes and can be used to calculate multiple algorithms automatically by using scripts. The software has multiple built-in functions and algorithms. MATLAB is frequently used by engineers to perform and to visualize complex calculations. Multiple customized algorithms have been used within our different studies.

Statistical analysis

All statistical analysis was performed using commercially available software programs, $p < 0.05$ was regarded as significant.

Paper I. In paper I, StatisticaTM (StatSoft, Tulsa OK, USA) was used for comparison between the different recordings. The values within the stated region and peaks were summarized and student t-test were used for statistical analysis.

Paper II. In paper II, the difference between the specific devices was shown by visualization which is common within engineering resulting in no specific statistical analysis.

Paper III. In paper III, IBM SPSS version 23 was used for statistical analyzes. To determine the correlation between measured and estimated frequencies the Pearson correlation coefficient was used. To determine the statistical differences in power distribution the two-tailed student t-test was used to compare the different groups of recordings.

Paper IV. In paper IV, the difference between the specific LVADs was evaluated with visualization in multiple graphs. No specific statistical analysis was used.

Summary of results

Acoustic analysis of a mechanical circulatory support. Paper I

The acoustics from the HMII could be recorded by an iPhone and transferred to a computer for further analysis. A frequency spectrum consisting of clear peaks and regions were found and to facilitate statistical analysis, the spectrum was divided in these regions and the sum of amplitudes was calculated. Changes with increase in speed resulted in significant changes in multiple regions and peaks. See figure 9 and table 3.

When simulating different clot situations with both ball valves and artificial thrombus masses from gelatin the frequency spectrum was significantly changed. The most significant changes were in the lower regions of the frequency spectrum. See figure 9 and table 3.

Figure 9. Change in the frequency spectrum at increased pumps speed curves (upper left panel) shows example of change in acoustic fingerprint when pump speed increased from 6000 to 700 to 8000rpm. The spectrum in the software audacity imprinted in the right corner. Acoustic changes in red when narrowing the inflow and outflow tubes with 50% respectively (left panel), and at different clots passed through the pump. R= Regions (R1:1000-6500; R2: 8500-14000; R3 15000-21000) Hz. P=Peaks (P1:0-1000; P2: 6500-8500; P3: 14000-15000; P4: 21000-23000) Hz. Frequency (x-axis) in 0-23000Hz, and amplitude (y-axis) in -dB. Figure from ²⁷¹

When controlling the pump monitor, a decrease in power consumption and flow occurred when the in-and out-flow tubing was narrowed. Compared to baseline (Power: 4.0, 3.9, 4.2W; Flow: 3.8, 3.8, 3.8 L/min) the power was decreased to 3.2W and 2.1L/min when the inflow tubing was reduced by 50%. When the outflow tubing was narrowed the power decreased to 2.7W and flow to 2.1 L/min. The artificial clots resulted in a decrease in power (2.7W, 2.4W) whilst the blood clot resulted in a 48% increase to 7.4W. The monitor showed no estimation of the flow while the clots were passing thru the pump. Uncertainty of the adequacy of the iPhone as a device for audio collection arose. The background for different peaks within the frequency spectrum could not be determined.

	Peaks and Regions (no. of Frequencies)											
	Change in noise level dB: mean (SD) and mean %											
	P1 (11)	R1 (64)	P2 (23)	R2 (64)	P3 (12)	R3 (69)	P4 (12)					
Change at increased speed (rpm)												
6 000 to 7 000	2 (2)* 4%	3 (2)** 5%	4 (3) ns 0%	5 (3)** 8%	7 (3)** 18%	5 (4)** 6%	4 (3) ns 7%					
7 000 to 8 000	2 (2)* 5%	5 (2)** 10%	4 (2) ns 1%	5 (2)** 8%	5 (3) ns 6%	5 (3)** 7%	7 (5)** 14%					
8 000 to 9 000	3 (2)** 7%	3 (2)** 3%	5 (5) ns 2%	5 (2)** 8%	6 (2)** 12%	4 (2)** 5%	9 (4)** 15%					
9 000 to 10 000	3 (2)** 8%	2 (1) ns 2%	3 (3) ns 4%	3 (2)** 4%	3 (2)** 5%	4 (2)** 5%	3 (2) ns 6%					
Change from baseline												
Pump inflow tube narrowed 50%	2 (1) ns 3%	4 (3)** 5%	5 (2)* 7%	4 (3)** 4%	2 (1) ns 3%	2 (8)* 3%	6 (4)** 7%					
Pump outflow tube narrowed 50%	8 (4)* 16%	11 (4)** 19%	16 (4)** 31%	4 (3) ns 5%	8 (3)** 10%	3 (3)** 4%	3 (2)** 4%					
Clot 1	9 (5)** 19%	20 (5)** 29%	19 (5)** 29%	8 (5)** 10%	7 (3) ns 8%	10 (3)** 10%	7 (3)** 9%					
Clot 2	10 (5)** 20%	22 (6)** 32%	20 (6)** 31%	10 (5)** 12%	8 (4)* 9%	10 (3)** 10%	10 (4)** 12%					
Blood Clot	12 (7)** 24%	22 (7)** 31%	16 (7)** 24%	6 (5)** 7%	7 (6)** 9%	5 (4)** 5%	6 (7)** 8%					

Table 3. R= Regions (R1:1000-6500; R2: 8500-14000; R3 15000-21000) Hz. P=Peaks (P1:0-1000; P2: 6500-8500; P3: 14000-15000; P4: 21000-23000) Hz.**P<0.005. *P<0.05. ns, no significant change. Rpm, revolutions per minute. A significant change in frequencies from the baseline acoustic fingerprint was detected in all experimental settings. Significant acoustic changes and the largest numeric change were seen in low frequencies when artificial clots and blood clots passed through the pump. Table from ²⁷¹

Sound analysis of a left ventricular assist device: A technical evaluation of iOS devices. Paper II.

The recordings from HMII within mock loop circuit and implanted in a patient appear similar in both time and frequency domain. Ambient and background noise affects the recordings. When the recordings were analyzed in time domain, a sine wave with an overlying saw-tooth signal became visible for the HMII in both patients and in mock loop circuit, see figure 10. The overlying “saw-tooth” signal is a high frequency signal at 7,2 kHz due to the pulse width modulation (PWM) and disappears when the pump is suddenly turned off. The PWM also generates harmonics seen as a peak at 14.4 kHz. This is a system parameter that was also visible in paper I. The fundamental frequency is located at the set speed appearing as a clear peak within the spectrum and frequency peaks appear by its side, side lobes. These peaks might stem from slowly changing amplitude of the low-frequency oscillations. The low-frequency component can be reproduced by parametric models that clearly apply to the underlying, fundamental frequency.

Figure 10. The figure shows the recordings from mock loop and patient with HMII. A periodicity, underlying sine wave with an overlying high frequency, saw-tooth signal can be seen. The overlying, high frequency signal originates from Pulse Width Modulation. The signal from mock loop and patient appear similar. Figure from ²⁷²

The iOS-devices appeared to pick up more ambient noise and were lower in sound volume. The oscillation that is seen with the dedicated equipment is not as clear for the iOS-devices, but a periodicity could often be asserted and the underlying, low frequency sine wave can be reconstructed, see figure 11. The low-frequency spectra revealed visible but not prominent peaks at the pump frequency and its harmonics. The frequency spectrum of HMII is complex and holds multiple peaks and harmonics that make the use of sound analysis for thrombosis detection challenging. The use of iOS-devices needs further evaluation and should benefit from a high-end microphone.

Figure 11. A comparison of the dedicated equipment, iPhone and iPod in time domain show that all of them are periodic (left). The PWM can be seen for all devices as a superimposed saw-tooth signal. The underlying sine wave, representing impeller rotation, can be reconstructed (right; dedicated recording equipment (green), iPhone (red), and iPod (blue)). Figure from ²⁷²

Sound analysis of the magnetically levitated left ventricular assist device HeartMate 3™. Paper III.

The HM3 holds different properties compared to other LVAD due to the absence of mechanical bearings. The sound from HM3 can be recorded with both dedicated and an electronic stethoscope. The sound appears similar in vivo and in vitro. When the sounds were plotted in time domain, an underlying sine wave and a shift in amplitude and frequency could easily be seen when the artificial pulse were active. These changes were not as clear with the electronic stethoscope as with the dedicated equipment, see figure 12. The major proportion of signal power (96.7%) is within pump frequency ± 40 Hz indicating that the signal of interest is in the low frequency range. When the artificial pulse was activated, peaks at +29.5Hz and -30.5Hz appeared in the frequency spectrum. These peaks correspond to an increase/ decrease of speed of approximately 1800rpm. This finding differs from the manufacturers manual but were consistent for all recordings, see figure 13. The electronic stethoscope was not as good as the Shure microphones at finding the fundamental frequency and in some recordings with electronic stethoscope a peak with higher amplitude and more power were seen, most often corresponding to a harmonic. All patients showed similarities in

the frequency spectrum with peaks at the fundamental frequency and harmonics, see figure 14. Dedicated microphone system is superior to the electronic stethoscope but both methods may be used for acoustic sampling.

Figure 12. Recordings of the HM3 in a mock loop circuit with microphone and the electronic stethoscope. The change in frequency and amplitude due to artificial pulsation can easily be seen for the microphones. The changes are not as clear for the electronic stethoscope. Figure from ²⁷³

Figure 13. The sound from HM3 in a mock loop presented in frequency domain. The fundamental frequency (100Hz) corresponds to the highest peak. This is not as clear for the electronic stethoscope but is visible and the harmonics are clearly seen. The peaks adjacent to the fundamental frequency correspond to the increase/decrease in speed that results in artificial pulsation. Figure from ²⁷³

Figure 14. Recordings from the four in vivo recordings presented in a low frequency spectrum up to 1 kHz after normalization (area under curve = 1). Pump frequency and artificial pulsation peaks are clearly visible. Multiple harmonics can be seen. All recordings look alike with minor changes due to speed. -20db equal to 0.01W/Hz. Rpm=revolutions per minute. Figure from ²⁷³

In-vitro study of the impact of LVAD loading on mechanical performance. Paper IV

The pump head, flow rate and data presented by the pump monitor were measured over a wide range of pump conditions. Acoustic signal was used to assess the time variations of the flow due to changes in rpm. For HMII the flow was steady and for HM3, quasi-steady. For both pumps, clot analogs remained within the pump housing. The linear relationship between flowrate and power consumption of both HMII and HM3 was valid in a limited range of operation and depended on the pump loading. Increment of afterload, by adjusting the piping length and outflow valve resistance affected the pump efficiency by decreasing the slope and the flow at specific rpm, see figure 15.

Figure 15. The measured flow-rate vs the pump speed in revolutions per minute (rpm) under different downstream conditions. HMII with a short and long circuit (a). HM3 pumping against three different downstream levels of resistance determined by the outflow valve seen in figure 8.

For HM3, the in-and outflow constriction affect pump efficiency where an intermediary obstruction resulted in the highest efficiency, see figure 16. The insertion of clot analogues resulted in an increased pump head due to increments in rpm but the slope decreased. The HM3 showed better resistance to increased number of clot analogs.

Figure 16. Measured flow vs pump speed in revolutions per minute (rpm) during mixed up-and down-stream levels of resistance for HM3. Minimum (1) to maximum (4) preload (PL) and afterload (AL) were altered. The highest efficacy is seen for intermediate in-and outflow restriction whilst the lowest flowrate is observed for higher outflow restriction.

Mechanical power output is defined as the total head in the circuit times the flowrate in W. The mechanical power output can be used to determine pump efficiency by comparing mechanical power output towards power output measured from the monitor. The best efficiency is seen for clean circuits. HM3 is more efficient than HMII and less prone to be affected by clot analogues, see figure 17. Both pumps show the highest efficiency at the highest pump speed. The flowrate from the monitor might be misleading but might be adjusted by fitting a parabolic curve. For a specific power input, the flowrate from the monitor and measured flow rate can differ, this due to surrounding features such as different constriction.

Figure 17. Mechanical power output vs pump speed in revolutions per minute (rpm) for HMII and HM3. Adding clot analogs to the circuit reduce the power output of both HM2 and HM3. HM3 seems to be less prone to be affected by clot analogs. Note that the scale is different for the two pumps.

Discussion

As the prevalence and incidence of HF increases, the number of patients that deteriorates to advanced HF with the need of advanced therapies is suggested to increase. This might also increase the number of patients in need for LVAD. The newest LVAD, HM3 has shown great results in the clinical studies, with both survival benefits as well as lower frequencies of adverse events.²²⁰ The number of pump thrombosis and malfunctions is low. This implies the need for further methods for detection of malfunction since the clinicians might not be aware of the risk as was the case for HMII.

Mock Loop

The mock loop circuits are a promising way to safely change the surrounding conditions as the pump is working. The mock loop can be constructed in multiple ways with different preload, afterload, and viscosity settings. This facilitates for studies on flow patterns, pump efficacy, and sound without the need of animals for implantation. On one hand, the use of water as medium results in a lower dissipation rate of turbulence. On the other hand, generation of flow instabilities and turbulence in the pumps is due to shear layer and centrifugal instabilities. Different viscosities of the fluid within the mock loop circuit and different acoustic positions have previously

been studied by Yost.²⁷⁴ The power, flow, pulsatility and peak harmonic frequency were left unchanged as viscosity was increased. The results indicate that the use of water as a medium is sufficient to study the acoustics. The difference in preload and afterload does not seem to affect the amplitude for peak harmonic frequency, which also indicates that sound analysis might be a valid method with low disturbance from other factors that might affect pump function.²⁷⁴ The sound recordings from patients and mock loop are similar for both HMII and HM3, shown in paper II and III and by Yost.^{263, 274} However, all studies, including ours, are mostly based on a small number of patients or clinical situations which impact the validity of the method. The first step to further assess the method could be to perform a larger scale simulation in mock loop circuit with daily recordings. The mock loop circuits allows for simulation at a larger scale with artificial thrombus at specific locations, for validation of the method, and examination of different recording devices as shown with HVAD by Feldman²⁶⁴

Recording devices and analysis

The use of handheld, easy to use recording devices is essential for developing the method so that it can be used in clinical settings. Different recording devices have been used in the different studies within the field. The iOS-devices, used within paper I, hold many features that are appealing, but the built-in high pass filter impacts the recordings. The HM3 and HVAD work in a lower speed than HMII, with a fundamental frequency, below 100Hz which make the iOS-devices even more dubious as a recording device for these devices. In Yost et al. an electronic stethoscope, of the same brand as used in paper III, was used for sound recording.^{263, 274} Validity of the electronic stethoscope was never discussed. As shown in paper III, the electronic stethoscope is more susceptible for disturbances and less efficient in determining the fundamental frequency. In Kaufman et al. a data acquisition device with a built-in microphone was used, the specification for the microphone is not however reported.²⁶¹ In paper II and III we used microphones with a relatively linear frequency spectrum as a reference method. These recordings were clearer for both HMII and HM3 recordings, thus indicating the need for validation of the recording devices. If a specific, low-frequency peak, infrasound, as found for Centrimag, ECMO system is found to indicate thrombosis is yet to be determined.²⁶⁵ For these low frequencies, a high end microphone or hydrophone is needed. In conclusion, further studies need to validate the easy to use, handheld devices before they are adopted as a clinical mean to evaluate pump function.

Within the studies, different ways and software have been used to analyze the sounds from the LVAD. A critical approach is the use of normalization so that the different peaks are not based on differences in volume. This has been performed in paper II and III, as well as Kaufman et al.²⁶¹ In paper I, a freeware used for sound recording was used to perform signal analysis, this resulted in power distribution at specific,

predefined frequency, not related to LVAD frequency. This might have affected the outcome, but it should not affect the area under the curve which was compared between the different recordings. This further implies that custom software, such as MATLAB is more sufficient for valid analysis.

For most studies, FFT has been used which is a solid method. If a harmonic or specific peak is shown to be associated with malfunction or thrombus in the future is yet to be determined. If that is the case, additional methods such as Continuous wavelet transform analysis, frequently used in studies on valvular disease can be a more relevant method.²⁷⁵ A way to compare the recording devices is if the recordings can be used to estimate pump frequency. Since the most power is in the fundamental frequency, i.e. pump speed, the amplitude of this peak should be the highest one. Yet, there is no consensus in how to assess malfunction or thrombosis of LVAD, but the use of customized software such as MATLAB further increases knowledge and facilitates characterization over the whole frequency spectrum enabling calculation of PSD. This results in that the power within a specific region can be compared between pumps with no adverse events and those with adverse events.

Implication of the results

Paper I arose from a clinical situation, which makes the studies and this thesis more applicable. It was one of the first studies on acoustic analysis of LVAD and an application of modern technology. The result was promising and showed similar results as Yost et al., but in need for technical evaluation of different devices.²⁷⁴ Today, the diagnosis of pump thrombosis or malfunction is based on multiple indirect measurements such as lab-results, pump parameters, x-ray, and echocardiographic examinations.²³² A pump exchange may have an impact on patient outcome as well as a substantial financial impact.²³⁴ Some of the parameters shown on the pump monitor might not be reliable, as shown in paper IV. This paper also shows the need to optimize patient factors, such as fluid status and afterload to maximize pump efficiency. These results are based on mock loop pressures and need to be validated in clinical settings or animal studies where hemodynamic alternations and vascular tonus can adapt to the different pressures. The lack of specific measurements on the monitor further increases the need of an additional method for diagnosing the presence of pump thrombosis or malfunction.

From a clinician point of view, an easy, handheld device with high sensitivity for detection would be optimal. Such a device could be an iPhone or electronic stethoscope since they both are commonly used. Despite the positive results of multiple studies on sound analysis, the clinical implication is yet low. Further studies might result in an application of artificial neuronal networks that can diagnose malfunction of the LVADs by just performing the recording. Another method might be

by monitor pump function with a built-in sensor that reacts to changes in specific frequency regions. Another way to minimize the need for outpatient monitoring might be remote monitoring with sound recordings sent to hospital for analysis. Routinely follow-ups with telephone calls have been shown to lowering the number of adverse events, and could easily be accompanied by a sound analysis to assess pump function in relation to clinical status.²²⁵

Conclusions

The main conclusions of the thesis are as follows.

1. It is possible to record and analyze sound produced from different LVAD and the sound holds information of pump function, both in vivo and in vitro, and the frequency spectrum is similar.
2. Different devices can be used for recording, but the more dedicated equipment is superior to the more handheld devices that are easy to use. These devices might however still be used as screening devices.
3. The sound contains of multiple peaks and harmonics that mostly are related to pump frequency.
4. The flow measurement on the monitor might not be valid. Optimization of fluid status and afterload of the patient can further increase pump efficiency.

Future perspectives

According to paper I-III, the use of acoustics as a mean to analyze pump function, and perhaps to determine thrombosis, might be an additional method to assess pump function. There are however multiple challenges. The critical point is to determine a specific change in the frequency spectrum that is due to the presence of thrombosis or malfunction. To facilitate this, the flow within the pump must be further studied to determine vortex phenomenon and its frequencies. Perhaps these frequencies are in the range of 1 Hz.

A multicenter trial in which the aim is to study the outcome of HM3 as destination therapy within a Swedish cohort consisting of 70 patients in each study-arm is enrolling. The trial is called SweVAD and is currently ongoing with randomization to

treatment with LVAD or optimal medical therapy. Within this trial, the sounds from the HM3 will be recorded at every outpatient follow up and at every adverse event. Data collection is ongoing at three sites, Lund, Gothenburg and Stockholm. This trial will hopefully further determine the efficacy of sound recording as a mean to find mechanical failures or pump thrombosis. If future trials of acoustic analysis show good results, the companies that provide the devices might be interested in the technology and further develop methodology.

If a specific parameter is indicative of pump thrombosis there are accelerometers that react to that specific frequency that can be used and neuronal network adopted within the device. If the total number of peaks within the spectrum seems to be more valid, the use of an accelerometer with a broader frequency spectrum can be used to alert the caregiver if an increase in peaks is found.

To further evolve the method, interdisciplinary approaches are needed, preferably with engineers with excellent knowledge in flow and signal analysis and medical doctors with knowledge of HF and LVAD treatment. One approach could be simulating thrombosis in a computer model to determine flow paths and to use these results in mock loop circuits for acoustic and vibrational analysis.

Svensk sammanfattning

Hjärtsvikt är ett allvarligt tillstånd med konsekvenser för både patient och samhälle då 1,5–3% av befolkningen beräknas lida av hjärtsvikt, en siffra som ökar i takt med ökad ålder. Bakomliggande orsak till hjärtsvikt kan vara många men högt blodtryck och kranskärslssjukdom är de vanligaste. Kostnaden för samhället är hög och studier har beräknat den årliga kostnaden i Sverige till 5-7 miljarder. Behandling av hjärtsvikt utgörs framför allt av medicinsk behandling i syfte att rädda liv och minska symptom genom att hämma de hormonsystem som bidrar till vätskeansamlingen och ärrbildning i hjärtat. Trots att den medicinska behandlingen är framgångsrik i praktiken och studier så är 5 års mortaliteten fortsatt 45-60%. För patienter som uppfyller prespecifierade kriterier kan implanterbara defibrillatorer och pacemakers förbättra prognosen.

För yngre patienter med uttalad hjärtsvikt så är hjärttransplantation den enda botande behandlingen. Tyvärr är tillgängliga organ inte tillräckligt många och årligen avlider patienter i väntan på transplantation.

För vissa patienter kan behandling med långtids-assist av vänster kammare (LVAD) vara en behandling i väntan på hjärttransplantation eller som slutgiltig behandling. Behandlingen med LVAD har flertalet komplikationer såsom blödningar, infektioner och trombos. Trombos i LVAD har förekommit sedan starten av implantation men ökade signifikant mellan 2012–2014. Detta medförde ett ökat behov av att enkelt kunna diagnostisera dess förekomst. Flertalet parametrar, bland annat flöde och strömkonsumtion används för att diagnostisera trombos i pumpen. Idén att kunna diagnostisera blodpropp i de mekaniska hjärtpumparna med hjälp av ljud var grunden för detta avhandlingsarbete.

Syftet med denna avhandling var att utveckla och utvärdera användandet av ett konstruerat cirkulationssystem för att kunna studera ljudet från LVAD, utvärdera olika inspelningsutrustning och studera effekten av afterload på pumpens effektivitet.

Två olika cirkulationssystem skapades för att möjliggöra inspelning, införa artificiell trombos samt justera tryckförhållanden i systemet. En iPhone/ iPod™ användes som inspelningsutrustning då distansmonitorering är eftersträvad men även ett elektroniskt stetoskop utvärderades. Ljudet från HeartMate II™ studerades under olika förutsättningar och inspelningen jämfördes mot dedikerad utrustning. Även ljudet från HeartMate 3™ studerades och jämfördes med ljudet från pump implanterad i patienter. Effektiviteten och flödesförändringar vid förändringar i tryckförhållanden studerades för både HeartMate II™ och HeartMate 3™

Resultatet av de olika studierna visar att ett experimentellt cirkulationssystem kan användas för att simulera olika förhållanden som pumparna arbetar under och att ljudet från pumparna är liknande de som framträder vid inspelning från patienter. Detta gäller för både HeartMate IITM och HeartMate 3TM. Resultaten visar att iPhone/iPodTM och elektroniskt stetoskop skiljer sig åt avseende kvalitet på inspelningarna men samtliga testade modeller kan användas. Det dedikerade systemet ger en tydligare ljudprofil medan de andra modellerna är mer lätthanterliga i den kliniska miljön. I det konstruerade cirkulationssystemet kan förekomst av blodpropp simuleras samtidigt som ljudet från pumpen spelas in. Vid dessa försök sågs med iPhone/ iPodTM förändring i amplitud av frekvensspektrumet för HeartMate IITM. I det konstruerade cirkulationssystemet kan flöde samt tryck mätas och ändras vilket påverkar pumpens effektivitet. Flödet, uppvisat på monitorn, påverkas av afterload där HeartMate 3TM är mer resistent mot artificiella proppar i pumpen. Effektiviteten hos både HeartMate IITM och HeartMate 3TM är bäst om det inte föreligger något hinder i systemet. Flödet på monitorn kan vara vilseledande då det uppmätta flödet och flödet på monitorn skiljer sig åt beroende på omgivande faktorer.

Sammanfattningsvis lägger studierna i denna avhandling en grund för vidare utveckling av ljudanalys av mekaniska hjärtpumpar men det krävs ytterligare forskning för att detektera en specifik förändring som indikerar blodpropp.

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“Feci quod potui, faciant meliora potentes”

– Jag har gjort vad jag kunnat, må nu de, som kan, göra bättre

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