UMEÅ UNIVERSITET

In the Hands of Ohm

Hemodynamic Aspects in Pulmonary Hypertension

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Till den andfådde

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Abstract

Congestive heart failure (CHF) is one of the most challenging diseases in terms of health care demand and mortality, in the western world. Despite major breakthroughs in the fields of diagnosis and treatment over the three last decades, the management of CHF still remains challenging.

CHF is defined as inability of the heart to supply sufficient blood flow to meet the needs of the body. This definition however, may be an oversimplification of a complex pathophysiological process since patients with overt CHF may have normal, or even supernormal cardiac output at the expense of increased filling pressures, which subsequently leads to the development of post capillary pulmonary hypertension (PH). In the presence of advanced CHF, clinical signs and symptoms are obvious at rest. However, the majority of affected individuals do not experience any discomfort at rest and may demonstrate normal findings when assessed. Small increases in systemic blood pressure and or venous return, caused by activity may result in severe elevation of filling pressures if left ventricular compliance is significantly decreased. This example highlights the need to perform cardiac investigations during stress to provoke symptoms. Increased pulmonary vascular resistance (PVR), commonly found in pre-capillary PH, is a condition that shares many symptoms with CHF, and is also associated with poor prognosis. Even though the disease is located within the lung vessels, it is highly important and challenging task differentiating pre- and post-capillary PH. Since treatment differs considerably and may be detrimental in case of misdiagnosis, additional sensitive and reliable screening methods are crucial to aid in differentiation.

Methods

Out of the four studies included in this thesis, three were conducted solely at Norrland's University Hospital, while patients in the third study were recruited and examined at Uppsala Akademiska Hospital. All included patients had idiopathic dyspnea and were admitted for right heart catheterization (RHC), which is gold standard with regards to hemodynamics. Echocardiographic examinations were performed simultaneously with RHC, except in the Uppsala study, wherein echocardiography were performed within 3 days to the RHC.

Echo-Doppler derived pulmonary artery acceleration time (PAcT) is an easily assessed parameter, indicating elevated pulmonary artery systolic pressure (PASP) and pulmonary artery resistance (PVR). PAcT was tested as a screening method for identification and differentiation of pre and post- capillary PH in a cohort of 56 patients (study 1).

The ability to calculate PVR non-invasively, using novel echocardiographic measurements, was made by replacing the invasive pressure and flow components that constitutes the foundation of the PVR = (mean pulmonary artery pressure – Pulmonary capillary wedge pressure (PCWP)) /cardiac output), with novel echocardiographic measurements. PVR = mPAP-Chemla – Left atrial strain rate during atrial systole (LASRa) / Cardiac Output-Echo (study 2).

Invasively measured left ventricular filling pressure in response to passive leg lifting, and its ability to predict pathological increase in left ventricular filling pressures during supine bicycling, was tested in a population of 85 patients with normal left ventricular ejection fraction (LVEF) and suspicion of CHF based on NT-proBNP levels alone were investigated (Study 3).

Finally, an evaluation of standard and novel Doppler echocardiographic parameters, potentially useful in identifying patients who may develop increased filling pressures during passive leg lifting (PLL), was carried out (study 4).

Results

Study 1: PAcT correlated negatively with pulmonary artery systolic pressure (PASP) ($r = -0.60$, $p < 0.001$) and PVR ($r = -0.57$, $p < 0.001$). PAcT of <90 ms had a sensitivity of 84% and a specificity of 85% in identifying patients with PVR ≥ 3.0 WU. Regardless of normal or elevated left sided filling pressures, PAcT differed significantly in patients with normal, compared to those with elevated levels of, PVR ($p < 0.01$). A significant difference was also found on comparison of the PAcT/PASP ratio ($p < 0.01$), with a lower ratio among patients with PVR ≥ 3.0. WU.

Study 2: We prospectively used Doppler and 2D echocardiography in 46 patients with sinus rhythm which revealed that left atrial strain rate during atrial systole (LASRa) had the highest significant positive correlation with PCWP ($r^2 = 0.65$, $P < 0.001$). By adopting a linear line of best-fit, LASRa may therefore be substituted for PCWP. Subsequently, LASRa was substituted into the PVR equation. This novel echocardiographically derived PVR calculation, significantly correlated with RHC generated PVR values ($r^2 = 0.69$, $P < 0.001$) and minor drift (+0.1WU) when assessed by Bland Altman analysis.

Study 3: Only 22% (11/51) of patients with elevated NT-proBNP had PCWP above normal levels at rest. However, in response to PLL, 47% of patients developed

elevated PCWP, and the majority of this 47% subsequently developed pathological pressure levels while performing supine cycling exercise. Thus, the likelihood of developing high LVFPs during exercise could be determined by PLL, with a sensitivity and specificity of 90%.

Study 4: At rest, left atrial volume indexed to body mass index (BMI) (LAVI) and mitral deceleration time (DT) were independently related to PCWP during PLL. However, during PLL univariate regression analysis revealed LASRa (β = -0.77, P <0,001) and E/LVSRe (β = 0.47, P < 0,021) most related to $PCWP_{PLL}$. Multiple regression analysis fortified LASRa and E/LVSRe as relevant independent parameters useful in the assessment of filling pressure during PLL.

Conclusion

A PAcT < 90ms is strongly suggestive of increased PVR (>3.0 WU). Based on study 1, there is clear evidence suggesting that these findings apply irrespective of LVFPs. PAcT can potentially serve as a rapid screening tool for estimation of PVR, however, is not useful if the exact level of PVR is required. In this case, an established PVR calculation method is preferred, and could be performed with higher precision by inclusion of echocardiography derived LASRa as a surrogate measure of PCWP. Insufficient LV compliance results in the inability to cope with increased cardiac preload. Nt-proBNP is secreted when the myocardium is stretched, however only a small portion of patients within the CHF group (study 3) had a high PCWP at rest. Nearly half of the study population with elevated NT-proBNP showed increased PCWP during PLL, which is indicative of underlying ventricular stiffness. By performing this preload increasing maneuver, patients predisposed to developing high filling pressure during supine cycling could be identified with high sensitivity and specificity. Echocardiography, in comparison with RHC, is more accessible, safer and requires less resources and time, thus is an appealing option in the quest to identify additional, non-invasive methods reflective of invasive pressures, which could be useful in the assessment of filling pressure during different loading conditions. LAVI at rest, LASRa and E/LVSRe during PLL, proved independently related to PCWP during PLL.

Abbreviations

AUC - area under the curve

BNP- B-Type Natriuretic Peptide

CHF – congestive heart failure

COPD – chronic obstructive pulmonary disease

CVP- Central Venous Pressure

CTEPH - chronic thromboembolic pulmonary hypertension

DLCO - diffusing capacity of the lung for carbon monoxide

dPAP – diastolic pulmonary artery pressure

DPG - diastolic pulmonary pressure gradient

ECG - electrocardiogram

edLVEDP - effective distending pressure of LV at the end of diastole

eeRAP – end-expiratory right atrial pressure

FPs – filling pressures

GOLD - Global Initiative for Chronic Obstructive Lung Disease

HF – heart failure

HFmrEF - heart failure with mid-range ejection fraction

HFpEF - heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

IVRT – isovolumic relaxation time

LA – left atrial

LAVI – left atrial volume index

LV – left ventricle

LHD - left heart disease

LVEDP – intra-cavitary left ventricular end diastolic pressure

LVEDV – left ventricular end diastolic volume

LVEF – left ventricular ejection fraction

LVFPs – Left ventricular filling pressure

mPAP - mean pulmonary artery Pressure

NPs – natriuretic peptides

NT-proBNP - N-terminal pro-brain natriuretic peptide

RAP - right atrial pressure

RVOT – right ventricular outflow tract

PAcT- Pulmonary artery acceleration time

PASP - pulmonary artery systolic pressure

PCWP - pulmonary capillary wedge pressure

PH - pulmonary hypertension

PR – pulmonary regurgitation

PLL – passive leg lifting

PVH – pulmonary venous hypertension

PVR - pulmonary vascular resistance

proBNP - pro-Brain Natriuretic Peptide

RAP – right atrial pressure

RHC - right heart catheterization

ROC - receiver operating characteristic

RV – right ventricle

SVR - systemic vascular resistance

TPG – trans-pulmonary pressure gradient

TRV – tricuspid regurgitant velocity

WU- Woods Units

Original articles

I: Tossavainen E, Soderberg S, Gronlund C, Gonzalez M, Henein M Y, Lindqvist P. Pulmonary artery acceleration time in identifying pulmonary hypertension patients with raised pulmonary vascular resistance. Eur Heart J Cardiovasc Imaging 2013 Sep;14(9):890-7

II: Tossavainen E, Henein M Y, Gronlund C, Lindqvist P. Left Atrial Intrinsic Strain Rate Correcting for Pulmonary Wedge Pressure Is Accurate in Estimating Pulmonary Vascular Resistance in Breathless Patients. Echocardiography. 2016 Aug;33(8):1156-65

III: Tossavainen E, Wikström G, Henein M Y, Lundqvist M, Wiklund U, Lindqvist P. Passive leg lifting in heart failure patients predicts exercise induced rise in left ventricular filling pressures. Clinical Research in Cardiology, currently under major revision.

IV: Henein Michael Y, Tossavainen Erik, A'roch Roman, Soderberg Stefan, Lindqvist Per. Can Doppler echocardiography estimate raised pulmonary capillary wedge pressure provoked by passive leg lifting in suspected heart failure? Clin Physiol Funct Imaging. 2019 Mar;39(2):128-134

Enkel sammanfattning på svenska

Avseende dödlighet och sjukhuskrävande vård är hjärtsvikt en av de största utmaningarna vi har i västvärlden. Den procentuella andelen av befolkningen som har sjukdomen är drygt två procent i Sverige och antalet som insjuknar varje år, ses bara öka. 5-årsöverlevnaden med hjärtsvikt är cirka 50 %, vilket innebär att prognosen är sämre än för de flesta former av cancer. Stora framsteg har gjorts de senaste tre årtiondena, avseende diagnostik, men även behandling. Numera kan man medelst ultraljudsundersökning av hjärtat (TTE), utföra detaljerad värdering av den sammandragande förmågan i hjärtats muskulatur. Kranskärlsröntgen med beredskap för ballongsprängning finns nu tillgängligt vid alla större sjukhus, vilket gör att hjärtmuskelvävnad kan räddas vid en akut hjärtinfarkt. Mediciner såsom ARNi, ACE-hämmare, betablockad och MRA är nu etablerad medicinering hos dessa patienter, sedan de visat sig motverka de ogynnsamma effekterna vid hjärtsvikt med nedsatt ejektionsfraktion (EF). Detta till trots är det många som inte har rätt diagnos och som sedermera saknar potentiellt livsförlängande medicinering.

Ungefär hälften av patientpopulationen med hjärtsvikt, har till synes ingen nedsättning av den kontraktila förmågan i vänster kammare och detta tillstånd omnämns ofta hjärtsvikt med bevarad EF. Beskrivningen är emellertid inte helt korrekt, när man med modern teknik kan identifiera avvikelser i rörelsemönstret, med ökad radiell rörlighet, för att kompensera den nedsatta sammandragande funktionen i längsriktning. Detta utgör förklaringsgrund till patientens besvär, fynd som dessa skall beaktas, när hjärtsvikt oavsett typ är behäftad med likartat dålig prognos. Behandlingsalgoritmen för hjärtsvikt med nedsatt EF är bevisat gynnsam, däremot har vi i dagsläget ingen medicinsk behandling som med övertygande effekt visat sig användbar, vid hjärtsvikt med bevarad EF.

Det finns flera definitioner på vad hjärtsvikt egentligen är, varav den mest frekvent förekommande slår fast att hjärtsvikt beror på otillräcklig pumpförmåga för att förse kroppens organ med tillräcklig mängd blod och därmed tillgodose kroppens behov. Denna definition kan tyckas något förenklad och i vissa avseenden missvisande, när uppenbar klinisk hjärtsvikt med bevarad eller ökad hjärtminutvolymkan kan föreligga på bekostnad av höga fyllnadstryck. Vid hjärtsvikt ses ofta trycket i lungcirkulationen förhöjt och i dessa situationer är det tryckalstrande området lokaliserat efter lungkapillärbädden, definitionsmässigt postkapillär pulmonell hypertension.

Vid avancerad hjärtsvikt föreligger ofta tydliga kliniska tecken, symptom och undersökningsfynd, redan i vila. Merparten har dock inga besvär i vila och kan ha normala undersökningsfynd i vila, medan minsta belastning i form av ökat

venöst återflöde eller ökning av blodtryck, kan förorsaka drastiska förändringar av fyllnadstryck, om vänster kammare är stel och har svårigheter att härbärgera ökade blodvolymer. Det finns således ett behov av att belasta till symtomutveckling, för en fullödig hemodynamisk utvärdering av hjärtfunktion.

Ökad resistans i lungcirkulationen (PVR), återfinns ofta hos individer med prekapillär pulmonell hypertension. Området som driver på utvecklingen av pulmonell tryckstegring är i dessa fall lokaliserat innan lungkapillärbädden. Trots att vi nu egentligen inte pratar om en hjärtsjukdom, utan en sjukdom i lungartärerna, är symptom och prognos likartad. Att särskilja sjukdomarna från varandra kan vara utmanande, men ack så viktigt, när behandling är vitt åtskild och till och med kan vara direkt skadlig om felaktigt använd.

Metoder: Den första, andra och fjärde delstudien är i alla avseenden utförda vid Norrlands Universitetssjukhus(NUS), medan patienterna i tredje studien är inkluderade, data insamlande och undersökta, vid Akademiska Sjukhuset, följt av statistiskanalys vid NUS. Samtliga patienter var remitterade för hjärtkateterisering (RHC) pga, andfåddhet, där genes behövde klarläggas invasivt. TTE utfördes hos alla patienter i nära anslutning till RHC, vilken är Gold standard, för värdering av tryck och flöden. Accelerationstiden i arteria Pulmonalis (PAcT), d.v.s. tiden från att flödet startar till att maximal flödeshastighet är uppnådd, är förhållandevis enkel att mäta. I delarbete 1, testade vi dess användbarhet som screening metod för att identifiera förhöjd PVR. I delarbete 2, undersöktes förmågan att kvantifiera lungkärlsresistans genom att ersätta ingående tryck och flöden, med ultraljudsgenererade värden. PVR beräknas genom att subtrahera ocklusionstrycket i en lungartärgren (PCWP), från medeltrycket i arteria pulmonalis (mPAP), följt av division med hjärtminutvolymen (CO). I delarbete 3 undersöktes NT-proBNPs relation till vänster kammares fyllnadstrycksrespons vid passivt benlyft (PLL) och PLLs förmåga att identifiera patologiskt stigande fyllnadstryck vid liggande cykling bland studiedeltagare med bevarad EF. I det fjärde delarbetet undersöktes vilka ultraljudsparametrar som är mest användbara för att identifiera vilka som utvecklar förhöjda fyllnadstryck under PLL, i en population med normala dito i vila.

Resultat

1: PAcT visade sig korrelerat till systoliskt tryck i arteria Pulmonalis(PASP) ($r = -0.60$, $p < 0.001$) och till PVR ($r = -0.57$, $p < 0.001$). Dessutom visade det sig att PAcT < 90ms har 84 % -ig sensitivitet och 85 % -ig specificitet för att upptäcka förhöjd PVR > 3.0 Wood Units. Förekomst av vänsterkammarsjukdom påverkade inte PAcTs förmåga att identifiera PVR-sjukdom. Både bland patienter med förhöjda samt normala fyllnadstryck var PAcT signifikant åtskild beroende på PVR($p<0.01$). Något mera höggradig korrelation till PVR observeras för

PAcT/PASP (r=-0.67, p<0.001), vilket dock inte förbättrade sensitivitet eller specificitet.

2: Bland 46 patienter med sinusrytm fann vi att left atrial strain rate during atrial contraction (LASRa) hade den högst förklaringsgraden till uppmätta nivåer av PCWP(r^2=0.65, p<0.001). Genom att använda den räta linjens ekvation, skapade vi ett surrogatmått för PCWP med hjälp av LASRa. Ultraljudsbaserad PVR-beräkning(r^2=0.69, p<0.001) visade på god överensstämmelse med invasivt genererad PVR, utan att någon större systematisk glidning(+0.1 WU) kunde observeras vid Bland-Altman analys.

3: Endast 22 % av patienterna med hjärtsvikt hade förhöjt PCWP > 15mmhg i vila, dock utvecklade 47 % av patienterna med hjärtsvikt PCWP >15 mmHg under pågående PLL, varav merparten också nådde gränsen(PCWP>25mmhg) för förhöjda fyllnadstryck under liggande cykling. Utveckling av arbetsinducerad hjärtsvikt, där fyllnadstrycket under arbete är mer än 25mmhg, kunde med PLL bestämmas med 90 % ig sensitivitet och specificitet.

4: LAVI och decelerationstiden över mitralis, visade sig i vila i oberoende relaterade till PCWP under PLL. Vid ultraljudsundersökning under pågående PLL, visade univariat analys att parametrarna LASRa (β = -0.77, P <0,001) och E/LVSRe (β = 0.47, P < 0,021) i högst utsträckning var relaterade till PCWP-nivå. Multipel regressionsanalys befäste LASRa och E/LVSRe som höggradigt relevanta oberoende faktorer, relaterade till fyllnadstrycksnivå under pågående PLL.

Diskussion

Baserat på den första delstudien, så bör man misstänka att förhöjd lungkärlsresistans föreligger om PAcT är kortare än 90ms, oavsett om vänsterkammarsvikt föreligger eller ej. PAcT fungerar som ett screeningverktyg för att enkelt identifiera patienter med förhöjd PVR, dock har den uppenbara begränsningar om exakt resistansnivå efterfrågas. Vid dessa frågeställningar, är en PVR-beräkning att föredra, vilket i delarbete 2 bevisats kunna göras med hög precision ultraljudsmässigt, när det ultraljudsgenererade måttet LASRa användes som surrogatmått för PCWP. En betydande del i förklaringsmekanismen bakom att LASRa är inverst korrelerat till PCWP, är att stelhet i vänster kammare motverkar blodets flöde från förmak till kammare under förmakkontraktionen. Om vänster kammares eftergivlighet är nedsatt, leder det ofrånkomligt till oförmåga att härbärgera ökat venöst återflöde, vilket är en form av preloadkänslighet. Höga tryck i vänster kammare leder till att hjärtmuskeln sträcks ut, vilket triggar NT-proBNP utsöndring. I delarbete 3 hade samtliga patienter med misstanke om CHF per definition förhöjda nivåer av nt-proBNP, men detta till trots hade endast en mindre andel

höga fyllnadstryck i vila. Vid preloadprovokation i form av PLL utvecklade närmare hälften patologisk PCWP-stegring, merparten av dessa visade sig vara samma individer som tryckmässigt hade svårt att tolerera liggande cykling. Således identifierades individer med benägenhet för att utveckla höga fyllnadstryck redan vid PLL. RHC är avseende mätning av exakta trycknivåer bättre än ultraljud, men undersökningen är behäftad med några faktorer som gör den mindre tilltalande, däribland kostnad, risken för skada och inte minst tillgänglighet. Mot bakgrunden av svårigheterna att i vila diagnostisera hjärtsvikt med bevarad EF, vore det önskvärt att kombinera belastande undersökning med den utbredda tillgången till TTE. Denna kombination belyses i delarbete 4, där PLL identifierar LASRa och E/LVSRe som höggradigt relaterade till vänster kammares fyllnadstryck under belastning, vilket i förlängningen speglar grad av vänsterkammarsjukdom.

Introduction / Background

The first ever invasive blood pressure measurements were carried out by experimental scientist Stephen Hale on a horse in 1711. He cannulated an artery on the horse´s neck allowing the blood to enter a 9 foot tall glass tube on which he marked and measured fluctuations in the blood level. In 1929 year Doctor Werner Forssmann was the first to demonstrate that cardiac catheterization could safely be performed in humans. Forssmann used himself as a test subject passing a ureteral catheter into the right auricle of the heart whilst documenting it by x-ray. The publication of his article created havoc in Berlin and resulted in withdrawal of his clinical privileges. The technique was improved during the 1930s, and thereafter refinements were made by Cournand, Ranges, and Richards in 1941 making the technique suitable for direct and accurate hemodynamic measurements in the human cardiovascular system.

Congestive Heart Failure (CHF)

Heart failure (HF) is a clinical syndrome characterized by symptoms such as breathlessness, ankle swelling and fatigue, and signs including elevated jugular venous pressure, pulmonary crackles and peripheral oedema. These signs and symptoms are caused by a structural and, or functional cardiac abnormalities, resulting in a reduced cardiac output and, or elevated intra cardiac pressures at rest and, or during physical stress (1).

The diagnosis of chronic HF in non-acute patients relies on clinical history, clinical signs and electrocardiography (ECG). Conditions such as hypertension, history of coronary artery disease (CAD), exposure to cardio toxic drugs/radiation, orthopnoea and the use of diuretics increases the probability of HF. Physical investigation includes assessing for ankle oedema, rales, murmurs and jugular venous dilatation, in conjunction with the presence of ECG abnormalities. If any of these elements are abnormal, BNP or NT-proBNP should be measured and if increased above normal levels sent for additional assessment including echocardiography.

The main terminology used to describe HF is based on the echocardiographic measurement of LVEF; HF with normal LVEF (≥50%) is typically considered HF with preserved EF (HFpEF), and patients with LVEF < 40% are categorised as HF with reduced EF (HFrEF).Over the last few years a third category has evolved, which includes those with an LVEF in the range of 40–49%, defined as HF with mid-range LVEF (HFmrEF) (2). Even though there is an overlap between the types of HF, differentiation based on LVEF is meaningful due to underlying aetiological differences, demographics, co-morbidities and response to therapies.

Heart Failure with Reduced Ejection Fraction (HFrEF)

The current diagnostic algorithm for non-acute HF considers predisposing aetiological factors, including clinical history, physical examination findings, ECG morphology and natriuretic peptide levels. While most CHF risk factors of are universal, some are overrepresented among patients with reduced EF. Patients of male gender, previous history of MI, LBBB, smoking, hyperkalemia and increased levels of NT-proBNP or hs-TnT have increased risk, specifically for new onset HFrEF (3, 4). If the diagnostic algorithm cannot rule out CHF, echocardiography for the assessment of structure and function is warranted.

One of the most important pieces of information provided by echocardiography which aids in the assessment of CHF is the assessment of systolic function via LVEF. The most wide spread and recommended way to assess LVEF is using the modified Simpson's biplane method. Patients with HFrEF have a poor prognoses and the level of LVEF is associated with survival (5). However, novel techniques for assessing deformation and tissue velocities have evolved during the past decade and now present the ability to identify subtle wall motion abnormalities. Left ventricular global longitudinal strain (LV-GLS) has gained increasing focus, as it is able to identify impaired systolic function even among HFpEF patients (6), but also has been found to be the best predictor of adverse outcome in HFrEF (7). Furthermore, LV-GLS has been proven by some studies to be an independent predictor of all causes mortality in HFrEF, after adjustment for all the other univariate predictors of mortality, though is less reliable in women and patients with AF (7). A recent study by Alenzei et al provides data suggesting that LV-GLS reliably can be assessed using only apical 4-chamber view, instead of multiple views, in patients without significant regional wall motion abnormalities (8).

In addition to echocardiography, imaging modalities including magnetic resonance imaging (MRI), coronary angiography, cardiac computed tomography (CT), chest X-ray, positron emission tomography, single photon emission computed tomography and conventional TTE during stress may be indicated and should be used to fully grasp aetiology, viability, ischemia, and comorbidities.

Heart Failure with Mid-Range Ejection Fraction (HFmrEF)

The classification HFmrEF was introduced in 2016 by the European Society of Cardiology, in reference to patients with HF and a mildly reduced ejection fraction of 40–49%. HFmrEF resembles HFrEF in many aspects, for example aetiology is often shared, for example; CAD and dilated cardiomyopathy (DCM) are more commonly the cause, than in HFpEF (1). Changes in LVEF seems to occur quite often over time, with reclassification of HF subtype as a consequence. Deteriorating or improvement of LVEF correlates strongly to course of disease progression and mortality (9). Medications associated with prolongation of life in HFrEF are repeatedly shown, however are less convincing evidence presented supporting the use of standard HFrEF medications in HFmrEF, though some

studies supportive of the use of ARB, beta-blockers and MRAs in HFmrEF (10-12). Biomarkers of ventricular wall stress and inflammation were both related to HFmrEF and displayed an intermediate profile, whereas HFrEF is more strongly associated with NT-proBNP and HFpEF is more associated with inflammatory biomarkers (13). Currently available studies do not provide enough data to conclude outcome differences between HFmrEF and HFpEF patients (14, 15). LVEF may change over time, though it seems like it increases due to positive response to heart failure medication in approximately the same extent as it decreases because of treatment resistant disease progression (16, 17). Prognostic alterations seem to be significantly influenced by change in LVEF. Deteriorating LVEF in patients with a previous diagnosis of HFpEF (LVEF ≥50%) to HFmrEF (LVEF 40–49%) were found to have a worse prognosis than both former HFrEF patients with improved LVEF who reached HFmrEF criteria and in contrast to patients with stabile HFmrEF (15, 16). Rastogi presented some interesting finds regarding HFmrEF categorization and outcomes; firstly, more than 90% of the study population had prior HF diagnosis based on LVEF > 50% or < 40%. Secondly, prior HFpEF diagnosis with deteriorating to LVEF of 40-49% had more advanced diastolic abnormalities in comparison to HFmrEF patients with improved LVEF. There were no differences in respect to HF medication within subgroups. Overall these findings suggest heterogeneous aetiology, despite similar LVEF.

Several studies have now shown treatment effects of conventional HFrEF medication in HFmrEF patients. In the Candesartan in Heart failure - Assessment of moRtality and Morbidity (CHARM) study Candesartan had a positive effect increasing LVEF in HFmrEF patients. In a large review study by Cleland et al, a positive effect in terms of LVEF improvement and cardiovascular death was observed for beta blockers in both HFrEF and HFmrEF, however no positive prognostic effect were observed in patients with atrial fibrillation (AF). In a subsequent study on the TOPCAT cohort Solomon et al showed a benefit of Spironolactone in HFpEF patients defined by LVEF ≥ 45%. However were the positive effect of MRAs only observed in patients with LVEF ranging from 45–55% and particularly in men with CAD and other features traditionally associated with HFrEF.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Prerequisites to diagnose HFpEF are LVEF ≥ 50%, symptoms and signs suggestive of CHF, elevated natriuretic peptide levels (BNP>35 pg/ml and/or NT-proBNP > 125 pg/mL) and echocardiographic signs consistent with diastolic dysfunction (18). In such patients echocardiographic examinations commonly reveal additional structural and or functional abnormalities indicating HFpEF. Nagueh states that at least 1-3 of the following echocardiographic findings need to be present for a diagnosis of HFpEF; Left ventricular hypertrophy, left atrial enlargement (left atrial volume index (LAVI) >34 mL/m2) and functional alterations consistent with diastolic dysfunction (elevated E/e´, E/A, right ventricular –

right atrial (RV-RA) pressure gradient and reduced LV deformation, indicated by reduced global longitudinal strain (GLS).

Signs and symptoms may be minimal and difficult to differentiate at early stages of HFpEF, due to coexisting comorbidities such as COPD, which are frequently present within this patient cohort. Furthermore, diuretic treatment masks symptoms as well as NT-proBNP level, making these patients challenging to diagnose. In order to diagnose HFpEF a diastolic stress test can be performed, either with echocardiography or catheterisation (19).

Supine bicycle exercise with echocardiographic assessment of E/e′, mitral E/A, RV-RA peak gradient, LV-GLS, stroke volume and cardiac output changes with exercise, may be beneficial in the work up. Alternatively, invasive assessment of PCWP and or LVEDP at rest, followed by exercise is recommended (20).

Patients with AF are particularly difficult to diagnose with HFpEF by means of echocardiography, since structural abnormalities as well as natriuretic peptides are heavily influenced by the underlying arrhythmia. AF patients seems notably more prone of developing elevated FPs. The relationship between AF and HFpEF in patients presenting with dyspnoea during stress has been explored with RHC by Reddy et al. The incidence of exercise induced HFpEF meeting RHC criterion, were significantly higher among AF-patients compared to patients in sinus rhythm. The odds ratio after adjustment for baseline characteristics for HFpEF association to persistent/permanent and paroxysmal AF, was 22.1 and 4.86 respectively (21). This suggests that AF is a specific marker of HFpEF, but if it is causative or merely a complication to underlying LV compliance problem remains unanswered.

Recent studies regarding HFpEF indicate 2D and Doppler echocardiographic indexes may not differ greatly from those observed in a comorbidity-matched population, indicating that HFpEF at least to some extent is a systemic disease (22). Some studies report that declining cardiac function is responsible for declining exercise tolerability and disease progression, while others state that disease progression is due to peripheral factors (23). Comorbidities have been shown to be associated with microvascular and myocardial abnormalities. Peripheral muscle biopsies in elderly patients with HFpEF compared to age matched controls, demonstrated lower capillary to muscle fibre ratio, however little attention has been focused on peripheral mechanisms of HFpEF (24, 25).

Typically, patients suffering from HFpEF are elderly women(4, 26) with diabetes mellitus (27), obesity (28), AF (3, 4) and arterial hypertension with or without LV-hypertrophy (29). Global ischemia has been put forward as potential mecha-

nism for development of diastolic dysfunction in these patients, which makes perfect sense, as relaxation is known to be the most energy-consuming phase of the cardiac cycle. Consequently diastolic abnormalities occur before systolic dysfunction and symptoms of angina (30). Thus key factors of CAD such as hypertension are overrepresented in HFpEF. Furthermore, age, female gender and diabetes are associated with diffuse microvascular involvement, hence potentially responsible for underlying stabile CAD (31). There are more contributing risk factors such as renal dysfunction (4), chronic obstructive pulmonary disease (COPD) (32) and sleep apnoea (33), however if these conditions are independently related to the increased risk of development of HFpEF remains to be determined.

Ventricular diastolic compliance (C = ΔV/ΔP)

The combination of elevated left ventricular end diastolic pressure (LVEDP) and normal or reduced left ventricular end diastolic volume (LVEDV) are key findings in HFpEF, and are suggestive of elevated chamber stiffness. The diastolic pressure-volume (P-V) relation, measured invasively by catheterisation, is the most accurate way to assess diastolic function, however this method seldom feasible, hence, the inevitable need for other methods to assess the nonlinear relation of diastolic P-V alterations.

The close relationship between preload, afterload and end diastolic P-V was nicely presented in a study by Leite-Moreira; An upward shift of the diastolic P-V relation was identified upon increased afterload, the addition of preload increase on top of afterload provocation, exaggerated end diastolic P-V relationship in a non-linear fashion. A steeper diastolic P-V curve will result in greater LVEDP if LVEDV remains unchanged, thus indicating increased intrinsic ventricular stiffness. Transient ischaemia, as well as conditions such as cardiac fibrosis or amyloidosis, increases myocardial stiffness and as a result the diastolic P-V slope gets steeper (Figure 1). Hence, end-diastolic P-V relation addressed as delta-volume / delta-pressure reflects ventricular end diastolic compliance, which in these HF scenarios is decreased.

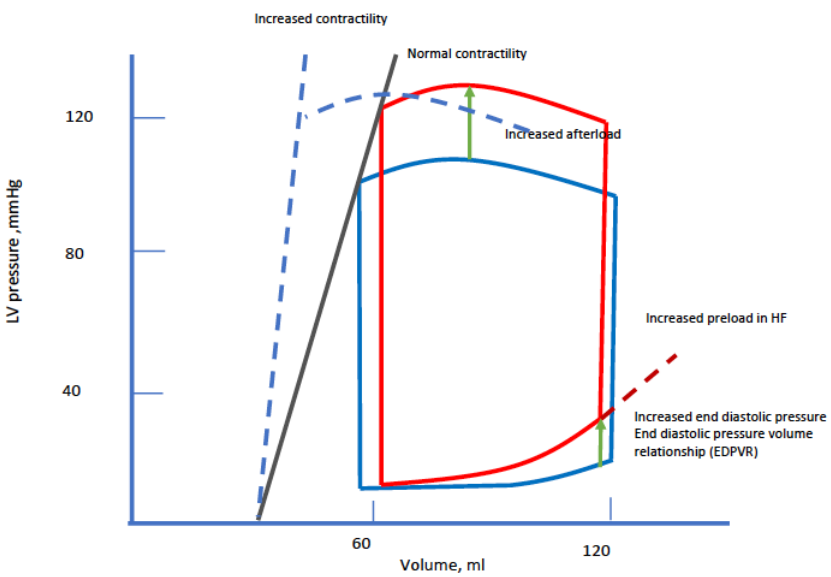

Figure 1. Pressure volume relationship and the effect of altering loading conditions.

According to Frank-Starlings Law of the heart increased fluid loading increases SV, as long as the ventricle is preload responsive. Pre-load responsiveness refers to the myocardium's ability to increase contractile force in proportion to increased myocardial stretch, and is attained as long as effective distending pressure and diastolic sarcomere elongation do not exceed their upper thresholds.

The preload state before commencement of fluid loading is crucial in the generation of SV increase. Irrespective of contractile state the heart will increase SV in response to an increased fluid load if the preload state was low to begin with (Frank-Starlings mechanism), however, this effect is less pronounced and disappears sooner in HF (Figure 2). The increase in SV is highly dependent on the recruitment of contractile reserve, as the predominant effect of fluid loading is an increase of EDV. Even if fluid responsiveness is highly preload dependent, it is worth stressing that it is not the same as preload. SV increase is accompanied and associated to increase in FPs, to which both are dependent on state of contractility, pre-infusion preload and afterload. If only static measures of FPs are assessed, the amount of myocardium recruited to increase contraction is overlooked, making the utilization of only FPs to predict fluid responsiveness less suitable in the assessment of a dynamic process. The inability to increase SV is highly suggestive of HF, stressing the use of preload alterations in the assessment of patients with dyspnoea to conclude cardiac involvement and potentially unmask HF.

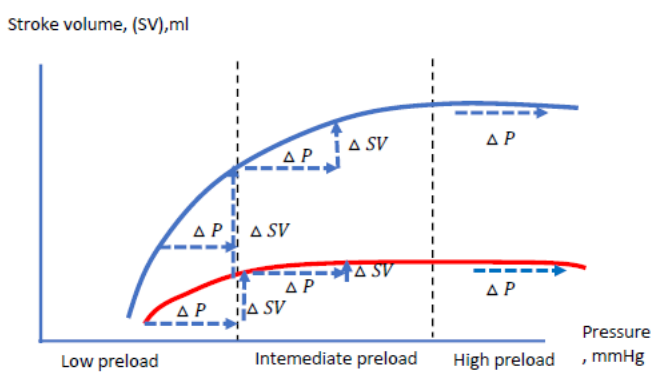

Figure 2. Response to fluid loading. Normal heart in blue, HF red line.

Pulmonary Hypertension (PH) and Pulmonary Artery Hypertension (PAH)

The definition of PH as mPAP ≥ 25mmHg is somewhat arbitrary, nevertheless has been found to indicate a poor prognosis, regardless of etiology (34-36). The Bernoulli equation is used to translate TRV to pressure (Pressure = velocity2 x 4) (37). Echocardiographic findings suggestive of PH are primarily based on systolic TRV> 2.8 m/s (ESC guidelines) (38). Galie et al state that the probability of PH increases with increased TRV (39). Since TRV only reflects the pressure gradient between RV and RA, the addition of RAP to TRV makes sense in order to quantify pulmonary artery systolic pressure (PASP). Given the wide array of difficulties associated with assessment of RAP, peak TRV is favored in the assessment of PH, not PASP, as it is more achievable, however in patients with mild TR, the TRV might be difficult to assess. Echocardiographic contrast may improve the Doppler signal, allowing for attainment of a TRV signal. Despite a strong correlation between TRV and RV to RA systolic pressure gradient, Doppler generated pressure gradients may be misleading on an individual basis and therefore other measures reinforcing the suspicion of PH should be obtained (40). Thanks to the formula established by Chemla et al, calculation of mPAP can accurately be predicted from systolic (s)PAP (mPAP = 0.61 x SPAP + 2mmHg) (41). Peak pulmonary regurgitant (PR) velocity can also facilitate mPAP estimation (mPAP = 4 x peak-PR-velocity2 + RAP) (42). The end diastolic PR-velocity enables estimation of diastolic (d)PAP from the following formula (dPAP = end-PR-velocity2 x 4 + RAP), however might pulmonary regurgitant estimations of pulmonary pressures may be unreliable in conditions associated with high RVEDP, for example pericardial constriction (42, 43). Right ventricular systolic myocardial motion (S'), assessed by tissue Doppler imaging (TDI) of the free wall, is useful in identifying elevated PASP. Maximum S' of < 12 cm/s is suggestive of pressure elevation above normal (44). Lateral tricuspid annular dispersion assessment by TDI, might be useful in identifying PH. RV-IVRT > 75ms is considered substantially prolonged and is associated with PH, while RV-IVRT < 40ms has a highly negative predictive value for PH (45).

PA mid-systolic notching and short PA acceleration time are easily assessed and are strong indicators of elevated PVR, however they do not provide information about the exactly level of PVR (46-48). A methods to grade PVR are presented by Abbas et al in 2003, utilizing the ratio of peak TRV to VTI-RVOT, with an upper limit of normal of ≤ 0.15 , and calculation of PVR by the formula PVR = (peak TR-velocity / VTI-RVOT) x 10 (49).

RV and, or RA dilatation, hypertrophy and flattening of the interventricular septum are also useful observations, when putting the PH puzzle together.

As a rule of thumb in the assessment of PH, a fairly high frame rate is needed, in order to avoid missing changes rapidly taking place. Narrowing the sector enables higher frame rate. Consider agitated saline if the image or TR jet are of poor quality. Achieving an accurate Doppler angle, parallel with flow or myocardial motion, often requires an off axis, non-conventional, echocardiographic views (50).

PH as a concept is not a disease on its own, however a distinct sign of pathology located within the pulmonary arteries or somewhere in the post pulmonary capillary circulation. Conceptually, the distinction in between pre and post capillary hypertension is crucial, however this not possible by solely assessing at the TRV. In order to ascribe PH as pre or post capillary PH, additional information regarding PVR and LV status is required, in particular measures of LV filling pressures. Echocardiographic parameters typically associated with elevated LV filling pressures are high E/e´, E/A, and enlarged LA-volume. Over the last decade has measurements of LV and LA deformation emerged, presenting promising data of improved conformity in respect to FPs. Just as important is the development of echocardiographic parameters related to PVR, as pre and post capillary PH might co-exist.

Irrespective of the etiology, PH is defined as mPAP ≥ 25mmHg at rest, even though available data does not support mPAP of more than 20 mmHg in healthy individuals (51). Currently, the clinical significance of mPAP between 21 to 24mmHg is unclear and should be interpreted with caution together with other hemodynamic and clinical indices associated with PH. Pre-capillary PH is defined as a PCWP ≤ 15mmHg, while post-capillary PH account for those with PCWP > 15 mmHg. PAH is hemodynamically characterized by the presence of pre-capillary PH, with a supplementary criterion of absence of other clinical conditions, associated with pre-capillary PH, for instance chronic thromboembolic pulmonary hypertension and lung diseases. Diagnosis of combined PH requires a PCWP > 15mmHg, with the additive criteria of elevated diastolic pressure gradient (dPAP – PCWP) > 7 mmHg and or PVR > 3 WU. Combined-PH is fairly common in left heart disease and relates to disease severity. Any type of left heart disease may trigger the cascade that leads to combined-PH, starting with venous congestion, followed by pulmonary artery constriction, impaired NO and endothelin availability, and finally vascular remodeling. However, these changes are merely the product of the underlying left heart condition (52) and should be treated accordingly. Small, single center studies have reported improved hemodynamics, decreased symptoms and increased exercise capacity with PAH-specific medications, though are large multicenter studies to support these findings are required. In a study by Bonderman et al, Riociguat failed to improve PAP in a cohort of

patients with reduced LVEF (53). The randomized, double blind, phase 2 MELODY-1 study recently evaluated the effect of Endothelin receptor antagonists in patients with left heart disease PH, without producing any evidence which was supportive of that strategy (54). Together with the FIRST trial in mind, which was interrupted because of increased mortality in CHF patients receiving Epoprostenol, the use of PAH specific treatment in this setting lacks evidence and should not be used in PH-LHD outside clinical trials (55). However, the use of intravenous PAH specific drugs in PAH patients is potentially lifesaving, while oral PAH medication are proven to postpone disease progression (56). Given the positive effects of PAH medications when indicated, they are not to be withheld because of fear of serious drug related side effects, but rather there is a need to improve diagnostics.

NT-proBNP

BNP was discovered in 1988 after isolation from the porcine brain from which it gained its original name “brain type natriuretic peptide”. Subsequently, BNP was found to be synthesised and secreted from the ventricles of the human heart. There are other peptides originating from the heart that shares many features of BNP, however these are currently less studied and have not been validated in a HF setting.

The endogenous function of the heart is mediated by the hormone proBNP, predominantly secreted upon LV myocardial stretch (57). Soon after secretion the pro hormone splits into B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP). The release of BNP activates diuresis, peripheral vasodilation and inhibits the Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic nervous systems. The half-life of BNP is 20 minutes, whereas NT-proBNP has a half-life of 120 minutes, which explains concentration differences in serum samples, in which NT-proBNP approximately six times higher than BNP levels (58).

NT-proBNP < 125 nano grams/L is proposed by the European Society of Cardiology as cutoff value for normal levels. This provides a very high negative predictor value (0.94-0.98) in both acute and non-acute settings. The positive predictive values are though significantly lower, making NT-proBNP useful in ruling out HF, however not accurate enough to establish a diagnosis.

As part of the Irbesartan study in HFpEF patients, multivariate analysis identified AF as the strongest associated baseline risk factor of increased NT-proBNP, with the presence of AF increasing NT-proBNP fivefold (59). Besides AF, mcKelvie stated that age, diabetes and female sex are not only common in HFpEF, but also associated to NT-proBNP levels (60). Interestingly Luchner et al also found weight gain inversely related to NT-proBNP. The kidneys are responsible for the main clearing mechanism of NT-proBNP, which explains the high levels of NT-proBNP commonly observed in patients with impaired renal function. There is data suggestive of a direct release of NT-proBNP upon acute ischemic events, not related to increased wall stress. In acute coronary syndrome (ACS) studies like the FRISC II study, non-ST elevation myocardial infarction (NSTEMI) patients had high levels of NPs, supportive of direct NT-proBNP release associated to myocardial cell injury (61). Later NT-proBNP is proven strongly associated with mortality in patients with unstable CAD (62). NT-proBNP levels have also been demonstrated to be associated with the extent of inducible ischemia and CAD, which suggests that NP levels might be influenced by other mechanisms than wall stress, in particular in CAD patients (63).

Breathlessness and fatigue are typical symptoms of HF, irrespective of LVEF status. Currently, no standard clinical investigation protocol exists to diagnose HF, however, should HF be suspected if clinical history and physical examination (including ECG) include typical signs and symptoms and raised NPs, with respect to NPs close relationship to left ventricular filling pressures and left ventricular size.

Transthoracic echocardiography (TTE) is the last step in the ESC proposed algorithm in the establishment of a HF diagnosis, providing not only additional criteria for diagnosis, but also information about cardiac chamber dimensions, volumes and function facilitating the categorisation of HF type. Typically HFrEF is accompanied by higher NT-proBNP levels than seen in HFpEF despite similar symptoms and exercise capacity, making it more likely to overlook diagnosis and symptoms in HFpEF patients with deceivingly low NT-proBNP levels. Furthermore, measurements of diastolic function are difficult to assess in the early phases of HFpEF as compensatory mechanisms often mean that echocardiographic criteria for grade of diastolic dysfunction are not neatly fulfilled.

HFpEF is structurally characterised by a non-dilated LV (sometimes hypovolemic) often accompanied with myocardial hypertrophy, which, overall does not increase wall stress significantly, even though LVEDP is elevated. This is explained by Laplace's Law:

NT-proBNP = Wall stress = LVEDP x LV-radius / 2 x LV wall thickness, (figure 3).

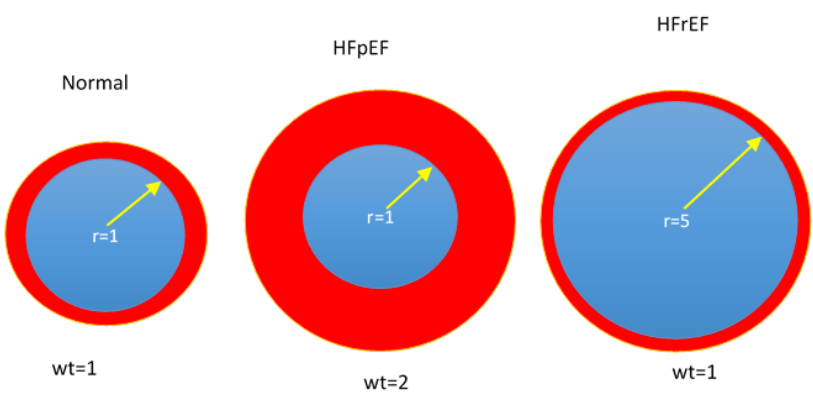

Figure 3. Laplace law

The consequence of having decreased diastolic LV compliance, together with a small ventricular size, may result in deceivingly low NP levels, not consistent with demonstrated exercise capacity. In order to avoid misdiagnosis, awareness of how NPs are related to PCWP and ventricular size, as well as the impact that wall thickness imposes, are important when NPs are widely used to assess the degree of 'stress' the heart is experiencing.

Pulmonary artery pressures from right heart catheterization

The gold standard for determining PVR and pulmonary pressures, includes measuring pulmonary hemodynamics, invasively with a fluid-filled catheter. Measurements of mean pulmonary artery pressure (mPAP) are utilized to determine the presence of pulmonary hypertension. Intrathoracic pressure levels affect all measured pressures including mPAP. While patients with COPD may have a positive intrathoracic pressure, patients with restrictive lung disease may have a highly negative intrathoracic pressure. In this setting it is worth stressing the importance of taking the intrathoracic pressure variations into consideration, to minimize the risk of misinterpreting results, as the measured value are composed of both the intrathoracic and transmural pressure.

The normal PVR response to exercise includes recruitment of pulmonary microcirculation in order to maintain relatively low pulmonary pressure, despite increased CO. The degree of COPD has been shown to be associated with the occurrence of PH (64). Portillo et al demonstrated similar findings, despite borderline (mPAP 20 – 24mmHG) pulmonary pressure at rest (65). The degree of COPD according to Gold classification was related to PVR and TPG, as well as development of EIPH mPAP > 30mmHg at submaximal exercise. As COPD progresses, PVR appears to become more fix, diminishing pulmonary circulation prerequisites to increase CO during exercise (65). Abnormal increase in pulmonary pressures in COPD patients has been documented by other Sims et al and also demonstrated to be associated with poor results from the 6 minutes walking test (66). In addition Portillo et al stresses the importance of abnormal pulmonary gas exchange, highly predictive of PH, regardless of COPD severity (65). In a COPD investigative series presented by Chaouat et al. severe PH was predominantly associated with less pronounced air flow limitations, advanced arterial hypoxemia, higher partial pressure of CO_2 and lower diffusing capacity of carbon monoxide (DLCO) than in patients with moderate PH (67). Overt PH in COPD is only seen

in less than 1% of patients, while frequently observed in the clinical course of idiopathic pulmonary fibrosis (IPF), though both are associated with higher mortality (68, 69). Patients with a combination of both emphysema and pulmonary fibrosis (CPFE) are prone to developing overt PH, a devastating complication associated with the poorest prognosis of all types of PH (70). Furthermore CPFE-PH is not necessarily associated with severe spirometric or lung parenchyma abnormalities seen on CT, but rather affected by highly depressed diffusion capacity, making the differentiation between CPFE-PH and IPAH difficult.

Histopathological studies of HFpEF patients with PH have described pathological remodelling of the pulmonary vasculature that resembles the vessel changes seen in patients with PAH (71). However, left heart disease (LHD) accompanied by PH is characterized by fibrosis and myofibroblast proliferation, and to a lesser extent affected by plexiform lesions and intimal proliferation, with is often observed in PAH patients (72). Gerges et al stresses the importance of grading the degree of vascular remodelling in PH-LHD, because post capillary-PH patients with transpulmonary gradient (TPG) > 12mmHg had worse prognosis if diastolic pulmonary gradient (DPG) exceeded 6mmHg (73).

Pulmonary artery pressures from Doppler echocardiography

Estimation of pulmonary artery pressures using non-invasive methods (Doppler echocardiography and phonogram) were presented in 1981 by Hatle and co-workers who measured isovolumetric relaxation time; the time interval from pulmonary valve closure (phono) to tricuspid valve opening (Doppler). Hatle et al found a prolonged time interval was related to an increased pulmonary pressure (74). This finding is still pertinent today with Lindqvist et al confirming these findings using up to date pulsed tissue Doppler techniques (75).

In 1983 Kitabake et al found a curve-linear relationship between pulmonary artery flow profile and mean pulmonary pressures using pulsed Doppler technique (acceleration time/ ejection time) (76). This finding has later been confirmed in a recent study (48).

In 1984 Yock et al found a strong correlation between pulmonary artery systolic pressure and the RA-RV pressure gradient using the continuous wave Doppler technique and the Bernoulli equation. They used assessment of the jugular veins to estimate right atrial pressures (37). This was supported by Berger et al in 1985 (77).

In 1988, Simonson et al found that the size and motion of the inferior vena cava in response to respiration related to RA pressures (78). This methods is today is today an established method recommended for the estimation of RA pressure (40). However, recent studies have shown its limitations (79).

Pulmonary capillary wedge pressure from right heart catheterization

Pulmonary capillary wedge pressure (PCWP) in the context of cardiac catheterization refers to the pressure that is obtained when occluding one of the arterial branches of the pulmonary circulation, most often performed by inflating the balloon at the tip of the catheter. Since the tip is located within the pulmonary artery and occluding the lumen, the rationale of the nomenclature pulmonary artery occlusion pressure (PAOP), pulmonary capillary wedge pressure (PCWP) and pulmonary artery wedge pressure (PAWP) seems logic and are used interchangeably.

Due to hydrostatic pressure within the cardiovascular system there are diastolic pulmonary vascular pressure gradients with higher pulmonary artery pressure (PAP) and pulmonary venous pressure (PVP) at the basal parts of the lungs, in comparison to the apical parts, when in an upright position. The level of PAP and PVP has to exceed alveolar pressure (P-alveolar) to obtain a true PCWP. When alveolar pressure exceeds PVP, the capillary beds collapses, which in turn disrupts the continuous column of blood from the atria to the catheter, making these locations not suitable for obtaining PCWP values. According to West criteria, apical (West 1) areas of the lung have greater alveolar pressure, than PAP and PVP, West 2 (mid area), PAP > P-alveolar > PVP, whereas the basal part (West3) PAP > PVP > P-alveolar (80)(galvin). On the catheterization table, patients are in a supine position, the ratio P-alveolar over PVP is decreased, making most of the lung a West zone 3 area. Differences according to ventilation and lung perfusion are not as pronounced in ventral parts of the lung, however sensitive to positive end-expiratory pressure (PEEP) in supine position. Because of the alveolar pressure augmentation it induces, with significant risk of non-zone 3 located catheter tip, the risk of alveolar pressure measurements instead of PCWP is often observed as a large respiratory swing. Increased RV afterload and intrathoracic pressure, as well as the reduction of LV preload are associated with PEEP, making hemodynamic assessments challenging.

PCWP waves are transmitted through the capillary bed with a resulting significant time delay in comparison to direct LVEDP measurements. The time delay, are attributed to the distance that the pressure wave must transverse. These conditions need to be taken into consideration since they can lead to discrepancies in PCWP and LVEDP (81).

Mitral stenosis as well as pulmonary venous stenosis and pulmonary occlusive disease, result in anatomical narrowing's between wedge position and the LV. Pressure gradients are thereby present making PCWP higher than LVEDP. Exaggerated differences between mean PCWP and LVEDP are also seen when large V-waves are present, for example in such conditions as mitral regurgitation, stiff LA-syndrome and atrial fibrillation. Reversed trans mitral flow, less compliant

LA, accelerated LA fibrosis and loss of LA-'booster pump' function, are factors impairing LA harboring properties, producing profound pressure elevation in the LA and pulmonary veins during ventricular systole (82).

It may seem confusing to measure pressures which reflects the left atrial pressures within the pulmonary circulation however, in the absence of resistance to flow this becomes irrelevant and the pressure at the tip of the catheter reflects the stationary blood pillar originating within the left atrium. Thus PCWP equals LAP, when the balloon is inflated.

$$P_{wedge} - P_{LAp} = Flow \times Resistance$$

$$\textit{When flow is zero: } P_{wedge} - P_{LAp} = 0 \times Resistance$$

$$\textit{Thus: } P_{wedge} - P_{LAp} = 0$$

$$\textit{Which makes: } P_{wedge} = P_{LAp}$$

Even though PCWP is similar to LVEDP, they are not entirely equal, except at the very end of diastole when trans-mitral pressure gradient and flow ceases. In accordance with several studies, which states that end expiratory wedge pressure (eePCWP) is the best surrogate measure of end expiratory LVEDP, most centers have adopted this approach and also recommended by esc guidelines (38). However, in specific patient cohorts in which large intrathoracic respiratory pressure differences are found, such as obesity and COPD, the digital mean PCWP seems more reliable (83, 84). Assuming that negative inspiratory and positive expiratory intrathoracic respiratory pressures changes cancel each other out, digital mean PCWP over multiple respiratory cycles is also acceptable (85).

The mean PCWP reflects LAP during the entire cardiac cycle, and provides a measure of the hemodynamic burden that the LA imposes (indirectly diastolic LV operating compliance) on the pulmonary circulation. This makes digital mean PCWP the most relevant pressure to assess when considering pulmonary congestion, whereas LVEDP is more of a measure of LV diastolic compliance and LV-preload, (figure 4).

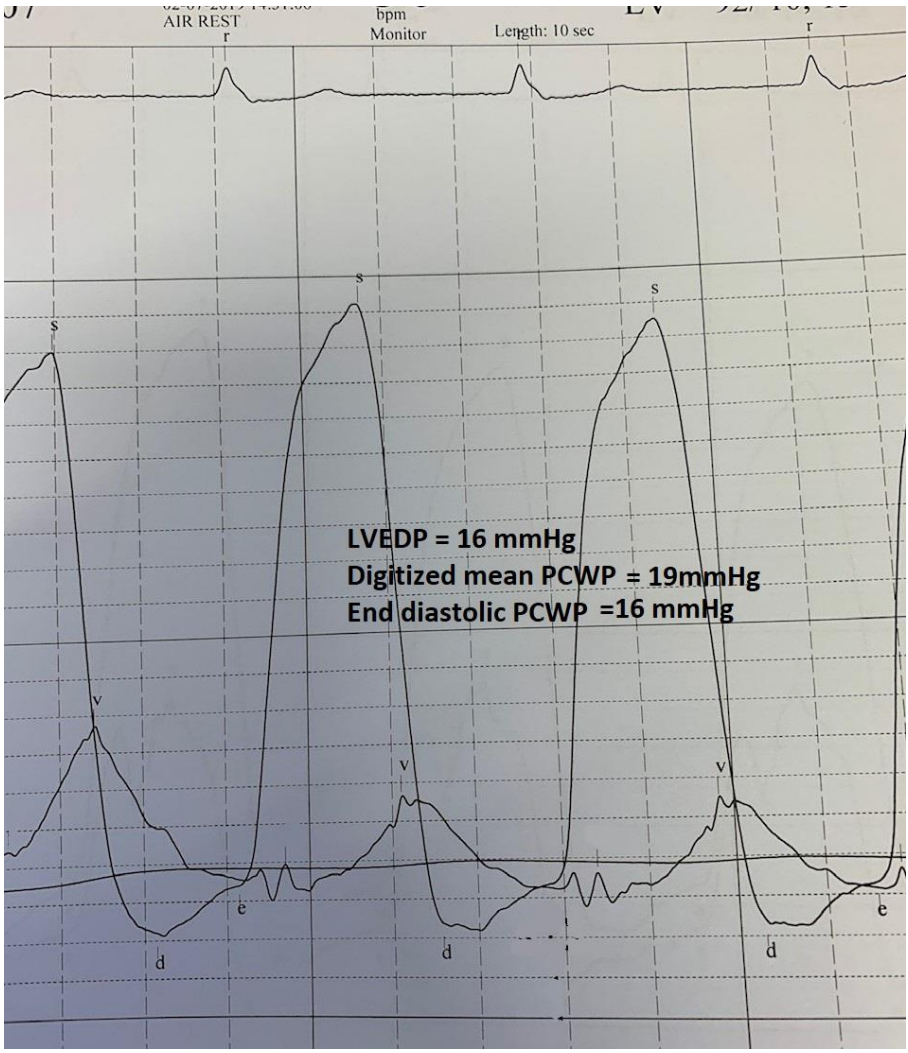

Figure 4. Superimposed LV and PCWP pressure

Prior studies provide inconsistent data regarding the usefulness of PCWP as an indicator of LVEDP. Systematic underestimation of LVEDP due to use of end-expiratory PCWP measurements has been described by Halpern et al (86). A later study by Dickinson et al (87) showed that heart rhythm has a profound effect on PCWPs ability to assess LVEDP. In sinus rhythm digital mean PCWP underestimates LVEDP within approximately 3 mmHg, whereas in AF mean PCWP overestimates LVEDP by approximately 5mmHg. This suggests that PH-patients in sinus rhythm may be wrongly classified as PAH, if assessment is based upon digital mean PCWP alone, however improved end-expiratory PCWP measurement

only the agreement for patients in sinus rhythm. Mechanisms to adequately explain this relationship are not fully understood, however pronounced respiratory fluctuations often seen among obese and patients with pulmonary disease may be part of the explanation (88). Hemnes et al found older age associated to underestimation LVEDP when mean PCWP were used (89). Large left atrial size, atrial fibrillation large v-waves and rheumatic valve disease were on the other hand associated with overestimation of LVEDP, when utilizing mean PCWP. Correlation between mean PCWP and LVEDP were modest ($r^2 = 0.36$, $p < 0.001$) and the mean difference of mean PCWP and LVEDP were -1.36mmHg.

Without flow, there would be no pressure; this intrinsic relationship was described by Otto Frank and Ernest Starling and gained wide acceptance in 1915, later known as Frank-Starlings Law. The law states that "the force acting to stretch the left ventricular muscle fibres at the end of diastole determines the resting length of the sarcomeres", which means that stroke volume increases in response to increase of volume of blood in the ventricles at end of diastole, to a point. As venous pressure increases, larger amounts of blood flows back into the ventricle, the blood stretches the myocardial fibres, which in turn leads to an increase in the force of contraction. LV preload is dependent on LVEDP, although not synonymous (90). The effective distending pressure of LV at the end of diastole (edLVEDP) is more appropriate than intra-cavity pressure LVEDP. edLVEDP = LVEDP – extra-cardiac pressure. Conditions associated with a substantial increase of extra-cardiac pressure can elevate external constraints more than LVEDP, thus in such cases preload is reduced in despite of LVEDP increase. Situations producing significant external pericardial constraint or surrounding pressure are for example PEEP, acute pulmonary embolism with increased RVEDP and pleural and pericardial fluid induced by CHF. These conditions may demonstrate absence of preload increase upon fluid administration, an effect which is attributed to the inability of the heart to increase effective distending pressure in comparison to intra-cavitary pressure. The potential discrepancy between LVEDP and edLVEDP in situations with elevated extra cardiac pressure, brings into question the usefulness of LVEDP as an indicator of preload. Right atrial pressure (RAP) and pericardial pressure are closely related. Calculating LVEDP by subtracting RAP from PCWP, thus provides a reasonable estimate of edLVEDP (91).

When the surrounding pressure is nearly zero, as in healthy individuals at the end of expiration, preload alterations are accurately reflected by change in LVEDP. Hence, LVEDV will rise along with edLVEDP, increasing sarcomere stretch and thus stroke volume. In general diuretic treatment works the other way around, reducing blood volume and thereby preload, which compromises contractile force and reduces stroke volume.

In COPD patients, the positive pressure within the hyper inflated lungs elevates the mean intrathoracic pressure (92), thus increasing respiratory swing. While the pressure of interest is intra-cardiac, intrathoracic pressures must not be neglected or thought irrelevant as they comprise part of the pressure that is measured. The oscillating intrathoracic pressure differences are far more pronounced during exercise and may by further overestimated if assessed at the end of expiration. Boerrigter et al proposes an oesophageal respiratory cycle correction strategy, which includes a pressure sensor placed in the oesophagus, to exclude respiratory swing and intrathoracic pressure abnormalities in COPD patients (93). The authors also found a good correlation in between eeRAP and intrathoracic pressure, later shown suitable as an alternative to the oesophageal approach in correcting respiratory variations in PCWP (93). Due to the close relationship between RAP and CVP ($r = 0.95$), both are suited to correct for pericardial pressure abnormalities in daily practice (94). Whether LVEDP would be a preferable method to overcome respiratory swing is questionable, when LVEDP also is affected by surrounding pressures and highly influenced by upstream pressure changes (83).

Viewed in the light of current guidelines, end expiratory wedge is favored, when intrathoracic pressures at the end of exhalation is more equivalent to atmospheric pressure (95), as well as based upon CHF-studies assessing its relation to LV-diastolic pressure. But according to a study by LeVarge et al, the risk of inverse misclassification applies if end expiratory PCWP are used routinely (83). The clinical phenotype proved to be better in line with respiratory mean PCWP, highlighting the need to individualize method when assessing LV filling pressures, as well as taking clinical symptoms and signs into consideration, before classifying PH as PVH or PAH. Furthermore, Levarge et al suggests that LVEDP respirophasic variations are highly correlated to simultaneous respirophasic PCWP alterations. With these similarities in mind, apparent risk of misclassification applies for both methods. This type of conformity seems perfectly logic as long as the blood pillar are not interrupted by pressure generating anatomical changes such as pulmonary venous- or mitral stenosis. If this type of post capillary obstacles exists, higher PCWP than LVEDP should be anticipated.

However, inverse pressure relationships exist where PCWP is lower than LVEDP (86). A convincing explanation for this inverse relationship, though not presented. These results highlights the importance of avoiding the conclusion that a patient has PAH without evaluating the LVEDP. The fact that measured LAP in several studies is lower than LVEDP, questions the robustness of the method, since these pressure circumstances appears non physiological, as diastolic trans mitral flow would cease during such conditions. LVEDP is a measurement made at one single time point, whereas mean PCWP is a composite measure, taking

many contributing factors into consideration including ventricular filling pressures. A minimal pressure gradient has to be present to maintain blood flow, however when the PCWP/LVEDP gradient is increased Mascherbauer et al showed that this gradient is strongly related to pronounced DLCO decrease as well as more advanced HFpEF disease (96). Furthermore, the authors found that mean PCWP, but not LVEDP, was associated with patient outcomes. This may be attributed to the fact that mean PCWP is a better measure of pulmonary congestion, furthermore that pulmonary fluid overload is associated to reduction of DLCO, higher PVR and RV dilatation (97). DLCO < 45% has been put forward as a strong predictor of adverse outcomes by affecting vascular remodelling, which in turn may be explained by longstanding PCWP elevation rather than LVEDP (98).

Leg lifting and fluid challenge

Data from fluid loading and passive leg lifting (PLL) studies reveals high FPs among patients with normal pressures at rest, supporting the argument for non-maximal stress testing. Bush et al found a non-significant biventricular FPs increase of 1-2 mmHg upon 1L pre warmed saline, administered over 6-8 minutes in healthy subjects, however dramatic pressure increase were observed in patients with constrictive pericardial disease (99). Despite having normal FPs at rest, both PLL and active leg lifting (ALL) can elucidate diastolic compliance disturbances, and thus are useful in stratifying early HFpEF. On multivariate analysis, age and E/e´ remained predictors of LVEDP increase during active leg lifting, however LV-mass did not, highlighting that changes are mainly due to hemodynamic factors related to ventricular stiffness rather than structural abnormalities (100). Level of LVEDP increase during leg lifting correlated to severity of symptoms, reinforcing explanatory power of the examination (100). Biventricular filling pressure patterns in healthy individuals separated by age, are nicely investigated in a study from 2017 by Wolsk et al (101), PVR and systemic vascular resistance (SVR) at rest were correlated to age, however interestingly no other hemodynamic factors. LVFPs were assessed as end expiratory wedge. LVFPs increased with age during PLL. Adopting a 95% confidence interval PCWP-PLL were found to be in the range from 15 mmHG to 18 mmHg among 60 – 80 years old subjects, suggesting an upper limit of normal of eePCWP of 18 mmHg for the oldest cohort.

PCWP during stress

The PVR-equation PVR = (mPAP – PCWP) / CO may be rearranged as mPAP = PVR x CO + PCWP. Knowledge of this relationship is essential when assessing LVFPs invasively, though more important non-invasively at rest and even more so during exercise. CO and mPAP are part of a routine assessed by TTE, while PCWP is somewhat more challenging to assess by TTE. Pulmonary resistance is consequently the result of the three other components of the equation, which are difficult to assess by other means. Repeated studies fortify the perception of PVR as a constant or decreasing during exercise (65), in contrast to CO and PCWP, which increases depending on the workload and cardio pulmonary status. During the past years tricuspid regurgitation velocity (TRV) has evolved as one of the most valuable tools for assessing LVFPs, due to its relationship to pulmonary pressure, which in turn is partially constituted by PCWP. Pulmonary pressures within normal ranges makes PVR disease and elevated LVFPs highly unlikely, though possible in low flow states.

Left ventricular preload is crucial in respect to CHF and LV filling properties are often ascribed as PCWP or LVEDP. With regards to the concept of preload, pressure cannot be evaluated in isolation and should always be assessed in reference to stroke volume and change of stroke volume, as they are significantly affected by each other. The ratio of PCWP/CO > 2 during exercise, has been proposed as a cut off where after LV dysfunction should be suspected, even when LVFPs are normal at rest. PCWP/CO slope > 2 is common and predictive of HF, thereby challenging current invasive HFpEF definitions (102).

The relation in between pulmonary pressure and LVFP is particularly interesting when stressing the cardiopulmonary system. Over the past years, mean pulmonary pressure at peak exercise > 30mmHg, together with mPAP / CO > 3 has been proposed as the definition of exercise induced pulmonary hypertension (exPH) (103). exPH is an early sign of pathology indicative of pulmonary vascular disease, or left heart disease or a combination of the two, in patients with normal or borderline elevation of pulmonary pressures at rest, forming a divergent patient category in need of follow up. To clarify the underlying hemodynamic mechanism behind exPH, PVR, PCWP and exercise-PCWP is crucial. Eisman et al recently presented a study addressing the difficulties and prognostic benefits of identification of hemodynamic alterations in HFpEF, in patients presenting with dyspnea and normal PCWP at rest. Exercise-PCWP / CO > 2 was found in 41% of patients and was highly associated with decreased peak VO2 and adverse cardiac outcomes (102).

Doppler echocardiography and left side filling pressures

In healthy hearts, variations in preload and diastolic function are facilitated by good compliance in the left ventricle which allows for generation of increased stroke volume (Frank Starlings mechanism). However, if the LV becomes stiff, most commonly due to fibrosis or hypertrophy, the LV lose its compliance and pressure within the LV increases. Increase of LA pressures is the only way to maintain diastolic filling of the LV and thus abnormal diastolic function. This could easily be measured by RHC but this is impossible to do in every patient suffering from diastolic dysfunction. Therefore, Doppler echocardiography is recommended in clinical practice. In 1972 Konecke et al, showed the relationship between trans-mitral flow assessed by M-mode and LV filling pressures (104). This pattern was later confirmed using pulsed wave Doppler by Appleton and coworkers in 1988 (105).

Today Doppler echocardiographic parameters are well defined and used in clinical practice as a standard method for estimation of LV filling pressures (figure 5).

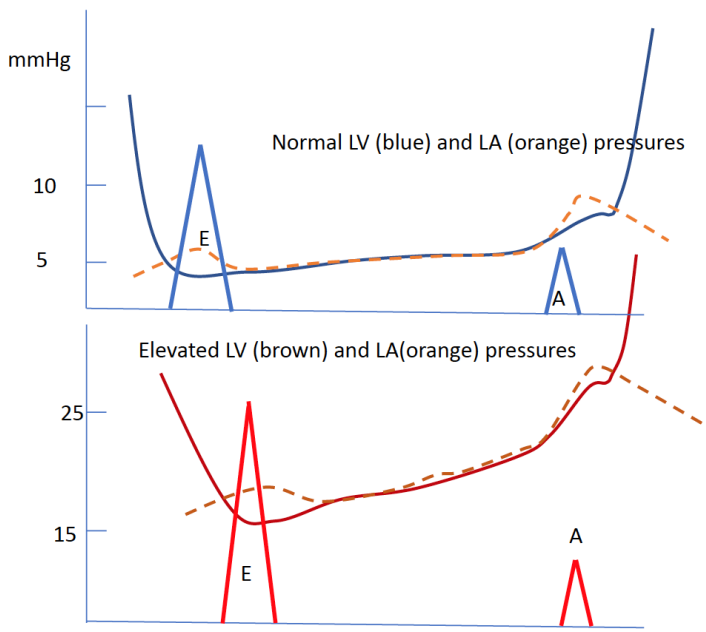

Figure 5. Trans-mitral flow and LV and LA pressure superimposed. Upper in normal filling pressures and lower elevated filling pressures.

Recommendation were published 2009 by Nagueh et al which suggested an algorithm, based on Doppler echocardiography, to grade diastolic dysfunction (106). This recommendation was later updated, focusing on identifying patients with elevated filling pressures. Both recommendations used trans-mitral flow (fig 6A) , pulmonary venous flow (fig 6E), pulsed tissue Doppler analysis of early diastolic myocardial flow (e') (Fig 6 C), left atrial volume(fig 6B) and estimation of pulmonary arterial pressures (fig 6D). The methods proposed were described in both HFpEF and HFrEF patients. In addition, LV long axis deformation or strain measured using 2D global longitudinal strain (GLS) might also be useful (fig 6F).

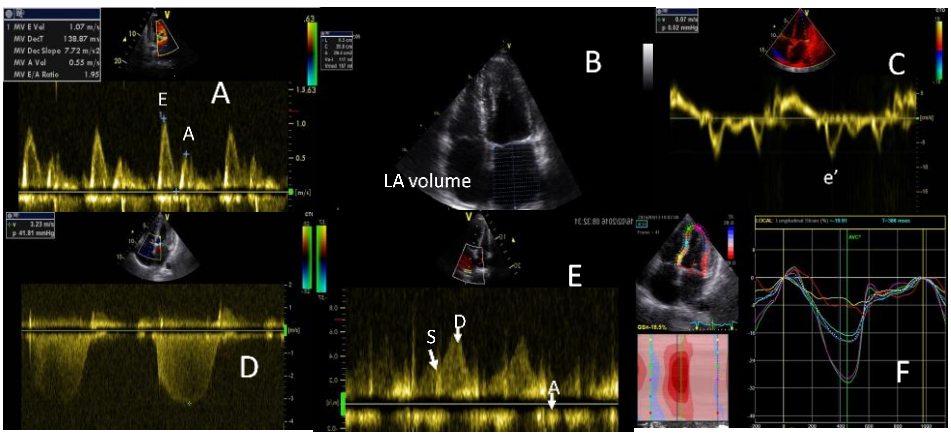

Figure 6A-F.

However, the use of cardiac stress was sparsely described in both recommendations. Nonetheless, a number of studies have shown the use of stress to identify elevated LV filling pressures, especially in patients with HFpEF. This is shown using supine bicycle exercise (107), hand grip maneuver (108) and passive leg lifting (109), (110), as well as a leg massage machine, which increases preload (111). The main findings of these studies were that patients with abnormal increase in LV filling pressures, were found to have increased E/A, E/e' and estimated pulmonary pressures as well as lower systolic functional reserve, lower increase in stroke volume and cardiac output.

Overall Aim

To investigate the possibility to improve the diagnosis in heart failure and the differentiation in between pre and post capillary pulmonary hypertension, using Right Heart Catheterization and/or Doppler Echocardiography.

Specific aims

1. How can Doppler Echocardiography (DE) derived PAcT be used to identify patients with PVR > 3 WU in pre and post capillary PH patients?
2. How can we estimate PVR on an individual basis using DE?
3. How can Passive Leg Lifting (PLL) and exercise improve diagnosis of HF using RHC
4. How can DE be used to estimate changes in PCWP during PLL

Materials and Methods

Patients

All subjects in this thesis were recruited on the basis of their upcoming RHC. Dyspnoea on exertion was the main symptom for which patients were referred for RHC. In study 1, 2 and 4 data was prospectively collected at Norrland's University Hospital. Echocardiographic data was collected simultaneous and all were in sinus rhythm. Study 3 was a retrospective study conducted using data from Akademiska University Hospital, this cohort included patients with AF and echocardiographic examination were carried out within close proximity (±3days at most) to the RHC, accordingly not necessarily simultaneous. Clinical diagnosis was determined from the medical records. Patients with poor acoustic windows, heart transplanted, presence of significant intra cardiac shunts, large vitium organicum cordis or incomplete RHC data were excluded and digitized mean PCWP were used consequently in all four studies.

Study 1

Pulmonary hypertension is the product of a problem within the pulmonary vasculature or somewhere within the left heart, though frequently difficult to pin point. Ascertaining raised PVR is proven a clinical prioritised objective. Various echo parameters has been put forward to assess PH, which in itself indicates poor user friendliness and or insufficient robustness of the method. From the pulmonary artery velocity time integral (VTIrvot), pulmonary acceleration time (PAcT) was defined as the interval between the onset of ejection and the peak flow velocity, (figure 7). We hypothesised that PAcT and PAcT/PASP would reflect elevated PVR better than other frequently used methods. In order to adjust for heart rate PAcT / $\sqrt{RR}$ was used.

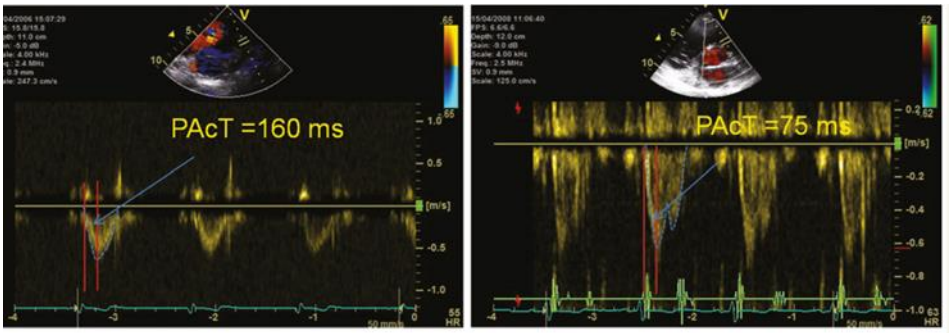

Figure 7. PAcT in normal (left) and in patient with pre-capillary pulmonary hypertension (right)

Study 2

Even though echocardiography is efficient and establish method for identifying PH in patients, differentiating pre from post capillary PH is still challenging especially in regards to an accurate assessment of PVR deviation. Based on our previous findings showing a strong correlation between LASRa and PCWP, we hypothesized that LASRa could be a substitute for PCWP in the established PVR formula; $PVR_{echo} = mPAP_{echo} - PCWP_{LASRa} \ / \ CO_{echo}$

Study 3

How LVFPs reacts to preload increase induced by PLL is not fully understood. We hypothesized that the response to PLL in dyspnoeic patients would be highly related to NT-proBNP considering its close relationship to wall stress and LVEDP. LVEF ≥ 50% and pulmonary resistance within normal range, were prerequisites for inclusion into this study. This decision was made with the intension to assess a subset of HF patients, which are known to be difficult to identify and differentiate at rest, irrespective of investigative modality.

Study 4

Dyspnoea on exertion is common, however is aetiology often multifactorial. Rapidly elevating filling pressures with alternating loading conditions is frequently observed in CHF, irrespective of LVEF. Improvement of non-invasive assessment

of volatile filling pressures is warranted, since Doppler echocardiographic measures such as E/e`, have not been able to present convincing, unambiguous proof that they represent accurate PCWP during stress. Patients in sinus rhythm with clinical signs of HF who underwent RHC were assessed at rest and with their legs lifted passively (PLL) and rested on a large pillow angled at 45 degree. Pressures by RHC and Doppler echocardiography assessments were performed after 2 minutes. Standard measures of chamber size, flow and velocities were recorded at rest and during PLL, as well as post processing analysis for LA and LV myocardial deformation. PCWP > 15mmHg at rest and during PLL were considered elevated in accordance with guidelines at that time.

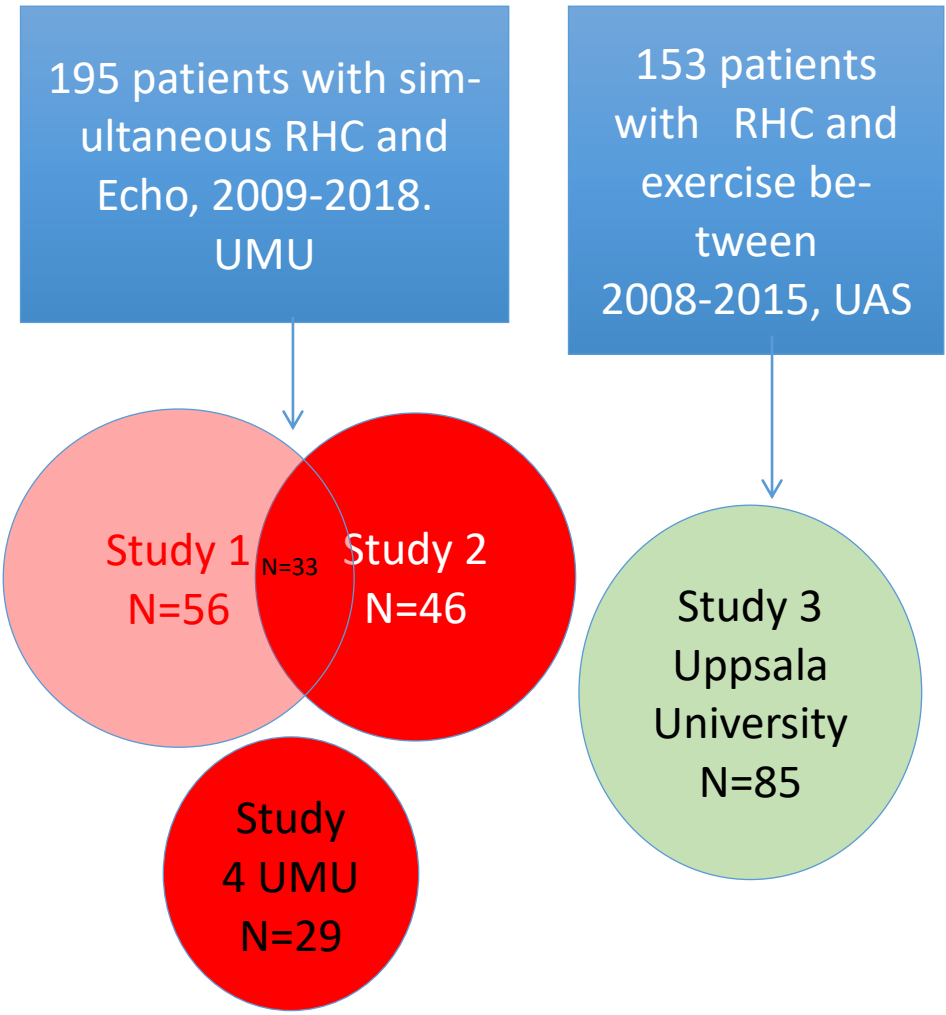

Figure 8. Patient selection the thesis

Ethics

The study protocol for studies 1, 2 and 4 was approved by the regional ethics committee of Umeå. Study 3 complied with the declaration of Helsinki and was approved by the Ethical approval board in Uppsala. All patients gave informed consent.

Right Heart Catheterization

Invasive pressures and flow measurements were recorder in all four studies. All patients studied were rested in the supine position, long-term medications were kept unchanged. Standard RHC was performed using a 7 Fr sheath via the internal jugular, cubital or femoral vein. Transducers were zeroed at mid-thoracic level, which was established by means of spirit level and yardstick in each patient. A fluid-filled catheter was advanced through the lumen of the inserted sheath, in order to measure digitized mean, right atrial, right ventricular, pulmonary artery, and PCWP. PCWP was verified based on characteristic waveforms and appearance on fluoroscopy. In cases of uncertainty, wedged oxygen saturation and or LVEDP was added. SBP was measured by oscillometric arm cuff sphygmomanometer. An increase of 8% between superior vena cava and the pulmonary artery was used to rule out significant intra cardiac shunts. CO was determined by thermodilution and, or the direct Fick method. Arterial-venous oxygen content difference was measured directly as the difference between systemic arterial and pulmonary artery oxygen content. Expired gas analysis was carried out with an Oxycon device to determine Oxygen consumption.

Doppler-Echocardiography

A GE Vivid 7 or 9 system (GE Medical Systems, Horten, Norway) equipped with an adult 1.5–4.3 MHz phased array transducer was used for all examinations. Standard views from the parasternal long and short axes and apical four- and two-chamber views were acquired. Flow velocities were obtained using pulsed- and continuous-wave Doppler techniques as proposed by the American Society of Echocardiography and European Association of Echocardiography. All Doppler recordings were made at a sweep speed of 50–100 mm/s with a superimposed ECG (lead II). LA volume was only measured from the four-chamber view, either by manually drawing maximum LA volume or adopting the area length method, and both at the very end of ventricular systole. The equation published by the European Society of Cardiology and American Society of Echocardiography was used to calculate CO**.** Peak early (E) diastolic velocity and E-wave DT and the E/A ratio was calculated from the trans-mitral flow signal. Visualisation of the trans-pulmonary valve jet, was obtained from the short-axis view. Either the parasternal right ventricular inflow view or the apical four-chamber view was used to assess retrograde systolic trans-tricuspid regurgitant flow, reflecting PASP**.** The modified Bernoulli equation $P = 4xV^2$ was used to assess peak tricuspid pressure drop.

Myocardial deformation was assessed from the apical four-chamber view and analysed off line using (GE, EchoPAC version BT 13, 113.0, Waukesha, Wisconsin, US) in study II and IV, while (GE Medical Systems, EchoPAC version 5.0.1 Waukesha, US) were used in study I. Care was taken to avoid foreshortening of atrial and ventricular walls in order to avoid inclusion of the LA appendage and pulmonary veins in analysis. A point and click technique was used to delineate the endocardial boarders of the LV, where after strain and strain rate were calculated. At least 4 out of 6 segments were required to have suitable tracking in order to be adequately analysed. The average of three consecutive cardiac cycles was used to determine measures of deformation.

Biomarkers

Level of NT-proBNP is reported in study II, III and IV, while Troponin T only was reported in study II. Analysis were performed at the clinical chemistry laboratory in Umeå University Hospital (study II and IV), while blood samples in study III were analysed at the clinical chemistry laboratory in Akademiska Hospital. Biochemical analysis for Troponin T and NT-proBNP were performed on a Cobas 8000 modular multianalyser (Roche Diagnostics, Basel Switzerland), with reagents from the same manufacturer. Troponin T was analysed with a high sensitive method (Troponin T hs STAT, catalog no. 05092728190) with a lowest level of detection 3 ng/L. The total coefficients of variation (CV) were 5.4% and 2.0% at levels of 29 and 2362 ng/L, respectively. NT-proBNP was analysed with proBNP STAT (catalog no. 05390109190). The total CV was <6% at both levels 100 and 4000 ng/L.

Statistics

Normally distributed baseline characteristics of the study cohort (studies 1-4), RHC parameters (studies 1- 4) and echocardiographic characteristics (study 1, 2 and 4) were expressed as mean, together with one standard deviation. Medians and interquartile was also used to describe characteristics of the cohort in study 4.

Study 1

One way ANOVA was used to determine whether there were any statistically significant differences in baseline characteristics and hemodynamic parameters, between the four groups with separate hemodynamic profiles. Pearson´s correlation coefficient was used to test the association between echocardiographic parameters and RHC data. In order to evaluate the best discriminating factor to identify PVR ≥ 3.0 ROC curve analysis was performed. In order to test what cut off to use in order to correctly identify and exclude elevated PVR, accuracy analysis was performed.

Study 2

The association between echocardiographic parameters and RHC data was tested with Pearson´s correlation coefficient. Bland-Altman analysis was performed to ensure that there was a good agreement between the two methods. Intra-class correlation coefficient was performed to test the reliability of measures made by different investigators. ROC curve analysis was performed to depict the diagnostic ability of echocardiographic parameters related to PCWP. The predictive power and performance of echocardiographically assessed PVR was expressed as sensitivity, specificity, accuracy, Youden´s index, negative predictive value and positive predictive value.

Study 3

Student's *t*-test and Fisher's exact probability or X^2-test, were used in the group comparison of patients with normal respectively elevated NT-proBNP (Study 3). Paired *t*-test was used to compare RHC data during different loading conditions (study 3). Specificity, sensitivity and accuracy were calculated to predict elevated PCWP from resting NT-proBNP

Study 4

Median and percentiles were used to describe resting data and Mann-Whitney U test to identify differences in patients according to PLL response. The association

between echocardiographic parameters and RHC data was tested with Pearson´s correlation test, at rest and during PLL. Multiple backward regression analysis was performed, to identify the strongest independent echocardiographic parameter related to PCWP. Specificity, sensitivity and the accuracy of echocardiographic parameters in identifying elevated $PCWP_{PLL}$ were tested.

Results

Study 1

Patient characteristics

In total 60 Patients were eligible for inclusion, however 4 patients were subsequently excluded based on circumstances listed above. The study population constituted of 56 patients with varying aetiologies. 23 (41%) of the 56 patients were male. 32 patients had PVR associated conditions, 21 had primarily left heart disease, whereas 3 had conditions neither associated to pulmonary vascular disease nor left heart disease. Digitalized mean PCWP < 12 and PVR < 3 was considered as normal.

RHC

Hemodynamically, 7 (13%) patients had perfectly normal resting RHC (group 1), 25 (45%) patients had pre capillary PH (group 2), 9 (16%) had a combination of pre and post capillary PH (group 3) and 15 (27%) had post capillary disease (group 4).

Echocardiography

PAcT was significantly shorter in groups 2 and 3, 84ms ± 23 and 75ms ± 18 respectively, in comparison to group 1 (136ms ± 41) and group 4 (117ms ± 29). PAcT correlated modestly to PASP (r= -0.6, P<0.001) and to PVR (r=0.57, P< 0.001). Quadratic regression improved the correlation with PVR (r= -0.61, P< 0.001) (figure 9). Applying the quadratic regression model resulted in PAcT ≤ 90 ms 85% specificity and 84% sensitivity, as well as a negative and positive predictive value of 81% and 88% respectively in identifying PVR ≥ 3.0.

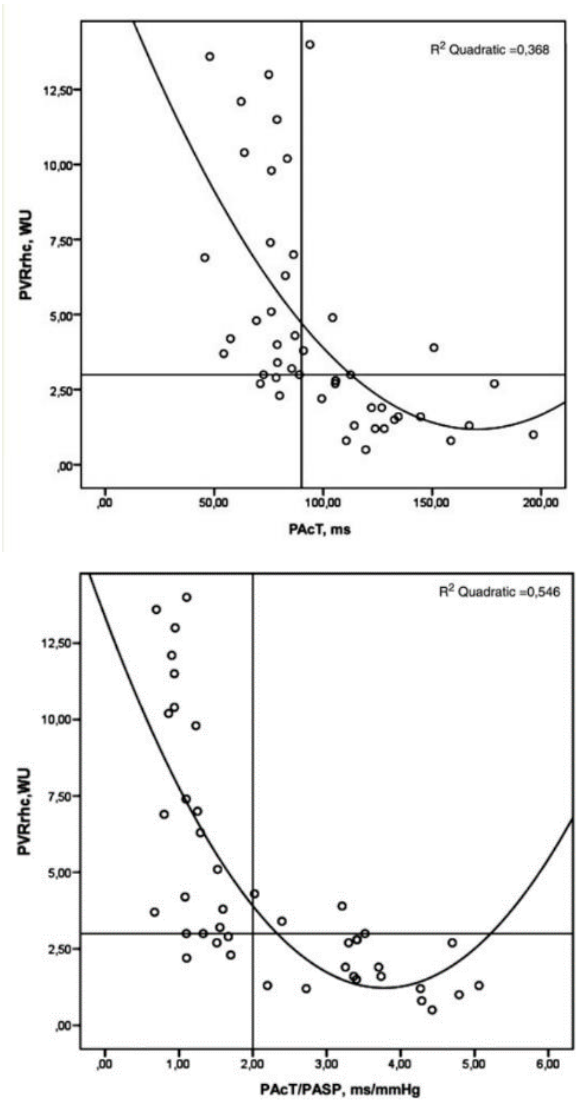

Figure 9. PAcT (top) and PAcT/PASP (bottom) and its relationship to PVR.

PAcT/PASP was more strongly correlated with PVR (r=-0.67, P<0.001) and (r= -0.74, P<0.001) in the quadratic regression model. PAcT/PASP < 2 was 83% sensitive and 79% specific in identifying PVR ≥ 3.0.

ROC curve analysis showed that TRV/VTIrvot, RV-IVRT, RV free wall strain and RV systolic myocardial velocities all had less discriminatory power to identify PVR ≥ 3.0 in comparison to PAcT and PAcT/PASP.

Performance of accuracy calculations found that a PAcT of 96ms to be the most accurate (83%) cut off value for PAcT to discriminate normal from PVR ≥ 3.0.

Study 2

Patient characteristics

57 patients with dyspnoea on exertion were recruited, however 9 patients were subsequently excluded due to poor image quality and 2 because of significant intra cardiac shunts.

Out of the remaining 46 patients, 22 (48%) were classified as having PAH, 19 (41%) had PH due to post capillary pathology, 1 (2%) had CTEPH and 4 (9%) had normal hemodynamics at rest. All were in sinus rhythm.

RHC and Echocardiography

LASRa (figure 10) had the strongest correlation with PCWP (r= -0.81, P<0.001), LASRe (r=-0.77, P<0,001), LA-volume (r=0.67, P<0.001), PALS (r=0.56, P<0.001) PACS (r=0.52, P<0.001), LV-GLS (r=0.44, P<0.002), LVSRa (r=0.61, P<0.001), mitral E/A (r=0.66, P<0.001). The correlation between PCWP and LASRa was however weaker among patients with PVR ≥ 3.0 (r^2= 0.52, P < 0.001).

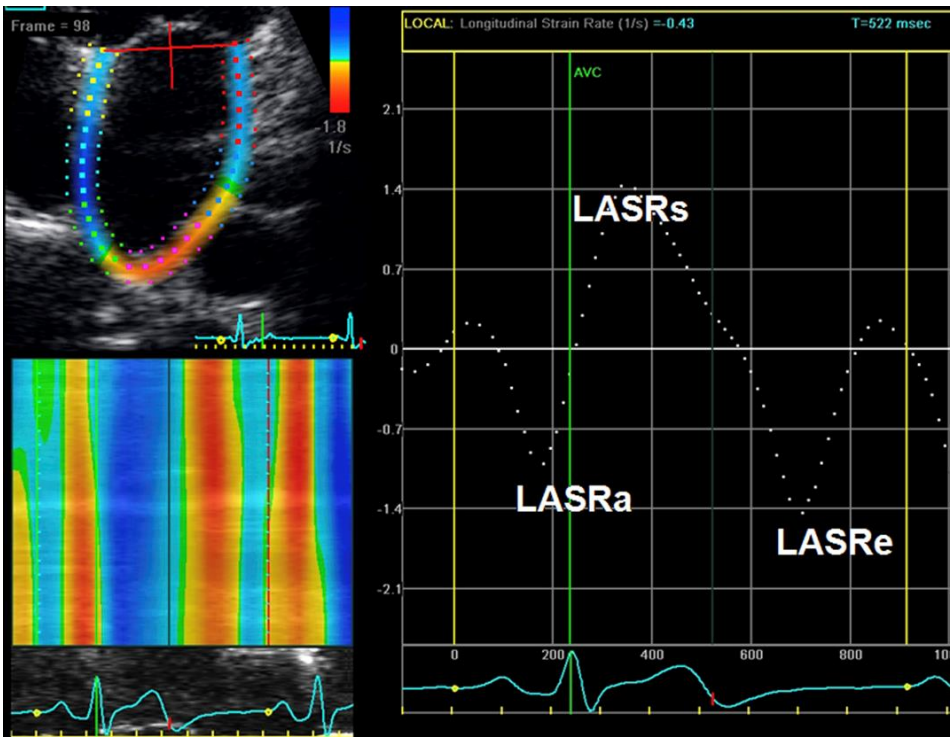

Figure 10. Strain rate is approximately zero at the R-wave of the ECG. Ventricular systole induces positive left atrial strain rate (LASRs), while ventricular relaxation is accompanied with negative strain rate during the early diastolic emptying of left atrium (LVSRe). At atrial contraction, left atrial strain rate (LASRa) is negative.

Based upon the equation of the straight line from the scatterplot of PCWP to LASRa, an equation was generated enabling PCWP assessment on an individual basis;

$PCWP_{LASRa} = 26.1 - 11.1 \times LASRa$

Inter observer variability between investigators for LASRa was tested with inter class correlation = 0.89, which supports LASRa as an investigator independent tool useful for assessment of PCWP.

Echocardiographically derived estimations of PVR were possible by adopting novel echocardiographic measurements which mimicked values of the PVR-formula. The correlation between PVR_{RHC} and PVR_{Echo} was $r^2 = 0.69$, $P < 0.001$. The mean differences between PVR_{RHC} and PVR_{Echo} was -0.1 wood units and the linear correlation ended up very close to the line of identity. The frequently used Abbas model (TRV/TVI_{RVOT}) had a less convincing correlation $r^2 = 0.38$, $P < 0.001$ and a significantly lower estimate of mean PVR than direct invasively measured PVR values. $PVR_{RHC} - PVR_{Abbas} = -1.0$ wood units.

$PVR_{Echo} = (mPAP_{Echo} - (26.1 - 11{,}1 \times LASRa)) / CO_{Echo}$

Study 3

Patient characteristics

85 patients met the inclusion criteria for this study, 42 of which were female. Patients with NT-proBNP ≥ 125 ng /litre (eBNP), had more ACE-Inhibitors (71% vs 42%), diuretics (41% vs 9%) and beta blockers (59% vs 21%), were older (65 years vs 49 years), had a history of AF or atrial flutter (33% vs 6%), had a history of ischemic heart disease (18% vs 3%), had lower estimated glomerular filtration rate (59 ml/min vs 94 ml/min) and performed less work during supine bicycle exercise (61 W vs 44 W). Interestingly, NYHA class did not differ.

RHC

At rest the pulmonary vascular resistance, mPAP and PCWP values were higher, though within normal range for the eBNP group.

Interestingly, we found mean $PCWP_{PLL}$ highly accurate for predicting PCWP response to a submaximal supine bicycle exercise, (figure 11). $PCWP_{PLL} > 15$ mmHg had a 91% sensitivity and 92% specificity for predicting exercise induced PCWP of >25 mmHg in patients with EF > 50% referred for unexplained dyspnea.

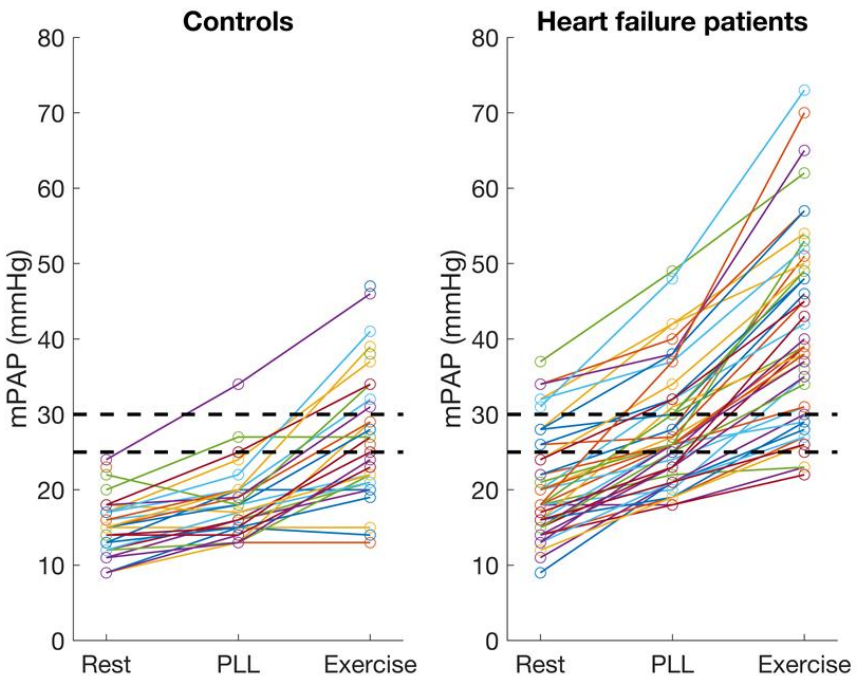

Figure 11. mPAP at rest, passive leg lifting (PLL) and exercise in normal-BNP (left) and elevated-BNP (right). Dotted line represents 25 and 30mmHg as cut off values for normal values at rest and exercise.

Study 4

Patient characteristics

29 patients met the inclusion criteria for this study (22 females). All patients had normal filling pressures at rest and no severe valvular dysfunction. All participants were limited by dyspnoea on exertion. At rest, mitral DT and LAVI were the only parameters that were significantly different in patients with elevated PCWP-PLL compared to normal PCWP-PLL.

RHC and Echocardiography

At rest, analysis showed that LASRa and E/LVSRe correlated with PCWP at rest (r = -0.41, P < 0.032) and (r = 0.61, P < 0.001) respectively.

LAVI and mitral-DT were the only resting echocardiographic parameters that were significantly different between patients with or without elevated PCWP during PLL. However were LAVI and LASRa at rest identified as most strongly related to $PCWP_{PLL}$ in univariate regression analysis ($\beta = 0.56$, $P < 0.018$) and ($\beta = -0.56$, $P = 0.002$). Mitral-DT was also significantly related ($\beta = -0.39$, $P = 0.041$).

These 3 parameters were subsequently entered into the multivariate analysis, resulting in LASRa being found to have the strongest relationship to $PCWP_{PLL}$ ($\beta = -0.51$, $P = 0.004$). The inverse relationship between LASRa and PCWP is illustrated by this example, (figure 12).

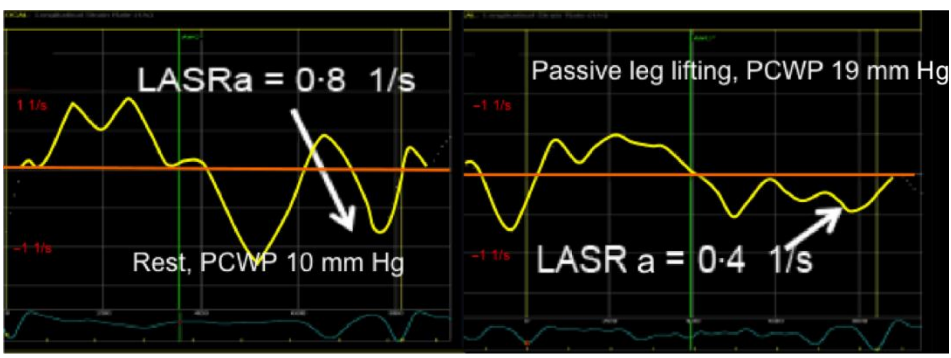

Figure 12. At rest left panel and during passive leg lifting right panel. The inverse relationship between LASRa and PCWP is further reinforced by its dynamic properties, with reduced LASRa upon increased PCWP at PLL.

In regards to PLL, univariate regression analysis revealed LASRa ($\beta = -0.77$, $P < 0.001$), E/LVSRe ($\beta = 0.47$, $P = 0.021$) and E/e´ ($\beta = 0.40$, $P = 0.040$) to be most related to $PCWP_{PLL}$. E/e´ was correlated for E/LVSRe and therefore not included in the multivariate regression analysis, whereas LASRa ($\beta = -0.58$, $P = 0.002$) and E/LVSRe ($\beta = -0.46$, $P < 0.001$) remained strong indicators of elevated filling pressures.

The trustworthiness of $PCWP_{PLL} \leq 0.9$ to identify $PCWP_{PLL} > 15$mmHg was tested. The close relationship between $LASRa_{PLL}$ and $PCWP_{PLL}$ is reflected by a sensitivity of 80% and specificity of 100%.

Discussion

Identification of the genesis and mechanics responsible for the symptom of dyspnoea is the first crucial step in order to be able to reduce morbidity and mortality related to CHF. Echocardiography has a central part in the diagnostic algorithm, but RHC is still the gold standard for the assessment of pressure and flow. Even though serious complications associated to RHC are rare, the small risk of pulmonary artery rupture, air embolism and in particular arrhythmias is always present, hence a non-invasive alternative would be preferable (112).

Diseases associated with increased PVR, irrespective of concurrent left heart disease, is coupled with high morbidity and mortality (34). In PAH and CTEPH, arterioles are subjected to narrowing and stiffening of the vasculature, making the arterioles less compliant which results in an increased pulse pressure (113). Furthermore, previous studies have demonstrated that an increased pulsatile load is related to a higher pulse wave reflection amplitude occurring earlier in the cardiac cycle, which in turn invades systole (114). The time it takes for the pulse wave reflection to have an impact on pulmonary artery flow is a function of the distance to the reflected point of origin (115). A healthy reflected pulse wave reaches central parts of the pulmonary artery during diastole, thus does not invading right ventricular ejection time and consequently does not reduce pulmonary artery flow. If the pulse wave reflection reaches the pulmonary artery during the ejection time, augmentation of pulmonary artery pressure develops, increasing pulmonary pulse pressure and reducing flow, which shortens time to maximum PA-flow (116). Previous studies on pulmonary artery acceleration time have mainly focused on the ability to identify PH, and to a lesser extent proven its ability to identify PVR elevation (117). In the absence of a reliable tricuspid regurgitant velocity jet our, findings become even more interesting, with an excellent ability of PAcT < 90 ms to identify PVR > 3 irrespective of pre- or combined PH. In order to calculate and quantify level of PVR, PAcT lacks the accuracy that is needed, however PAcT is a great screening instrument of PVR elevation (48).

PCWP is often overlooked in non-invasive attempts to calculate PVR (49). This is probably partly due to difficulties of accurate quantification of LVFPs, but also in regard to PCWPs lesser contribution to pulmonary pressures. From previous studies by Henein et al, LASRa´s relation to PCWP has been explored and has been shown to be highly correlated (118). Utilising LASRa´s ability to assess LVFPs enabled us to present a refined non-invasive PVR formula highly related to PVR-RHC.

The intrinsic contractile properties of the LA-booster pump function during atrial contraction, together with the afterload that the LV imposes, forms the main contribution and obstacle to LA contraction, hence also a determinant of

LASRa. In conformity with ventricular function, stretching of the myocardium leads to increased contractile force, in accordance with the mechanism of preload established by Frank and Starling (Frank-Starlings law of the heart), hence preload elevation should lead to increased LASRa, yet LASRa decreases in patients which develop high filling pressures with PLL, indicating the afterload dependency of the LASRa assessment.

Based on the studies included in this thesis LASRa assessments of FPs should be encouraged, both at rest and during PLL, and it is worth stressing that a functional approach, including an easily performed stress test, should always be a consideration. As a sonographer the time has past when inconclusive echocardiographic data at rest is the limit of the diagnostic ability of echocardiography. Now, additional echocardiographic tools and methods such as exercise echocardiographic examination can be employed when the patient's characteristics and symptoms disagree with resting echocardiographic findings. Kovacs et al have presented an official European Respiratory Society statement supporting the use of cut off values during exercise; mPAP > 30mmHg, mPAP/CO > 3.0, as a definition of exercise induced PH (EIPH). Even though mPAP is based upon RHC data, conversion of echocardiographic estimated PASP to mPAP is feasible using the formula presented by Chemla et al, confirmed in our study 2.

Identifying EIPH by means of TRV is achievable in most cases non-invasively, however in isolation TRV is not specific for pre or post capillary hypertension. Obokata et al endorse a non-invasive strategy, presenting excellent sensitivity and a negative predictive value, suggesting exercise echocardiography as a non-invasive strategy to rule out HFpEF (19). However, Obokata relied on mitral inflow E/e´ ratio during exercise, which did not perform as well as LASRa and E/LVSRe in our PLL-study, study 4.

The EIPH criteria of ex-mPAP > 30mmHg and ex-mPAP/CO > 3 is well suited for identification of pathology, either in the pulmonary circulation or related to left heart pathology. The EIPH design also enables pulmonary pressures to exceed 30mmHg as long as cardiac output rises equivalently, for example in athletes.

With the inability to increase PVR upon exercise in mind, total pulmonary vascular resistance (TPVR), (which is the same as mPAP/CO) increase during exercise has to be attributed to PCWP increase, not matched by flow increase, regardless of level of PVR. This results in delta-TPVR being specific for underlying post capillary disease, while exTPVR (exmPAP/CO) > 3 indicates elevated PVR and/or LVEDP.

TPVR = mPAP / CO = (TPG + LVEDP) / CO = TPG/CO + LVEDP/CO

Consequently:

Delta TPVR = TPVR-ex - TPVR-rest

Delta TPVR = (TPG-ex/CO-ex + LVEDP-ex/CO-ex) - (TPG-rest/CO-rest + LVEDP-rest/CO-rest)

Assuming TPG/CO is static

Delta TPVR = LVEDP-ex/CO-ex – LVEDP-ex/CO-ex

At this point exact cutoff values for delta-TPVR are not established, however based upon our research a delta-TPVR > 1 mmHg / L should be considered.

I am convinced there are advantages adopting a functional rather than static approach in the assessment of FPs. Besides TTE parameters previously validated such as LAVI and E/A ratio, pulmonary artery pressures and CO are almost always attainable at rest and during stress. Differences in between TTE and RHC are present regarding pulmonary pressures and CO at rest, however these differences are not attenuated with stress, providing less delta differences thus further supporting the delta-TPVR approach. Stressing patients to a level that generates a very high heartrate aggravates TTE assessment, endorsing a submaximal workload strategy and leg lifting.

Is it possible to have CHF with normal PCWP and normal LVEF?

In my opinion the answer is yes. If solely looking at filling pressures, one might say that it is impossible, however cardiovascular hemodynamics are intricate and affected by many factors. Wall stress induces generation of proBNP, which is an endogenous defence mechanism, reducing afterload and promoting diuresis, which might decrease FPs on the expense of reduced sarcomeric stretch, hence decreasing cardiac output.

With reference to pressure size and mechanics of left ventricle, which corresponds to wall stress, it is understandable that NPs are lower in HFpEF than in HFrEF, though diagnostic values applies similarly (119). In study 3, we investigated the connection between NT-proBNP and CHF expressed in terms of presence or development of elevated FPs on exertion. Normal NT-proBNP demonstrated excellent negative predictive value, while patients with NT-proBNP levels above the reference interval displayed great differences in response to PLL and exercise. The unpredictable response in patients with elevated NT-proBNP

stresses the need to alter loading conditions, however method of choice to challenge the cardiovascular system are less important, when both PLL and supine bicycle exercise identifies patients unstable FPs.

Level of intrathoracic pressure is dependent on respiratory phase, pleural- and pericardial effusion etc. In my opinion, current normal values might not be correct if zero levelling towards intrathoracic pressures would be made by routinely, though more correct. Given that all cardiac pressures are affected by intra thoracic pressure alterations, the best way to assess all pressures should be during the same respiratory cycle and preferentially at the end expiration phase. If choosing to express pressures as mean and digitalized mean out of several cardiac cycles, this strategy might constitute the most reasonable way to handle large respiratory pressure alterations (85).

Assessment of FPs, factors to take into consideration;

1. Make sure you have a proper West zone 3 position, a and v -wave should be present. When in doubt, consider controlling saturation while in wedge position and/or LVEDP assessment.

2. Anatomical alterations may be creating pressure gradients in between tip of the catheter and LV

3. Assess pre-test probability in light of, for example; medical history, clinical signs, TTE, ECG

4. Assess end expiratory wedge pressure at the very end of diastole, which coincides with the R-wave on surface ECG. In situations where pericardial or intrathoracic pressures are suspected to be elevated, consider adjusting according to level of RAP, CVP or respiratory swing, if a trans oesophageal pressure sensor aren´t available

5. If there is any suspicion of left ventricular disease, do not settle with a resting examination. What kind of challenge performed is not crucial, PLL and supine bicycle exercise works well to provoke filling pressure abnormalities.

Conclusion

PAcT > 90 ms is strongly suggestive of increased PVR (>3 WU), and is applicable irrespective of LVPFs. PAcT serves as a quick screening tool, however is not useful if the exact level of PVR is required. In this scenario an established PVR calculation is preferred and could be performed with high precision adopting non-invasively, echocardiography derived LASRa as a surrogate measure of PCWP.

Insufficient LV compliance results in the inability to cope with an increased cardiac preload. Nt-proBNP is secreted when the myocardium is stretch, however only a small portion of patients with elevated NT-proBNP, had high PCWP at rest. However, nearly half of our study population with elevated NT-proBNP showed increased PCWP during PLL, which is indicative of underlying ventricular stiffness. By performing this preload increasing maneuver, patients predisposed to developing high filling pressures during supine bicycling could be identified with high sensitivity and specificity. Echocardiography in comparison to RHC, is a more accessible, safe and less resource consuming, thus is an appealing option in the quest to identify methods that are highly related to invasive pressures which could be useful in the assessment of FPs during different loading conditions. LAVI at rest, LASRa and E/LVSRe during PLL, proved independently related to PCWP during PLL.

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