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Ambulatory Fontan pressure monitoring: Results from the implantable hemodynamic monitor Fontan feasibility cohort (IHM-FFC)

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ABSTRACT

Background: Implantable invasive hemodynamic monitoring (IHM) using the CardioMEMS™ HF system has been shown to reduce heart failure (HF) hospitalizations. IHMs have not yet been used in congenital heart disease (CHD). We aimed to evaluate feasibility and mid-term outcomes of IHM use in the single ventricle/Fontan population.
Methods: Six adult Fontan patients (>1 HF admission, NYHA FC >3) were enrolled (30 ± 7 years old, mean pulmonary artery pressure (mPA) 16 ± 4.7 mm Hg). Heart failure mediated events (HFME) were evaluated for 12 months: CV medication change, hospital admission, paracentesis, and change in orthotopic heart transplant (OHT) listing status.
Results: The IHM device was successfully placed in all participants. In total there were 671 IHM transmissions and 25(3.7%) HFME. The mean PA pressure across all episodes was 18.2 ± 6.6 mm Hg (range 6–40 mm Hg). Higher mPA pressures were associated with greater odds of having a HFME (OR 1.17 [1.09, 1.25], $p < 0.0001$). Mean PA pressure had good ability to discriminate transmissions associated with HFME (AUC 0.76 [0.654, 0.866]), with mean PA pressures >24 mm Hg or individual mPA change >4 mm Hg, best discriminating transmissions associated with HFME.
Conclusions: In the first feasibility series of adult Fontan patients undergoing CardioMEMS™ implantation we demonstrate early technical success and no device-related adverse events. We propose that ambulatory mean PA pressures >24 mm Hg or individual mPA change >4 mm Hg may be associated with more HFME. Further large-scale studies in this population are recommended.

1. Introduction

Complex congenital heart disease (CHD) characterized by a single functioning ventricle was associated with poor survival until about 40 years ago when the Fontan procedure was developed [1]. Although this palliation has improved survival to adulthood, intrinsic limitations exist even in the most ideal conditions [2]. The Fontan circuit creates a unique form of indolent heart failure (HF) characterized by chronic systemic venous hypertension and low cardiac output. Over decades the elevated central venous pressure, chronic congestion and low cardiac output result in HF with worsening functional capacity, hospitalizations and ultimately either early cardiovascular mortality or transplant.

In the non-congenital heart disease population hemodynamic guided heart failure management has been shown to be effective in reducing HF hospitalization rates. Invasive hemodynamic monitoring (IHM) using the CardioMEMS™ HF system is a validated tool to measure pulmonary artery pressures (mPA) in patients with New York Heart Association functional class (NYHA-FC) III HF symptoms [3]. In non-CHD patients, frequent monitoring of PA pressures and targeted treatment intervention based upon this data resulted in reduced HF hospitalizations [4].

Hemodynamic guided heart failure management has not yet been described in CHD patients, particularly those with a Fontan palliation. In this study we aimed to evaluate the safety and feasibility of CardioMEMS™ IHM in Fontan patients, describe real-time hemodynamic assessment in this cohort and report mid-term outcomes in Fontan patients managed with the CardioMEMS™ IHM.

2. Methods

2.1. Patient population & implantation

Adults ≥18 years of age with single ventricle anatomy and Fontan palliation known to be NYHA FC III or greater with at least 1 admission in the previous year for acute decompensated heart failure (current FDA indication for CardioMEMS™ placement) were offered enrollment in this prospective feasibility study (target enrollment n = 6). Any

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patient with known pulmonary artery stenosis or Fontan obstruction was excluded, as were patients with a contraindication to full dose anticoagulation or women who were pregnant. Between May 2015 and November 2016 there were 6 patients enrolled and implanted with the CardioMEMS™ IHM. All enrolled patients underwent successful IHM implantation with the CardioMEMS™ device. The first device was placed by a combined adult and pediatric interventional team at an adult hospital with extensive experience in the placement of this device; the following 5 implants were completed by the same combined adult/pediatric interventional team at a free-standing affiliated pediatric hospital. Details regarding anatomic location selected, device placement and calibration have previously been described [5].

Two patients were prescribed Coumadin prior to implantation and continued full dose anticoagulation post-device placement. Patients who were not taking full dose anticoagulation were prescribed Coumadin (Goal INR 2.0–3.0) and Aspirin 81 mg daily for 1 month post device placement. At that time if there was no further indication for therapeutic dose anticoagulation, Coumadin was discontinued and Aspirin was continued indefinitely.

2.2. Data collection and follow-up evaluation

Baseline clinical information was reviewed at the time of enrollment including: underlying anatomy, prior cardiac surgeries, imaging studies, current medications, most recent exercise testing and previous laboratory data. All patients had laboratory testing repeated prior to IHM implantation (complete blood count, comprehensive metabolic panel and coagulation testing). In addition to subjective assessment of functional class (NYHA FC), in patients that did not have any recent objective evaluation of exercise tolerance (V02 within the prior 6 months) cardiopulmonary exercise testing was completed (V02). Finally, all participants completed a Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Subjects were instructed how to use the CardioMEMS™ device to transmit readings after placement and prior to hospital discharge. For the first week after discharge, subjects were contacted by the study team to encourage transmission and verify that remote transmission was successful. One subject had interference from an implantable loop recorder, which was later removed and permitted successful subsequent transmissions. All participants were instructed to remotely transmit a reading once a day. Participants were not contacted to submit any additional readings after the first week post-implantation unless they reported a change in clinical status. Transmissions were reviewed by the study team on a weekly basis, however because this was a feasibility study in a new population, participants were treated similar to the control group of patients in the CHAMPION-HF study, in that no cardiovascular treatment changes were instituted unless there was a change in clinical status such as shortness of breath, worsening edema or weight gain [3].

All patients were followed for a minimum of 12 months post implant. As standard of care, all patients were evaluated clinically at 1-, 6-, and 12-months. At the 6- and 12-month visits NYHA FC was assessed, laboratory measurements were drawn and the MLHFQ was repeated. At the 6-month visit exercise testing was repeated (V02) in all subjects. All patients were monitored for clinical signs of pulmonary thromboembolic events, however no routine imaging was ordered unless clinically indicated. Four participants underwent an "IHM-Monitored VO2" on cycle ergometer where real-time exercise hemodynamics were transmitted each minute of the exercise study. For these subjects a ramping protocol was used with workloads selected to achieve individual volitional exhaustion between 8 and 12 min [6]. Breath-by-breath gas analysis was recorded continuously throughout exercise using a metabolic cart that was calibrated for flow and gas concentrations prior to each test while patients were monitored on a 12-lead ECG. Peak VO_2 was selected as the highest 20-s average VO_2 recorded in the last 60 s of exercise to exhaustion with an associated RER >1.05. VE/VCO2 slope was calculated using all exercise data points [7]. Pulmonary artery pressures were recorded at baseline and every 1-min of exercise to peak. Blood pressure via manual auscultation and oxygen saturation (pulse oximetry) were recorded every-other-minute throughout the exercise study.

All transmissions were evaluated to determine if they occurred in the context of a "Heart Failure Mediated Event" (HFME). HFME were defined as changes in clinical status or treatment due to underlying worsening of HF and included: cardiac medication change, hospital admission, paracentesis or change in heart transplant listing status. Transmissions occurring up to 2 weeks prior to a HFME were defined as being associated with the event.

2.3. Statistical analysis

Descriptive analysis of the data was performed using 1-way analysis of variance or student *t*-test for continuous variables where appropriate and Chi-square to evaluate categorical variables. Descriptive data are reported as mean ± SD or frequency n (%) where appropriate. We performed logistic regression to evaluate the association between mean PA readings and HFME (individual and group), using an optimum threshold of mean PA pressure using Youden's J statistic. As a sensitivity analysis, the process was repeated for subjects 1 and 6 separately (the two subjects with sufficient sample size), with similar results. Moreover, to account for repeated measurements per patient, a binomial mixed effects model was applied after excluding subjects 3 and 5 (due to absence of any events, to facilitate model convergence), and results were also similar. Only results from the primary analysis are reported. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) with two-sided *p*-values of <0.05 considered statistically significant.

3. Results

3.1. Baseline characteristics

Four men and 2 women were enrolled in this feasibility study (30 ± 7 years-old, V02 17 ± 9 mL/kg/m^2, Fontan pressure 16 ± 5 mm Hg). Single ventricle anatomy resulted in a systemic morphologic left ventricle in 4 participants (Tricuspid atresia n = 2, Pulmonary atresia-intact ventricular septum n = 1, Superior-inferior ventricles with criss-cross atrioventricular valves with pulmonary atresia n = 1) a systemic morphologic right ventricle in the remaining 2 participants (double outlet right ventricle n = 2). Lateral tunnel was the most common Fontan anatomy (lateral tunnel = 4, Extracardiac = 2). Systolic ventricular function was normal in most subjects (n = 4) (abnormal systolic function in 2: mild dysfunction n = 1, severe dysfunction n = 1). In this cohort 2 subjects had advanced Fontan failure (with preserved systolic function) and were listed for isolated heart transplant. During the course of the study one participant advanced listing from status II to status Ia followed by eventual de-listing due to high surgical risk for transplant; this patient remains alive and is currently treated medically for advanced disease. A second subject that was initially listed as status II chose a palliative route rather than listing escalation. All subjects performed exercise testing with the exception of one patient who was not able to exercise independently (Table 1, Online Supplement Table I).

All participants had successful placement of the CardioMEMS™ IHM device (Fig. 1, G). The device was placed in the left pulmonary artery in 4 patients and in the right pulmonary artery in 2 patients due to LPA hypoplasia. No procedure-related complications occurred in this feasibility cohort (Hemodynamics available in Online Supplement Table II). Representative angiography at the time of device placement is shown in Fig. 1 (H–K) and Online Supplemental Videos. During the follow-up timeframe there were no clinical pulmonary venous thromboembolic events (VTE). One patient (Subject 2) presented with shortness of breath 530 days after device placement and received computed tomographic angiography (CTA) which showed no evidence of thromboembolic event. A second patient (Subject 5) with hypoxia 28 days post implant and had a CTA which also showed no evidence of pulmonary thromboembolism. No other patients had symptoms necessitating clinically indicating imaging studies to evaluate the pulmonary arteries. Clinically indicated pre- and post-device placement pulmonary artery imaging testing is reported in Online Supplement Table III.

3.2. Transmissions, heart failure mediated events (HFME) and exercise

At 12 months follow-up, subjects transmitted 9 ± 10 readings per month. There was no significant difference between baseline and follow-up exercise tolerance (MLHFQ 40 ± 30 vs. 50 ± 34, $p = 0.51$); peak VO2 (17 ± 8 vs. 14 ± 5, $p = 0.18$) (Online Supplement Fig. I). Monthly averaged pulmonary artery pressure readings and heart rates transmitted for each subject, along with details regarding HFME are outlined in Online Supplement Fig. III. Mean PA pressure was variable among subjects with the lowest average mPA readings 15 ± 3 mm Hg and the highest 23 ± 3 mm Hg. Heart rate control was also variable, with some subjects consistently transmitting normal heart rates (60–110 bpm) and others who had several episodes of tachycardia (HR > 100 bpm) (Fig. 1, A–F).

There were 671 IHM transmissions and 25 (3.7%) which were associated with a HFME. The mean PA pressure across all episodes was 18.2 ± 6.6 mm Hg (range 6–40 mm Hg). Subject-level data including average IHM readings and association with HFME are detailed in Table 2. Mean PA pressure values were higher among transmissions associated with a HFME as compared to those without an event ($p < 0.0001$). Moreover, higher mPA pressures were associated with significantly greater odds of having a HFME (OR 1.17 [1.09, 1.25], $p < 0.0001$). Mean PA pressure had good ability to discriminate transmissions associated with HFME from transmissions without HFME, with an area under

Table 1
Descriptive baseline patient characteristics.

Characteristic	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
CHD diagnosis	PA-IVS	TA-PS, VSD	TA	DORV, PA	DORV, MA hypoplastic LV, TAPVR	Superior-inferior ventricles with criss-cross AAV, PA
Surgical palliation	AP Fontan later converted to lateral tunnel Fontan	Extracardiac Fontan, fenestrated	Lateral tunnel Fontan, fenestrated	Extracardiac Fontan, fenestrated	Lateral tunnel Fontan, fenestrated	Lateral tunnel Fontan, fenestrated
Site of IHM implantation	LPA	LPA	RPA	LPA	LPA	RPA
Arrhythmia	AF, SSS, PM	None	SSS, PM	None	None	AF (sotolol)
NYHA class	III	III	III	III	III	III
Systolic function, method of diagnosis	Mild dysfunction, TTE	Normal, TTE	Normal, TTE	Normal, TTE	Severe dysfunction (RVEF 26%), cMRI	Normal, TEE
AVV regurgitation	Mild	Mild	Trivial	Trivial	Moderate	Moderate
Liver disease, method of diagnosis	Fibrosis, biopsy	None, F0 Fibrosure	Fibrosis, Biopsy	Fibrosis stage: F1–F2 Fibrosure	Cirrhosis, MRE	Cirrhosis, US
MELD	12[a]	7	12[a]	10	13	16
Creatinine (mg/dL)	1.04	0.64	0.66	1.03	0.77	0.81
Albumin (mg/dL)	3.4	4.3	4.8	4.1	3.8	4.1
Baseline mPAP (mm Hg)	22	12	13	15	12	22
Baseline VO2	17.5	12.2	–	19.5	30.1	5.8
Listed for OHT	Yes, Status II (heart only)	No	Yes, Status II (heart only)	No	No	No
Other comorbidities	Restrictive lung disease	Endocarditis CVA NSAID-induced GIB Osteomyelitis Narcotic use	Autism	Pulmonary AVMs Chronic anemia JRA Hypothyroidism NSAID-induced GIB	None	None

AAT: Antiarrhythmic therapy, AF: atrial fibrillation, AP: Atrio-Pulmonary, AVMs: Arteriovenous Malformations, AVV: Atrioventricular valves, CHD: Congenital Heart Disease, cMRI: Cardiac Magnetic Resonance Imaging, CVA: Cerebral Vascular Accident, DORV: Double outlet Right Ventricle, D-TGA: D Transposition of the Great Arteries, GIB: gastrointestinal bleeding, IHM: Implantable Hemodynamic Monitor, JRA: Juvenile Rheumatoid Arthritis, LPA: Left Pulmonary Artery, LV: Left Ventricle, MELD: Model for End Stage Liver Disease, MA: Mitral Atresia, mPAP: Mean Pulmonary Artery Pressure, MRE: Magnetic Resonance Elastography, NSAID: Non-Steroidal Anti Inflammatory Drug, NYHA: New York Heart Association, OHT: Orthotropic Heart Transplant, PA: Pulmonary Atresia, PA-IVS: Pulmonary Atresia-Intact Ventricular Septum, PM: Pacemaker, RPA: Right Pulmonary Artery S/P: Status Post, SSS: sick sinus syndrome, TA: Tricuspid Atresia, TA-PS: Tricuspid Atresia-Pulmonary Stenosis, TAPVR: Total Anomalous Pulmonary Venous Return, TEE: Transesophageal echocardiography, TTE: Transthoracic Echocardiography, US: ultrasound.

[a] Denotes MELD XI used due to patient history of warfarin use.

the receiver operator characteristic curve (AUC) of 0.76 (0.654, 0.866). Based upon the ROC curve results, the optimum threshold value of mean PA pressure which best discriminated transmissions associated with HFME from those where no HFME occurred was a mPA ≥24 mm Hg (sensitivity 64%, specificity 78%; Online Supplement Fig. II). We performed the same analysis evaluating change in mPA pressure for each subject, and found that individual increase in mPA by 4 mm Hg, although not terribly sensitive, was highly specific in discriminating HFME with an AUC of 0.66 (0.52, 0.80) (sensitivity 32%, specificity 93%; Online Supplement Fig. III).

The IHM- Monitored VO2 test was performed in 4 of 6 patients. Resting mPA was disparate among the patients, measuring <10 mmg in some and >30 mm Hg in others. There did not appear to be any significant change in mPA with exercise until the groups were separated based upon morphologic single ventricular anatomy. Statistical analysis with this low number of subjects has limitations; however there appeared to be a trend toward less change in mPA pressure with exercise in subjects with a morphologic LV as compared to a morphologic RV (8 ± 1 mm Hg vs. 11 ± 2 mm Hg, $p = 0.3$; Fig. 2).

4. Discussion

As more adults with complex CHD survive to adulthood [8,9], late heart failure becomes increasingly important as it is the most common end-stage complication in moderate and severely complex CHD [10,11]. Ambulatory hemodynamic evaluation of the Fontan circuit has not yet been evaluated, and there is a clinical need to define how ambulatory hemodynamics can be optimized to improve functional capacity and decrease morbidity/mortality associated with end stage heart failure. Our early feasibility study implanting and monitoring the CardioMEMS™ IHM in Fontan patients has shown that in a small number of early implants there were no procedure-related complications. We have also shown that HFME were associated with IHM transmissions ≥24 mm Hg, perhaps indicating that there may be an ambulatory Fontan pressure threshold above which Fontan patients experience objective findings of heart failure. Finally, we show that it is possible to obtain ambulatory exercise hemodynamics in Fontan patients with the IHM device.

4.1. Heart failure in single ventricle anatomy

Heart failure in single ventricle/Fontan anatomy is not the same as heart failure in biventricular anatomy. The Fontan circulation relies on re-direction of systemic venous blood to the pulmonary arteries in the absence of a subpulmonic ventricle. This results in passive flow of blood through the pulmonary vasculature and a single functioning ventricle which is used to support systemic circulation. In Fontan patients, pulmonary blood flow is dependent upon a gradient between central venous pressure (CVP) and a combination of ventricular end diastolic pressure and resistance of flow across the pulmonary vascular bed. Therefore, in patients with a prior Fontan operation, pulmonary vascular resistance (PVR) plays a crucial role in modulating ventricular filling, and thus cardiac output [12]. The long-term effects of a Fontan circulation lead to several extracardiac complications including congestive hepatopathy, liver cirrhosis, and ultimately liver failure [13,14].The liver is not the only organ affected, and frequently renal dysfunction, protein losing enteropathy, and plastic bronchitis can also be seen [15,16]. Although not specifically proven, many of these complications can be secondary to elevated CVP along with chronic congestion and low cardiac output. Over decades this results in the deterioration of exercise tolerance and worsening functional capacity, both of which are associated with worsening quality of life [17,18]. Ultimately these sequelae result in increased rates of hospitalization, diuretic titration, and consideration for transplant. Theoretically IHM ambulatory monitoring in the Fontan patient may be advantageous so that clinicians can guide therapy even before the patient feels symptomatic.

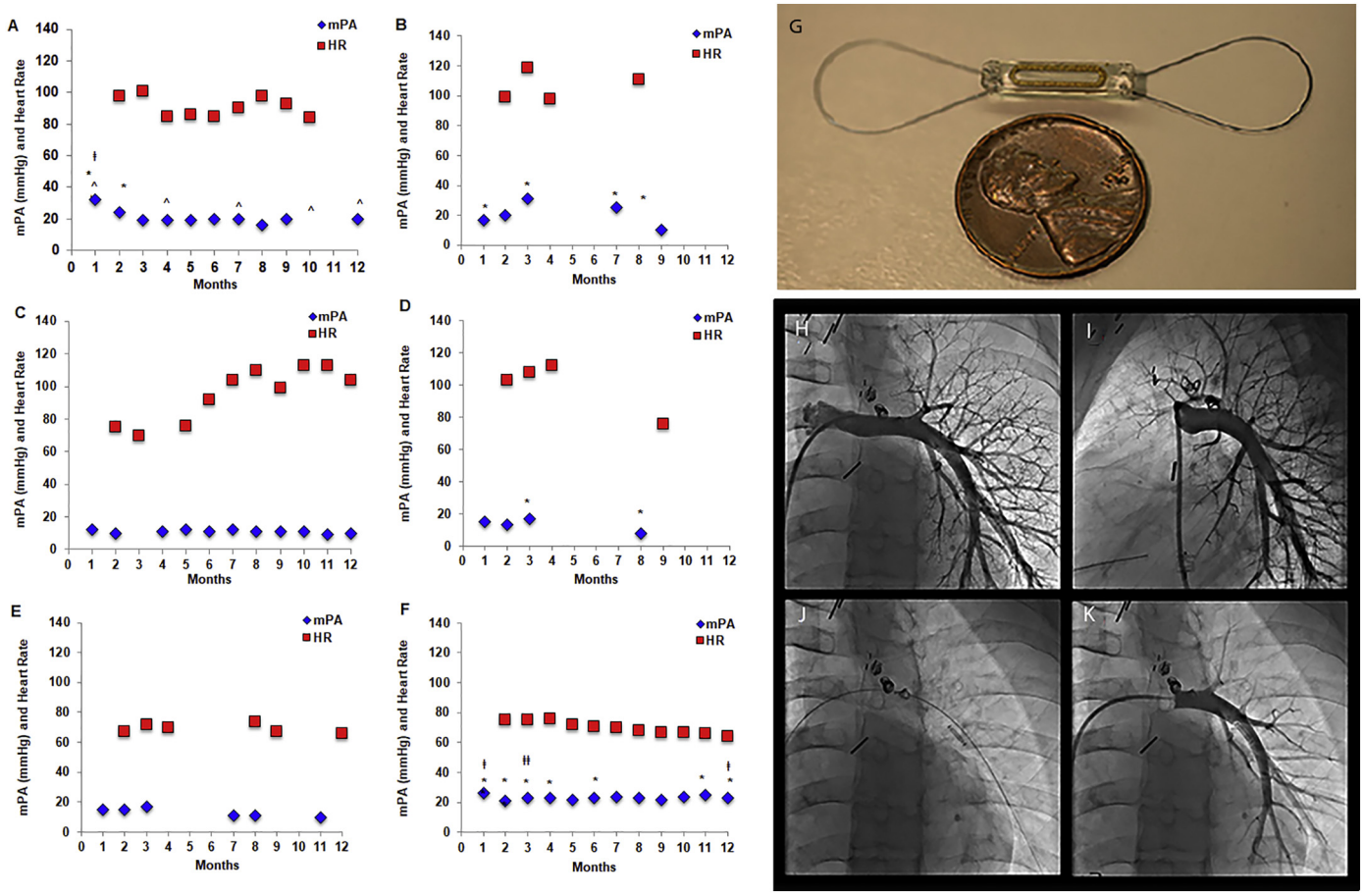

Fig. 1. Hemodynamics and imaging with CardioMEMS™ placement. Average monthly mean pulmonary artery pressure readings (blue diamonds) and heart rates (red boxes) in the six adult Fontan patients (A–F) with HFME events: *Medication change, ‡Decompensated HF Admission, ^Paracentesis. CardioMEMS™ device compared for size next to U.S. penny (19.05 mm diameter) (G). Angiography demonstrating injection of contrast and measurement of the left pulmonary artery (LPA) on AP (H) and lateral (I), deployment of the CardioMEMS™ device (J), and injection of contrast after placement of device with no evidence of stenosis of the LPA (K).

4.2. Heart failure treatment in the Fontan patient

Traditional heart failure therapies are less well studied in CHD than non-CHD populations. Heart failure medications such as beta-blockers and ACEi/ARB are often prescribed in CHD based upon evidence from acquired heart failure studies [19], hoping that the same effects on the neurohormonal system [20], ventricular remodeling [21] and fibrosis [22] are similar for the CHD group. Use of these medications in the Fontan population is even less studied than other forms of CHD, making it difficult to determine what optimal therapy is in this group, and more importantly, how the natural history of heart failure can be changed, if at all. Adjusting pulmonary vascular resistance can, at least in part, potentially modify the hemodynamic effects of a Fontan circulation. Several studies have aimed to explore the role of pulmonary arterial hypertension (PAH) medications in Fontan patients, as altering PVR may improve cardiac output. These studies have shown improvement in exercise capacity in this population with single-dose [23,24], and short-term (6 weeks) phoshodiesterase type 5 inhibitor administration [25]. More recently, similar results were shown when an endothelin receptor antagonist was taken for 14 weeks [26]. Ambulatory hemodynamic evaluation of the Fontan circuit in these patients has not yet been evaluated, and there is a clinical need to define how hemodynamics can be optimized to improve functional capacity and decrease morbidity/mortality associated with end stage heart failure. Although no patients in our cohort were receiving PAH targeted medications, evaluation of the Fontan patient prescribed targeted PAH therapy who also has an IHM may be the next logical area of study.

In our study we also highlight that ambulatory Fontan pressure readings were successfully obtained from the IHM device. Although we analyzed the data based upon underlying anatomy, the number of patients is too small to draw any significant conclusions about this. Nonetheless, the data does provide hypothesis-generating information about the role that underlying anatomy (morphologic left versus right ventricle in the systemic position) may play in late hemodynamics and exercise. Further study delineating specific risk factors in groups of different single-ventricle patients would be useful to help determine how treatment strategies may differ. An ambulatory IHM may be one useful tool to assist in the ongoing evaluation and monitoring of these patients as they age.

Table 2
Transmissions and HFME.

Subject	ALL		No HFME		HFME	
	N[a]	Mean ± SD	N[a]	Mean ± SD	N[a]	Mean ± SD
1	77	23 ± 6	74	23 ± 6	8	29 ± 5
2	6	20 ± 8	3	18 ± 4	4	22 ± 11
3	234	11 ± 2	233	11 ± 2	0	–
4	22	15 ± 3	20	15 ± 3	2	13 ± 6
5	37	15 ± 3	37	15 ± 3	0	–
6	295	23 ± 3	278	23 ± 3	11	25 ± 4
Total	671	18 ± 6	645	18 ± 7	25	24 ± 6

HFME: Heart Failure Mediated Event, PAP: Pulmonary Artery Pressure.
[a] Number of transmissions.

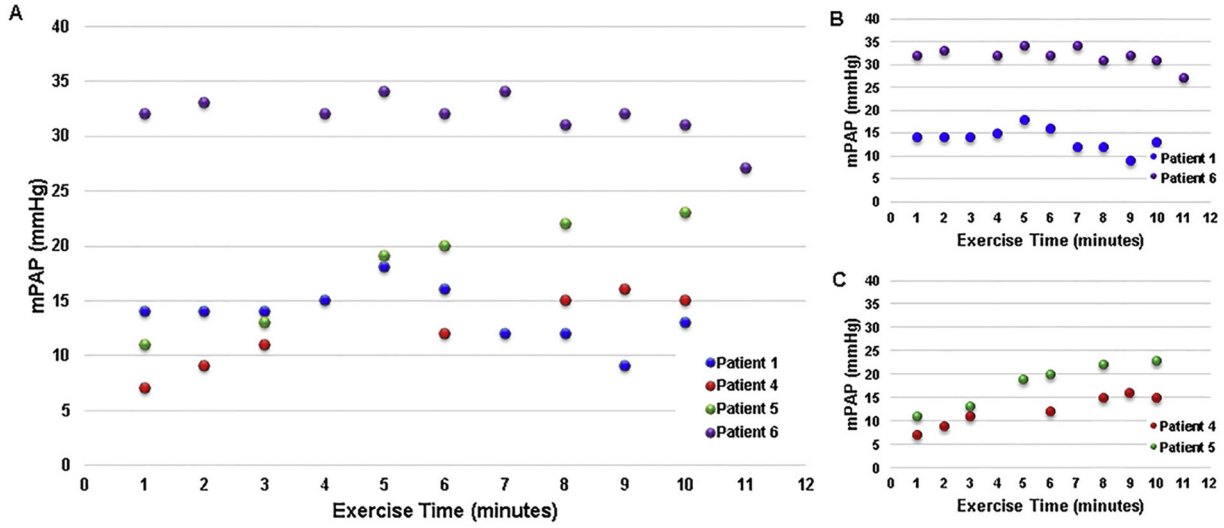

Fig. 2. IHM-monitored VO2. Mean pulmonary artery pressures (mm Hg) at each 1-min interval of exercise in four of the six patients (A). Mean pulmonary artery pressures over time in patients with systemic left ventricle (B) and patients with systemic right ventricle (C).

4.3. Limitations

There are several limitations in this early feasibility study. Our enrollment is small, and although it is an important 'first-look' at IHM use in a unique population, the ability to generalize these findings is limited. The single-ventricle anatomy is heterogeneous, and so the ability to identify associations and/or draw conclusions applicable to the Fontan population-at-large, is narrow. With respect to follow-up, there were a relatively low number of individual device transmissions, making it difficult to discriminate an absolute mPA cut-off at which the likelihood of HFME occurs; this may be better defined in a larger study where daily transmissions occur. In this study medical therapy was not adjusted based upon transmitted pressures, however future studies should further evaluate not only feasibility and safety, but mPA pressure guided therapy in the Fontan population. Finally, although there were no clinical venous thromboembolic events in this group, the concern for VTE risk in a sluggish Fontan pathway is not negligible, and requires the care team to have a high index of suspicion with any change in clinical status.

5. Conclusions

Our new data from the first small series feasibility study of adult Fontan patients undergoing CardioMEMS™ implantation and monitoring demonstrated technical success and no device-related adverse events. We describe ambulatory hemodynamic monitoring of patients with Fontan physiology, and propose that ambulatory mean PA pressures ≥24 mm Hg or individual mPA change >4 mm Hg may be associated with more HFME. We have shown that perhaps, change in ambulatory Fontan pressures with exercise may be more important in the patient with a morphologic systemic right ventricle. Further large-scale studies of IHM monitoring, HFME and exercise ambulatory hemodynamics in this heterogeneous population are important to better understand and treat heart failure as this group ages.

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