Accelerometer-based monitoring of left ventricular assist device: tromboembolism and pump thrombosis detection in HeartWare HVAD

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1. Preface

This thesis is submitted to the University of Oslo for the degree of Philosophiae Doctor. The research presented was carried out at The Intervention Centre, Oslo University Hospital, under the supervision of professor Per Steinar Halvorsen, professor Arnt Eltvedt Fiane, professor Erik Fosse, and Doctor Andreas Espinoza. The research was funded by the South-Eastern Norway Regional Health Authority.

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Itai Schalit

3. Summary

Heart failure is a major public health challenge in the developed countries. Its incidence increases with age. Heart failure may progress to end-stage heart failure, defined as pronounced heart failure symptoms at rest, or at minimal physical activity, despite maximal medical treatment. The gold standard treatment for end-stage heart failure is heart transplantation. Organ supply is however insufficient and 10% of the individuals enlisted die each year on the waiting list.

Left ventricular assist device (LVAD) is an implantable pump which can support the failing left ventricle, either as a bridge to transplantation or as a permanent solution for patients inelligable for transplantation. LVAD treatment reduces mortality and increase the quality of life, and its use is expected to increase in the coming years. It has, however, considerable complications, including stroke and pump thrombosis. As for today, there is no diagnostic method that detects thromboembolism passing through the pump. Traditional LVAD thrombosis detection rely on blood tests, imaging modalites, and change in LVAD power consumption. There is a consensus that LVAD thrombosis diagnosis is suboptimal, which is reflected in efforts to find new diagnostic methods. Acoustic spectral analysis of pump sounds is a way to track changes in the LVADs vibration pattern. Increased third harmonic amplitude (pump speed x 3) has been shown to be a marker of pump thrombosis. Though promising, the method has some disadvantages as low signal quality and intermittent nature, which leads to low reproducibility between studies. Accelerometer sensor is an alternativ method to capture pump vibrations which may not suffer the same disadvantages.

In this thesis we tested a novel acceleroemter-based detection of thromboembolism and pump thrombosis in LVAD. We hypothesized that the accelerometer would detect changes in the third harmonic amplitude under thromboembolism and pump thrombosis, and that it would perform better than pump power consumption, the only continuous monitoring method at the moment.

We also hypothesized that analyzing amplitude changes in the nonharmonic frequencies would further improve the method's diagnostic power.

LVAD vibrations were recorded by an accelerometer attached to the HeartWare HVAD housing. We tested the accelerometer in a series of experiments using in vitro and in vivo models. Signal changes under thromboembolic events (injection of thrombi into the pump) were compared with control interventions, which included pump speed change, preload and afterload manipulation, and saline bolus injections. As the frequency domain is more suitable for vibration analysis, the signal was converted using fast Fourier transform.

Thromboembolic events led to increased amplitude in a continuous range of frequencies including the third harmonic. As the third harmonic normally has low amplitude and is minimally affected by hemodynamic changes, it proved to be a good marker for the detection of thromboembolic events (paper I and paper II), with area under the curve in ROC analysis above 90%. The accelerometer performed better than the HVAD power consumption which demonstrated area under the curve below 76%. Testing the change in the nonharmonic frequencies further improved the positive predictive value of the method by 8.3% (paper III).

A subgroup of the thromboembolic events led to persistent signal changes indicative of pump thrombosis. Despite persistent changes in the accelerometer signal, HVAD power consumption showed minor changes (0.2 W [IQR 0.3]) and did not reach the current cutoff value for the diagnosis of pump thrombosis (paper I and paper II). Persistent signal changes affected either the third harmonic, or the nonharmonic frequencies. Nonharmonic amplitude change was present in 8.3% (5/60) while third harmonic amplitude change was present in 21.6% (13/60) of thromboembolic interventions, on the pooled data. Only one thrombus injection led to concomitant change in both third harmonic and nonharmonic amplitude. Combining the two types of signal changes led to 36% improvement in the positive predictive value of the method compared with using third harmonic amplitude change alone (paper III).

Accelerometer is a new modality in LVAD monitoring. It shows promise in the diagnosis of pump thrombosis. It replicated previous findings demonstrating that the third harmonic is a sensitive and specific marker for pump thrombosis. It also demonstrated that changes in the nonharmonic region can be used in the diagnosis of pump thrombosis. The lack of dependency between third harmonic and the nonharmonic frequencies suggests that they have a different underlying etiology which may improve our understanding of different forms of pump thrombosis.

The accelerometer shows promising results not only in the detection of pump thrombosis, but also in the detection of thromboembolic events. Since up until now, there has been no diagnostic method for the detection of thromboemboli passing through the pump, the number of silent thromboemboli in LVAD patients is unknown. Infective endocarditis is a condition where emboli, originating from the heart, enter the systemic circulation. Peripheral emboli cause abscesses and therefore are easy to detect. Extrapolating from the distribution of thromboemboli in infective endocarditis, peripheral embolization is grossly underdiagnosed in LVAD patients. Detection of subclinical emboli may allow for intervention before function loss occurs. Considering the mortality and morbidity that ensue due to stroke, this may have considerable effect on the LVAD population.

We concluded that accelerometer attached to the pump will open the door for reliable, continous, real time monitoring of LVAD. Accelerometer based monitoring will be a considerable improvement compared with pump power consumption and acoustic spectral analysis based monitoring.

4. Sammendrag

Hjertesvikt er et økende problem i den vestlige verden. Insidensen øker med alder. Terminal (endestadium) hjertesvikt er definert som symptomer på hjertesvikt i hvile eller med minimal aktivitet, på tross av optimal medisinsk behandling. Hjertetransplantasjon har vært det eneste behandlingsalternativet til denne pasientgruppen. Organtilgjengeligheten er i midlertid begrenset, og hvert år dør 10% av pasientene på ventelisten.

Left ventricular assist device (LVAD) er en implanterbar hydrodynamisk pumpe som kan avlaste den sviktende venstre ventrikkelen, enten som en bro til transplantasjon eller som en mer permanent løsning for pasienter som ikke kan transplanteres. Behandling med LVAD reduserer dødligheten og øker livskvaliteten til hjertesviktpasienter, og bruken er forventet å øke i de kommende årene. LVAD behandling har imidlertid alvorlige komplikasjoner, deriblant hjerneslag og pumpetrombose. Frem til nå har man ikke kunnet diagnostisere tromber som passerer gjennom pumpen (tromboembolisme). Tidligere har man basert diagnosen av pumpetrombose på labratorieprøver, radiologiske undersøkelser, og endring i strømforbruket til pumpen (pump power). Det er konsensus at diagnostikk av pumptrombose er mangelfull, og dette reflekteres i bred innsats for å finne bedre diagnostiske metoder. Akustisk spektralanalyse av pumpelyder er en måte å spore endringer i vibrasjonsmønstret til pumpen. Økt amplitude av den tredje harmoniske frekvens (pumpehastighet x 3) har vist seg å være en markør for pumpetrombose. Metoden har imidlertid mange ulemper, som dårlig signalkvalitet og dens intermitterende natur, og dette er en årsak til lav reproduserbarhet mellom studier hvor akustisk spektralanalyse brukes. Bruk av akselerometer er en alternativ metode for monitorering av pumpevibrasjoner hvor man kan unngå disse problemene.

I dette arbeidet testet vi en ny akselerometerbasert metode for diagnostisering av tromboembolisme og pumpetrombose i LVAD. Vår hypotese var at et akselerometer kan detektere tromboembolisme og pumpetrombose via endring i amplituden av den tredje

harmoniske frekvens, før økning i LVAD strømforbruk indikerer pumpetrombose. En annen hypotese var at analyse av amplitudeendringer i de nonharmoniske frekvensene i akselerometersignalet ville kunne øke metodens diagnostiske treffsikkerhet.

Et akselerometer ble festet utenpå en HeartWare HVAD pumpe, og det ble gjort opptak av pumpevibrasjonene. Siden vibrasjonsmønsteret er lettere synlig i frekvensdomenet, ble opptaket omgjort ved hjelp av fast Fourier transformasjon. Akselerometeret ble testet med både in vitro og in vivo modeller.

Injeksjoner av trombemasser ble sammenlignet med kontrollintervensjoner, som inkluderte endringer i pumpehastighet, preload og afterload, samt saltvanninjeksjoner.

Tromboembolisme førte til økning i amplitude i et bredt frekvensområde inkludert den tredje harmoniske frekvens. Siden den tredje harmoniske frekvens har lav amplitude ved normal LVAD funksjon og er lite påvirket av hemodynamiske forandringer, viste den seg å være en god markør for pumpetrombose (paper I og paper II), med areal under kurven på ROC analyse over 90%. Akselerometeret hadde høyere diagnostisk styrke samenlignet med LVAD strømforbruk, som hadde areal under kurven på ROC analyse under 76%. Ved å legge til endringer i de nonharmoniske frekvensene økte den positive prediktive verdien av metoden med 8,3% (paper 3). En undergruppe av trombene førte til vedvarende signalendringer, som indikerte pumpetrombose. På tross av vedvarende endret akselerometersignal var HVAD strømforbruket minimalt endret (0,2 W [IQR 0,3 W]) og nådde ikke diagnostisk terskelverdi for pumpetrombose. Vedvarende signalendringer påvirket enten den tredje harmoniske frekvens eller de nonharmoniske frekvensene. Vedvarende amplitudeendringer i de nonharmoniske frekvensene var tilstede i 8,3% (5/60) av trombeinjeksjonene, mens vedvarende amplitudeendringer i den tredje harmoniske frekvens var tilstede i 21,6% (13/60). Kun en trombeinjeksjon førte til kombinert endring i nonharmonisk og tredjeharmonisk amplitude. Ved å kombinere de to signalendringene økte den positive prediktive verdien med 36% sammenlignet med å bruke den tredje harmoniske frekvensen alene.

Akselerometeret er en ny metode innen LVAD monitorering. Det viser lovende resultater for diagnostikk av pumpetrombose. Våre resultater støtter tidligere funn, og bekrefter at endringer i den tredje harmoniske frekvens er en sensitiv og spesifikk markør for pumpetrombose. Våre resultater viser også at endringer i de nonharmoniske frekvenser kan brukes i diagnostikk av pumpetrombose. Vi observerte at endringer i den tredje harmoniske og de nonharmoniske frekvensene var uavhengige av hverandre, som tyder på ulike underliggende etiologier. Forståelse av de underliggende årsakene til de to signalforandringene vil øke vår forståelse for ulike typer pumpetrombose.

Akselerometeret viste gode resultater ikke bare i pumpetrombose-deteksjon, men også i deteksjon av tromboemboliske hendelser. Frem til nå har man ikke hatt noen diagnostisk metode for å detektere trombepassasje gjennom pumpen, og derfor er antallet stumme embolier hos LVAD pasienter ukjent. Perifere embolier hos pasienter med infeksiøs endokarditt kan lett diagnostiseres grunnet abscessutvikling. Dersom man ekstrapolerer fra distribusjon av embolier hos pasienter med infeksiøs endokarditt, er perifere tromboembolier grovt underdiagnostisert hos LVAD pasienter. Påvisning av subkliniske embolier gir et intervensjonsvindu før funksjonstap. Med tanke på mortalitet og morbiditet etter hjerneslag har dette stor betydning for LVAD populasjonen.

Vi konkluderte at akselerometer festet utenpå en HeartWare HVAD pumpe vil være en døråpner for kontinuerlig, sanntid monitorering av LVAD. Monitorering med akselerometer er en betydelig forbedring sammelignet med monitorering av LVAD strømforbruk og akustisk spektralanalyse.

5. List of Papers

Paper I

Schalit, Itai; Espinoza, Andreas; Pettersen, Fred-Johan; Thiara, Amrit P.S.; Karlsen, Hilde; Sørensen, Gro; Fosse, Erik; Fiane, Arnt E.; Halvorsen, Per S.. **Accelerometer Detects Pump Thrombosis and Thromboembolic Events in an In vitro HVAD Circuit.** ASAIO Journal (American Society for Artificial Internal Organs: 1992) Sep/Oct 2018;64(5):601-609. doi: 10.1097/MAT.0000000000000699.

Paper II

Schalit, Itai; Espinoza, Andreas; Pettersen, Fred-Johan, Snartland, Steinar; Ringdal, Mari-Ann L.; Hoel, Tom N.; Skulstad, Helge; Fosse, Erik; Fiane, Arnt E.; Halvorsen, Per S.. **Detection of Thromboembolic Events and Pump Thrombosis in HeartWare HVAD Using Accelerometer in a Porcine Model.** ASAIO Journal (American Society for Artificial Internal Organs: 1992) Jan 2020;66(1):38-48. doi: 10.1097/MAT.0000000000000954.

Paper III

Schalit, Itai; Espinoza, Andreas; Pettersen, Fred-Johan; Skulstad, Helge; Fosse, Erik; Fiane, Arnt E.; Halvorsen, Per S.. **Improved Detection Of Thromboembolic Complications In left ventricular assist device By Novel Accelerometer-Based Analysis.** ASAIO Journal 2022; Publish Ahead of Print. doi: 10.1097/MAT.0000000000001654

6. Glossary

CMRI = cardiac magnetic resonance imaging

CRT = cardiac resynchronization therapy

CTA = computer tomography angiography

ECG = electrocardiography

ECMO = extracorporeal membrane oxygenation

EF = ejection fraction

EPPY = event per patient-year

HFpEF = heart failure with preserved ejection fraction

HFmrEF = heart failure with midrange ejection fraction

HFrEF = heart failure with reduced ejection fraction

HVAD = HeartWare VAD

HVAD physiological conditions = uncomplicated HVAD supported circulation

HVAD flow estimation = The flow value presented by the HVAD monitor

IQR = interquartile range

LDH = lactate dehydrogenase

LVAD = left ventricular assist device

Measured flow = Flow as measured by M3 ultrasonic flowmeter (Spectrum Medical, Cheltenham, England).

ROC = receiver operating characteristics

RVAD = right ventricular assist device

7. Motivation

The incidence and prevalence of heart failure is expected to increase, and consequently also the number of patients suffering from end-stage disease. As left ventricular assist device (LVAD) is a life-saving treatment for end-stage heart failure, its use is expected to increase despite the risk for severe complications.

Complications from LVAD therapy include bleeding, pump thrombosis, stroke, infection, aortic insufficiency, and right heart failure. Hemostasis-related complications, including bleeding, pump thrombosis, and stroke, are a considerable source for morbidity and mortality. Shear stress effects and contact activation of the coagulation cascade from LVAD therapy, induces combined hypercoagulability and bleeding diathesis. This poses clinical challenges both in management of complications, and in decisions regarding anticoagulation regime. Monitoring of hemostasis-related complications is important but lacking.

LVAD thrombosis may lead to pump malfunction and is considered a medical emergency. It may lead to either hypoperfusion due to reduced pump output or to stroke secondary to thrombus embolization from the pump. Stroke is a major cause for morbidity and mortality, and early diagnosis is essential for optimal management. As most pumps have no thromboembolic events detection, there is practically no information regarding silent emboli. Adjustment of anticoagulation prior to loss of function is therefore impossible. The magnitude of this problem is unknown.

The modern LVAD is a hydrodynamic pump that is placed, literally, in the heart of the circulatory system, a highly dynamic, quickly changing environment. Optimal monitoring should be continuous, reliable, and safe, preferably without breaching the blood barrier. Pumps maintain a predictable, pump-type specific, vibration pattern. Under pathological conditions this vibration pattern is disrupted, presenting new characteristic features. Vibration analysis using accelerometer fulfills the above requirement for continuous monitoring while maintaining patient

safety. Based on previous findings using acoustic spectral analysis, we expected to find characteristic, reproducible, vibration ‘fingerprints’ that may improve LVAD monitoring.
In this work we intended to test the ability of accelerometer-based vibration analysis to detect thromboembolic complications in LVAD.

8. Introduction

LVAD is an implantable pump used in the treatment of end-stage heart failure. It is implanted into the left ventricle and pumps blood into the aorta. Understanding the need for LVAD, its utility, and its complication management requires understanding of the clinical settings in which it is used. We start with a description of heart failure, the underlying pathology necessitating LVAD use.

8.1. Heart failure

8.1.1 Definitions

Heart failure is defined by the European Society of Cardiology as follows:

> "Heart failure is a syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress." [1]

Other definitions might vary to some degree but all point to pathophysiological intracardiac compensatory responses in an attempt to maintain adequate cardiac output. As the disease progress one may reach end-stage heart failure (refractory heart failure, or terminal heart failure).

> 'End-stage heart failure' is defined as a condition in which pronounced heart failure symptoms are present at rest, or at minimal physical activity, despite maximal medical treatment.'[2]

It is important to acknowledge that the term 'end-stage heart failure' is misleading to a certain degree. Heart failure may have different etiologies, hemodynamic profiles, clinical challenges,

and course. This definition implies a chronic course where the end-stage arrives at the end of a gradual deterioration. This may be the case, for example when the underlying etiology is non-ischemic dilated cardiomyopathy. Other conditions, however, may lead to decompensated heart failure after an acute course, as can be seen with severe myocarditis, or post-infarction heart failure. The term also suggests that after reaching the 'end-stage' there is no way back. The potential for recovery in acute course is uncertain in some cases, which make fast and decisive decision making necessary and challenging. In this thesis the term 'end-stage heart failure' is used as defined above, and denotes the point where a decision regarding heart transplantation, mechanical circulatory support, or palliative strategy has to be taken.

8.1.2. Demographics

According to the European Society of Cardiology, one to two percent of the adult population in developed countries suffers from heart failure. Its incidence increases with age, affecting over 10 percent of adults over 70 years of age.[1] According to the Norwegian Health Institute, there are about 50.000-100.000 (0.9-1,8%) individuals suffering from heart failure in Norway, and heart failure prevalence over 75 years of age is about 10%.[3] Heart failure is responsible for at least 5% of all acute hospital admissions to medical wards.

The situation in the USA is similar, with heart failure afflicting estimated 6.2 million Americans over 20 years of age. Based on the current data, the prevalence of heart failure is expected to increase by 46%, from 2012 to 2030, leading to over 8 million heart failure patients in the adult population.[4]

With improvement in prevention of hypertension, diabetes mellitus, and improvement in invasive cardiology, there is a trend showing reduction in the incidence of heart failure related hospital admissions, but increase in its prevalence.[5] The increased prevalence is, at least partly, due to improved heart failure survival.

8.1.3. Pathophysiology

Heart failure is a complex syndrome with an array of symptoms, signs, clinical features and course which not always correlate with one another. The condition may affect the left ventricle, right ventricle or both. Valvular disease may be present or absent. Its course can be acute or chronic.

Heart failure severity was, traditionally, described based on symptomatology which led to the New York Heart Association (NYHA) classification. Despite its popularity, the NYHA classification correlates poorly to echocardiographic parameters and biomarkers used to evaluate heart failure and it provides no information about the etiology of the heart failure.[6] An alternative is the American College of Cardiology and the American Heart Association classification (ACC-AHA) which includes in the assessment the presence of structural heart changes, without more closely defining them.[7]

A more pathophysiological approach classifies heart failure based on the main pathophysiological feature, such as systolic dysfunction, diastolic dysfunction, or a combination of the two. Systolic dysfunction is characterized by decreased contractility with dilated remodeling of the left ventricle leading to high wall tension (increased afterload).[8] Diastolic dysfunction is characterized by relaxation abnormality which leads to a rapid rise in end-diastolic pressure and low end-diastolic volume. It is often present with concentric hypertrophic ventricular remodeling with low wall tension (normal to reduced afterload). A certain degree of diastolic dysfunction may coexist with predominantly systolic dysfunction.[9-13]

Ejection fraction (EF) measurements may help classify heart failure based on the predominant underlying pathophysiology.[1,7] Systolic dysfunction usually leads to heart failure with reduced ejection fraction (HFrEF), defined as EF below 40%. Diastolic dysfunction usually leads to heart failure with preserved ejection fraction (HFpEF), defined as EF above 50%. Patients with EF

between 40% and 50% is a new category in the new guidelines defined as heart hailure with mid-range ejection fraction (HFmrEF). This new category was defined due to gap of knowledge regarding the predominant heart failure component in this patient group.

The most common etiologies for HFrEF are idiopathic dilated cardiomyopathy or specific cardiomyopathies with a dilated phenotype.[1,14] Idiopatic dilated cardiomyopathy is of unknown cause in 70% of cases and hereditary in 30%. Specific cardiomyopathies with a dilated phenotype are associated with post-infarct heart failure, myocarditis, valvular disease, chemotherapy, and pregnancy.

The most common etiologies for HFpEF are hypertensive heart disease, hypertrophic cardiomyopathies, and restrictive cardiomyopathies. Hypertrophic cardiomyopathy is hereditary (60%) or idiopathic (40%).[14] The minority of hypertrophic cardiomyopathy (5-10%) develop left ventricular dilation late in the course of the disease. Restrictive cardiomyopathies may involve the myocardium or the endocardium.

8.1.4. Diagnosis

The diagnosis of heart failure relies mainly on clinical history, physical examination, biomarkers, ECG and echocardiography.[1] In some cases, invasive pressure measurements may assist in the correct diagnosis.

Adjuvant cardiac imaging modalities include cardiac magnetic resonance imaging (CMRI), non-invasive stress investigations (echocardiography, CMRI), invasive coronary angiography and CT Angiography (CTA).

The diagnosis of HFpEF is more difficult to establish.

8.1.5. Treatment

Medical treatment of heart failure is multimodal.[1] It focuses on prevention and improvement of heart failure predisposing factors (e.g. coronary artery disease, hypertension, etc.), reducing the workload of the failing heart (e.g. reducing afterload), improving symptoms (e.g. reducing volume overload and pulmonary congestion), and prevention of life-threatening complications (e.g. arrhythmias). Many of the medications used have more than one function in the treatment of heart failure. The details of medical treatment of heart failure is beyond the scope of this thesis.

Cardiac resynchronization therapy (CRT) might be used under HFrEF (EF<35%) NYHA class 3, which do not respond to medical treatment, when the ECG QRS complex duration is longer than 130 msec.

Patients who develop end-stage heart failure may be eligible to mechanical circulatory support or heart transplantation.

8.1.6. Treatment of end-stage heart failure

End-stage heart failure correlates to the New York Heart Association (NYHA) class 4, or the American College of Cardiology and the American Heart Association (ACC-AHA) stage D, and accounts for approximately 5% of the cases.[15] The definite treatment of end-stage heart failure is either heart transplantation or mechanical circulatory support.

8.1.6.1. Heart transplantation

Survival after heart transplantation has improved over the years, with one-year survival rate of 95% and 10-years survival rate of 60%. Median survival today is 12,5 years. The most common

indications for heart transplantation are non-ischemic dilated cardiomyopathy (52%) and ischemic cardiomyopathy (32%).[16] The number of grown-ups with congenital heart disease undergoing heart transplantation is expected to increase in the future.

Organ supply is however insufficient and 10% of the individuals enlisted die each year on the waiting list.[17] In Norway this number is as low as 5%, which is the consequence of good resource management and good collaboration between the Scandinavian countries. In an attempt to compensate for persistent donor heart shortage, extended criteria for donor hearts are increasingly used. Such criteria include donation after circulatory death donors, heart supported with ex-vivo perfusion, and donations from hepatitis C positive donors.[16] One accepts higher donor age in Europe in order to improve organ availability.[18]

Almost 50% of the patients who eventually undergo heart transplantation are supported temporarily with left ventricular assist device (LVAD).[16,19,20] LVAD use as “bridge to transplantation” does not seem to adversely affect post-transplant mortality. On the other hand, extra-corporeal membrane oxygenation (ECMO) use as “bridge to transplantation” has been shown to increase post-transplant mortality considerably, with up to 45% one-year mortality rates.[16,19]

In an attempt to reduce mortality on the heart transplant waiting list, a new allocation system was implemented, independently from each other, first in France, in 2004, and then in the United States, in 2018.[21,22] These allocating systems prioritized organs to the sickest patients, many of them on ECMO. This led to increased post-transplant mortality. Jasseron et al defended this allocation system pointing that there is a survival benefit for the individual patient on ECMO. According to their conclusion, transplantation should be a primary treatment option for patients on ECMO. After implementing the new regulations in the United States, Ventura et al leaned toward a utilitarian argument against the new allocation system.[23] They argued that with the development in technology, survival rates with LVAD support approach post-transplant survival rates, at least in the short-term. As LVAD physiology differs from ECMO physiology and

has not been shown to increase mortality it is a viable option for patient stabilization and rehabilitation before eventual heart transplantation. This will allow prioritizing transplantation to patients who will gain the utmost benefit from donated hearts and increase the overall benefit of heart transplantation. [23]

8.1.6.2. Mechanical circulatory support in the treatment of end-stage heart failure

For many years the only definitive treatment for end-stage heart failure was heart transplantation. It is still considered to be the gold standard. Long-term mechanical circulatory support was developed out of necessity, due to low organ availability or rapid clinical deterioration with complicating conditions and relative contraindication for transplantation. As mechanical circulatory support improved, it became an important tool in the arsenal clinicians use treating end-stage heart failure.

It is necessary to acknowledge the short-term mechanical circulatory support devices. Their purpose is to support the failing heart temporarily, providing adequate cardiac output, giving the treating team time to assess the situation and choose an adequate long-term strategy. Short-term mechanical circulatory support devices include extra-corporeal membrane oxygenation (ECMO), Impella, and intra-aortic balloon pump (IABP). These devices have little bearing on this work and will be mentioned only briefly in the relevant sections.

8.2. Mechanical circulatory support

8.2.1. Evolution

The first mechanical circulatory support device was the precursor of the heart-lung machine. It was built and used by Dr. John H. Gibbon Jr. under open heart surgery in 1953. This is today

the standard circulatory support under open heart surgery. In time this type of circulatory support gave rise to extra-corporeal membrane oxygenation (ECMO).

Attempts at developing total artificial heart (TAH) began at 1964 under the leadership of Dr. Domingo Liotta. Despite considerable efforts, building a well functioning TAH, for long-term circulatory support, proved more difficult than expected. The survival in *in vivo* experiments did not exceed 24 hours. The TAH project was temporarily abandoned and efforts were averted to developing LVAD. The first non-commercial LVAD was implanted by Dr. DeBakey in 1966. The patient recovered and the LVAD could be removed.

The first heart transplantation was performed at 1967. Due to positive initial result the new technique was enthusiastically adopted. Organ scarcity led to the first attempt of using a TAH as 'bridge to transplantation' in 1969. The patient survived 64 hours until an organ was available. The patient died 32 hours after transplantation due to overwhelming sepsis.

The enthusiasm around heart transplantation was short lived. Immunosuppression was a new field and transplanted patients died due to infections or organ rejection. Transplantation was therefore abandoned for a decade, and efforts were averted to LVAD development.

The first generation commercially available LVAD was a pulsatile implantable pump, the Heartmate XVE. Ten thousand pumps were implanted between 1991 and 2012. These were complex positive displacement pumps and their durability was limited to two years.

The second generation of pumps were continuous flow LVADs (CF-LVADs). They were built for reliability and durability. The first pump was Hemopump, with a design that later inspired the percutaneously inserted temporary circulatory support, the Impella®. The second pump was the Jarvik Heart, a pump with blood-washed bearings. This opened the door to a new generation of pumps including the popular Heartmate II LVAD. These axial pumps utilized the ancient idea of the Archimedes screw. They were simple in design and durable, which made long-term circulatory support possible.

The next advancement was the development of the centrifugal pump. This opened the door for a combined hydrodynamic and magnetically levitated impeller that did not require bearings at all. The first commercial pump using this principle was the HeartWare HVAD. This pump gained popularity and became the second most implanted pump after Heartmate II. The HeartWare HVAD was withdrawn from the market in June 2021 due to patient safety issues. This decision was taken due to high incidence of neurological adverse events compared with Heartmate 3, and reports of pump failure to start leading to multiple death cases.

The Heartmate 3 is a fully levitated new centrifugal pump. It was compared with the Heartmate II axial pump in the Momentum 3 investigation. The Heartmate 3 demonstrated superiority concerning hemostasis-related complications.[24,25]

This illustrates the enormous fast progress that is continuously made in the field of mechanical circulatory support.

8.2.2. Clinical impact

It is difficult to overstate the effect that the development in LVAD technology has had on the treatment of end-stage heart failure. It offers a solution to a patient group which, up to recently, had no treatment alternatives. Starting from the humble ‘bridge to transplantation’, LVAD use expanded to new patient groups with an array of new indications. The role of LVAD as ‘destination therapy’ is now well established, and the great majority of patients are treated under this indication.[26] Other indications include ‘bridge to decision’, ‘bridge to candidacy’, and ‘bridge to recovery’. With the new indication ‘bridge to decision’ comes an acknowledgement of the element of uncertainty with regard to patient’s outcome. This is especially important under an acute course of disease where medical treatment cannot be established and the chance for recovery is unclear. With the new indication ‘bridge to recovery’ there is an acknowledgement of the potential benefit LVAD has compared with ECMO.[23]

One of the striking conclusions of the Momentum 3 investigation lie not in the difference between centrifugal and axial pumps, but in the fact that mechanical circulatory support with Heartmate 3 provides short-term survival rate that is comparable to heart transplantation.[23-25] The limited organ availability combined with improvement in LVAD technology led to change in organ allocation, as previously mentioned, and heart transplantation is reserved, in some countries, to cases where mechanical circulatory support is failing.[27]

Considering the magnitude of heart failure in the population and the trajectory of MCS until now, LVAD use is expected to increase in the coming years.

8.2.3. The modern LVAD

The modern third generation LVAD is a hydrodynamic pump, small enough to be implanted in the thoracic cavity. Its inflow cannula is implanted through the left ventricular wall into the left ventricle. A graft connects the outflow cannula to the aorta (figure 1). Blood is pumped through the LVAD and into the aorta bypassing the aortic valve.

The pump is connected to a controller by a percutaneous driveline. The controller is responsible for powering the pump and in HeartWare HVAD must always be connected to two power sources. The controller also collects and log information from the pump. The controller interfaces with the monitor through a data port.

The pump monitor provides an interface by which one controls selected parameters as pump speed or hematocrit, and view real time data or logged information (figure 2). The HVAD interface provides the current pumps speed, the pumps power consumption and the estimated pump flow. Blood flow through the pump depends on the pumps head pressure which is defined as the pressure gradient between the inflow cannula and the outflow graft. The HeartWare HVAD measures the pump power consumption. It then uses a pump head curves to estimate flow. The pump head curves are predetermined relationship between the head pressure and

expected flow and work under the assumption the the HVAD is undamaged. Intra-pump thrombosis may lead to increased friction between the impeller and the pump housing. HVAD power consumption increase in turn to maintain the pump speed which leads to overestimation of flow.

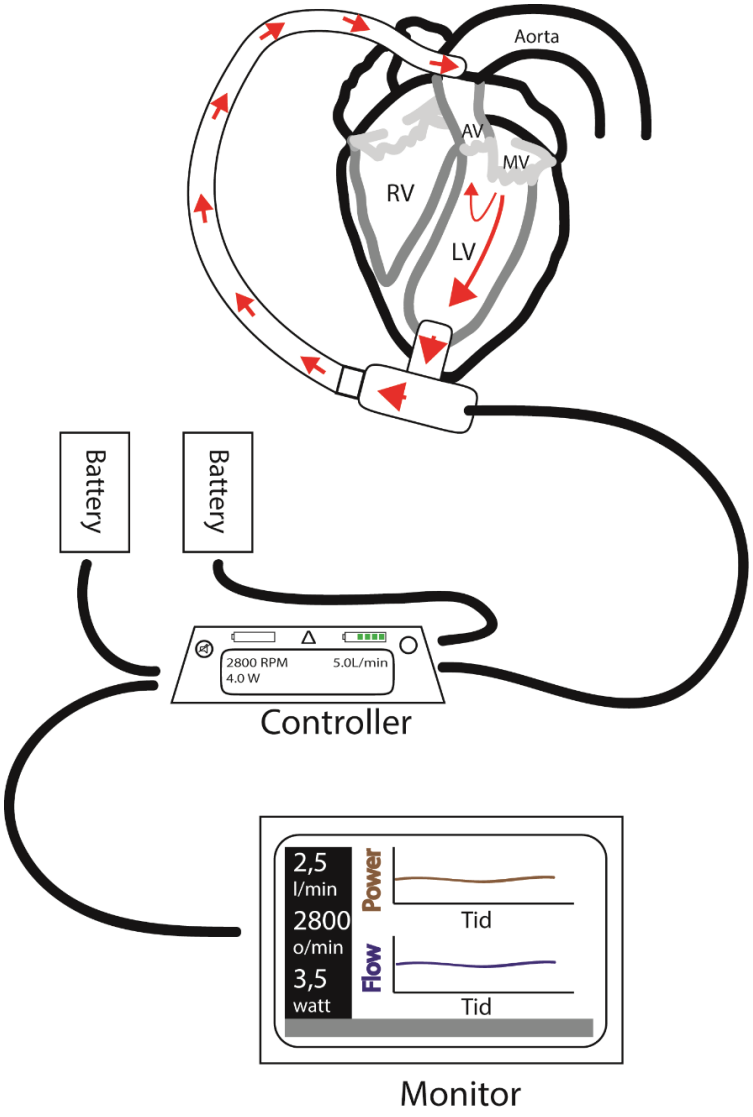

Figure 1. Typical LVAD set up. The inflow canulla is implanted into the left ventricle. The LVAD pumps blood from the left ventricle into the aorta bypassing the aortic valve. The LVAD is connected to a controller that is responsible for its power supply. Information from the LVAD is logged at the controller. The controller can be connected to a monitor which can present real time data or logged information. The monitor interface permits adjustment of selected parameters as pump speed or hematocritt. LV = left ventricle, RV = right ventricle, MV = mitral valve, AV = aortic valve.

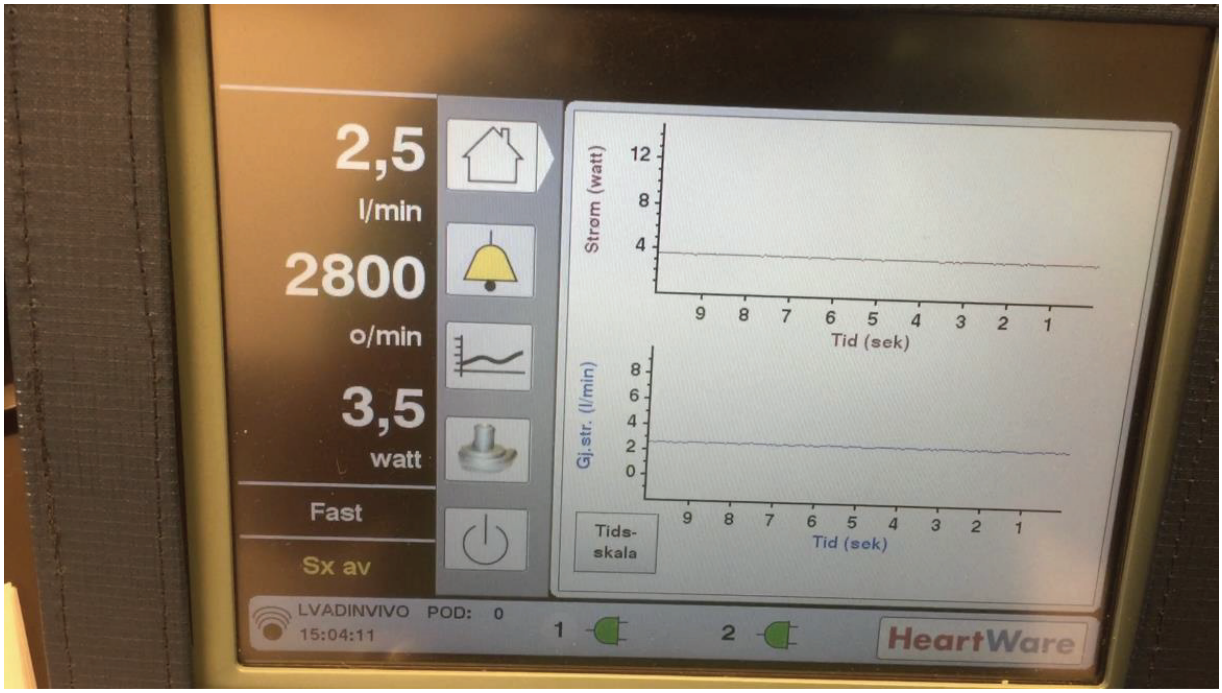

Figure 2. HeartWare HVAD monitor. The monitor presents continuous real time data. Pump pwer consumption (watt), estimated flow (l/min) and pump speed (RPM).

8.2.4. LVAD complications

LVAD patients continue to suffer from an array of severe complications, despite considerable improvement in technology. Most complications are frequent in the early phase (90 days) and decline significantly thereafter.[28] Early mortality (within one year) can be reliably predicted by the preoperative evaluation of the patients, while late mortality becomes more dependent on the burden of complications and is much more difficult to predict.[29]

Complications can be grossly grouped based on their relation to the coagulation system. In some publications, complications due to altered coagulation are referred to as 'hemocompatibility related complications'. This term creates a strong etiological link to hemocompatibility issues and may cause confusion, as intracardiac thrombus and thromboembolism is not limited to the LVAD population. The term '(non-) hemostasis-related complications' is used in this thesis, as it avoids this problem. The main non-hemostasis-related

complications include major infections, aortic insufficiency, and right heart failure. The main hemostasis-related complications include pump thrombosis, thromboembolism (stroke, non-CNS thromboembolism), and bleeding.

8.2.4.1. Non-hemostasis-related complications

Non-hemostasis-related complications are not the focus of this work and will be discussed only briefly.

8.2.4.1.1. Infection

Infection tops the complication statistics, together with bleeding, with early phase infections rate of 1.349 events per patient-year (EPPY), and late phase infection rate of 0.440 EPPY.[28] Freedom from infection is only at 58.9% after 12 months. Severe infection is the major cause of death in 5.7% of LVAD patients. Infections can be further divided into three groups: LVAD-specific, LVAD-related, and non-LVAD infections.[30] LVAD-specific infections can occur only in LVAD patients, including pump, graft infections, or driveline focus. LVAD-related infections may occur in other patients but require further clarification in LVAD patients, including infectious endocarditis, blood born infections, mediastinitis, sternal wound infections, and mycotic aneurism. Non-LVAD infections are infections that are unlikely to be related to the LVAD, for example cholecystitis, urinary tract infection, etc.

The presentation of LVAD-specific or LVAD-related infections is usually non-specific and demands careful evaluation of the source of infection, which may be challenging. Investigations should include careful history, physical examination, LVAD function evaluation, surgical wound and percutaneous driveline exit site examination, laboratory studies, microbiological cultures (including blood, airway secretion, urine, and cutaneous infection site if present), and imaging tests (chest X-ray and echocardiographic examination).

Empiric treatment should start as soon as microbiological cultures have been secured. Treatment should be adjusted based on the culture result. Severe sepsis cases may require pump exchange, in which case the pump and graft should also be sent to microbiological examination.

8.2.4.1.2. Aortic insufficiency

Lack of aortic valve opening is considered to be a key factor in the development of aortic valve insufficiency, aortic valve commissure fusion, and aortic root thrombosis.[31,32] These complications may be detrimental to ventricular recovery, reduce exercise tolerance, and may increase shear stress damage to the blood due to recirculation.[33] Despite difficulties in demonstrating improved survival, strategies to maintain aortic valve opening are still recommended.

8.2.4.1.3. Right heart failure

Right heart failure is a feared complication. Its presence increase mortality significantly and it is registered as the primary cause of death in 11% of patients.[26,34] The degree of preoperative right heart failure varies.[35] Preoperative evaluation of postoperative right heart failure risk is challenging, and new scoring systems and methods are continuously evaluated.[34] The development or progression of post-implantation right heart failure is multifactorial. The right ventricle has to accommodate for changes in preload, afterload, left ventricular morphology, and interventricular septum restriction. Temporary factors that aggravate acute onset right heart failure include increase pulmonary resistance after bypass, systemic inflammatory response syndrome, and blood transfusion. Most right ventricular dysfunctions have early onset though late onset is also reported and represents progression of intrinsic ventricular dysfunction. Treatment of right heart failure requires manipulation of contractility, preload and afterload to

unload the right ventricle while maintaining adequate circulation. As the modern LVAD is preload dependent, this may be challenging. Severe right heart failure may require the use of ECMO or right ventricular assist device (RVAD).

8.2.4.2. Hemostasis-related complications

LVAD patient anticoagulation regime has to balance between the risk of thrombosis and bleeding. This patient group suffers simultaneous increased bleeding and thrombosis risk, due to underlying pathophysiological derangement of different parts of the coagulation system. Hypercoagulability is secondary to surface activation of platelets and the coagulation cascade.[36] On the other hand, LVAD shear stress leads to the development of acquired von Willebrand syndrome.[37,38] This creates an especially challenging situation where anticoagulation has to be administered to a patient with underlying bleeding diathesis.

The hemostasis-related complications, especially pump thrombosis and thromboembolism, are at the center of this work and will be discussed in detail.

8.2.4.2.1. Bleeding

Epidemiology

Bleeding is the leading complication in the LVAD population, together with infection.[28] The rate of major bleeding in the early phase (< 90 days after device implantation) is 1.433 EPPY, and it falls to 0.347 EPPY at the late phase (> 90 days after device implantation).

Major bleedings can be further divided into gastrointestinal bleedings and non-gastrointestinal bleedings. Both gastrointestinal and non-gastrointestinal bleedings are common during the early phase with rates of 0.699 EPPY and 0.243 EPPY respectively. Bleeding early in the postoperative period is predominantly surgical bleeding. Non-gastrointestinal bleeding rate fall dramatically in the late phase (0.01 EPPY), while gastrointestinal bleeding rate show only

moderate fall (0.249 EPPY). Epidemiological studies have shown that gastrointestinal bleeding occurs in up to 60% of patients.[39,40]

Patients developing gastrointestinal bleeding are at risk for recurrent bleedings with increased hospital readmissions. They also have higher non-device-related infection rate compared with the rest of the LVAD population.[41]

Based on the Momentum study, gastrointestinal bleeding burden in the Heartmate 3 supported patients is lower than the control, but still considerable (0.31 EPPY vs. 0.49 EPPY respectively).[25]

Pathophysiology

The pathophysiology of bleeding in LVAD patients is multifactorial. Early bleeding is usually surgical. Contributing factors beyond the surgical procedure include initiation of anticoagulation and antiplatelet drugs, thrombocytopenia, and renal failure. Treatment on ECMO before device-implantation may contribute to coagulopathies and thrombocytopenia in a subgroup of patients. Factors that may contribute for the high late-phase bleeding rate include acquired von Willebrand syndrome, arteriovenous malformations/angiodysplasia, renal failure and platelets dysfunction.

Acquired von Willebrand syndrome and angiodysplasia

The von Willebrand factor is a multimeric glycoprotein which interact with different elements in the coagulation system. It has binding sites for factor VIII, platelet surfaces, and collagen. Its activity is highly dependent on the size of the multimers. When activated the multimers are broken by the proteolytic enzyme ADAMTS13 into smaller segment with procoagulant activity. It has also been shown that the von Willebrand factor has antiangiogenic properties. The von Willebrand factor also acts as a carrier protein for factor VIII and protects it from degradation.

Normally the von Willebrand factor is circulating in a coiled form. This protect its multimers from enzymatic cleavage by the proteolytic enzyme ADAMTS13 and maintain the procoagulant potential of the molecule until it is activated.[37,38,42]

It has been shown that sheer stress leads to the von Willebrand factor uncoiling, exposing it to the proteolytic activity of the ADAMTS13. The degradation of the von Willebrand multimers increases the risk of bleeding through several mechanisms. Primarily it has reduced activity in platelets binding and activation. Its down regulation also may lead to factor VIII deficiency. The reduced antiangiogenic activity leads to increased arteriovenous malformations especially in the gastrointestinal tract which are often a bleeding site in LVAD patients.

An increase in gastrointestinal bleeding episodes has been observed in patients using continuous flow LVAD compared with the previously used pulsatile devices, which support the notion that sheer stress plays a major role in the pathogenesis of gastrointestinal bleedings.[43-45]

Diagnosis

Evaluating the cause of bleeding in LVAD patients is demanding. Interpretation is difficult due to thrombocyte dysfunction, thrombocytopenia, low VWF:ristocetin cofactor activity, and the use of antiplatelet therapy.

Testing the von Willebrand factor (VWF) should include VWF:antigen test, VWF:ristocetin cofactor (RCo) activity, VWF:collagen binding activity, VWF:RCo/VWF:antigen ratio, and FVIII:C. VWF multimers should be quantified using agarose gel electrophoresis and densitometry.

Thromboelastography and thromboelastometry may be useful.

It is important to emphasize that despite the fact that most LVAD patients develop acquired von Willebrand disease, not all patients suffer bleeding episodes. This led to the development of the ‘two hit model’, which assumes that additional factors are needed. Additional factors may include infection (sepsis), gut hypoxia, or high levels of angiopoietin-2.[46]

Treatment

Early surgical bleeding should be treated accordingly by the surgeon.

Late gastrointestinal bleeding should be evaluated with upper and lower endoscopy to identify the source of bleeding. Active bleeding from a vascular malformation should be treated with clips or argon plasma coagulation. Often the source of bleeding cannot be identified.

When severe bleeding occurs an adjustment of anticoagulation should be considered. Vitamin K antagonist can be reversed using prothrombin complex, and heparin effect may be reversed using protamine sulphate. It is important to remember that LVAD patients with active gastrointestinal bleeding are also at high risk of pump thrombosis and stroke.[47]

Knowledge of the best medical treatment strategy is lacking, as no randomized controlled trial has been performed.

Desmopressin, which is used to treat bleeding episodes in patients with hereditary von Willebrand disease, has been used only sporadically in LVAD patients. Its limited use may be due to the fact that desmopressin is contraindicated in patients suffering from heart disease, and its limited effect due to high degradation of the VWF multimers.

Some suggests the use of plasma-derived VWF or FVIII/VWF concentrate. Though this strategy has been published in one case report, it is important to remember that the infused VWF will be exposed to the same pathophysiological conditions, and thus will be degraded at the same rate as the patients endogenous VWF, which increases the cost and reduces the utility of this strategy.

Omega-3 fatty acids have anti-inflammatory and antiangiogenic properties. Imamura et al has shown in a retrospective study that the use of 4 g/d omega-3 therapy led to one-year GI bleeding free rate of 97% compared with 73% in the control group.[48] This important finding should be confirmed in a controlled, randomized trial.

8.2.5. Pump thrombosis

LVAD thrombosis is a special case of pump malfunction in which a thrombus mass is located in any of the different parts of the pump and can potentially lead to circulatory failure.[49] Despite the fact that pump thrombosis is not the most common complication, its severe consequences, from life threatening circulatory collapse to the need for pump exchange, earn it special attention.

Epidemiology

Initial data suggested low incidence of pump thrombosis in both Heartmate II and HeartWare HVAD before 2013.[50-52] An unexplained increase in pump thrombosis was reported in 2014.[53-56] The pump thrombosis rates fell since but never returned to the levels before 2011. The rate of pump thrombosis varies somewhat over time even when based largely on the same database.[26,28] The current rates reported put early pump thrombosis rates at 0.183 EPPY (< 90 days after implantation) and late pump thrombosis rate at 0.087 EPPY (> 90 days after implantation).[28] Axial pumps have higher pump thrombosis rates than centrifugal pumps.

Pathophysiology

LVAD promotes blood clot formation via several mechanisms. First and foremost, the contact with the foreign material of the pump and the shear stress on blood elements activate the coagulation cascade leading to a hypercoagulability. Other factors that promote thrombus formation include areas of low flow, areas of turbulence, and heat spots (e.g. produced by mechanical bearings).

Three forms of pump thrombosis can be distinguished: pre-pump thrombosis (26%), intra-pump thrombosis (70%), and post-pump thrombosis (4%).[57] Pre-pump thrombosis is usually the consequence of thrombus mass, originating from the heart chambers, blocking the inflow cannula. Intra-pump thrombosis refers to thrombus inside the pump which interferes with the

impeller movement. It often does not lead to total flow obstruction until late in the process.[58] Post-pump thrombosis refers to thrombus mass at the outflow graft. Its main pathophysiological feature is flow obstruction.

Thrombus material in areas of high flow leads to high shear stress and hemolysis. Some patients may appear with hemoglobinuria as the presenting symptom which mandate immediate investigation to exclude pump thrombosis. On the other hand, massive thrombosis with flow occlusion may lead to minimal hemolysis due to limited flow through the pump.

Diagnosis

The diagnosis of pump thrombosis relies on several modalities including clinical assessment for heart failure signs, evidence of intravascular hemolysis, alteration in pump parameters, imaging modalities, and acoustic analysis of pump sounds. Systematic diagnostic algorithms have been published to optimize the accuracy and efficiency of the diagnostic process.[57]

Hemolysis parameters

Increase in hemolysis parameters is a sign of erythrocyte damage, and in the LVAD patient it should indicate intra-pump thrombosis with erythrocyte damage due to shear stress. Hemolytic parameters include high levels of lactate dehydrogenase (LDH), high free hemoglobin, low haptoglobin or increased reticulocytes. When free hemoglobin is high the presenting symptom can be hemoglobinuria which is considered an emergency.[54,59]

LDH values 2.5 times the high normal values are considered pathologic. Five-fold increase in LDH considered diagnostic for pump thrombosis with high sensitivity (100%) and specificity (92.5%).[60] There is no clear consensus regarding threshold values for other hemolysis parameters, though LVAD patients with increased hemolysis parameters suffer over eight-fold increase in adverse events.

Centrifugal pumps cause less hemolysis than axial pumps.[61] It is rare to see chronically elevated LDH in HeartWare HVAD. It appears late in the course, and usually pump power is already affected.[62]

Pump power and flow

Pre-pump thrombosis leads to acute obstruction of the inflow cannula. This will lead to low flow phenomenon which is presented by low power consumption and low flow estimation.[57] This process is usually acute with abrupt drop in flow.

Intra-pump thrombosis, as usually presented in the literature, refers to thrombus mass that either attaches to the impeller or block the spaces between the impeller and the pump house.[49] This may cause an increased power consumption and overestimation of flow.[54] Heartmate II demonstrates high power transitions relatively frequently that are not pump thrombosis induced.[61] An isolated elevation in pump power and flow should be interpreted with caution. HeartWare HVAD parameters are considered to be reliable.[63]

Post-pump thrombosis may lead to gradual reduction in flow which may help distinguishing it from the abrupt fall in flow due to pre-pump thrombosis.[54,57]

It is important to notice that these two potential complications, flow obstruction on one hand and intra-pump thrombosis on the other, affect pump parameters in opposite directions.[58] Concomitant flow obstruction and intra-pump thrombosis may be present with normal pump parameters.

Imaging modalities

'Ramp test' is a specialized ultrasound-based investigation which may assist in the diagnosis of flow obstruction. Ramp test is a systematic investigation of the relationship between pump speed and end-diastolic diameter. [60] Increasing pump speed will normally lead to unloading of

the left ventricle. Failure to unload the left ventricle is indicative of flow obstruction due to pump thrombosis. Aortic insufficiency may lead to abnormally high left ventricular preload and ramp test under these conditions should be interpreted with caution. [64]

Other relevant imaging modalities concentrate on visualization of position and patency of the inflow and outflow cannulas, and include angiography, CT/CT angiography, and echocardiography.

Acoustic spectral analysis

Acoustic spectral analysis is a method which can capture changes in the pump's vibration pattern under pump thrombosis. Auscultation is an integral part of the cardiological physical examination, and physicians noticed early that pump sounds change under pathological LVAD conditions, such as flow obstruction. Subjective analysis was quickly replaced with pump sound recording and systematic acoustic signal analysis. Already in 2006, Makino et al demonstrated in total artificial heart early detection of impending failure using artificial neuronal-network-based analysis of acoustic signals.[65] Shortly after Slaughter et al. developed and demonstrated a diagnostic method for the detection of pump damage before failure ensued in Heartmate XVE, a first generation pulsatile LVAD, using a systematic analysis of the acoustic signal (in the time domain) by a blinded interpreter.[66] This sprung enthusiasm in the field, leading to several publications between 2011 and 2013 supporting the feasibility and utility of sound-based monitoring of both Heartmate II and HeartWare HVAD.[67-70] Bartoli et al, in a review article from 2014, referred to harshening of pump sound, on auscultation, in response to flow occlusion, and suggested following changes in pump sound as a mean to test treatment efficacy.[59] Acoustic signal analysis in the time domain was supplemented by signal analysis in the frequency domain using Fast Fourier Transform (FFT).

Kaufmann et al, in 2014, suggested that the third harmonic amplitude (the amplitude of the frequency corresponding to pump speed x 3) is a sensitive and specific marker of pump

thrombosis in HeartWare HVAD.[58] This criterion was later included in the pump thrombosis diagnostic algorithm in the Berlin Heart Center.[57] Three other studies using HeartWare HVAD managed only partly to confirm these findings.[71-73] Feldman et al suggested an alternative method to diagnose pump thrombosis based on the number of peaks in the spectrogram.[72] Despite disagreement about the optimal signal analysis method, several studies demonstrated that pump thrombosis detection using acoustic spectral analysis was superior to the traditional pump power based method.[58,72,73]

There have been several other reports investigating acoustic spectral analysis for the diagnosis of pump thrombosis in Heartmate II.[74-78] The studies differed in design and signal analysis method. Different authors concluded that acoustic spectral analysis may assist in the diagnosis of pump thrombosis, but concrete diagnostic criteria seemed elusive.[77]

Attempts to expand the use of acoustic spectral analysis in the monitoring of LVAD is reflected in a study by Sunbom et al which evaluate iOS devices as a potential candidate for acoustic signal recording of pump sounds at home, comparing it with dedicated equipment.[77] The iOS recordings were inferior to the acoustic signal captured by the dedicated equipment.

In conclusion, there is a general agreement that acoustic spectral analysis is feasible and has the potential to improve the diagnosis of pump thrombosis.

New methods in the diagnosis of pump thrombosis

New approaches for the diagnosis of pump thrombosis are being continuously developed. This constant effort is an indication of the need for better diagnosis. One of the promising new approaches is monitoring circadian rhythm alterations in pump power. Another approach is utilizing machine learning to combine multiple currently used parameters to create a more efficacious algorithm.[73]

Both of these methods produce promising results, but their overall utility is still to be determined.

Pump thrombosis treatment

Pre-pump thrombosis

Pre-pump thrombosis used to be an indication for emergency pump exchange. Now a backwash maneuver is an acceptable first choice alternative, attempting to resolve this pathology without surgical intervention.[57] A carotid protection is placed, and the pump is stopped for 10 seconds. The thrombus washes back to the ventricle and exit through the aorta into the systemic circulation. This procedure should be done in a hybrid operating theater for the eventuality of maneuver failure or carotid protection failure. In case the backwash maneuver fails, and the pump is still occluded, one proceeds to pump exchange. In case the carotid protection device fails, one proceeds with thrombectomy. One should always do angiography to exclude peripheral arterial embolus in a critical site. It is of significance to this work that one not always finds the thrombus after backwash maneuver, as it suggests that silent thromboembolism is a plausible event under LVAD treatment.[57]

Intra-pump thrombosis

The treatment for pump thrombosis is either pump exchange or thrombolysis. Pump exchange is a major high-risk surgery, which is further complicated by an unstable patient. The prognosis of patients surviving pump exchange is worse than the prognosis after first time implantation. Thrombolysis also puts the patient at risk of severe complications, such as intracranial bleeding.[79] There are different treatment strategies, including intensifying anticoagulant therapy with heparin and GpIIb/IIIa inhibitors or the use of thrombolytics. Thrombolytics in turn can be administered systemically or intra-cardially. The use of tissue plasminogen activators (rTPA) increases the chance of resolving the thrombus to 50-70% in HVAD. There is however a considerable chance of recurrence, reducing success rate to 21%.[62,79,80]

Post-pump thrombosis

Occlusion of the outflow graft is a relatively rare but severe complication. Underlying causes can be thrombotic occlusion of the graft, kinking of the graft, or stenosis of the aortic anastomosis. Stenting is the treatment of choice. When the underlying problem is thrombotic occlusion, stenting should be done after a carotid protection device has been placed.

8.2.6. Thromboembolism (stroke and non-CNS thromboembolism)

Epidemiology

The rate of stroke in LVAD (not including the Heartmate 3 pump) patients range from eight to seventeen percent.[81-86] This has been shown to be greater than in the general advanced heart failure population.[86,87] It is slightly higher in the 'destination therapy' group compared with the 'bridge to transplantation' group, probably due to 'destination therapy' patients being sicker. Females are at two-fold increased risk for stroke than men.[88] The last data from the INTERMACS rapport asses stroke rates to be 0.294 EPPY in the early phase (< 90 days after implantation), with a subsequent fall to 0.094 EPPY in the late phase (> 90 days after implantation).[28]

Stroke may be ischemic or hemorrhagic. Some studies demonstrated similar incidence between the two groups, while other demonstrated overweight to one of the forms. This is most probably a consequence of the different cohorts.

Stroke is more common in centrifugal pumps than axial pumps during the first three months but show similar rates afterwards.[26] Mortality, however, is not reflecting this difference in stroke rates. These data do not include the new Heartmate 3 pump. The Momentum 3 study, comparing the new centrifugal Heartmate 3 pump with the axial Heartmate II pump, showed reduced rates of disabling stroke in Heartmate 3 (3.9%) compared with Heartmate II (5.9%).[25] A study by Chiang et al demonstrated one-year stroke-free survival of 76.8% for HeartWare HVAD

and 84.3% for Heartmate 3.[89] Stroke in Heartmate 3 tended to be more debilitating than in HeartWare HVAD (83% vs. 54% respectively).[89,90]

In patients supported with LVAD, stroke leads to 2-fold increase in mortality. Survival rates two years after stroke is 53.9% compared with 74.7% in stroke-free patients. A new study by Hariri et al demonstrated that each new stroke episode increases mortality by 42% in those alive at one year and by 24% in those alive at three years support.[29] Not surprisingly, mortality rate is especially increased after hemorrhagic stroke. Patients who survive stroke need long rehabilitation and report decreased quality of life.

Arterial non-CNS thromboembolism are diagnosed in much lower rates than stroke.[28] Early phase rates are at 0.024 EPPY (<90 days after implantation), and falls to 0.003 EPPY in the late phase (> 90 days after implantation).

Pathophysiology

LVAD patients demonstrate higher propensity to right-sided stroke.[84,86] This suggests that the thromboemboli originates from the pump outflow canula. Interestingly, this tendency to right sided stroke is associated with concomitant infection.

Other predisposing factors for stroke include hypertension, atrial fibrillation, aortic cross clamping during implantation, previous stroke history and diabetes mellitus.

Diagnosis

As for today, thromboembolic events leading to stroke are diagnosed based on their clinical consequences, e.g. cerebral ischemia. In a review article, Rich et al mention that the HeartWare HVAD pump may register thrombus ingestion with acute increase in power consumption.[80,91] There is no data provided regarding the relation between change in power consumption and the

size of thrombus. Nor is it integrated to any diagnostic guidelines. To the best of our knowledge, there is no current method systematically attempting to identify silent thromboemboli.

Treatment

Treatment today is either preventive or reactive after the damage has been done. Anticoagulation regimen suggestions were published in guidelines for mechanical circulatory support, by the International Society for Heart and Lung Transplantation (ISHLT) in 2013.[92] These guidelines were criticized in a clinical expert consensus document published in 2019 for being based on manufacturers recommendations and expert opinion, and not subjected to clinical trials.[93] This document, however, do not offer an alternative regime. As a rule, different centers have their own protocol for anticoagulation. Left atrial appendage closure has been shown to reduce the incidence of thromboembolic events.[94] Some centers supply anticoagulation with dipyridamol or clopidogrel in the case of previous TIA/stroke or pump thrombosis.

8.3. Accelerometer

An accelerometer sensor may be used as an alternative method to capture pump vibrations and can be utilized in a similar manner to acoustic signal in the diagnosis of pump thrombosis. It has, however, some potential benefits. The next section provides an overview over accelerometer technology and its current uses in medicine and other relevant fields.

8.3.1. Principle of action

An accelerometer is a sensor that measures proper acceleration. ‘Proper acceleration’ is zero at free fall and is affected by gravity in all other conditions. This is different from ‘coordinate

acceleration' which shows acceleration in relation to a certain coordinate system. Commercial devices often utilize piezoelectric plates or capacitive components to translate force into acceleration measurement. Piezoelectric plates produce electrical current when deformed by external force. This electrical current is proportional to the deforming force and after calibrated can estimate the ensuing acceleration.

By combining accelerometer sensors (e.g. piezoelectric plates) positioned in perpendicular planes, one can build three-axis accelerometer which provides acceleration components in a cartesian coordinate system.

8.3.2. Accelerometers in the industry

Accelerometers are found in a variety of devices, from highly advanced navigation and flight stabilizing systems to mundane smart phones. They may serve a critical role, where reliability is crucial, and malfunction may lead to severe consequences, or they may serve for entertainment purposes only. An example of accelerometer use, where reliability and durability are critical, is in the monitoring of rotating machinery in oil drilling using vibration analysis.

8.3.3. Accelerometers in medicine and cardiology

Accelerometers has been used extensively in medicine to measure physical activity in both adults and children.[95,96] As the technology developed, other uses for accelerometers emerged, for example, automatic evaluation of compression depth during heart lung resuscitation and evaluation of residual neuromuscular blockade under anesthesia.

Since 2005, our group has been investigating the use of accelerometers in cardiology. The use of accelerometers for the detection of myocardial ischemia has been investigated in porcine models and in clinical trials, and demonstrated high efficacy.[97-99] Krogh and other members of our group developed and validated algorithms for gravity compensation using the combination

of accelerometer and gyro-sensor. Gravity compensation transform proper acceleration to coordinate acceleration.[100,101]

Initially, professor Ole Jacob Elle, from our group, used a fast Fourier transform based approach to diagnose myocardial ischemia.[102] Most detection algorithms, at a later stage, were based on signals in the time domain (the raw acceleration, the integrated velocity, and the integrated displacement signals). Analyzing the signal in the time domain allows for analysis of the different phases of the cardiac cycle for specific signal changes. This is a more intuitive and hypothesis generating approach for a clinician as it is easily comparable to parameters obtained with echocardiography. Our group has been developing algorithms to monitor aortic valve opening and preload estimations based on accelerometer signals in healthy hearts.[103,104]

8.3.4. Vibration analysis and accelerometers

Vibration is a mechanical back and forth movement oscillating around a baseline. Although vibrations can have a random pattern, we normally use this term to describe a repetitive, regular phenomenon. When regular, vibrations can be accurately described based on their periodicity, magnitude, and phase (alignment in time). Using ‘fast Fourier transform’ a signal in the time domain can be represented in the frequency domain which is more suitable to characterize its vibration pattern. ‘Vibration analysis’ is a well-established method for describing a system based on its vibrating components.

8.4. Fast Fourier transform (FFT)

‘Fourier series’, named after the French mathematician Jean-Baptiste Joseph Fourier (1768–1830), is a mathematical theorem stating that an arbitrary continuous mathematical function can be described as a sum of trigonometric functions of different frequencies. This means that a mathematical function in the time domain has an alternative representation in the frequency

domain. A digital signal is a discrete mathematical function in the time domain. It matches points in time to corresponding values. The ‘discrete Fourier transform’ is an algorithm to calculate a signals alternative representation in the frequency domain. The ‘fast Fourier transform’ is a considerably more effective algorithm to calculate the ‘discrete Fourier transform’.

The significance, importance and strength of signal representation in the frequency domain is its simplicity and elegance in describing repeated phenomena. Each repeated phenomenon in a system is represented by its frequency, amplitude, and phase (alignment in time). A sine wave is the simplest example of repeated phenomenon. Sound waves are maybe the best known example of complex wave interaction. Acoustic spectral analysis using FFT is a standard method used in the analysis and modulation of sound.

8.4.1. Vibration analysis in LVAD

Mechanical devices with moving parts often have a characteristic vibration pattern. This vibration pattern often changes under malfunction. Vibrations can be easily recorded using an accelerometer. Transforming intervals of a signal from the time domain to the frequency domain, using FFT, and comparing them is a common method to detect and analyze changes in vibration pattern. Changes in the vibration pattern is often characteristic to the underlying problem.[105]

Accelerometer-based vibration analysis is not limited to fault detection. There are both patents and articles regarding accelerometer-based flowmeters in both water industry and oil industry.[106,107]

One central advantage of vibration analysis in general and accelerometer-based vibration analysis in particular is that the signal recording is non-invasive. It can be done from the surface of the apparatus, while monitoring moving part that are not available for direct inspection.

9. Aim of thesis

Despite continuous efforts and improvements in LVAD technology, its complication rates are still considerable. The focus of this thesis is the diagnosis of pump thrombosis and thromboembolism.

It is difficult to balance the combined hypercoagulability and bleeding diathesis, and despite improvement in pump design, these complications are unlikely to disappear in the near future. As for today, the majority of LVAD implantations are done under ‘destination therapy’ indication. This means that pump longevity is of utmost importance. For that reason, third generation LVADs are built for durability and reliability. As a consequence, monitoring is extremely limited. In order to decrease the hemostasis-related complications, any monitoring method for LVAD patients should preferably avoid breaching the blood barrier. Pump sound analysis is a relatively new method for pump monitoring that fulfills this requirement. Despite promising results in each individual study, the method has some disadvantages.

Acoustic signal recorded at the skin is muffled by surrounding tissues which reduce its quality. Some authors chose to average the signal to overcome this challenge. This reduces stochastic noise but prevents detection of acute intermittent signal changes.

Despite promising results in each individual study, challenges in reproducibility between investigation has been an issue. Signal acquisition depends on replicating the examination accurately, e.g. measuring at the exact same position on the chest wall. And even if succeeding in doing so, the underlying tissue acoustic characteristics may have changed from one investigation to the next (due to e.g. pleural effusion, lung consolidation, upper displacement of the diaphragm), which may affect the recordings.

The last disadvantage of acoustic spectral analysis is its intermittent nature, limiting its diagnostic benefits.

Accelerometer-based vibration analysis of LVAD may overcome these limitations. Signal acquisition by accelerometer attached to the pump house can produce a continuous, real-time, high-quality, standardized signal which is minimally affected by surrounding tissues.

The main aim of the study was to investigate the ability of a three-axis accelerometer, attached to HeartWare HVAD, to detect thromboembolic events and pump thrombosis using previously described vibration patterns, namely, third harmonic amplitude elevation.[58] Second, we aimed at finding new relevant vibration patterns to improve the diagnosis of thromboembolic events and pump thrombosis. Third, we aimed at using a semi-automatic method to demonstrate the feasibility of full automation in the future.

10. Hypotheses

We hypothesized that:

1. Accelerometer can detect thromboembolic events through acute changes in the third harmonic.
2. Acute changes in the third harmonic amplitude is more sensitive and specific than changes in pump power.
3. Accelerometer can detect prolonged changes in third harmonic indicative of pump thrombosis.
4. Accelerometer is superior to traditional use of pump power in the diagnosis of pump thrombosis.
5. Changes in the nonharmonic amplitudes can further improve the diagnosis of thromboembolic events and pump thrombosis.

11. Material and methods

We tested our hypotheses in two sets of experiments. The first set used an in vitro model. Three pilot experiments were used for model building, protocol testing, and signal analysis development. The pilot experiments were followed by three experiments for data collection. The second set of experiments used an in vivo model. Seven Noroc pigs were used for model building and protocol testing. They were followed by seven experiments using Noroc pigs (90 ± 9 kg). Signal analysis was based on the methods developed from the in vitro model.
We investigated thromboembolic events and pump thrombosis detection using the accelerometer third harmonic amplitude in vitro (Paper I) and in vivo (Paper II). The data collected in the in vivo and the in vitro experiments were used to investigate the additive value of changes in the accelerometer nonharmonic frequencies in the detection of thromboembolic events and pump thrombosis (Paper III).

11.1. Experimental models

The pump of choice in our models was HeartWare HVAD from the following three reasons. First, it was one of the two most implanted pumps on the market. Second, when we started our experiments, it was the only pump in which acoustic spectral analysis was taken into clinical use. And third, HeartWare HVAD was the pump of choice in our center, and we had experience and expertise with this pump.

11.1.1. In vitro experiments

11.1.1.1. In vitro model

A mock circulatory loop was built using an explanted HeartWare HVAD (HeartWare®, Medtronic, Minneapolis, Minnesota, USA) (figure 3). We used a simple circular configuration

connecting the pump and reservoir using polyvinyl chloride (PVC) tubes in series. The HVAD was suspended in an elastic chamber to mimic changing hemodynamic conditions. The afferent limb was supplemented with a side port which was used for the injection of thrombus material into the circuit, mimicking thromboembolic events. There were no contractile elements in the model. Clamps on the afferent and efferent limbs of the model were used to manipulate preload and afterload respectively.

A three-axis accelerometer (KXM52-1040, Kionix, Inc., NY, USA) was attached to the HVAD casing in order to record vibrations continually on a dedicated computer. The pressures in the afferent (preload) and efferent (afterload) limbs were monitored using a patient monitor (Siemens AG 7000C, Munich, Germany). Flow was measured using M3 ultrasonic flowmeter (Spectrum Medical, Cheltenham, England) on the efferent limb.

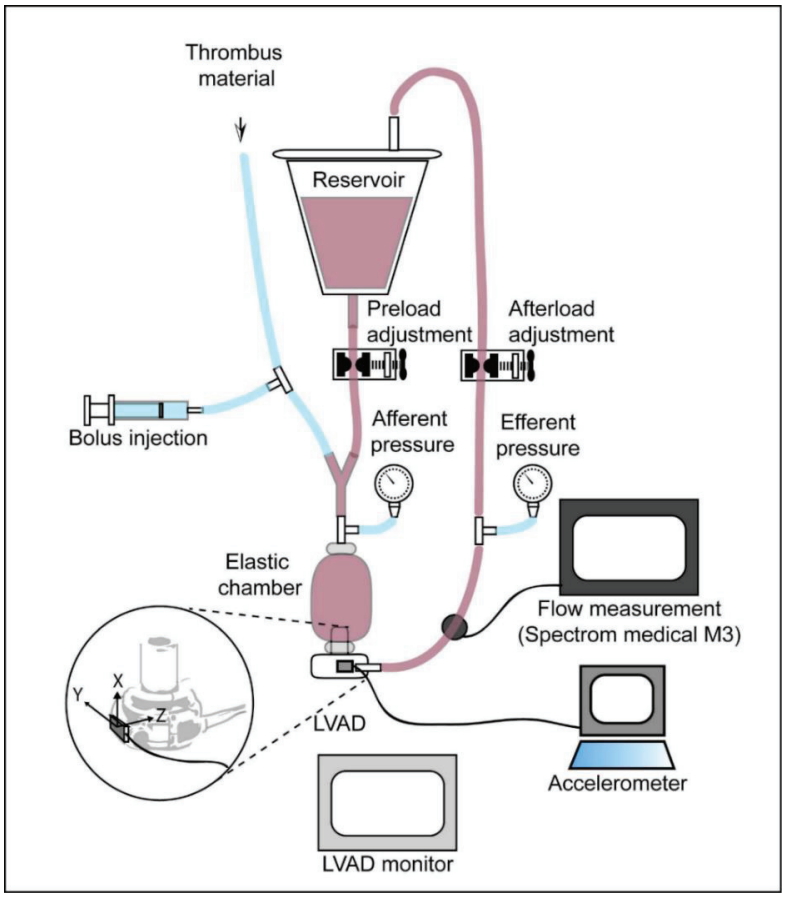

Figure 3. In vitro model. The elastic chamber simulated changing wall tension conditions. The accelerometer placement on the left ventricular assist device is highlighted with orientation of the measured three-dimensional accelerations in the X, Y, and Z directions.

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11.1.1.2. Experimental protocol

In describing the experimental protocols and results we use two terms, '**interventions'** and '**events'.**

- The term 'intervention' refers to a part of the experiment, composed of a series of manipulations of a concrete parameter. The parameters could be one of the following: pump speed, afterload, preload, saline bolus injection, or thromboembolism. Each individual change of the parameter of interest was referred to as an 'event', which means that each intervention was composed of a number of events.
- The term 'event' refers to a concrete manipulation (change) of the parameter of interest. For each event we documented its effect on the accelerometer signal, HVAD power consumption, pump speed, preload, and afterload.

The interventions were grouped into thromboembolic interventions and control interventions. Control interventions included pump speed change, afterload increase, preload decrease and saline bolus injections. We intended to confirm a low amplitude of third harmonic during the control interventions, so they were performed before the thromboembolic interventions. The order of the control interventions was randomized.

The pump speed change intervention included pump speeds between 2400 and 3200 rpm (with 200 rpm intervals) in randomized order. Both preload decrease and afterload increase targeted flow reduction of 20% to 80% from baseline (with 20% intervals) in randomized order. The aim of the saline bolus injection was to test whether it led to signal changes, as saline bolus injection was part of the procedure for thrombus introduction into the mock circulatory loop.

Thromboembolic interventions included two series of five thrombus injections into the mock circulatory loop. Thrombus size varied between 0.2 ml and 1 ml (with 0.2 ml intervals). The

order of thrombus size was randomized. A full description including a schematic illustration of the interventions can be seen in figure 4.

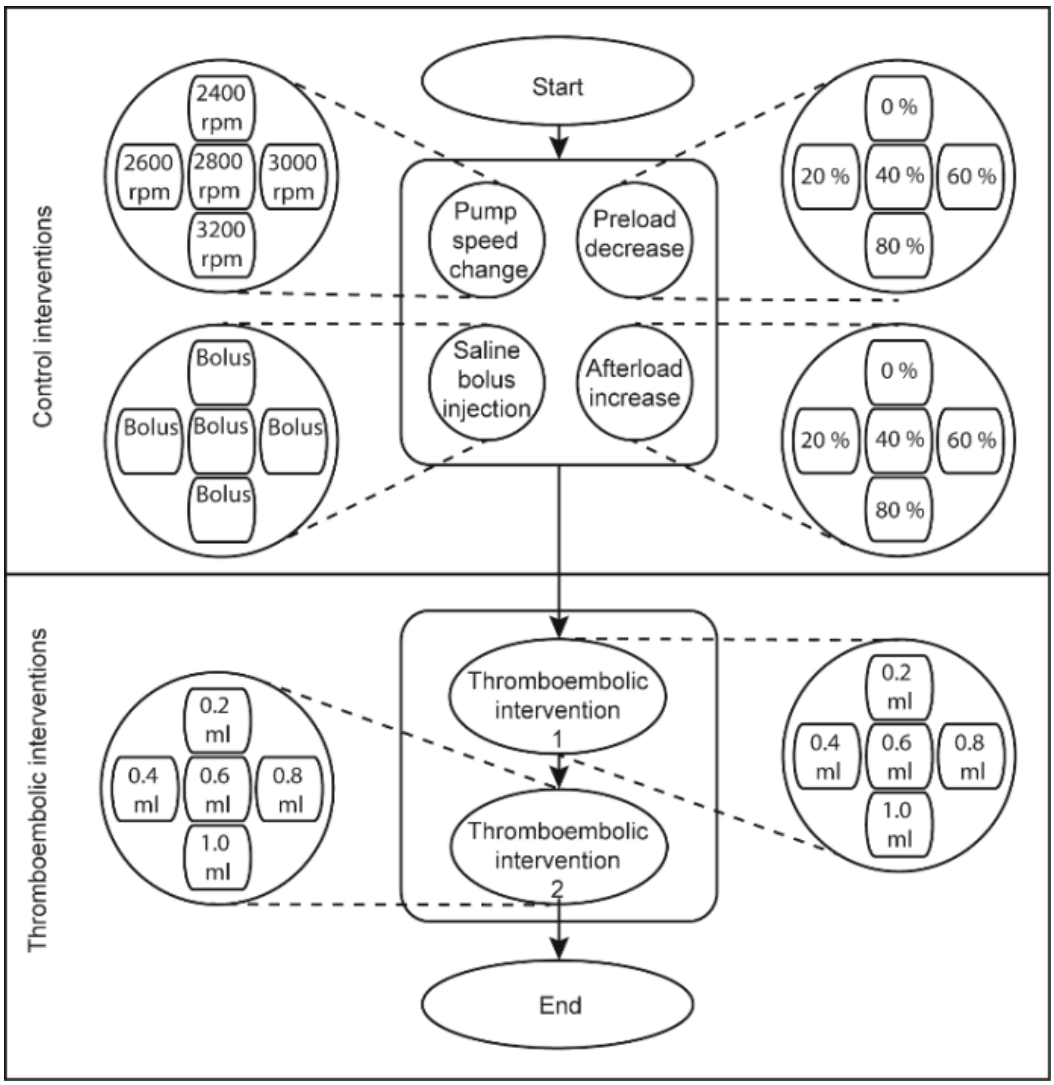

Figure 4. In vitro protocol. Interventions are divided into two main groups: control interventions and thromboembolic interventions. The control intervention order was randomized. Each intervention was composed of a series of events as shown by the expanded bubbles. The order of the events within each intervention was randomized. Pre- and afterload manipulations were achieved by flow reduction of a certain percent from the baseline flow and indicated as percentages in bubbles for these interventions. Thromboembolic events differed from each other by the thrombus volume injected into the model as indicated in the bubbles for these interventions.

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11.1.2. In vivo experiment

Institutional approval was obtained (13/5,551), and the experiments were carried out in accordance with Norwegian National Legislation on animal experimentation.

11.1.2.1. In vivo model

A HeartWare HVAD (HeartWare®, Medtronic, Minneapolis, Minnesota, USA) was implanted in seven Noroc pigs (90±9 kg) under cardiopulmonary bypass (figure 5). A three-axis accelerometer (KXM52-1040; Kionix, Inc, Ithaca, NY) was attached to the HVAD's outer casing. The pump graft was supplemented with 5 cm long polyvinyl chloride (PVC) tube with side port. This was used for post-pump pressure measurements and graft flow measurements. Flow was measured using M3 ultrasonic flowmeter (Spectrum Medical, Cheltenham, England). The pump graft was supplemented with clamping system distal to the pressure measurement point. The left atrium was cannulated to allow thrombus injection into the left heart. Heart failure was established by ligation of the diagonal branches of the left anterior descending artery, aiming at a minimum HVAD to cardiac output ratio of 0.5.

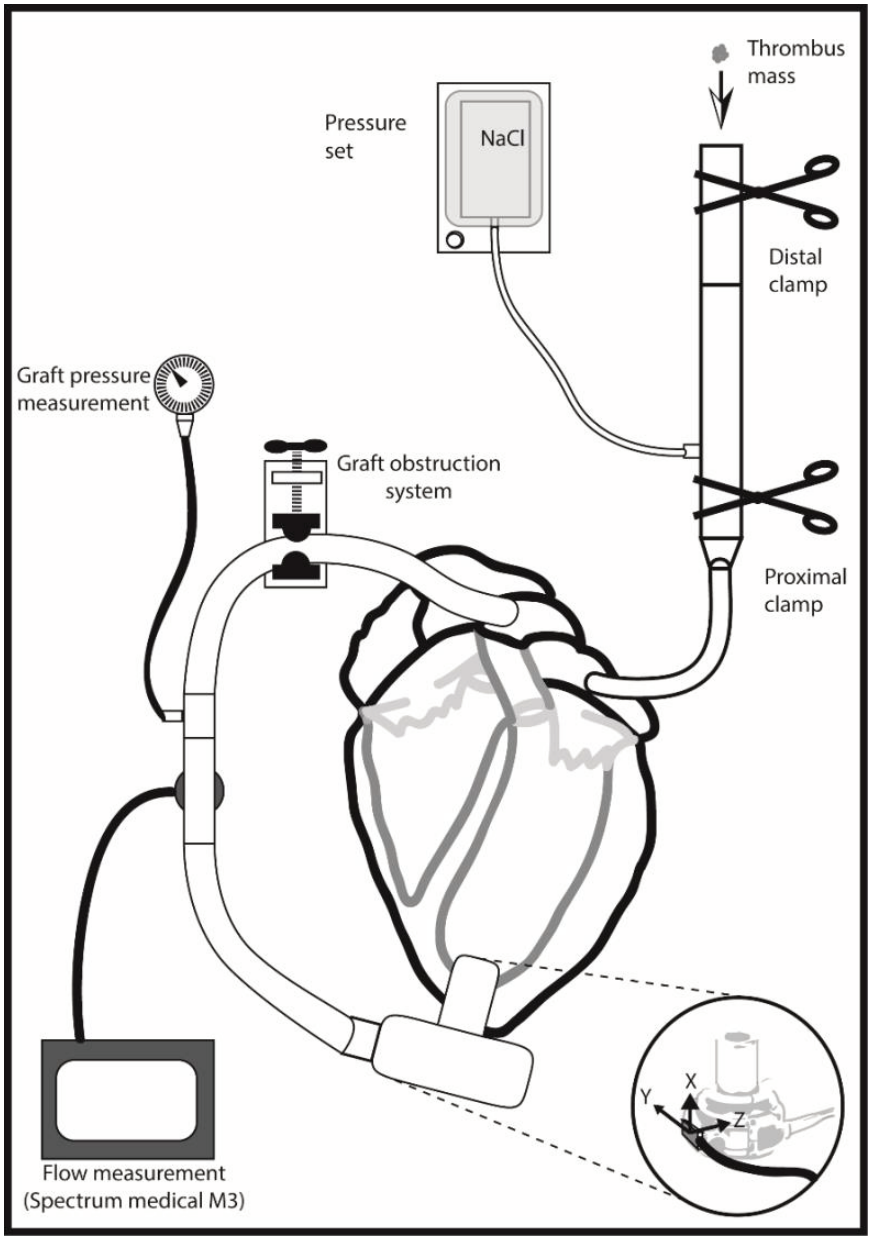

Figure 5. In vivo model. The HeartWare HVAD was implanted in the left ventricle with a graft (20 cm long) connecting the HVAD to the aorta, equipped with ultrasonic flow meter, pressure set, and graft obstruction system. A cannula (20 Fr) was introduced into the left atrium for thrombus injection. During the thromboembolic interventions, a thrombus was placed into the cannula and flushed into the left atrium using a saline bolus injection. A three-axes accelerometer was attached to the HVAD housing as shown in the circular figure.

11.1.2.2. Experimental protocol

The interventions were divided into thromboembolic interventions and control interventions (figure 6). Control interventions included pump speed change, afterload increase, and saline bolus injections. We did not perform preload manipulation due to the risk for hemodynamic instability. We intended to confirm a low amplitude of third harmonic during the control interventions, so they were performed before the thromboembolic intervention. The order of the control interventions was pump speed change, followed by graft obstruction, and finishing with saline bolus injections.

The pump speed change events included pump speeds of 1800 rpm, 2200 rpm, and 2600 rpm in this order. Afterload increase targeted flow reduction of 0%, 50%, 25%, 50%, and 0% from baseline flow, in this order. The aim of the saline bolus injection was to test whether it led to signal changes, as it was part of the procedure for thrombus introduction into the left atrium. Thromboembolic events included a series of up to 10 thrombus injections, depending on the animal hemodynamic stability and pump function. Thrombus size varied between 0.3 ml and 0.4 ml. A full description including a schematic illustration of the interventions can be seen in figure 6.

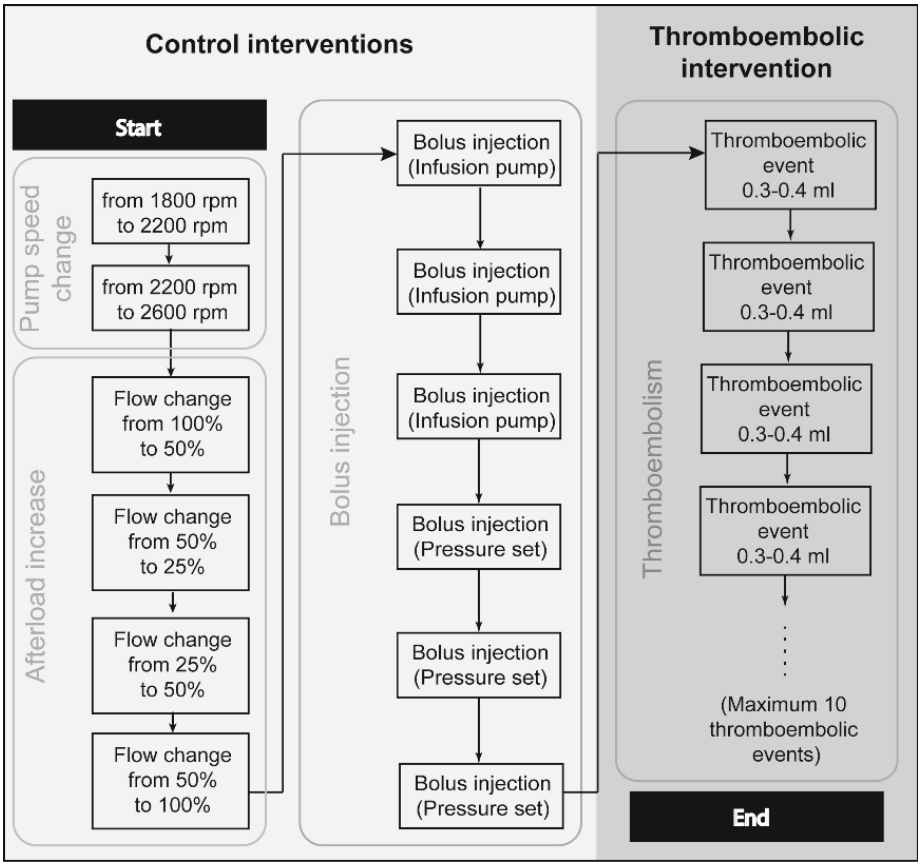

Figure 6. In vivo protocol. The experimental protocol was divided into control interventions followed by a thromboembolic intervention. The control interventions included pump speed change, graft obstruction to a target flow reduction as measured by ultrasonic flowmeter, and bolus injection using either infusion pump (given over 1 min) or pressure set (10 s long injection using pressure set pressurized to 300 mm Hg).

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11.2. Thrombus material preparation

Thrombus material was used in both the in vitro and the in vivo experiments. The preparation procedure was similar. Non-heparinized blood was collected in 20x10 ml clot activator tubes and centrifugated for 15 minutes in 2500 rpm at 4˚C. The blood was then left to coagulate for at least one hour.

11.3. Accelerometer signal analysis

The three-axis accelerometer signals were recorded on a dedicated computer with sampling rate of 500 samples/s. It produced three acceleration signals corresponding to the accelerometer axes X, Y, and Z (Gx, Gy, and Gz). Further signal analysis was performed in Matlab (R2013b, MathWorks Inc., Natick, MA). The individual signals were first analyzed using sliding window fast Fourier transform (Matlab, Signal Processing Toolbox, spectrogram function utilizing Hamming window) with windows of approximately 8 seconds (2^{12} samples/500 samples/s = 4096/500 s ≈ 8.192 s) and 75% overlap between windows. This was done in order to reduce cardiac cycle related variation in the signal. The amplitude was calculated using the 'abs' function and the phase was calculated using the 'angle' function.

11.3.1. The components of the normal LVAD spectrogram

The non-pathological LVAD spectrogram can be divided into the harmonic frequencies, including the fundamental frequency corresponding to pump speed and its harmonics, and the nonharmonic region including all the other frequencies. A harmonic frequency is the fundamental harmonic multiplied by an integer.

The nonharmonic region generally demonstrated homogenous areas of low amplitude with two exceptions.

1. High amplitude in the low frequencies in the in vivo experiment due to effect of heart motion. This was confirmed by visual comparison of spectrograms from the in vitro and in vivo experiments demonstrating high amplitude in low frequencies only in the in vivo model (figure 7).

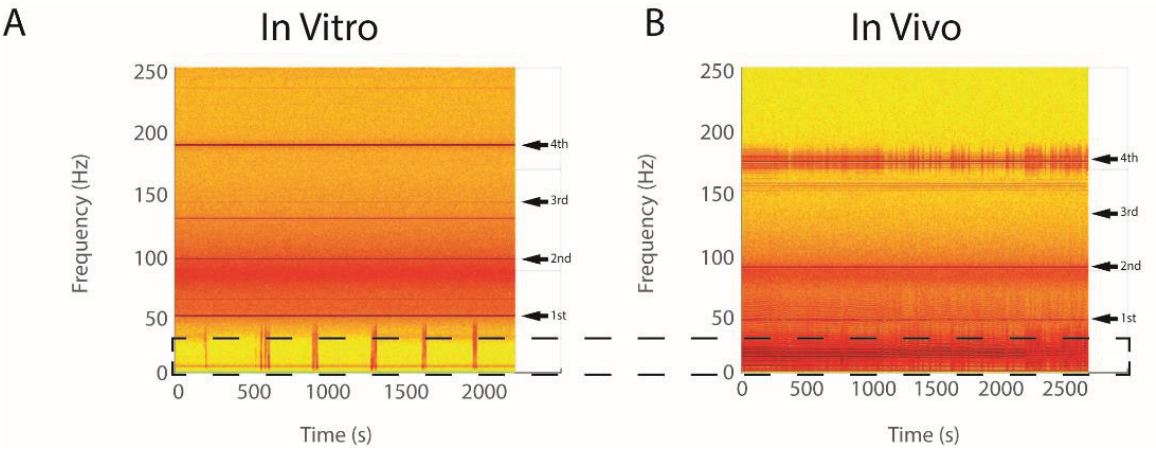

Figure 7. Spectrogram during saline bolus injections in vitro vs. in vivo. The amplitude is color coded (lowest: green; intermediate: yellow; high: red). The dashed line frames the frequencies between 0 Hz and 28 Hz (0-1700 rpm). The black arrows point at the 1st to 4th harmonic frequencies. **(A)** In vitro spectrogram demonstrating low amplitude in the lower frequencies region (framed). **(B)** In vivo spectrogram demonstrating distinct high amplitude in the lower frequencies region (framed).

2. High amplitude of uncertain origin, possibly from other vibration sources, spectral leakage, or resonance in the model.

11.3.2. The harmonic frequencies

The amplitude of the harmonic frequencies, including the third harmonic, were read directly from the spectrogram based on pump speed for each sliding window entry. This produced a signal in the time domain with sampling rate of approximately 30 samples/min (window size 4096 with 75% overlapping) for each harmonic frequency.

11.3.3. The nonharmonic frequencies

In order to evaluate the high amplitude areas in the nonharmonic region related to thromboembolic events we needed to mask the harmonic frequencies, heart motion related

phenomenon, and signal changes of other origins (external vibration sources, spectral leakage, or resonance in the model).

The amplitude of the low frequencies is highly affected by heart motion (figure 7) and all frequencies below 28 Hz (~1700 rpm) were directly masked.

Both the harmonic frequencies and high amplitude frequencies from other origin demonstrate a stable phase over time. We took advantage of that phenomenon and built a phase filter to mask these changes.

11.3.3.1. Phase filter

11.3.3.1.1. Phase Terminology

- **Organized phase –** A repeated phenomenon in the time domain is well described by its frequency, amplitude, and phase (figure 8A). This means that for a repeated phenomenon of frequency f, two FFT based periodograms, at time t1 and t2, will demonstrate a predictable shift in phase depending on the time interval between t1 and t2. In the case of a sliding window FFT the phase difference between two adjacent windows will be constant (figure 8B).
- **Disorganized phase** – When there is no repeated phenomenon in a certain frequency, the phase assigned to it will be random. In the case of sliding window FFT the phase difference between adjacent window is unpredictable.
- **Phase shift** – When a repeated phenomenon is disrupted (e.g. thromboembolism passing through an LVAD) the vibration pattern is disrupted. After the disturbance ceases (e.g. thromboembolism evacuated the pump), vibrations resume their previous pattern. The alignment in time, however, may be different than the previous alignment. In this case the signal demonstrates a ‘phase shift’ (figure 8C).

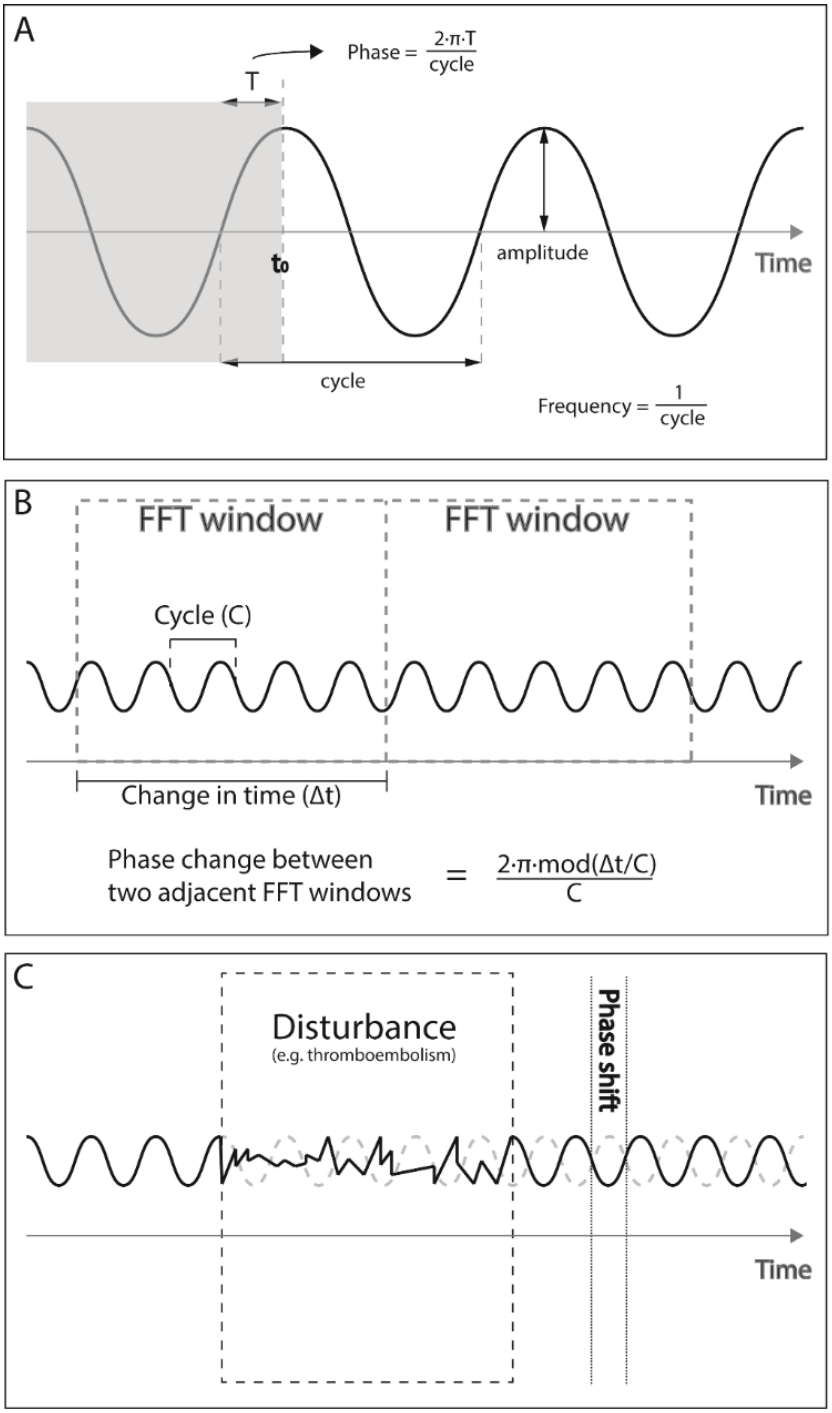

Figure 8. Phase terminology illustration. **(A)** A sinus wave is completely described by its frequency, amplitude and phase. **(B)** The change in phase as a function of change in time. **(C)** Phase shift after vibration pattern disruption.

11.3.3.1.2. Filter

Some phenomena are highly regular and demonstrate organized phase on the spectrogram. Based on data from the pilot in vitro experiments, we suspected that the impeller rotation led to organized phase in the fundamental frequency corresponding to pump speed and its second and fourth harmonic. The third harmonic also demonstrated an organized phase when its amplitude was above the background values (figure 9).

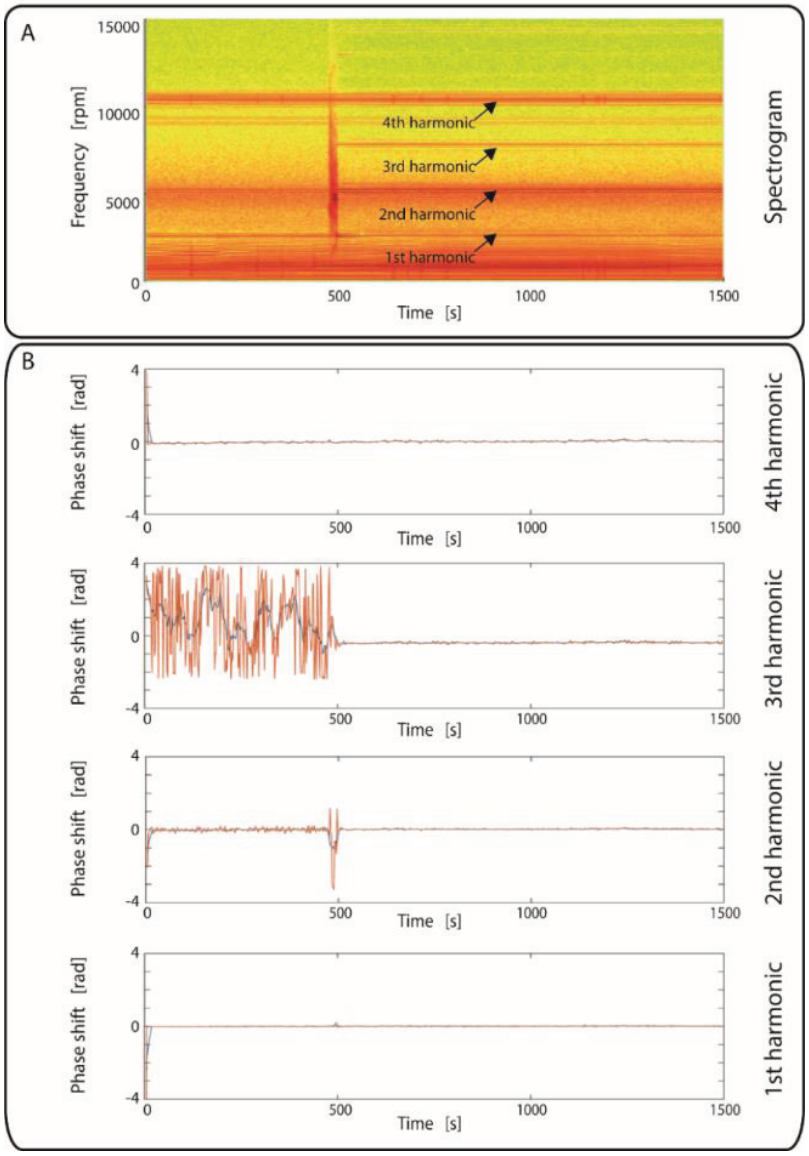

Figure 9. Phase shift under thromboembolic event. **(A)** Spectrogram. The amplitude is color coded (lowest: green; intermediate: yellow; high: red). A thromboembolic event led to a temporary global signal change affecting a continuous range of frequencies including the third harmonic. These changes subside into isolated third harmonic amplitude increase. **(B)** The phase shift data of the harmonic frequencies. As shown the first and second harmonic undergo phase shift 500 seconds into the recordings. The third harmonic demonstrates noise level signal on the spectrogram and disorganized phase before the thromboembolic event. This changes into organized phase as the amplitude increase about noise level after the thromboembolic event.

The nonharmonic amplitude normally does not demonstrate organized phase. An exception is frequencies in the nonharmonic range which represents regular vibration of external (non-pump related) uncertain origin (figure 10). A filter, taking advantage of this phenomenon, was used to mask all areas with organized phase. Practically, we chose to mask all areas which demonstrated locally low standard deviation of phase (Std(phase)< 0.5) (figure 10).
This led to over-filtering, but the remaining signal was sufficient for our purpose.

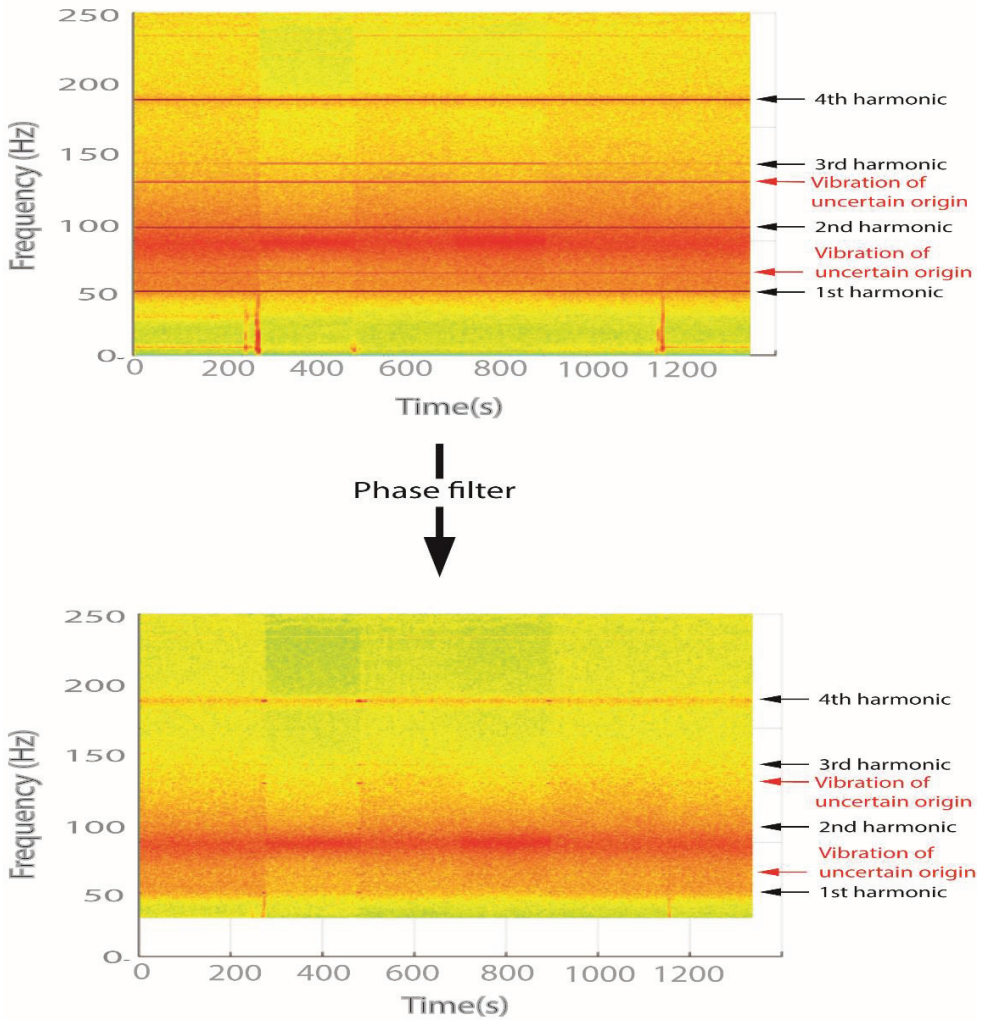

Figure 10. Phase filter example. Both the harmonic (black arrows) and vibrations of uncertain origin (red arrows) are filtered by the phase filter. The upper pannel is the non-masked spectrogram. The lower pannel is the masked spectrogram. The black and red arrows point to elements that were removed by the phase shift masking algorithm.

11.3.3.2. Nonharmonic signal

In order to quantify these signal changes, we used the previously described phase filter. As we were interested in the high amplitude areas of the nonharmonic region, we then masked all the spectrogram areas below the spectrogram average amplitude.

We calculated the average amplitude of the non-masked regions of the spectrogram for each sliding window entry. This produced a signal in the time domain with sampling rate of approximately 30 samples/min for the high amplitude nonharmonic regions of the spectrogram (figure 11).

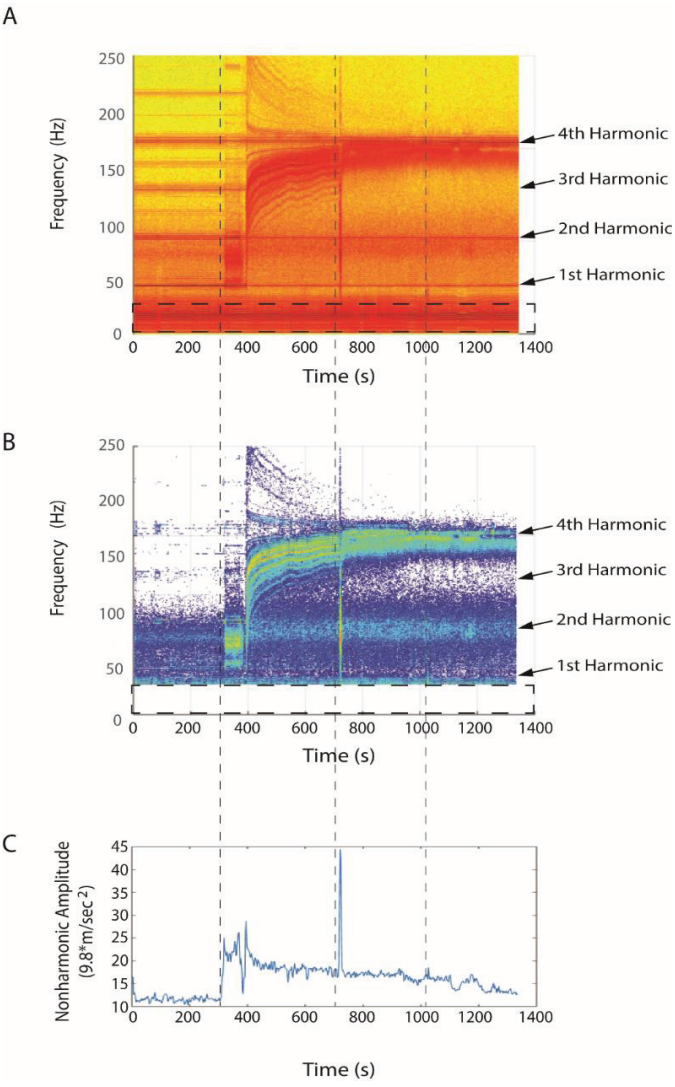

Figure 11. Example of signal analysis (in vivo) with extraction and quantification of accelerometer nonharmonic amplitude. The dashed vertical lines designate a thromboembolic event time. **(A)** The unmasked spectrogram. **(B)** The masked spectrogram. The low frequencies (below 28 Hz) and areas with organized phase including the harmonic frequencies are masked. The low component (below the spectrogram average values) is also masked. **(C)** The nonharmonic signal is constructed based on the masked spectrogram (B) as the average value of each sliding window.

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11.3.4. Event measurement

For each event, we noted the baseline third harmonic amplitude 20 seconds prior to the event. Each event was followed by 120 seconds hands-off period.

For paper I and paper II, we registered the maximum absolute deflection of the third harmonic amplitude within these 120 seconds and its exact timing. The third harmonic amplitude at the end of this two minutes hands-off period was considered to be a steady state value.

For paper III we registered the maximum absolute deflection of the nonharmonic amplitude within these 120 seconds and its exact timing. The last 60 seconds of the 120 seconds hands off period were considered to be steady state. The nonharmonic steady state value was presented as median and inter-quartile range (figure 12).

For each event, we calculated the amplitude and the amplitude change from baseline at the maximal deflection point and at steady state.

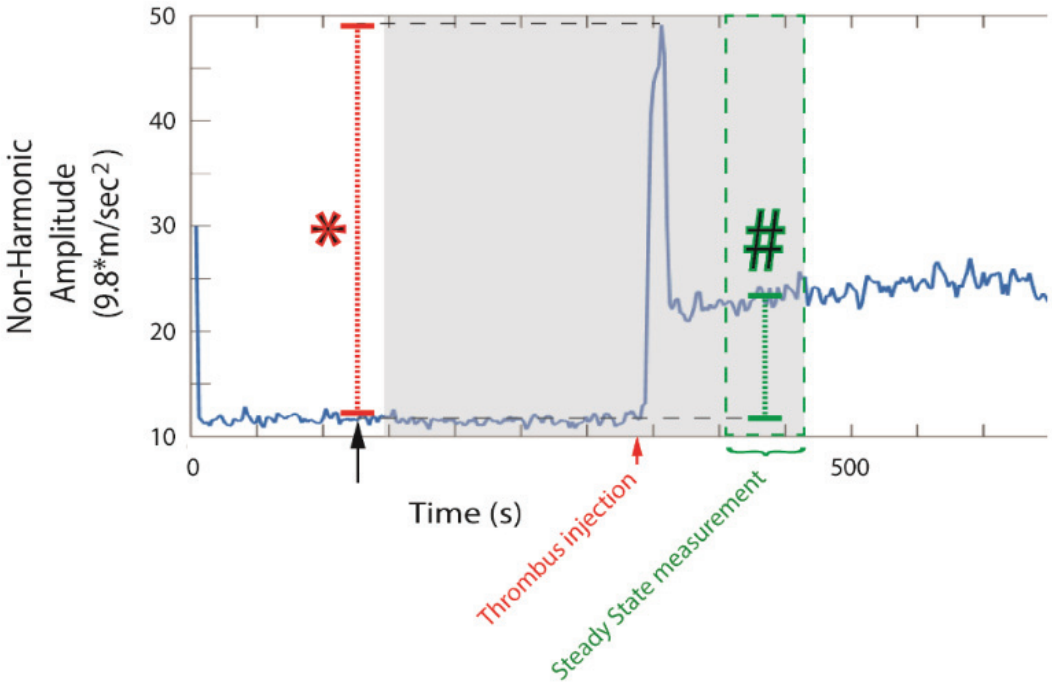

Figure 12. Event measurement algorithm. The nonharmonic signal illustrating a thromboembolic event. The gray rectangle represents the event period from start to end. The reference value at 20 seconds prior to event start (black arrow) is used to find and calculate the maximal acute change in the signal ('*' red dotted line). The time between the reference value and thrombus injection is a hands-on period in preparation for the thrombus injection. The last 60 seconds of the event were defined as the steady state period (green dashed rectangle). We calculated the median and interquartile range over the steady-state period and calculated the steady-state deflection in the signal (# green dotted line).

11.4. Statistical methods

Animals that did not survive to thrombus injections were excluded from the statistical analysis. Statistical analysis was conducted using SPSS v.21 (IBM, Armonk, NY). The values of the third harmonic, changes in third harmonic, change in the nonharmonic amplitude, pump power, and change in pump power parameters were reported as median and interquartile range (IQR). We used Mann-Whitney U test to compare the difference between the thromboembolic interventions

and the control interventions. A p-value ≤0.05 was considered statistically significant. Corrections of p-values for multiple testing were not made.

Receiver operating characteristics (ROC) analysis was used to estimate the sensitivity and specificity of the third harmonic amplitude, changes in third harmonic amplitude, change in the nonharmonic amplitude, pump power consumption, and change in pump power consumption parameters (paper I-III). Threshold values assuring specificity of one were calculated, based on the acute response to thromboembolic events, for both third harmonic change and nonharmonic amplitude change (paper III). Based on these threshold values the acute effect and steady state effect of thromboembolic events were divided into 4 groups:

1. Isolated nonharmonic amplitude change.
2. Isolated third harmonic amplitude change.
3. Concomitant nonharmonic amplitude and third harmonic amplitude change.
4. Nonharmonic amplitude or third harmonic amplitude change did not reach threshold levels.

The positive predictive values in the acute phase and steady state were calculated for third harmonic change, nonharmonic signal change, and the combined method using both third harmonic and/or nonharmonic amplitude change in order to illustrate the additive value of the nonharmonic signal (paper III).

12. Summary of the results

Paper I

Accelerometer Detects Pump Thrombosis and Thromboembolic Events in an In vitro HVAD Circuit. *ASAIO journal (American Society for Artificial Internal Organs : 1992) 2018;64:601-9.*[108]

This proof-of-concept paper investigated the feasibility of thromboembolic events and pump thrombosis detection in vitro, using the third harmonic amplitude and change in third harmonic amplitude as parameters.

The third harmonic frequency maintained low amplitude during all control interventions and was significantly higher in the thromboembolic intervention group ($p < 0.01$) (hypothesis 1) (figure 13A). During the thromboembolic intervention, 92% (23 of 25) of the thromboembolic events led to acute change in the amplitude of the third harmonic (hypothesis 1) whereas 64% (16 of 25) led to prolonged change in this parameter (hypothesis 3).

Qualitatively all accelerometer axes demonstrated similar signal changes. Sensitivity and specificity for detecting thromboembolic events were calculated in all axes for both third harmonic amplitude and the change in third harmonic amplitude. The sensitivity and specificity of the change in third harmonic amplitude was superior to the third harmonic amplitude in Gx and Gz, while it was the opposite for Gy. The best performing axis was the Z axis (parallel with the impeller plane), with the change in third harmonic amplitude parameter demonstrating area under the curve of 0.966 on the ROC analysis and sensitivity and specificity of 0.92 and 0.94 respectively (hypothesis 1) (figure 13C).

Both the HVAD power and the change in HVAD power performed poorly compared to the accelerometer (hypothesis 2). The ROC analysis showed area under the curve of 0.66 for the

HVAD power and 0.304 for the change in HVAD power (figure 13C). The optimal sensitivity and specificity pair for HVAD power parameter was 0.72 and 0.58 respectively.

The median change in pump power per thromboembolic event was 0.2 W (IQR 0.3), which is below the current diagnostic criteria for pump thrombosis (figure 13B), while the average change in third harmonic exceeded the calculated diagnostic threshold in 64% of the events, indicative of pump thrombosis (hypothesis 4).

This paper demonstrated the feasibility of accelerometer-based detection of thromboembolic events and pump thrombosis and its potential benefit in the diagnosis of these conditions compared with currently used methods.

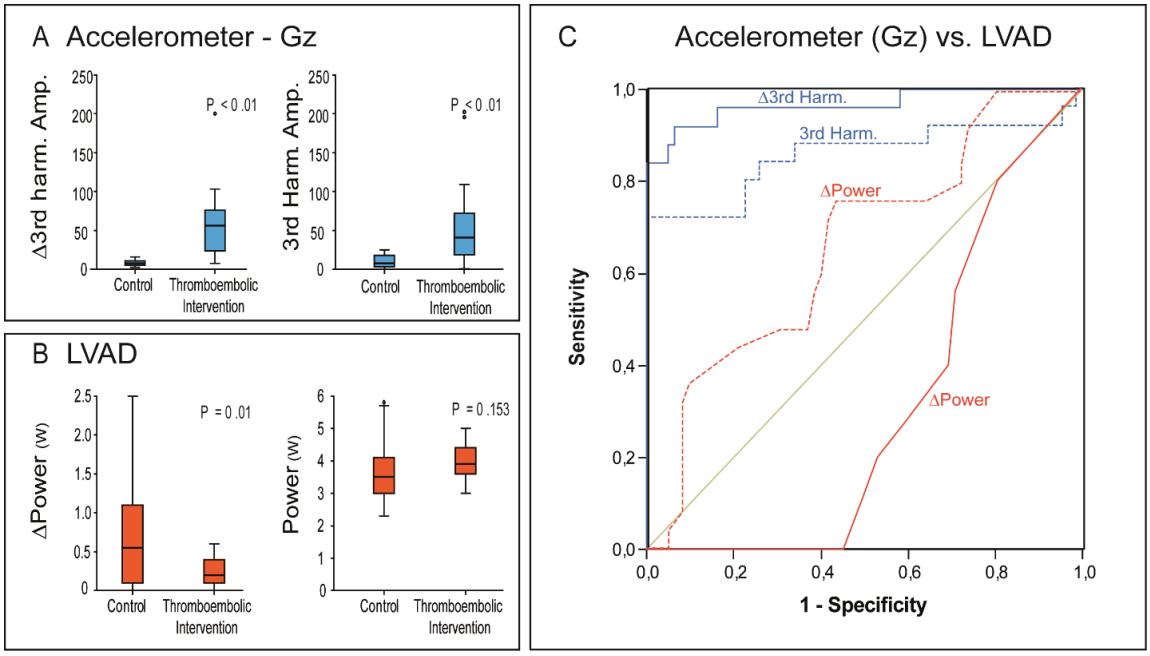

Figure 13. Statistical analysis in vitro data. **(A)** Block diagram of the third harmonic amplitude change (left panel) and third harmonic amplitude (right panel) in the accelerometer Gz axis. **(B)** Block diagram of the LVAD power consumption change (left panel) and LVAD power consumption (right panel). **(C)** ROC diagram of the accelerometer third harmonic amplitude and its change (blue colors) and HVAD power consumption (red colors). All values obtained at the point of maximal signal change during the 2-minute "hands-off" period.

Paper II

Detection of Thromboembolic Events and Pump Thrombosis in HeartWare HVAD Using Accelerometer in a Porcine Model. *ASAIO journal (American Society for Artificial Internal Organs) 2020;66:38-48.*[109]

This paper is directly related to paper I, and aimed at confirming in vitro findings in a relevant in vivo (porcine) model, namely the detection of thromboembolic events and pump thrombosis using the third harmonic amplitude change as parameter.

The target of 50% HVAD flow was achieved in all experiments with average HVAD flow to cardiac output ratio of 0.66. Since thromboembolism could pass either through the HVAD or through the aortic valve, we expected 21-25 of 35 thromboemboli to pass through the HVAD (35 thromboembolic events; 0.66 HVAD flow ratio; 10% error margin). Out of 35 thromboembolic events, 26 led to acute increase in third harmonic amplitude (74%). Thromboembolic events typically led to temporary changes in a continuous range of frequencies including the third harmonic, followed by either return to baseline or prolonged signal changes.

The change in third harmonic amplitude was higher in the thromboembolic intervention group compared to the control intervention group ($p < 0.01$), as seen in figure 14B, left panel (hypothesis 1). Though statistically significant, the difference in the pump power consumption between the two groups was much smaller ($p < 0.01$), as can be seen in figure 14B middle panel (hypothesis 2). The change in pump power consumption between the two groups was not statistically significant, as can be seen in figure 14B right panel.

All the accelerometer axes demonstrated similar qualitative information. We included all thromboembolic events in our statistical analysis even when presumed to pass through the aortic valve (n=35). The superior axis in the ROC analysis was the Z axis, with area under the curve of 0.954 and sensitivity and specificity of 0.74 and 1 respectively, for threshold value of

21.56 (figure 14A). The ROC analysis of the pump power showed area under the curve of 0.759 with sensitivity of 0.4 and specificity of 1 using cutoff value of 3.15 (hypothesis 2) (figure 14A). Of the thromboembolic events that lead to acute signal changes, 53% (14 of 26) lead to persistent third harmonic amplitude increase (hypothesis 3).

The median pump power under the thromboembolic interventions was 3.0 W (IQR: 2.9–3.3), and the median change in pump power was 0.1 W (IQR: 0–0.2), which are below the diagnostic threshold used in the diagnosis of pump thrombosis (hypothesis 4).

This paper replicated the findings made in paper 1 in a relevant in vivo model, confirming the feasibility of accelerometer-based detection of thromboembolic events and pump thrombosis, and demonstrating its potential benefit compared with conventional pump power monitoring.

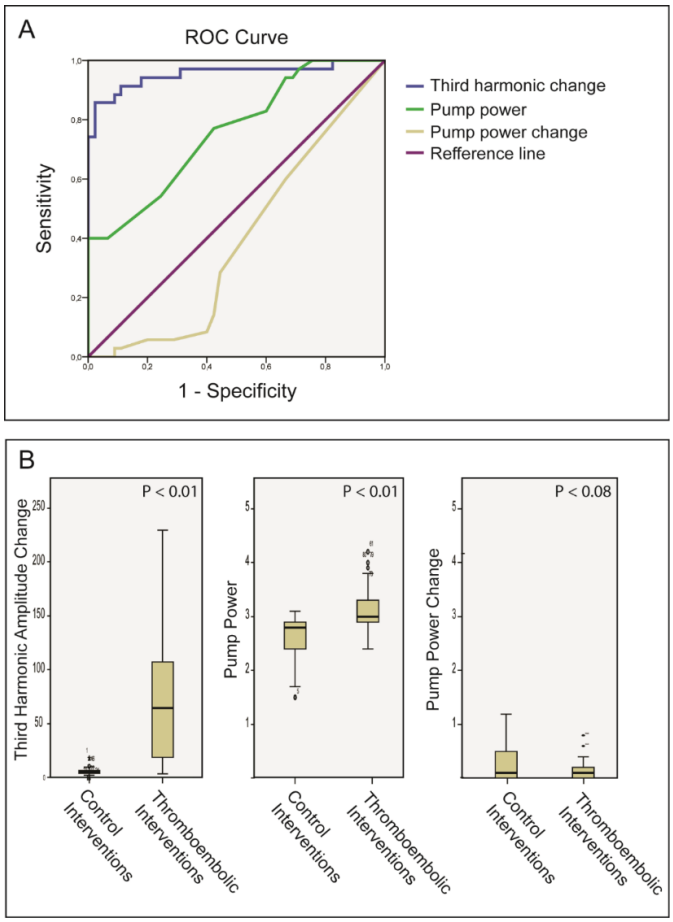

Figure 14. Thromboembolic event detection: 3rd harmonic amplitude vs. pump power. **(A)** Receiver operating characteristic curve of the third harmonic change in the accelerometer z-axis (blue), pump power (green), and pump power change (beige). **(B)** Box plots for the third harmonic change, the pump power, and the pump power change.

From: 'Detection of Thromboembolic Events and Pump Thrombosis in HeartWare HVAD Using Accelerometer in a Porcine Model.', by Itai Schalit et al. ASAIO Journal. Copyright 2020 by ASAIO Journal. Reprinted with permision.

Paper III

Improved Detection Of Thromboembolic Complications In Left Ventricular Assist Device By Novel Accelerometer-Based Analysis. ASAIO journal (American Society for Artificial Internal Organs) 2022;Publish Ahead of Print.[110]

In this study we tested whether changes in the nonharmonic frequencies can improve the detection of thromboembolism and pump thrombosis (hypothesis 5). We used data collected in the previously described in vitro and *in vivo* experiments.

We performed ROC analysis of the change in the nonharmonic amplitude in the acute phase. The ROC analysis area under the curve was 0.843 in vitro and 0.854 in vivo (figure 15B).

Thromboembolic events led to acute signal changes in the nonharmonic frequencies which was statistically significant compared with the control intervention both in vitro and in vivo ($p<0.01$) (figure 15A). During the acute phase, 50% (30/60) of the thrombi demonstrated combined third harmonic and nonharmonic amplitude change, while only 6.6% (4/60) demonstrated isolated nonharmonic amplitude change and 24% (14/60) demonstrated isolated third harmonic amplitude change, on the pooled data (figure 15 Acute signal changes). Combining the two types of signal changes led to 8.3% improvement in the positive predictive value of the method compared with using third harmonic amplitude change alone.

At steady state, acute signal change either subsided or transformed into a prolonged signal change. When prolonged signal changes were present, the signal demonstrated either nonharmonic amplitude change or third harmonic amplitude change. Nonharmonic amplitude change was present in 8.3% (5/60) while third harmonic amplitude change was present in 21.6% (13/60) of thromboembolic intervention, on the pooled data (figure 16

Steady state changes). Only one thrombus injection led to concomitant change in both third harmonic and nonharmonic amplitude. Combining the two types of signal changes led to 36% improvement in the positive predictive value of the method compared with using third harmonic amplitude change alone.

We concluded that changes in the nonharmonic amplitude can improve the diagnosis of thromboembolism and pump thrombosis (hypothesis 5).

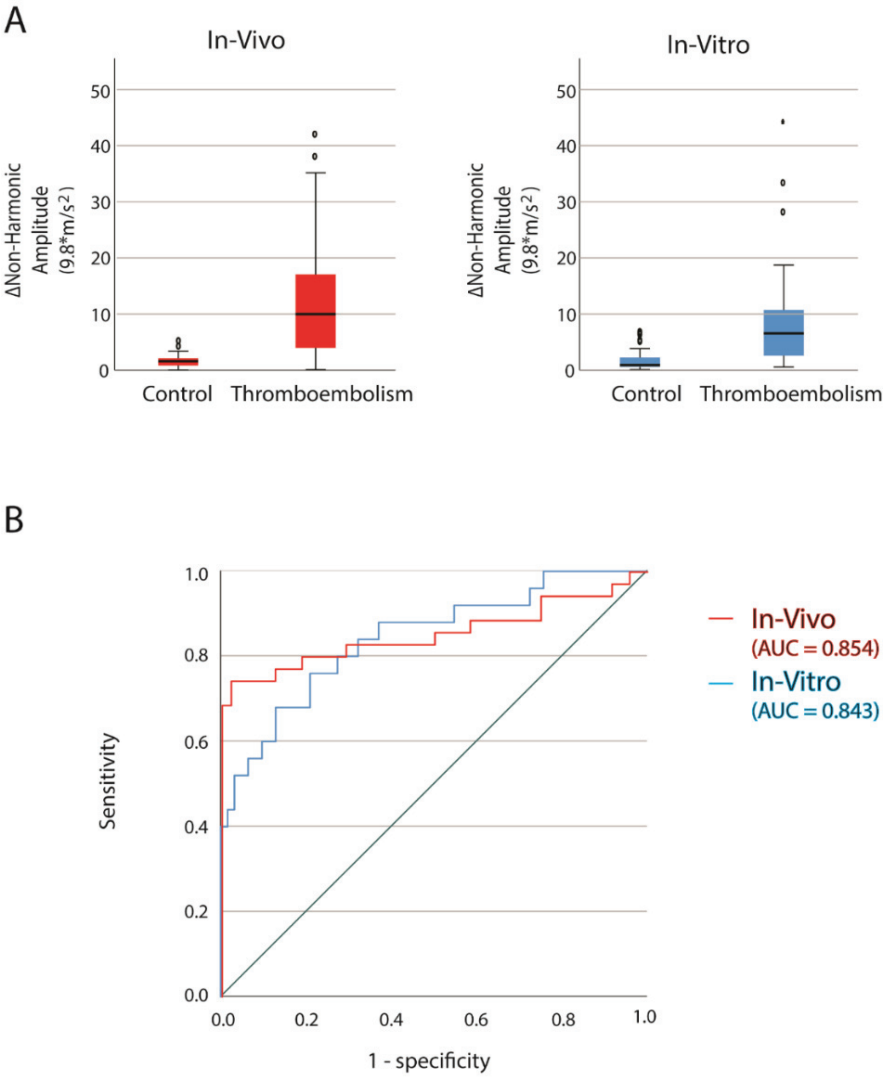

Figure 15. Acute changes in the nonharmonic signal. **(A)** Block diagram for the change in the nonharmonic amplitude signal. **(B)** Receiver operating characteristic (ROC) curve for the change in nonharmonic signals of in vitro and in vivo.

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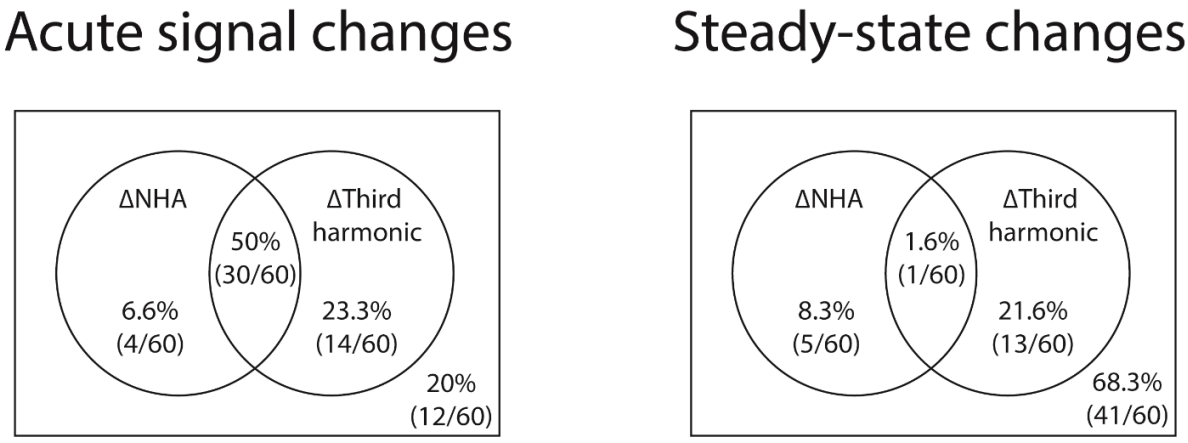

Figure 16. Venn diagram of the resulting signal changes on nonharmonic and third harmonic signals (pooled data).

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13. Discussion

13.1. Novelty

This is the first work describing the use of accelerometers in left ventricular assist device monitoring. The experimental results were promising. The accelerometer detected thromboembolic events with higher sensitivity and specificity than pump power in both in vitro and in vivo models (hypothesis 1 and hypothesis 2). More than 50% of the acute signal changes in response to thromboembolic events progressed to prolonged third harmonic amplitude increase indicative of pump thrombosis (hypothesis 3). Prolonged changes in third harmonic were significant even when the change in pump power consumption remained low, which demonstrated the superiority of the accelerometer compared with traditional pump power elevation (hypothesis 4). This thesis also demonstrates the utility of a novel signal analysis for diagnosis of both thromboembolism and pump thrombosis by the quantification of changes in the nonharmonic regions of the spectrogram (hypothesis 5).

13.2. LVAD monitoring with accelerometer in the clinical setting

The merit of accelerometer-based LVAD monitoring of thromboembolism and pump thrombosis depends on evidence that (1) it performs better than the traditional diagnostic criteria, (2) it performs better than acoustic spectral analysis, and (3) it may be integrated with new monitoring paradigms and combined with new diagnostic methods.

An accelerometer attached to the pump offers three desirable features:

1. Signal acquisition allows for easy continuous monitoring.
2. It provides standardized signal recording in a fixed position directly on the pumps casing.
3. It does not breach the blood barrier.

In order to appreciate the resulting clinical advantages, it is important to discuss the current gaps in LVAD monitoring and evaluate whether accelerometer-based monitoring can improve the current situation.

An overview of accelerometer-based HVAD monitoring of thromboembolism and pump thrombosis is presented in figure 17.

13.2.1 Thromboembolism

This thesis demonstrates that acute thromboembolism leads to temporary disruption in the pumps vibration pattern which can be captured by an accelerometer attached to the pump housing. The increase in the amplitude of a continuous range of frequencies on the spectrogram, as demonstrated in figure 18A, usually include a marked elevated third harmonic amplitude. The changes in the spectrogram can be quantified either by measuring the third harmonic amplitude (paper I and paper II) (figure 18B) or by calculating the nonharmonic signal (paper III) (figure 18C).

As thromboembolism is a single phenomenon, change in the third harmonic amplitude and the nonharmonic signal normally happens simultaneously and reflect one another. Anecdotal cases where nonharmonic changes spare the high frequencies (including the third harmonic) or cause isolated persistent third harmonic amplitude may also occur. This leads to a moderate increase in positive predictive value when both parameters are used, as demonstrated in paper III.

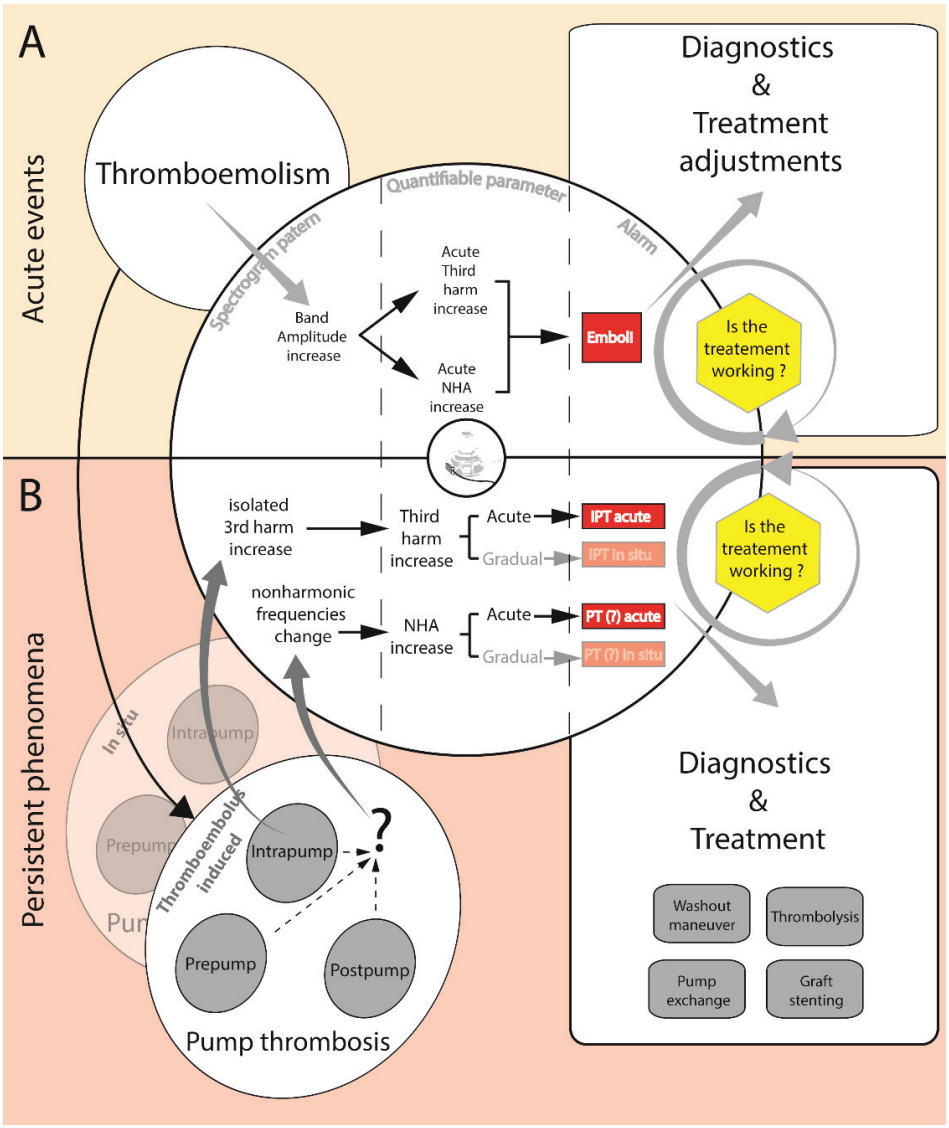

Figure 17. Overview of accelerometer-based HVAD monitoring of thromboembolism and pump thrombosis. **(A)** thromboembolism Leads to signal changes i an array of frequencies, can be detected through changes in either acute change in third harmonic or change in the nonharmonic frequencies. Alarm on possible thromboembolism should initiate investigation regarding the source of the embolus and adjustment of treatment. Efficacy of treatment can be evaluated by monitoring for repeated thromboembolic episodes. **(B)** Pump thrombosis causes either third harmonic amplitude change or changes in the nonharmonic frequencies. As they appear independently of one another they probably represent different etiological entities that may require different treatment. Elevation in third harmonic suggests intra-pump thrombosis. The etiology of changes in the nonharmonic frequency is, however, uncertain at the moment. Thrombosis in situ probably leads to gradual signal changes. Continuous monitoring with accelerometer may help classifying pump thrombosis as acute or gradual. As this was not investigated in our models, thrombosis in situ and gradual signal changes are printed in semitransparent format. Treatment efficacy may be evaluation by the degree of resolution of the signal changes.

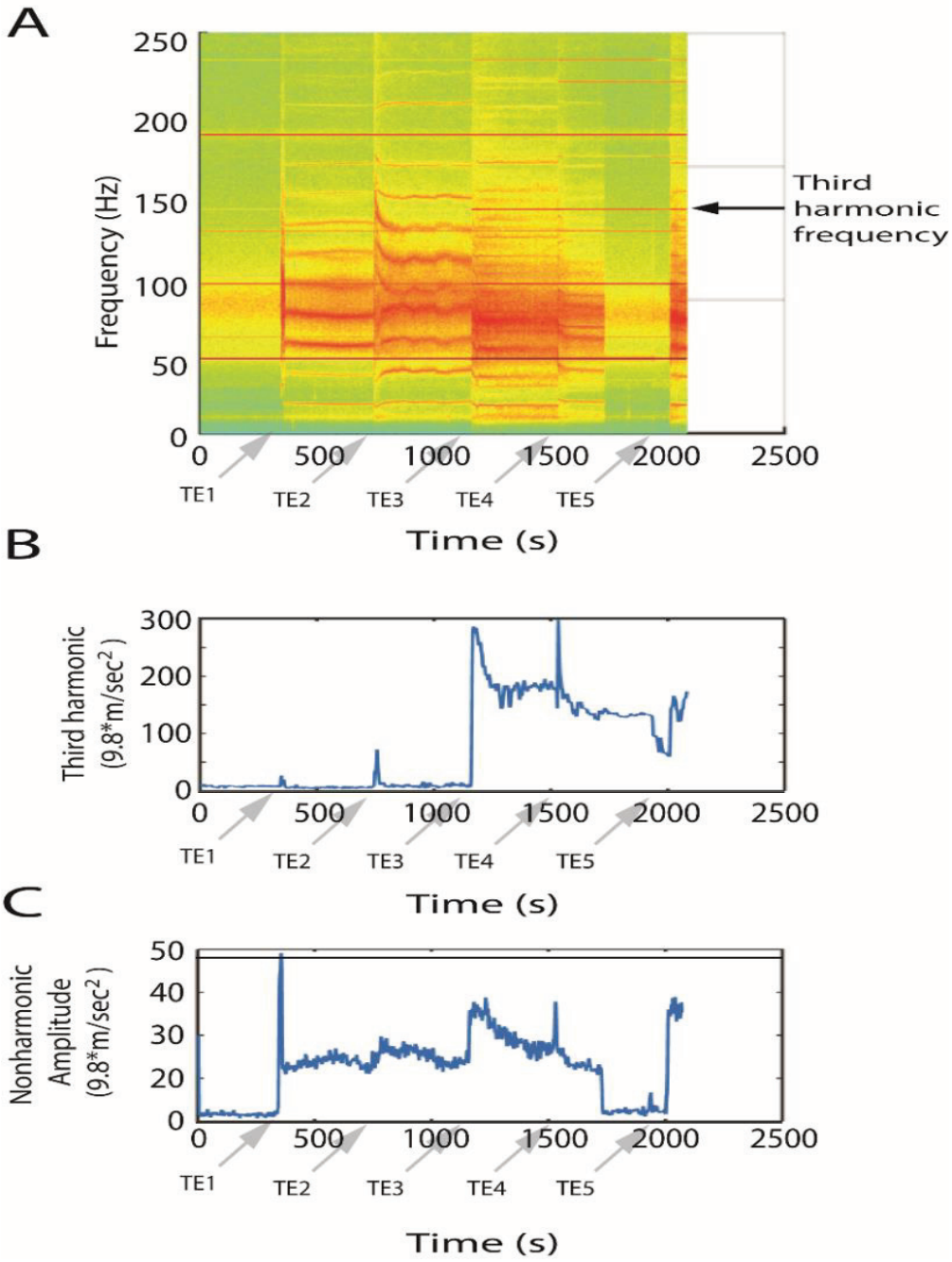

Figure 18. Example of thromboembolic intervention (TE). The gray semitransparent arrows designated TE1-5 point to the TE's injection times. **(A)** Spectrogram. **(B)** Third harmonic signal. TE1 and TE2 leads to acute third harmonic amplitude increase. TE3 leads to prolonged increase in the third harmonic amplitude which remains high through the intervention. **(C)** The nonharmonic signal. Change in the nonharmonic region appears after TE1. Between TE4 and TE5, changes in the nonharmonic regions subsided and its amplitude returned to its baseline.

Detection of acute elevations in third harmonic or nonharmonic signal can alarm the treating team of suspected thrombus ingestion and initiate a diagnostic investigation of the thrombus origin using imaging modalities. Anticoagulation regime can then be adjusted after consideration regarding bleeding risk. After treatment initiation, the accelerometer can be further used to monitor treatment efficacy.

13.2.1.1. The benefit of accelerometer-based detection of silent thromboembolism

Stroke is a devastating complication responsible for considerable morbidity and mortality in the LVAD population. Even the Heartmate 3 pump, despite technological improvement, demonstrate high stroke rates (0.07 EPPY).[24,25,111,112] As for today, there is no reliable method to diagnose thrombus ingestion by the pump.

Thrombus ingestion by the pump is an acute event and therefore capturing it depends on continuous monitoring. Currently, the only continuous LVAD monitoring modality is pump power. This thesis demonstrates the superiority of the accelerometer compared with pump power in this respect. An accelerometer attached to the pump can easily provide continuous pump vibration recording with no impact on the patient.

It is unknown how often silent thromboembolism occurs in the LVAD population. Peripheral thromboembolism may also occur, but its reported rate is considerably lower than stroke rates. Stroke rates are 10 folds higher in the early phase (< 90 days after implantation) and 30 folds higher in the late phase (> 90 days after implantation) than peripheral thromboembolism.[28] Considering that the blood supply to the brain accounts for 20% of blood flow the difference in incidence is striking. One can try and compare emboli distribution in LVAD patients with emboli distribution in infective endocarditis, as peripheral septic embolism from endocarditis is much

easier to diagnose due to the ensuing infection. Peripheral embolism in infective endocarditis accounts for 35-52% of all endocarditis related embolizations.[113,114] This suggests that peripheral thromboembolism is grossly underdiagnosed in LVAD. Another evidence supporting the occurrence of silent emboli in LVAD patients is the backwash maneuver used to expel thrombus mass occluding the inflow canula of the pump. It is common practice to search and locate the embolized thrombus after the maneuver using imaging modalities as conventional or CT angiography. In a study of four cases of backwash maneuver, only three thrombi were detected by angiography.[57] This supports the notion that a silent thromboembolism under LVAD treatment is more common than the current statistical evidence suggests and that it may pass undetected under today's monitoring.

Alarming the treating team of suspected thromboembolism by accelerometer may open the door for early intervention and help tailoring patient specific anticoagulation protocol before function loss occurs. This can lead to considerable advantages for both the individual patient, reducing mortality and maintaining quality of life, and for the health system, reducing treatment and rehabilitation costs.

13.2.2. Pump thrombosis

This thesis supports other investigations, demonstrating that pump thrombosis is associated with persistent change in vibration pattern seen as prolonged accelerometer signal changes (figure 17A). Persistent changes in the accelerometer signal may appear either as elevation in the third harmonic amplitude or in the nonharmonic frequencies. The accelerometer signal changes can be quantified by directly reading the third harmonic amplitude (figure 17B) or by quantifying the changes in the nonharmonic frequencies (figure 17C).

Figure 18 shows the potential use of accelerometer. As third harmonic and nonharmonic amplitude appears independently from one another, both should be sought after. When alarm is raised, a thorough investigation for the cause of pump thrombosis can be initiated and treatment strategy chosen. The accelerometer can help monitoring treatment efficacy through the resolution of signal changes, together with the normalization of pump parameters and blood tests.

13.2.2.1. The benefits of accelerometer-based monitoring compared with traditional LVAD monitoring

Traditional criteria for the diagnosis of pump thrombosis (signs of heart failure, hemolysis, pump parameters change, and imaging) offers relatively late diagnosis. This may explain the low success rate using thrombolysis.[80]

This was recently further elucidated by Semiz et al. that integrated acoustic spectral analysis with traditional diagnostic parameters in a machine learning based algorithm.[73] In their study patients diagnosed with pump thrombosis using traditional approach such as pump power elevation above the manufacturer recommendation, hemolysis, heart failure symptoms, or positive ramp test were administered thrombolysis. Resolution of symptoms were monitored using traditional parameters and acoustic spectral analysis. The algorithm then found and graded the relevant features for pump thrombosis. This allowed for comparison between different diagnostic methods. The study concluded that traditional methods were inferior to acoustic spectral analysis and that pump power on its own performed inferiorly to harmonic analysis alone. This is in agreement with findings from our studies that showed that traditional pump power analysis is inferior to accelerometer-based vibration analysis.

Another interesting finding in the study by Semiz et al, was that despite the normalization of both pump parameters and biochemical parameters after thrombolysis administration, the algorithm integrating acoustic signal analysis detected residual pump thrombosis in four pumps.[73] Indeed, three of the four pumps later developed residual pump thrombosis. The authors speculated that this is due to late diagnosis which precluded total thrombus lysis or structural damage to the pump at the time of diagnosis. This strongly supports that traditional diagnosis of pump thrombosis do not offer timely diagnosis with regard to medical intervention.

It has been shown that early thrombolysis may reduce the need for pump exchange.[80] This thesis showed that accelerometer can detect pump thrombosis before pump power increases. This may lead to early medical intervention with thrombolysis which may increase its efficacy and thereby reducing the need for pump exchange.

13.2.2.2. Measurement reliability and reproducibility of accelerometer signal compared with acoustic signal

Acoustic spectral analysis has been investigated for a decade now without reaching a diagnostic consensus due to somewhat conflicting results. Kaufmann et al found the presence of third harmonic to be diagnostic for pump thrombosis, while more recent studies by both Feldmann et al and Boilson et al. found third harmonic to be present without pump thrombosis.[58,71] Kaufmann et al also reported that the fourth harmonic had the highest amplitude, while Semiz et al. reported in a later study that the fourth harmonic was seldom the highest harmonic amplitude in their data set.[73] These contradictory results may be secondary to differences in the experimental model, measuring equipment, auscultation points, or signal analysis.

The study by Feldmann et al. was an in vitro experiment while the other three studies using HVAD were clinical studies of patients. Simulating the acoustic properties of the body is difficult.[72] A study by Yost et al., investigating pump thrombosis diagnosis in Heartmate II, demonstrated reduced amplitude in six of eight individuals compared with in vitro measurements. This suggests acoustic interference from surrounding tissues, and variation between individuals. An accelerometer attached to the pump may provide more consistent recordings.

Studies used different dedicated equipment. Differences in the presence or absence of third harmonic peak in different studies may be directly related to the equipment used. Sunbom et al. investigated Heartmate II, comparing iOS recording device with dedicated recording equipment, and concluded that iOS performed inferiorly, eliminating important parts of the signal.[77] This, though not surprising, supports the notion that recording equipment plays an important role in signal quality. Accelerometer attached to the pump will provide optimal signal quality and can assure a standardized signal acquiring method which will help reaching consensus.

The auscultation points also differed between different spectral analysis studies. Semiz et al used the mitral place, Kaufmann et al and Feldmann et al did not report the exact auscultation point.[58,73] Boilson et al tested multiple auscultation points; the second right intercostal space (aortic area), second left intercostal space (pulmonary area), fourth left intercostal space at the sternal border (tricuspid area), and fifth intercostal space, left mid-clavicular line (mitral area).[71] He concluded that the tricuspid area provided best quality and most consistent signal. This observation suggests differences in signal quality depending on auscultation point and can explain some of the differences between studies. In contrast, accelerometer will provide a standardized point with minimal influence of surrounding tissues, overcoming this limitation. This is reflected by the low inter-pump and inter-subject variation in our signal.

Another difference between the above-mentioned studies is signal analysis. Kaufmann et al. and Feldman et al. used signal averaging while Boilson did not.[58,71] Signal averaging is usually used to decrease stochastic noise and improve signal quality. The tradeoff is loss of temporal information. Our accelerometer signal was not averaged, enabling detection of short-lasting events such as thromboembolism.

Even more, Kaufmann et al normalized the harmonic amplitudes to the fourth harmonic amplitude, while Boilson et al normalized the harmonic amplitudes to the fundamental frequency (the first harmonic).[58,71] The accelerometer data showed little variability between measurements and therefore normalization was unnecessary, which is another advantage compared with acoustic spectral analysis.

Accelerometer-based analysis offers a solution for the utility of the third harmonic amplitude. It seems that the description of the third harmonic as absent by Kaufmann et al. was circumstantial to the equipment used and somewhat imprecise. The accelerometer data demonstrated low level third harmonic in all pumps as referred in paper I. The third harmonic became apparent when background signal level decreased, due to increased afterload or decreased preload, as shown in figure 17. Even when third harmonic amplitude increased above background signal level, it remained low under the large hemodynamic flow alterations during the control interventions both in vitro and in vivo and only increased significantly under pump thrombosis (figure 19). This shows that diagnosing pump thrombosis using the presence/absence of third harmonic (above background signal level) may be problematic, while using a third harmonic amplitude cutoff value is feasible and avoids this problem.

To summarize, an accelerometer-based LVAD monitoring can eliminate many of the methodological challenges of acoustic signal analysis. An accelerometer integrated into the pump by the manufacturer will provide a standardized equipment, eliminate differences in

auscultation point and reduce acoustic effects from surrounding tissues. Providing a standardized signal of high quality will help reaching a consensus regarding the best signal analysis method.

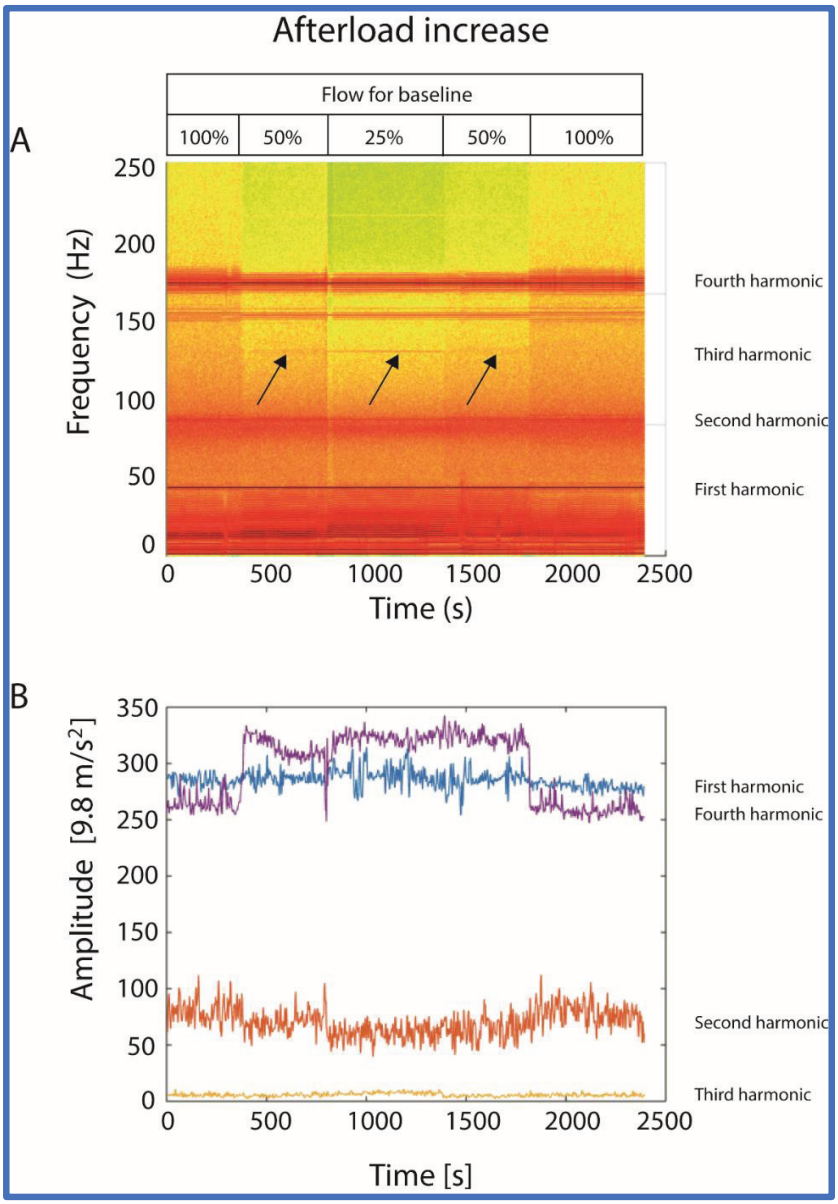

Figure 19. Third harmonic amplitude under graft obstruction. **(A)** The spectrogram (presented in paper 3) shows the third harmonic becomes apparent as background noise decreases under graft occlusion (black arrows). **(B)** The first, second, third, and fourth harmonic amplitude extracted from the spectrogram. The third harmonic maintains low amplitude all through the graft obstruction intervention.

13.2.2.3. Accelerometer-based distinction between thrombosis in situ and thromboembolism induced thrombosis

The ability to classify an event as acute or gradual depends on continuous monitoring. It is documented that pump thrombosis increases stroke risk.[59] In contrast, the causative connection between thromboembolism passing through the pump and the development of pump thrombosis is not clear and seldom discussed. A study by Jorde et al. showed that thrombolysis efficacy was higher in cases where pump power increase was gradual and not acute.[80] As vibration analysis with accelerometer is more sensitive and specific than pump power, continuous monitoring with accelerometer can improve classifying signal changes as acute or gradual. This will help in choosing the right treatment.

13.2.2.4. Accelerometer-based nonharmonic amplitude change contribution for pump thrombosis diagnosis

Paper III was the first paper using the nonharmonic region of the accelerometer-based spectrogram in the diagnosis of thromboembolism and pump thrombosis in LVAD. It showed that thromboembolism can lead to persistent change in the nonharmonic amplitude indicative of pump thrombosis. As changes in the nonharmonic region had no association with third harmonic change, a method utilizing both parameters improved the positive predictive value compared with a method that relied on only the third harmonic amplitude change. Beyond the increase in positive predictive value, the lack of association between the two parameters suggests that they represent different forms of intra-pump thrombosis.

In the literature intra-pump thrombosis is often used as an umbrella term, referring simply to thrombus mass within the pump. Intra-pump thrombosis may take different forms. Thrombus

may be central or peripheral. It may be attached to the impeller or to the pump housing. It may affect different parts of the impeller (e.g. primary, secondary, or tertiary blood flow pathways) (figure 20). As for today there are no methods to distinguish different forms of intra-pump thrombosis. It is reasonable to assume that thrombus location affects LVAD vibration pattern differently, in which case different signal changes will represent different pathologies. Unfortunately, studies utilizing acoustic spectral analysis usually try to show the superiority of one parameter over other parameters. The most studied part of the spectrogram involves the harmonic frequencies. Limited information exists regarding changes in the nonharmonic frequencies. Feldmann et al. demonstrated that the number of peaks on the acoustic frequency spectrum increased significantly (including new nonharmonic amplitude peaks) in response to artificial thrombus attachment to the tilted part of the impeller. Though morphology of signal changes in the nonharmonic region may take more than one form, examples where increased number of nonharmonic amplitude peaks occurred also in our data (figure 15).

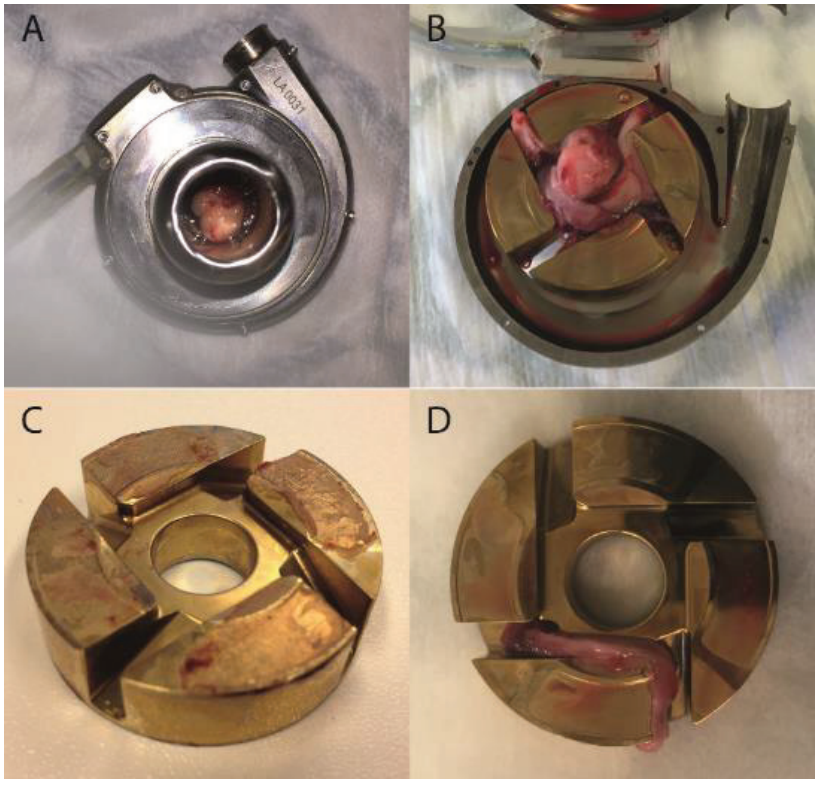

Figure 20. Different forms of pump thrombosis. **(A)** and **(B)** Central thrombus at the end of the experiment. **(C)** Residual deposition of fibrin on the impeller. **(D)** Thrombus filling one of the pumps primary blood flow pathway.

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It is important to acknowledge the possibility that different signal changes may represent different pathologies, as they may respond differently to treatment. Reliable diagnosis and distinction between these two signal changes may further improve intra-pump thrombosis classification and help answering questions about the most effective treatment strategy in each case.

13.2.2.5. Accelerometer-based monitoring and pump power circadian rhythm monitoring

New studies demonstrated that the normal pump power circadian rhythm is lost under pump thrombosis.[115-117] Both thrombus build-up inside the pump and pre-pump thrombosis led to loss of circadian rhythm that could be detected an average 12 days prior to pump parameters reaching diagnostic threshold.

Loss of circadian rhythm seems to be nonspecific concerning the underlying pathology, as it changes in both pre-pump and intra-pump thrombosis.[115-117] As pre-pump and intra-pump thrombosis may require different intervention, loss of circadian rhythm should be combined with other methods to help distinguishing these two conditions. Combining novel circadian rhythm analysis and accelerometer vibration analysis may improve clinical decision making, and should be further investigated.

Circadian rhythm analysis is based on pump power consumption. As accelerometer-based vibration analysis was more sensitive than pump power in the diagnosis of pump thrombosis, it will be interesting to check whether the accelerometer signal demonstrate circadian rhythm, and whether it is lost under pathological conditions. It is possible that accelerometer-based analysis detects alteration in circadian rhythm even earlier than pump power.

13.2.2.6. Potential for accelerometer-based monitoring using machine learning

The advantages of machine learning based algorithms is the ability to process large amounts of information and different parameters, and by that finding correlations that were previously hidden in the data. The quality of the result gilded by machine learning algorithms is directly related to the quality of the training data set that is available. Machine learning has been utilized by Semiz et al. in an algorithm that combined acoustic spectral analysis with conventional pump parameters, demonstrating improved pump thrombosis detection.[73]

Accelerometer signal can easily replace the acoustic signal and with better signal quality this can translate to better performing algorithms. This needs to be investigated.

New paradigms in machine learning, as deep learning algorithms, challenge human intuition and push the boundaries of what is possible. They, however, require large amounts of representative data. This data does not exist at the moment. Adding sensors by manufacturers and collecting representative data in order to then develop these algorithms may be a profitable investment in the years to come.

13.3. Methodological considerations and reliability of the findings

In this thesis the in vitro model in paper I was used to establish the relevant diagnostic criteria for pump thrombosis by accelerometer, and the in vivo model was used to validate the method in a clinically relevant model.

The in vitro model allowed for observations distinguishing heart motion related signal changes from pump related signal changes (figure 5). Comparison of the two models confirmed the logical assumption that heart related signal changes are responsible for the high amplitude of the low frequencies. Based on this observation we chose to mask the low frequencies in our

third study, as we were only interested in the pump related signal changes in the nonharmonic regions of the spectrogram.

The value acquisition from the signal was performed using a semiautomatic method, which received the intervention time and based on that found the relevant predefined signal changes without operator intervention. This can be easily fully automated by scanning the accelerometer signal continuously for signal changes in the third harmonic amplitude and in the nonharmonic signal.

The experimental protocol provided vigorous control interventions covering a large range of hemodynamic conditions and pump speeds. At the same time, we kept thrombus size in clinically relevant volume between 0.2 -1.0 ml in vitro, and 0.3-0.4 ml in vivo. Despite this the accelerometer distinguished thromboembolism related signal changes from control interventions with high sensitivity and specificity.

Our models had some disadvantages. In our in vivo model, thromboemboli were injected into the atrium and could pass either through the pump or through the aortic valve. We did not have a method detecting the course the thrombus took and therefore we included all thromboembolic events in the statistical analysis. This affected the sensitivity and specificity in the in vivo model.

Another weakness in our model was related directly to the fact that currently there is no reliable method to detect pump thrombosis. We based our pump thrombosis diagnosis on the assumption that persistent change in the vibration pattern after thrombus ingestion into the pump is evidence for a residual thrombus in the pump. As there is no gold standard, the only way to confirm the presence of pump thrombosis and its exact type is to open the pump after each thromboembolic event. This would have increased the number of animals and pumps needed 10 folds and was considered unethical. We therefore chose to open the pump only after all thromboembolic events were performed.

A third factor that has to be taken into account, is our use of open chest model. The decision to use open chest model was taken primarily in order to perform graft occlusion and thrombus

injection with direct visual confirmation. Another reason was the risk of arrhythmias and the ability to perform defibrillation and direct heart compression if needed. Closed chest model may lead to amplitude attenuation on the spectrogram and increase variability between subjects. Experiments investigating accelerometer performance under closed chest model should be performed.

13.4. Relevance of this thesis

This work is based on HeartWare HVAD which was recently removed from the market due to complications related to stroke rates and device malfunction. This puts the relevance of this work in question and demands a response.

First and foremost, HeartWare HVAD was one of the two most popular pumps in the recent decade and many patients still use this pump. According to the INTERMACS report from 2020, 6,565 centrifugal pumps with hybrid levitation have been implanted between 2010 and 2019, with peak implantation numbers in 2018.[28] Over 50% of implantations between 2015 and 2019 were performed as destination therapy. With 5 years survival rates of about 50% we should expect to encounter HVAD related complications in the coming years, and we should continue to develop diagnostic strategies for this patient group.

We currently test the hypothesis that vibrations captured by accelerometer attached to the pump's driveline may serve as an alternative to accelerometer attached to the pump.

Though we did not compare acoustic signal and accelerometer signal in our experiments, our data suggests that accelerometer signal has lower noise levels. With advancing technology and improved acoustic signal the data published in this thesis may be utilized using acoustic spectral analysis.

Second, it is important to acknowledge that despite improvements in pump technology, hemostasis-related complications are still a major cause for morbidity and mortality in the LVAD

community regardless of the pump type. Despite lower pump thrombosis rates, the Momentum 3 study still reports stroke rates of 0.07-0.08 EPPY and bleeding rates of 0.6-0.7 EPPY for the Heartmate 3 pump.[112] As LVAD causes changes in hemostasis with combined bleeding diathesis and hypercoagulability, the probability that these complications will be abolished in the near future are unrealistic. This means that optimal anticoagulation strategy and complication management require patient tailored strategy. Unfortunately, monitoring of LVAD patients remain lacking. This is reflected by continuous efforts to improve LVAD diagnostic using new modalities as acoustic spectral analysis[58,65-78,118], alteration in circadian rhythm[115-117], and machine learning based analysis[73]. Though this work describes signal changes in Heartware HVAD, it is reasonable to assume that the observations made are relevant with some modifications to other hydrodynamic pump types. Testing the spectrogram regions described here will be a good place to start an investigation of other pump types. This is supported by observations made using acoustic spectral analysis demonstrating that third harmonic is a marker for pump thrombosis not only in Heartware HVAD but also in Heartmate II.[71]

Third, this work describes general signal analysis methods, for example the phase filter, that should be tested on other pump types.

13.5. Limitations

Static models

The models in this thesis are static, meaning that the results are relevant for monitoring patients at rest. Analysis of the mobile patient will have to take into account orientation changes in the gravitational field, vibrations from external sources, and acute events from external sources. Orientation changes in the gravitational field can be recognized by a gyroscope. There are commercially available six axis sensors that has both accelerometer and gyroscope. Krogh et al. from our research group, developed and validated algorithms compensating changes in the

gravitational field.[100] Recognizing external sources of signal changes, regular or irregular, may be achieved by comparing accelerometer recordings at the surface, for example at the controller, with accelerometer recordings at the pump. Vibrations from an external source will most probably be more prominent at the surface of the body. Limiting the analysis to events that effect solely the LVAD accelerometer may help distinguishing acute thromboemboli from external mechanical events.

No direct comparison between acoustic spectral analysis and accelerometer

Accelerometer-based vibration analysis and acoustic spectral analysis are highly related methods. A direct comparison between the two methods will help determining the potential advantage of accelerometer-based monitoring. Evaluation of variation between individuals and measurements will help establish differences in measurements reproducibility of the two methods.

Open thorax model

We used an open thorax model. This may affect the vibration amplitude, and signal quality. It may also increase variability between patients and/or measurement. This can be investigated under close thorax conditions. Some of these questions may be best answered under chronic animal model or clinical trial, collecting data over a long period of time. It may be combined with efforts to establish the principles of dynamic monitoring of mobile patients.

Heartmate 3 was not tested

After the withdrawal of Heartware HVAD from the market, Heartmate 3 is the leading pump. It is important to recognize that the Heartmate 3 pump differs in levitation mechanism and impeller structure, and findings in Heartware HVAD cannot be automatically applied. Pump thrombosis rates seems to be much lower in this pump, and the impeller structure may make the detection

of thromboembolic events passing through the pump more challenging. The models and signal analysis methods described in this work can be used to investigated Heartmate 3, but new investigations should be performed in order to demonstrate the utility of accelerometer-based monitoring in this pump type.

Accelerometer attachment to the pump require manufacturer involvement

The modern LVADs are robust, state of the art, devices built for reliability, safety and durability. In the name of reliability and durability, the pumps are stripped of all unnecessary components, leaving device monitoring lacking. Adding new monitoring components to a pump already on the market is demanding and costly. The consequence is that all monitoring modalities on an implanted device are either included in the original design or excluded from it altogether, limiting the technological solutions to the insight of the developing team. Accelerometer sensors do not breach the blood barrier and poses minimal risk for patient safety. Despite this, integrating an accelerometer to an already approved pump as the Heartware HVAD seems demanding from a manufacturers perspective and limits its potential patient benefit.

14. Conclusions

This thesis represents the first step in utilizing accelerometer sensors in the field of circulatory assist devices. The main focus areas in this work were thromboembolic events and pump thrombosis detection in HeartWare HVAD using an accelerometer. The following conclusions can be drawn:

1. The accelerometer detected thromboembolic events (hypothesis 1) with higher sensitivity and specificity than pump power (hypothesis 2). This may help in the diagnosis of subclinical emboli and open the door for treatment adjustment before function loss occurs.
2. A subset of thromboembolic events led to prolonged increase in the accelerometer third harmonic amplitude which was associated with pump thrombosis (hypothesis 3). Persistent accelerometer signal changes were present before HVAD power indicated underlying pump thrombosis, which demonstrated the superiority of the accelerometer method (hypothesis 4).
3. Analyzing the nonharmonic region of the accelerometer spectrogram improved the positive predictive value of the method in the diagnosis of both thromboembolic event and pump thrombosis (hypothesis 5).

Accelerometer-based vibration analysis has two main advantages compared with acoustic spectral analysis, including measurements in a fixed position directly on the pump, and the possibility of continuous monitoring. Though the two methods were not directly compared, accelerometer-based monitoring seems like the natural next stage in LVAD monitoring. Hopefully this work is a first step in the utilization of accelerometer in LVAD monitoring and will encourage other works in the field of mechanical circulatory support.

15. New research areas

Detection of preload status

Exercise tolerance among LVAD patients is low. Modern LVADs are hydrodynamic pumps and offers some preload dependent autoregulation of LVAD flow. This can be determined by the pump head curve, which is the relationship between pressure gradient across the pump and flow. The response under exercise is, however, a complex combination of increased contractility, tachycardia, and vasodilation. Vasodilation may potentially increase the head pressure, but its effect may be counteracted by increased contractility at systole and short diastolic phase due to tachycardia. It has been shown that increased output under exercise is mainly attributed to increase myocardial work and not to pump flow.[119]

Monitoring preload conditions seems to be a key element in developing pump with dynamic automatic pump rate control. Our group has developed accelerometer-based algorithm that evaluate preload conditions in healthy hearts.[103] The ability to react dynamically to changes in preload is the first step in developing dynamic automatic pump rate control. This should be tested under LVAD physiology.

Ramp test

Echocardiography based Ramp test is used today in the diagnosis of pump thrombosis. Inadequate unloading of the ventricle under sequential increase in pump speed is a marker of flow obstruction due to underlying pump thrombosis.[60]

If accelerometer is able to estimate preload conditions, it can be used to automatize the ramp test and allow for prehospital periodic ramp testing to facilitate early pump thrombosis diagnosis.

Aortic valve opening detection

The detection of aortic valve opening is challenging and as for today is mostly based on intermittent evaluation with echocardiography with adjustments of pump speed. Our group has been working on detection of valve events using accelerometer.[104] This algorithm should be tested under LVAD physiology.

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