Trial Protocol

Official title:

ArrhythmiaS in Pulmonary arterIal hypeRtEnsion and right heart failure assessed by continuous long-term cardiac monitoring

ASPIRE

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Content

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease affecting both the pulmonary vasculature and the heart. PAH is characterized by a mean pulmonary artery pressure (mPAP) of ≥25 mmHg, pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg and PVR ≥ 3 WU (1). As a response to the changed vascular conditions, the right side of the heart adapts via hypertrophy and increased contractility by an increase in cardiomyocyte size and addition of sarcomeres (2). This is referred to as adaptive remodeling and compensates for the elevated afterload. However, as the disease progresses these compensatory mechanisms are insufficient and a ventriculoarterial uncoupling occurs (3;4). With further progression, the remodeling process becomes maladaptive leading to eccentric hypertrophy and dysfunction of the RV (fig.1). Ultimately, stroke volume declines, RV failure (RVF) develops and subsequent arrhythmias become a prominent phenomenon of PAH, which again may reduce right ventricular function (5;6). Furthermore, modulation in autonomic activity, delayed cardiac repolarization and right ventricular ischemia contributes to the pathobiology of arrhythmias.

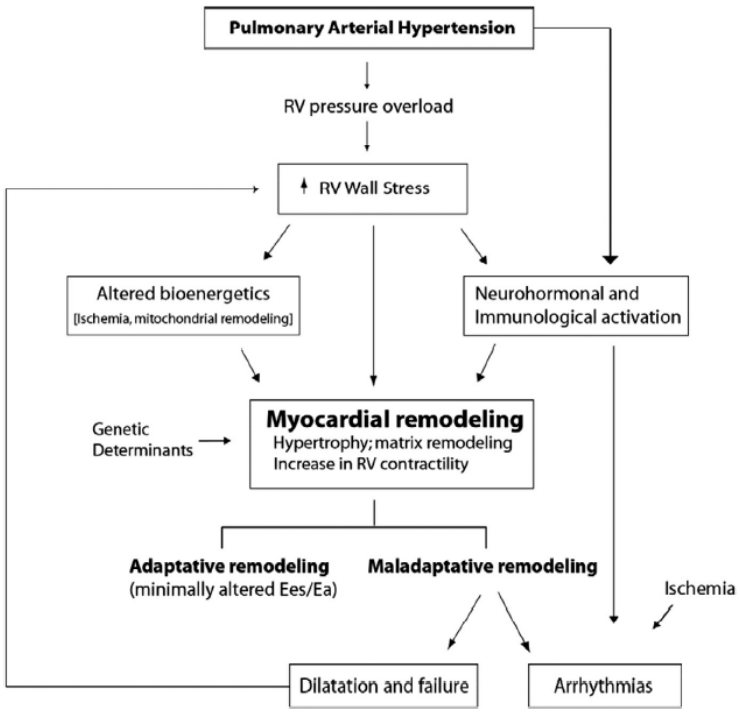

Figure 1 (3): Pathophysiological mechanisms of right ventricular failure (RVF) in pulmonary arterial hypertension (3). RV wall stress induces altered bioenergetics and activates the neurohormonal axis and an inflammatory response. These factors contribute to myocardial remodeling which is divided into adaptive and maladaptive remodeling. The latter is characterized by ventriculoarterial uncoupling and dilatation.

The incidence of supraventricular arrhythmias is between 8 - 35% (6-11) and considerably lower for ventricular arrhythmias (5;10-14). Cardiac parameters, such as right ventricular diameter, right ventricular longitudinal dimension and right atrial length, significantly correlate with an increased risk of arrhythmias (7). Supraventricular tachycardias (SVT) may compromise cardiac function and worsen the prognosis of patients with PAH (6), but information about their incidence and clinical role is based on a small number of retrospective studies (5;6;10;11;15). Additionally, permanent atrial fibrillation and prolonged QTc interval are associated with the highest mortality (16). The goal in management of arrhythmias is to maintain sinus rhythm either by pharmacological or device treatment.

This research project is the first study applying continuous long-term monitoring of arrhythmias in patients with PAH and right heart failure (RHF). The study specifically seeks to investigate following:

- The incidence and type of supraventricular and ventricular arrhythmias in PAH by continuous long-term monitoring
- The predictive value of both right and left ventricular cardiac magnetic resonance (CMR) imaging parameters for arrhythmogenesis in PAH.
- Optimization of specific therapy in PAH using continuous long-term arrhythmia monitoring

Project ASPIRE I:

Incidence and characteristics of supraventricular and ventricular arrhythmias in PAH

Background

A. Supraventricular arrhythmias

In a 6-year retrospective analysis of 231 patients with PAH and chronic thromboembolic pulmonary hypertension, Tongers et al. noted a cumulative supraventricular arrhythmia (SVA) incidence of 11.7% and an annual risk of 2.8% per patient (9). All patients were seen regularly at 1 to 6 monthly intervals, or whenever clinically indicated and 12-channel electrocardiograms (ECGs) were obtained. None of the patients was carrying any device that could record rhythm events continuously. The most common types of arrhythmia were atrial flutter (AFL) and atrial fibrillation (AF) diagnosed from standard surface ECG. AV nodal re-entry tachycardia (AVNRT) was less common and documented by standardized electrophysiologic studies. However, this cohort of PAH patients was not entirely homogeneous and the relative incidence of various types of SVA may vary based on the etiology of pulmonary hypertension. Other retrospective studies have reported an incidence of SVA in PAH of 8.4%, 22% and 35 %, respectively (9;5;10). In prospective studies the incidence of SVA in PAH and PH have been described as 15% in IPAH (7) and 20% in PAH and CTEPH(8) respectively.

B. Ventricular arrhythmias

RV failure is reported to account for approximately 38 % of death in a low-risk group and up to 63 % in a high-risk group (17), whereas sudden cardiac death accounts for 30%. Together, RV failure and sudden cardiac death represent the majority of deaths in patients with PAH (18-20). However, in contrast to patients with advanced left heart disease, malignant ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) are relatively rare in patients with PAH. In patients with PAH, pulseless electrical activity is often heralded by bradycardia. Hoeper et al. reported the outcome in 132 of 513 patients (26%) after cardiopulmonary resuscitation (12). The initial ECGs at the time of cardiopulmonary arrest showed bradycardia in 58 cases (45%), electromechanical dissociation in 37 cases (28%), asystole in 19 cases (15%), ventricular fibrillation in only 10 cases (8%), and other arrhythmias in 6 cases (4%).

C. Bradyarrhytmias

Ventricular tachycardia is less common, and relative bradycardia is an ominous sign, with bradyarrhythmias frequently observed in the setting of cardiopulmonary arrest. Clinical studies of defibrillator/pacemaker therapy for primary prevention against sudden death in PAH patients are lacking.

D. Heart rate variability

As PH progresses, the RV afterload increases, ultimately leading to impaired cardiac output and right-side heart failure. Consequently, the sympathetic nervous system activity (SNS) increases and the parasympathetic nervous system (PNS) decreases [12, 18]. The autonomic nervous system (ANS) regulates the sinus node, and can be assessed by heart rate variability (HRV) [19, 20]. The HRV illustrates the autonomic balance between the sympathetic and parasympathetic input, and is a noninvasive indicator of the autonomic input to the heart [21].

Reveal LINQ Insertable Cardiac Monitor

The Reveal LINQ Insertable Cardiac Monitor is a wireless and the smallest insertable cardiac monitor. The Reveal LINQ insertion procedure is minimally invasive, and requires short procedure time and clinical resources. It is placed under the skin of the chest and automatically detects and records abnormal heart rhythms for up to 3 years.

Figure 2. The Reveal LINQ Insertable Cardiac Monitor is supported by a CareLink Network and a patient monitor easy to use that features cellular technology. Alert notifications can result in earlier

clinical decisions compared to non-wireless devices (21). The Reveal LINQ is safe for use in an MRI setting.

CareLink® Remote Monitoring Network

The Medtronic CareLink Network ensures timely identification of clinically important issues, such as asymptomatic atrial fibrillation or device integrity issues (22). Data are automatically sent to the CareLink server from the device. In addition, patients can transmit device information from home (Figure 3), and clinicians can review device data when and where they choose on the Medtronic CareLink Clinician Website. The Medtronic CareLink Network provides comprehensive data comparable to an in-clinic device check, including full parameter summary, A-V conduction histograms and arrhythmia summary.

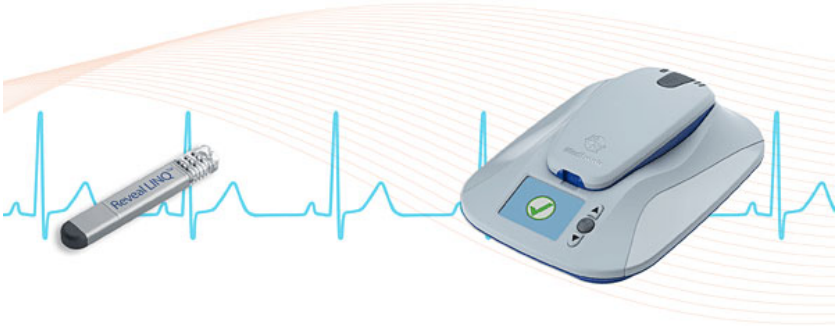

Figure 3 The Medtronic CareLink Network is fast and easy to use with scheduling flexibility, allowing patients to transmit data within a time range rather than at a set time. Clinic staff need not be present during transmissions.

Study Synopsis – ASPIRE I

Name of the study	Incidence and characteristics of supraventricular and ventricular arrhythmias in PAH (ASPIRE-I)
Study design	Single centre observational study in patients treated with PAH specific medication. Patients will be followed for 2 years after inclusion.
Study objectives	**Primary objective** To assess the incidence of arrhythmias in prevalent and incident cases of PAH using continuous long-term monitoring by Reveal LINQ insertable cardiac monitor. To assess heart rate variability in correlation to known risk markers in PH.
Methodology	The study will be conducted as a single center study at Copenhagen University Hospital, Rigshospitalet, DK-Denmark.
Trial duration	Enrolment duration: 9 months
Number of patients	40 patients. WHO Group I PAH: 10 with IPAH, 10 with CTD-aPAH, WHO Group III: 10 with pulmonary disease related PH and Group IV: 10 with CTEPH.
Study treatment	Patients with PAH/PH will be consecutively selected from the cohort of patients being treated with PAH specific medication, and incident cases will be enrolled prospectively.

Selection criteria	Inclusion criteria: The following patients will be included in the study: - Patients >18 years of age - Patients on current PAH specific medication must be stable for at least 3 months. - Patients can be included in WHO group 1 only with IPAH or CTD-aPAH and group IV, CTEPH Exclusion Criteria: - Patients who are unlikely to comply with the study protocol and procedures required by the study protocol. - Patients with any severe complication or comorbidity other than PAH which might determine the prognosis and functional level of the patient. - Need for escalation of PAH specific therapy - Patients who are already in specific treatment for arrhythmias. Concomitant treatments - Patients can be on the following treatments only if they have been at least treated for three months prior to inclusion and are planned to be continued during the whole study period: diuretics, digoxin, beta-blockers and amiodarone
Data collection	**At screening:** - PAH verified with right heart catheterization before start of PAH specific medication. - Basic demographic data including medication. - Physical examination and vital signs - 6 MWT - Digital ECG to verify rhythm at baseline **Care Link Network** - Device information send from home - Clinicians review device data on the Medtronic CareLink Clinician Website **Visits every 6 months** - 6 MWT - Lab tests, including NT-proBNP - Record concomitant medications
Statistical methods	SPSS/PASW Statistics 19 software (SPSS Inc, Chicago IL), SAS or R are used for all statistical analyses. In addition, descriptive time serial analysis will be done on heart rate variability and heart rate. Correlation statistics will be done to assess heart rate variability and heart rate in correlation to known risk markers in PH.
Endpoints	To assess the incidence of arrhythmias in patients with PAH.

Study Chart - ASPIRE I

	Screening	**Operation**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
		1	6 mo	12 mo	18 mo	24 mo
Informed consent	X					
Height	X					
Weight	X					
RHC`¤	X					
SPECT/CT	X					

LFT	X					
ECG	X	x	X	X	x	X
Echocardiography	X			x		x
6 MWT	X	X	X	X	x	X
Clinical data collection	X	X	X	X	X	X
Blood Samples#	X	x	X	x	x	x

¤ RHC;: right heart catheterisation for incident cases only. Prevalent cases have had RHC at the time of diagnosis. *CMR, cardiac index, RV size, stroke volume and pulmonary artery diameter including exercise measurements #Blood samples include haematology, liver chemistry (ALT, AST, LDH bilirubin) renal (creatinine, eGFR), and NT-proBNP.

Project ASPIRE II

Predictive value of Cardiac Magnetic Resonance, CMR-Derived RV and LV parameters for arrhythmogenesis in PAH

Background:

Several factors contribute to the arrhythmogenic shift in the electrophysiology of the heart in PAH/RHF. The major four predisposing factors for arrhythmias in PAH are 1. modulation in autonomic activity, 2. remodeling of the myocardium 3. delayed cardiac repolarization and 4. RV myocardial ischemia.

The function of the RV and the RA decreases when remodeling progresses. Li Wen et al. (7) examined the changes in cardiac parameters as measured by echocardiography and their associated risk of arrhythmias (Table 1).

Variable	Hazard Ratio [95% CI]	p Value
Right atrial diameter	1.80 [1.40-3.11]	<0.001
Right atrial length	2.08 [1.62-2.69]	<0.001
Right atrial area	1.07 [1.05-1.10]	<0.001
Right ventricular diameter	2.76 [2.07-3.70]	<0.001
Right ventricular longitudinal dimension	2.06 [1.49-2.81]	<0.001
mRAP	1.14 [1.08-1.19]	<0.001
PVR	1.08 [1.03-1.13]	0.001
Cardiac output	0.72 [0.55-0.95]	0.022

Table 1 Univariate analysis of risk factors for SVA in IPAH, modified after LiWen (7) CI: Confidence interval, mRAP: mean Right Atrial Pressure, PVR: Pulmonary Vascular Resistance.

Cardiac parameters measured by cardiac magnetic resonance (CMR) has not been used in the assessment and prediction of arrhythmias in PAH/RHF. However, arrhythmias often leads to clinical deterioration, right sided cardiac failure and is associated with a higher risk of death in patients with PAH (7;9;15).

CMR-derived RVEF is an independent noninvasive imaging predictor of adverse outcomes in this patient population (23;24). Van de Veerdonk et al. (25) confirmed that, in 110 patients with newly diagnosed PAH, CMR-derived RVEF measured at baseline was an independent predictor of mortality. In addition, they found that even though pulmonary vascular resistance measured at baseline was also predictive of mortality, after a year of PAH-targeted therapy, only changes in RVEF were associated with survival. This finding suggests that RVEF, as measured by CMR, is a clinically important determinant of prognosis.

Several studies have reported that, when using contrast-enhanced CMR in patients with PAH, *late gadolinium enhancement* (LGE) of the RV insertion points strongly correlated with multiple indices of RV function (26-30). The presence of late gadolinium enhancement of the RV insertion points seems to be a marker for more advanced disease and poor prognosis in patients with PH (31). Rydman et al. described that systemic RV LGE is strongly associated with adverse clinical outcome especially arrhythmia in transposition of the great arteries (32).

More recently, T1-mapping and extracellular volume fraction has emerged as novel techniques to assess myocardial involvement prior to overt RV dysfunction in experimental pulmonary hypertension (33). ECV was also increased in the RV in patients with pulmonary hypertension, even after adjusting for RV volume and ejection fraction (34).This has led to requests of further investigation of the roles of T1-mapping and ECV as methods of risk assessing patients with pulmonary hypertension (35).

Myocardial strain is defined as the percentage of change in tissue length. A study of strain velocity in the left ventricle in pulmonary hypertension showed that it predicted functional capacity and clinical worsening before significant changes in RVEF and SV (36). Today, CMR analysis software allow strain assessment using standard steady-state free precession cine-imaging of both the left and right ventricle, leading to requests of studies investigating the role of RV strain and strain velocities as predictors of adverse outcome in pulmonary hypertension (35).

Study Synopsis - ASPIRE II

Title of the study	Predictive value of CMR-Derived RV and LV parameters for arrhytmogenesis in PAH (ASPIRE-II)
Study design	Single centre observational study with CMR and insertable cardiac long term monitoring in newly referred and PAH patients treated with PAH-specific therapy. Patients will be followed for 2 years after inclusion.
Study objectives	**Primary objective** To evaluate CMR as a tool for providing noninvasive predictors for arrhythmias in patients with PAH. **Secondary objectives**

	- To assess change in 6 MWT - To assess hemodynamic changes with RHC - To assess hemodynamic changes in echocardiography - To assess the number of patients progressing one FC (Modified NYHA class) - To assess changes in NT-proBNP. - To assess Hospital admission for any reason - To assess Death or transplantation
Methodology	The study will be conducted as a single center study at Copenhagen University Hospital, Rigshospitalet, DK-Denmark.
Trial duration	Enrollment duration: 9 months
Number of patients	40 patients. WHO Group I PAH: 10 with IPAH, 10 with CTD-aPAH, WHO Group III : 10 with pulmonary disease related PH and Group IV: 10 with CTEPH.
Selection criteria	Inclusion criteria: The following patients will be included in the study: - Patients >18 years of age - Voluntary participation after giving informed verbal and written consent - Patients untreated with PAH specific therapy - Patients on current PAH specific medication independent of duration of therapy - Patients can be in WHO group 1 only with IPAH or CTD-aPAH, and group IV, CTEPH Exclusion Criteria - Patients who are unlikely to comply with the study protocol and procedures required by the study protocol. - Patients with any severe complication or comorbidity other than PAH which might determine the prognosis and functional level of the patient. - Renal insufficiency (GFR estimated <60 ml/min/ 1.73 m2). - Implanted ferromagnetic metal parts unsuited for CMR (ICD, cerebral clips) - Claustrophobia - Allergy or hypersensitivity to Gadovist Concomitant treatments - Patients can be on the following treatments only if they have been at least treated for three months prior to inclusion and are planned to be continued during the whole study period: diuretics, digoxin, beta-blockers, amiodarone
Data collection	**At screening:** - SPECT/CT will be performed at diagnosis for prevalent cases only and at screening for incidents cases to evaluate pulmonary embolism - LFT to exclude pulmonary disease: COPD and ILD - Echocardiography to exclude left heart disease - PAH verified with right heart catheterization before start of PAH specific medication - Basic demographic data including medication. - Physical examination and vital signs - 6 MWT - ECG - Lab tests including liver and renal function tests and NT-pro-BNP **Visits every 6 months or with increased symptomatology** - CMR with measurement of RV/LV volumes, CI (volumetric and flow), RVEF and pulmonary artery diameter according to standard criteria. Yearly measurement of RV fibrose (LGE, T1 mapping and ECV). The same MR-scanner must be used for all measurements.

	- 6 MWT - Lab tests, including liver and renal function tests including yearly eGFR, hematocrit and NT-proBNP - Echocardiography yearly and at 3 month after inclusion - Record concomitant medications - PAH medications
Endpoints	**Coprimary endpoints** - Change in cardiac index, right atrial size, RV size, fibrosis and stroke volume - Arrhytmias as assessed by Insertable Cardiac Monitors **Secondary endpoints** - Modified NYHA functional class - Reduction in 6 MWT in the study period. - NT-proBNP change in study period. - Change and /or escalation of PAH therapy - Respiratory hospitalization - Death or transplantation
Statistical methods	Repeated measurements of CI, right atrial size, RV size, fibrosis and stroke volume will be performed every 6 months. Two groups of subjects will be defined: 1. Patients with no change in CI, RV size and stroke volume, and 2.A group of patients where one of the measurement change more than 2 standard deviations. It is group-shift (Y/N) if a subject changes out of the 2 stdv band. Time to group shift will be analysed in a subsequent analysis. Cox-model analysis will be done on measurements of (1) cardiac index, (2) RV size, (3) stroke volume and (4) fibrosis to calculate the correlation with risk of developing clinical symptoms and clinical deterioration. In other words, this analysis will establish if the MR-measurements predict clinical outcome. SPSS/PASW Statistics 19 software (SPSS Inc, Chicago IL), SAS or R is used for all statistical analysis.

MRI protocol

Every six months, all subjects are scanned according to the protocol below. The scanning will take 60-80 minutes. MRI scans will be carried out on a 1.5 to 3.0 Tesla MRI scanner. At visit 1, 3 and 5 a cannula will be placed for contrast administration.
MRI studies will provide time-volume curves for LV and RVs filling and ejection fraction, peak emptying rate, peak filling rate and stroke volume will be calculated.
The measurements will provide time-flow curves for flow in the pulmonary trunk, pulmonary branch arteries and aorta. It will be possible to measure the distribution of flow to the right and left lung. Since the pulmonary trunk is often dilated with slow flow, it can be more accurately to measure the flow in the smaller branch pulmonary arteries. Angiography will also provide the flow distribution in the lungs and the different segments of the lungs.
After baseline scan subjects will be exercised by a MR compatible ergometer with a load of 1 watt per kg. Stress test will measure the physiological reserve in terms of changes in cardiac index and ventricular volumes. Finally, late enhancement will measure the degree of fibrosis in the left and right ventricle.

	Scannings protocol	Sekvens
1	Scout	SSFP, single shot
2	Transverse stack, no gaps – covers the hears	SSFP, 8 mm, 25 phases

3	LV vertical long axis (VLA)	SSFP, 8 mm, 25 phases
4	Scout LV, short axis	SSFP, single shot
5	The four standard views (4 chamber, 3 chamber, 2 chamber, LVOT coronal)	SSFP, 8 mm, 25 phases
6	LV short axis stack, no gaps	SSFP, 8 mm, 25 phases
7	RV long axis	SSFP, 8 mm, 25 phases
8	RV inlet-apex-outlet (3 points)	SSFP, 8 mm, 25 phases
9	RVOT – PA x 2 perpendicular views	SSFP, 8 mm, 25 phases
10	RVOT short axis	SSFP, 8 mm, 25 phases
11	Left pulmonary artery x 2 perpendicular	SSFP, 8 mm, 25 phases
12	Left pulmonary artery short axis	SSFP, 8 mm, 25 phases
13	Right pulmonary artery x 2 perpendicular	SSFP, 8 mm, 25 phases
14	Right pulmonary artery short axis	SSFP, 8 mm, 25 phases
15	Pre-contrast T1-mapping 4ch Pre-contrast T1-mapping short-axis T2-mapping 4ch T2-mapping short-axis	
	*Kontrast injection: Gadovist 1.5 mmol/kg	
16	*Rest myocardial perfusion scan	
17	PA flow	Velocity encoding, VENC 10 % above max velocity
18	LPA flow	Velocity encoding, VENC 10 % above max velocity
19	RPA flow	Velocity encoding, VENC 10 % above max velocity
20	Aorta flow	Velocity encoding, VENC 10 % above max velocity
	Post-contrast T1-mapping 4ch Post-contrast T1-mapping short-axis	
21	*Late enhancement LV short axis stack	Inversion recovery, FLASH
	Stress 1 watt/kg	
22	Transverse stack, no gaps – cover the heart	SSFP, 8 mm, 25 phases
23	PA flow	Velocity encoding, VENC 10 % above max velocity
24	Aorta flow	Velocity encoding, VENC 10 % above max velocity
25	LV short axis stack, no gaps	SSFP, 8 mm, 25 phases

* Contrast studies will only be performed at visit 1, 3 and 5.

LV: left ventricle, LVOT left ventricular aoutflow tract, RV, right ventricle, PA, pulmonary artery, LPA. Left pulmonary artery, RPA, right pulmonary artery.

Study Chart – ASPIRE II

	Screening	**ILR implantation**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
		1	6 mo	12 mo	18 mo	24 mo
Informed consent	X					
Height	X					
Weight	X					
RHC`¤	X					
SPECT/CT	X					

LFT	X					
ECG	X	x	X	X	x	X
Echocardiography	X			x		x
6 MWT	X	X	X	X	x	X
Clinical data collection	x	X	X	X	X	X
CMR		X§	x	X§	x	X§
Blood Samples#	X	x	X	x	x	x

¤ RHC;: right heart catheterisation for incident cases only. Prevalent cases have had RHC at the time of diagnosis. *CMR, cardiac index, RV size, stroke volume and pulmonary artery diameter including exercise measurements #Blood samples include haematology, liver chemistry (ALT, AST, LDH bilirubin) renal (creatinine, eGFR), and NT-proBNP.

Project ASPIRE III

Optimization of specific therapy in PAH using continuous long-term arrhythmia monitoring

Background

In most cases, onset of atrial tachyarrhythmias is related to clinical deterioration, and deterioration in exercise capacity by one functional class or more, and development of ascites and/or edema refractory to diuretic therapy (37). Restoration of normal sinus rhythm is invariably associated with clinical improvement. The onset of these arrhythmias could be a warning sign for deteriorating RV function and hence the need for increasing specific therapy for PAH. Although prospective and controlled data are lacking, these findings suggest that maintenance of sinus rhythm is an important treatment goal in patients with PAH, which contrasts with the clinical experience in left heart failure in non-PAH patients, where the rhythm control strategy seems to offer no mortality benefit compared to the rate control and systemic anticoagulation strategy (38).

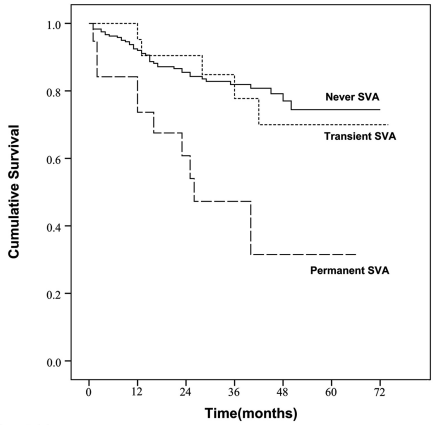

Figure 3: Kaplan-Meier estimates of survival in patients with PAH in relation to supraventricular arrhythmias (SVA; (7))

With regard to mortality, while AVNRT and AFL were invariably converted to sinus rhythm and were not associated with an increased risk of death (cumulative mortality<6%), the presence of persistent atrial fibrillation and failure to restore sinus rhythm were associated with a cumulative mortality of > 80% (9). AF may be a particularly malignant arrhythmia in patients with chronic PAH and RHF (10).

In terms of ventricular arrhythmias QT prolongation increases the risk for VAs and especially for torsades-de-pointes tachycardia. QTc interval in PH patients are generally longer compared to controls (454.8±29ms vs. 429.8±18ms, p<0.001) (16). A prolonged QTc interval correlated with deterioration of the RV, and when QTc was ≥480ms an increased risk of death was observed in a multivariate analysis (HR=3.09 [CI 95%; 1.61-8.38], p = 0.022). Furthermore, an analysis of CPR outcome in PAH patients showed that several arrhythmias are indicative of imminent cardiac arrest. The outcome of CPR in PAH-patients was critical, with a survival rate of 6% after 90 days (12).

With regard to therapies for SVTs in PAH patients, medical treatment with calcium-channel blockers and beta-blockers is considered to be deleterious due to their negative inotropic effects and their role is unfortunately limited. In the acute setting, amiodarone has been used for control of hemodynamically significant arrhythmias. The role of chronic, prophylactic antiarrhythmic drugs to maintain sinus rhythm remains questionable given significant potential side-effects. Nevertheless, the recurrent development of poorly tolerated arrhythmias may require its use on a long-term basis. Finally, interactions of medications must be carefully considered since for instance amiodarone may increase levels of bosentan, requiring close monitoring and adjustment. In a retrospective analysis of 22 patients with AFL and PAH due to pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension, Showkathali et al. demonstrated that AFL cavotricuspid isthmus ablation can be performed successfully and without complications, and was accompanied with a statistically significant improvement in functional class after ablation (39).

The role of cardiac resynchronization therapy (CRT) in patients with right heart failure due to PAH is currently uncertain. In an experimental model of PAH and right heart failure, investigators found that pre-excitation of the RV free wall in the absence of baseline conduction disturbances resulted in improved RV systolic function and reduced adverse left ventricular diastolic interaction (40). Another study demonstrated that resynchronization therapy acutely reduced ventricular dyssynchrony and enhanced RV contractility, left ventricular diastolic filling, and stroke volume in a patient suffering from right heart failure and ventricular dyssynchrony secondary to chronic thromboembolic pulmonary hypertension (41). In addition, recent analysis notes that pediatric patients with PAH manifest abnormal mechanical as well as electrical RV activation when compared to patients without PAH. These promising results warrant further investigations of CRT as a novel treatment for right heart failure secondary to PAH. However, without further data, the relative benefits versus risks of CRT in this setting remain unknown.

Study Synopsis – ASPIRE III

Title of the study	Optimization of specific therapy in PAH using continuous long-term arrhythmia monitoring (ASPIRE-III).
Study design	Single centre observational study with CMR in newly referred and PAH patients treated with PAH-specific therapy. Patients will be followed for 2 years after inclusion.
Study objectives	**Primary objective** To evaluate long-term monitoring of arrhythmias as a predictor tool for escalation of PAH specific therapy and prognosis in patients with PAH. **Secondary objectives** - To assess change in 6 MWT - To assess hemodynamic changes with RHC - To assess hemodynamic changes in echocardiography - To assess the number of patients progressing one FC (Modified NYHA class) - To assess changes in NT-proBNP. - To assess Hospital admission for any reason - To assess Death or transplantation
Methodology	The study will be conducted as a single center study at Copenhagen University Hospital, Rigshospitalet, DK-Denmark.
Trial duration	Enrollment duration: 9 months
Number of patients	40 patients. WHO Group I PAH: 10 with IPAH, 10 with CTD-aPAH, WHO Group III : 10 with pulmonary disease related PH and Group IV: 10 with CTEPH.
Selection criteria	Inclusion criteria: The following patients will be included in the study: - Patients >18 years of age - Voluntary participation after giving informed verbal and written consent - Patients untreated with PAH specific therapy - Patients on current PAH specific medication independent of duration of therapy - Patients can be included irrespective of pre-medication disease (WHO group 1) Exclusion Criteria - Patients who are unlikely to comply with the study protocol and procedures required by the study protocol. - Patients with any severe complication or comorbidity other than PAH which might determine the prognosis and functional level of the patient. Concomitant treatments - Patients can be on the following treatments only if they have been at least treated for three months prior to inclusion and are planned to be continued during the whole study period: diuretics, digoxin, beta-blockers and amiodarone
Data collection	**At screening:** - SPECT/CT will be performed at diagnosis for prevalent cases only and at screening for incidents cases to exclude pulmonary embolism - LFT to exclude pulmonary disease: COPD and ILD - Echocardiography to exclude left heart disease - PAH verified with right heart catheterization before start of PAH specific medication - Basic demographic data including medication. - Physical examination and vital signs - 6 MWT - ECG - Lab tests including liver and renal function tests and NT-pro-BNP

	Visits every 6 months or with increased symptomatology - 6 MWT - Lab tests, including liver and renal function tests including yearly eGFR and NT-proBNP - Echocardiography yearly and at 3 month after inclusion - Record concomitant medications - PAH medications
Endpoints	**Primary endpoints** - Arrhytmias as assessed by Insertable Cardiac Monitors **Secondary endpoints** - Modified NYHA functional class - Reduction in 6 MWT in the study period. - NT-proBNP change in study period. - Change and /or escalation of PAH therapy - Respiratory hospitalization - Death or transplantation
Statistical methods	SPSS/PASW Statistics 19 software (SPSS Inc, Chicago IL), SAS or R is used for all statistical analysis.

Study Chart – ASPIRE III

	Screening	**Operation**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
		1	6 mo	12 mo	18 mo	24 mo
Informed consent	x					
Height	x					
Weight	x					
RHC`¤	x					
SPECT/CT	x					
LFT	x					
ECG	x	X	X	X	x	X
Echocardiography	x			x		x
6 MWT	x	X	X	X	x	X
Clinical data collection	x	X	X	X	X	X
Blood Samples#	x	X	X	x	x	x

¤ RHC;: right heart catheterisation for incident cases only. Prevalent cases have had RHC at the time of diagnosis. *CMR, cardiac index, RV size, stroke volume and pulmonary artery diameter including exercise measurements #Blood samples include haematology, liver chemistry (ALT, AST, LDH bilirubin) renal (creatinine, eGFR), and NT-proBNP.

Limitations

Reveal LINQ Insertable Cardiac Monitor, ICM

The ICM used in this study is wireless and the smallest available device, and the insertion procedure is minimally invasive, and requires short procedure time and clinical resources. To be able to send device information from home cellular technology is required.

Cardiac magnetic resonance imaging, CMR

CMR has its own limitations. Unlike echocardiography, it is expensive and not widely available. Data acquisition and post-processing can be time consuming and the need for patients to lie flat in the scanner can be somewhat challenging. However, with improved technology, many of the parameters mentioned above can be attained in almost the same amount of time as a standard 2-dimensional echocardiography (2DE).

Conclusions and perspectives

Arrhythmias in pulmonary arterial hypertension and right heart failure are prominent problems with an incidence of up to 35%. Supraventricular arrhythmias are the most prevalent in patients with pulmonary arterial hypertension. Permanent atrial fibrillation is the most ominous supraventricular arrhythmias and at the same time the most difficult to treat, whereas transient episodes of supraventricular arrhythmias seem to have no effect on mortality. Right ventricular and atrial parameters correlate with an increased risk of supraventricular arrhythmias in idiopathic pulmonary arterial hypertension patients. Prolonged QTc is associated with an increased risk of death.

More data is needed to determine the optimal way to restore sinus-rhythm and manage arrhythmias in pulmonary arterial hypertension. In cases with atrial flutter, the most feasible and the safest therapy is radiofrequency ablation.

This is the first study to assess arrhythmias in a homogeneous patient population prospectively, equally distributed among the different subgroups of pulmonary arterial hypertension with long-term monitoring. The implantation of an Insertable Cardiac Monitor records the heart rhythm continuously, for up to three years, and saves ECG details immediately preceding and during arrhythmia. This approach in combination with MR scanning of RV haemodynamic parameters holds the promise for optimizing specific therapy in patients with PAH and right heart failure.

Risks and side effects

MR scan:

Contrast agents will be used in connection with the yearly MR-scan. This can have side effects such as nausea, dizziness or a minor impact on the patient's kidney function. In rare cases, MR scans with contrast agents can be associated with more severe side effects such as shortness of breath and rashes. If a patient develops reduced kidney function, contrast agents will no longer be used in the yearly MR controls.
The patient may have the same symptoms in connection with the bike test as with physical work load outside the scanner. The work load in the bike test will gradually be increased but will be stopped in case the patient feels discomfort.
No radiation will be used in the study.

Blood samples:

Withdrawal of blood samples entails a minor risk of infection at the place of insertion of the needle, and a risk of puncture of an artery or nerve damage. Those complications are very rare and will be treated. Nerve damage will often disappear by itself. The most common complication in connection with taking blood samples is the occurrence of a hematoma, which will gradually disappear.

Side effects of the insertion of a loop recorder:

Pain may occur in the area around the place where the loop recorder is implanted. The pain can be relieved by using painkillers, such as paracetamol. In very rare cases, the loop recorder can displace itself from its start position (1%), or it can cause inflammation (1%) or a hematoma under the skin (0.3 %). Finally, there is a risk of erosion in the pocket, in which the loop recorder lies (0.2 %) (42).

Biobank:

A biobank will be established in connection with the study. The biobank will enable the investigation of new hypotheses upon renewed authorization by The Danish Scientific Ethical Committee and the patient's renewed consent. In the test, 10 ml blood will be withdrawn for every visit (6 visits in total) and the excess amount of blood will be kept in the biobank. The material will be kept for up to 25 years after the ending of the study and will then be destroyed.

Information from the patient's journal

Release of any information from the patient's journal to the person in charge of the study will take place according to section 46, subsection 1 of the Danish Health Act. According to this section, information about an individual person's health, other private conditions and confidential information in patient journals etc. may be released to a researcher for the use in a concreate biomedical research project. Information about gender distribution, population distribution within various age groups, age distribution, blood pressure and weight may be obtained from a patient's journal. In addition, information may be obtained about symptoms in relation to PAH, medical treatment and possible concomitant diseases. This kind of information may be compared with data appearing from the loop recorder and the MR scans. Any information used for publication will be anonymized.

We adhere to the European regulation on protection of personal data.
The study has been announced to and approved by the Danish Data Protection Agency (J.nr. 2018-41-5331<)

Financial conditions:
We will apply for funding from external foundations. We will keep The Danish Scientific Ethical Committee currently informed about funding and also notify them when the final funding has taken place.
The study has been started by the initiative of consultant Jørn Carlsen

Recruitment of patients
The patients will be recruited from the cohort already treated at “Kardiologisk Klinik” for PAH. In addition, we will prospectively offer new patients participation in the study and obtain their acceptance.

Publication of test results:
We aim at publishing all results, whether positive, inconclusive or negative, in articles in international scientific journals. Such articles will be found on the internet at www.ncbi.nlm.nih.gov/pubmed by a search on “Carlsen J” and “Hastrup J” and the subject “pulmonary arterial hypertension”. If the test results are not accepted by international journals publication of the results will be made in national journals and in presentations at national and international conferences.

Abbreviations

2-DE	2-dimensional echocardiography
6 MWT	6-Minute Walk Test
AF	Atrial Fibrillation
AFL	Atrial Flutter
AVNRT	AtrioVentricular Nodal Reentry Tachycardia
BNP	Brain Natriuretic Peptide
CMR	Cardiac Magnetic resonance imaging
CO/CI	Cardiac Output/Cardiac Index
CPR	CardioPulmonary Resuscitation
CRT	Cardiac Resynchronization Treatment
CTEPH	Chronic ThromboEmbolic Pulmonary Hypertension
EPS	Electrophysiological Study
ECG	ElectroCardioGraphy
HR	Hazard Ratio
ICM	Insertable Cardiac Monitor
IPAH	Idiopathic Pulmonary Arterial Hypertension
LV	Left Ventricle
LVF	Left Ventricle Failure
mPAP	mean Pulmonary Arterial Pressure
mRAP	mean Right Atrial Pressure
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PH	Pulmonary Hypertension
PVR	Pulmonary Vascular Resistance
RA	Right Atrium
RHF	Right Heart Failure
RV	Right Ventricle
RVEDV	Right ventricular end-diastolic volume
RVESV	Rright ventricular end-systolic volume
RVEF	Right ventricle ejection fraction
SV	Stroke Volume
RVF	Right Ventricle Failure
SVA	SupraVentricular arrhythmia
SVT	SupraVentricular Tachycardia
VA	Ventricular Arrhythmia
VT	Ventricular Tachycardia

RHC: right heart catheterization
SPECT/CT: Single photon emission computed tomography/ Computed tomography

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