**MacGowan GA, Wrightson N, Robinson-Smith N, Woods A, Parry G, Gould K,
Schueler S.**

**[Myocardial Recovery Strategy with Decommissioning for the HeartWare Left
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Myocardial Recovery Strategy with Decommissioning for the HeartWare Left Ventricular Assist Device. --Manuscript Draft--

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Abstract:	To manage myocardial recovery in patients with the HeartWare left ventricular assist device (HVAD), we describe a minimally invasive approach ('decommissioning') that involves disconnecting the driveline and occluding the outflow tract through a small left thoracotomy incision leaving the device in situ, in conjunction with optimal medical therapies and comprehensive assessment of left ventricular recovery. Nine patients (all male, 37+/-12 years, all non-ischemic dilated cardiomyopathy) had an HVAD implanted for 766+/-343 days. When left ventricular function improved to mild impairment by echocardiography, patients underwent assessment at reduced flow (2578+/-148 to 1822+/-67 rpm) with documentation of compensated right heart hemodynamics and ejection fraction 52+/-8%. Eight of nine patients underwent decommissioning, and 1 patient had a hybrid procedure of percutaneous occlusion of outflow graft and surgical division of driveline. 2 patients died post operatively at 413 days (sepsis) and 810 days (heart failure). In conclusion, in selected patients with non-ischemic dilated cardiomyopathy a prolonged period of HVAD support in conjunction with heart failure medications can lead to recovery of left ventricular function. Surgical decommissioning is then an option to remove these patients from support. These patients are not however 'cured' and remain at risk for future deterioration in ventricular function and infections.

MacGowan et al 'Myocardial Recovery Strategy with Decommissioning for the HeartWare Left Ventricular Assist Device'

ASAIO-16310 R1

Response to Reviewers:

Dear Dr Slaughter,

Thank-you for your further comments. Below are detailed responses to the reviewer's comments.

Reviewer #3:

The authors have come back with some reasonable revisions.

- They changed some references in the intro, but actually didn't read the articles they references. The recent Wever-Pinzon paper is based on debunking the Intermacs concept that the rate of recovery is 1.3%. This paper should not be used to continually reinforce the Intermacs competing outcomes data.

Response: Apologies for the mistake. We have rephrased the opening 2 sentences to: 'Myocardial recovery in patients on left ventricular assist devices (LVAD) is well documented^{1,2}, and in appropriately selected patients can be achieved in 24% of implants³.

- With regards to rationale, the original question raised was not about the rationale for attempting to recover, but rather the rationale to decommission versus explant. They only really respond with a single statement with the natural orifice left behind. While this is a reasonable thought, others have put a titanium plug in to maintain the orifice as well. So, it is still unclear why decommissioning is better than other alternatives (besides the ease of doing it)

Response: The rationale is now more clearly stated. It is the combination of the uncertain long term future (possible need for further device) and avoiding a complicated operation (full explant procedure). Furthermore, as a plug is likely needed to fill the apical deficit, the decommissioning procedure uses the device as its own plug. Thus, the 'ease of doing it' it certainly a significant factor. We now state 'Thus, it has been proposed that remission rather than recovery is a more appropriate terminology when there is a risk of relapse in the future⁵. In that context, whether a definitive explant operation is needed initially should be questioned. A simpler operation, leaving the device in-situ, though occluding the outflow graft and severing the driveline using the device as its own apical plug will leave a natural orifice to re-implant a new device at a later date should that be needed.'

- with regards to timing, then, what is the average length of time that the patients were deemed recovered and then explanted.

Response: Patients waited an average of 94±64 days from the low flow assessment until the decommissioning procedure. This wait was due to logistical reasons rather than a specific wait and see strategy, and if the wait was prolonged from the low flow assessment to the

operation we would repeat the echo before the operation to ensure no change in function (which was never observed) (page 6 last line going to page 7)

- do they anticoagulate differently during their 5 days of low flow:

Response: We do not change the anticoagulation during low flow. The standard anticoagulation protocol is INR target 2.7 and aspirin 300 mg daily. Of course, we would not do the assessment if the INR was subtherapeutic. This is stated on page 6, 2nd paragraph.

Myocardial Recovery Strategy with Decommissioning for the HeartWare Left Ventricular Assist Device.

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Abstract:

To manage myocardial recovery in patients with the HeartWare left ventricular assist device (HVAD), we describe a minimally invasive approach ('decommissioning') that involves disconnecting the driveline and occluding the outflow tract through a small left thoracotomy incision leaving the device in situ, in conjunction with optimal medical therapies and comprehensive assessment of left ventricular recovery. Nine patients (all male, 37 ± 12 years, all non-ischemic dilated cardiomyopathy) had an HVAD implanted for 766 ± 343 days. When left ventricular function improved to mild impairment by echocardiography, patients underwent assessment at reduced flow (2578 ± 148 to 1822 ± 67 rpm) with documentation of compensated right heart hemodynamics and ejection fraction $52 \pm 8\%$. Eight of nine patients underwent decommissioning, and 1 patient had a hybrid procedure of percutaneous occlusion of outflow graft and surgical division of driveline. 2 patients died post operatively at 413 days (sepsis) and 810 days (heart failure). In conclusion, in selected patients with non-ischemic dilated cardiomyopathy a prolonged period of HVAD support in conjunction with heart failure medications can lead to recovery of left ventricular function. Surgical decommissioning is then an option to remove these patients from support. These patients are however not 'cured' and remain at risk for future deterioration in ventricular function and infections.

Key Words: Recovery, left ventricular function, HeartWare left ventricular assist device

Introduction:

Myocardial recovery in patients on left ventricular assist devices (LVAD) is well documented^{1,2}, and in appropriately selected patients can be achieved in 24% of implants³. This potentially offers patients with a history of end-stage heart failure an alternative to long term left ventricular assist device (LVAD) support with its potential complications, or transplantation with its associated risks. Two issues with myocardial recovery on LVADs are clear: 1) that patients with recent onset non-ischemic dilated cardiomyopathy are more likely to recover than long standing non-ischemic cardiomyopathy^{2,3,4}, or ischemic patients, and 2) there is a risk of future decline in ventricular function after recovery. For instance, in a recent report on recovery in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) at 1 year post explantation 18 out of 21 patients were alive without further intervention, 1 had died and 2 had undergone transplantation³. Thus, it has been proposed that remission rather than recovery is a more appropriate terminology when there is a risk of relapse in the future⁵. In that context, whether a definitive explant operation is needed initially should be questioned. A simpler operation, leaving the device in-situ, though occluding the outflow graft and severing the driveline using the device as its own apical plug will leave a natural orifice to re-implant a new device at a later date should that be needed.

In response to these issues we have developed a program of myocardial recovery with the HeartWare VAD (HVAD) that involves maximally tolerated standard heart failure therapies, monitoring of recovery for prolonged periods (usually well beyond 1 year), careful assessment of recovery at low HVAD flow rates, and then minimally invasive ‘decommissioning’ surgery which involves leaving the HVAD in-situ, though occludes the outflow graft and cuts the driveline through a small left thoracotomy incision without the

need to arrest the heart. In another patient a hybrid procedure of percutaneous outflow graft occlusion and surgical division of driveline was performed. We report the first 9 patients who have undergone this program who had devices implanted over a 7 year period.

Methods:

Between July 2009 and Sept 2016, 170 adult patients underwent implantation of the HVAD at the Freeman Hospital as a bridge to transplant. The strategy as indicated in table 1 was adopted to aid and assess myocardial recovery. In all patients flow rates of the device were set at time of implantation and set in part to allow some degree of aortic valve opening detectable by echocardiography. Patient details of those that were successfully decommissioned are presented in table 2. All patients were male. Eight of the nine patients were on pre-operative inotropes, 2 had intra-aortic balloon pumps, and 2 patients were on arterio-venous extracorporeal membrane oxygenation. Diagnosis was established by a combination of clinical presentation, family history, and myocardial histology. This study adhered to the terms of the United Kingdom Data and Protection Act and Freedom of Information Act, and was approved to obtain confidential information by the local Caldicott Guardian.

Echocardiograms were performed by experienced echocardiographers. Left ventricular dimensions were measured from parasternal long axis views. As left ventricular function is difficult to quantify in patients with the HeartWare device causing difficulty in obtaining apical windows, a scale of left ventricular function was used from 1-4 (1 = normal, 2 = mild, 3 = moderate, and 4 = severe impairment). As this was a semi-quantitative measurement, we also obtained computed tomography (CT) angiograms for measurement of left ventricular end-diastolic volume and ejection fraction for the final assessment pre-decommissioning at low flow. Right ventricular function with the echocardiograms were also measured using a semi-quantitative scale from 1-6 (1 = normal, 2 = mild, 3 = mild-moderate, 4 = moderate, 5 = moderate-severe, and 6 = severe). Right heart catheterization for measurement of right and left heart fillings pressures and thermodilution cardiac output was

performed, and a cardiopulmonary stress test for determination of peak exercise oxygen consumption.

Surgical Decommissioning: In order to keep the surgical trauma to the recovered myocardium to a minimum, a new surgical strategy was introduced⁶, not to remove the pump at all, but rather use the pump as a “plug”. A 5 cm antero-lateral thoracotomy was performed via the sixth intercostal space with the patient in the supine position. This small incision allows exposure of the HVAD pump, and removal of the 3 plastic rings covering the outflow graft. The outflow graft was exposed, encircled and divided. The drive line was then exposed at the lower end of the xiphoid or where it is brought out of the thoracic cavity, and divided (figure 1). In most cases it was feasible to pull out the driveline remnant distally at the exit site. In some cases an additional incision was required to allow removal. In the ninth case, a hybrid procedure was performed with percutaneous closure of the outflow graft and surgical division of the driveline. This was performed because the outflow graft could not be reached through the thoracotomy incision. Anticoagulation with warfarin was continued for an internationalised normalised ratio of 2 – 2.5 following decommissioning, and antiplatelets discontinued.

Data Analysis: Data are presented as mean $\pm$ standard deviation. Survival curves were composed using SPSS (version 22) and groups compared using the Tarone Ware test.

Results:

Nine patients have been surgically decommissioned from this cohort, which represents 5.2 % of the total number, and 10.0 % of those patients with non-ischaemic dilated cardiomyopathy (mean age 37 ± 12 , range 19 – 53 years; all male). Four other patients in the total cohort who are not included in this report had only partial myocardial recovery but serious complications requiring full VAD explantation: 2 with prior myocardial infarction (one with recurrent haemorrhage and one with adverse social conditions precluding discharge from hospital), one patient with idiopathic dilated cardiomyopathy and resistant VAD-related pseudomonas sepsis, and another with idiopathic dilated cardiomyopathy and non compliance-induced device thrombosis. Only one of these partially recovered patients was a long term survivor.

Mean duration of support was 766 ± 343 (range 205 – 1145) days and mean follow up post decommissioning was 695 ± 341 (range 330 – 1359) days. The mean hemodynamics of the successful low flow assessments are presented in table 3. The standard anticoagulation regimen was not changed during the low flow assessments (warfarin target INR 2.7 and aspirin 300 mg daily). On average there were 1.8 ± 1.0 of these assessments for each patient, repeated until patients had acceptable hemodynamics and left and right ventricular function on low flow. Criteria to proceed with surgical decommissioning were after 5 days of low flow investigations: unchanged left and right ventricular function by echocardiogram (with at worst mild left and right ventricular function), left ventricular ejection fraction > 40% on gated cardiac CT, and pulmonary arterial wedge pressure < 15 mm Hg and cardiac index ≥ 1.8 ml/min/m² on low flow. Reasons for not passing the low flow assessments were as follows: low cardiac output N=1, right ventricular function N=2, left ventricular function N=1, and abnormal pulmonary arterial wedge pressure N=3. Of note, all but 1 patient had recent onset heart failure. The mean time from the low flow assessment to the

decommissioning procedure was 94 ± 64 days. Mean post-operative length of stay was 6 ± 1 days.

One patient died at 413 days post decommissioning due to sepsis. This was a patient with poor mobility due to Becker's muscular dystrophy, obesity and previous methicillin sensitive *staphylococcus aureus* colonisation of his driveline who had been treated with long term suppression with flucloxacillin before the decommissioning. The final admission with sepsis was probably precipitated in part by non-compliance with the antibiotic regimen. Another patient died at 810 days post decommissioning with heart failure. One patient has had a complete VAD explant since the initial decommissioning because of recurrent sepsis. This patient and the remaining 6 patients are well and free from symptoms of heart failure.

Serial Echocardiograms: Results of serial echocardiograms pre and post decommissioning are presented in figure 2. On support, over time there are reductions in left ventricular end-diastolic dimensions, end-systolic dimensions, and improvement in left ventricular function grade. Of note it takes approximately 700 days for left ventricular function to improve to the level of mild impairment. Right ventricular function improves to mild to moderately impaired from between moderate and moderate to severe impairment at the time of implant. Following decommissioning, there is reduction in left ventricular function again, so that after 1 year post decommissioning, left ventricular function on average is between mild and moderate dysfunction. In the 7 survivors, 2 have normal left ventricular function, 3 mild, 1 moderate and 1 severe dysfunction. Left ventricular dimensions do not change, and right ventricular function remains between mild to moderately impaired.

Survival of the decommissioned cohort from the time of VAD implant was compared to all other HVAD patients implanted at this centre. For the non-decommissioned HVAD

cohort an event included death on the device, and death after transplant. Survival was significantly better in the decommissioned group compared to the non-decommissioned patients (figure 3).

Discussion:

We demonstrate in this study that in patients with predominantly recent onset, non ischaemic cardiomyopathy after a significant period of support with the HVAD on maximal medical therapies, careful low flow assessments and minimally invasive surgery leaving the HVAD in-situ but disconnected, that recovered patients can be safely removed from device support. The immediate surgical risk is low, but there are potential problems with long term follow-up with potential sepsis and deteriorating left ventricular function.

Minimally invasive surgery to reduce risk: Surgery to explant the device can carry significant risk. Birks and colleagues reported that 3 of 23 HeartMate II patients explanted died peri-operatively⁷. Frazier and colleagues⁸ have recently reported a modified technique to explant the HeartMate II device that involves leaving the inflow cannula in place and removing the rest of the device. Our technique with the HVAD takes this evolution one step further and retains the device in-situ. An alternative is a percutaneous approach using vascular plugs to close the outflow graft⁹, which we have also used in 1 patient. To-date our approach has not led to any immediate post operative adverse events, though there are potential long term problems. All patients have been left on an empiric dose of warfarin anticoagulation to maintain an INR of 2 – 2.5.

Recovery with the HVAD: The assessment of recovery with the HVAD as described shares a lot of the attributes described with other devices^{7,10,11,12}. There is a period of unloading and when function appears to improve assessments are performed at low flows. Compared to the study from Birks and colleagues with the Heartmate 2 device the development of recovery with increasing function and reduced dimensions in the current

study is significantly slower⁷. In their study the majority of patients achieved normal ejection fractions by 4-5 months. Other groups have shown the same phenomenon. Dandel et al¹⁰ have shown in a group of patients with a variety of LVADs (though not the HVAD) that the mean duration of support to allow explantation was 4.9 ± 2.8 months. Drakos et al¹² have likewise shown that the largest increase in ejection fraction on support was at 270 days. The reasons for this are unclear: there are 2 possibilities – 1) that the HVAD has intrinsic less unloading properties than other VADs, and/or 2) that our setting of aortic valve opening in all patients leads to less unloading. We have previously reported that with the HVAD¹³ at 200 days of support the left ventricular end-diastolic dimension reduces from 7.2 ± 1.0 to 6.9 ± 1.2 cm (at an average of 2522 ± 174 revolutions per minute). In other studies using other continuous flow devices there is apparently greater unloading. For instance, in a comparison of pulsatile and continuous flow unloading with the HeartMate II device, Kato et al¹⁴ have shown that after a median of 100 days support left ventricular end-diastolic dimension reduces from 6.8 ± 1.1 to 5.6 ± 1.5 . Likewise, Maybaum et al¹⁵ have shown greater unloading of the left ventricle in a study involving predominantly the Heartmate 2 device. However, Gupta et al¹⁶ with the HVAD have shown at 100 days that left ventricular end-diastolic dimension reduces from 7.1 ± 1.3 to 6.1 ± 1.4 cm, though at a higher mean pump speed of 2693 ± 139 rpm, specifically set so that the aortic valve was closed. Thus, the issue of slow left ventricular remodelling seems to be an issue of the HVAD settings rather than specifically related to the type of device. We do not know if allowing the aortic valve to open from implantation has benefits in terms of long term recovery. We do however know that an aortic valve that opens is likely to develop aortic regurgitation and thromboembolic events^{17,18}.

Long term outcomes: The long term outcomes of these patients compare favourably to those previously reported with the Heartmate 2 device. Birks et al⁷ have reported an

approximate 50% survival in recovered explanted patients at 750 days, which compares to approximately 50% survival at 2000 days in the current study (figure 3). One patient has died of sepsis and one of heart failure. There is potential for future deterioration in left ventricular function despite the optimal medical treatments, and sepsis, and so these patients cannot be considered cured⁵. Dandel et al have reported a 66% 5 year freedom for heart failure¹⁰. In a group of 27 explanted patients, Frazier et al⁸ have reported 1 transplant, 1 device reimplantation, 3 strokes and 2 deaths for a mean survival time post explant of 1097 ± 926 days. Leaving the device in situ leaves a natural conduit through which to place a new device should that be needed in the future. An alternative is repair of the apical defect, though we do not know if this has a beneficial impact on left ventricular function. Ideally, to minimise long term infection risk those patients who have had systemic infections while the device is operating should probably have a full explant procedure. Our patient who died of sepsis was a high risk patient for both an explant procedure (obesity with Becker's muscular dystrophy) but also at high risk for infection given history of colonisation with methicillin sensitive *Staphylococcus aureus*, so posed a difficult real world dilemma.

Conclusions: In selected patients with end-stage heart failure and non-ischemic dilated cardiomyopathy supported with the HVAD a prolonged period of device support in conjunction with optimal heart failure medications can lead to recovery of left ventricular function. Surgical decommissioning is then a practical option to remove these patients from support without the need for extensive surgery. Nevertheless, there is a risk of deterioration in left ventricular function and recurrence of heart failure in the long term.

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Figure Legends:

Figure 1. Chest X rays of the same patient immediately after VAD implant (left), and then post surgical decommissioning (right). Arrows point to the driveline. Post decommissioning the VAD is in situ, and the arrow indicates where the driveline has been cut. The contrast on the images has been increased so that the driveline is more easily seen.

Figure 2: Serial echocardiograms before decommissioning (left column) and post decommissioning (right). **A. and B.** left ventricular end-diastolic (LVEDD) and end-systolic dimensions (LVESD); **C. and D.** left ventricular function on a graded visual scale from 1-4 with 1 being normal and 4 severe; **D. and E.** right ventricular function on a graded visual scale from 1-6 with 1 being normal and 6 severe. At the bottom of each column is the number of scans available for each time point.

Figure 3: Survival of decommissioned patients (grey line) with all other HVAD patients (black). Survival is significantly better in the decommissioned patients ($P < 0.01$).

Table 1:**Strategy for Managing and Assessing Potential Patients for Decommissioning:**

1. Maximally tolerated standard heart failure therapies.
2. Serial echocardiograms until LV function rated as mild.
3. 5 Day low flow assessment.
4. Day 1: Echocardiogram on full flow and then reduced flow. If no change in function proceed with complete assessment.
5. Day 4: Right heart catheterisation and cardiopulmonary stress tests on low flow.
6. Day 5: CT angiogram and final echocardiogram on low flow.
7. Surgical Decommissioning if acceptable haemodynamics and no deterioration in echocardiogram at low flow.
8. Discharge on pre-operative maximally tolerated heart failure therapies. No antiplatelets. Warfarin for INR target range 2 – 2.5

Table 2: Patient Characteristics:

Patient	Age	Diagnosis	Duration of Heart Failure	Days on Support	Intermacs Class	Medications: (daily dose)
1	22	Familial Dilated Cardiomyopathy	1 st Admission	940	2	Bisoprolol 10 mg Lisinopril 20 mg Spiro. 25 mg Ivabradine 10 mg
2	25	Familial Dilated Cardiomyopathy	1 st Admission	837	1	Bisoprolol 10 mg Lisinopril 5 mg Eplerenone 25 mg Ivabradine 10 mg
3	53	Idiopathic Dilated Cardiomyopathy	1 year	1145	4	Bisoprolol 10 mg Lisinopril 15 mg Spiro. 25 mg Ivabradine 10 mg
4	19	Familial Dilated Cardiomyopathy	1 st admission	917	2	Bisoprolol 10 mg Lisinopril 20 mg Eplerenone 25 mg
5	39	Sarcoidosis	1 st Admission	1078	1	Bisoprolol 7.5 mg Candesartan 4 mg Prednisolone 15 mg
6	42	Becker's Muscular Dystrophy Cardiomyopathy	1 st Admission	861	1	Bisoprolol 10 mg Lisinopril 20 mg Ivabradine 10 mg
7	44	Idiopathic Dilated Cardiomyopathy	1 st Admission	205	1	Bisoprolol 2.5 mg Lisinopril 2.5 mg
8	35	Idiopathic Dilated Cardiomyopathy	1 st Admission	646	3	Bisoprolol 7.5 mg Hydralazine + Nitrates
9	51	Acute myocarditis	1 st Admission	225	1	Bisoprolol 5mg Lisinopril 15 mg

Spiro: spironolactone.

Table 3:

Pre-Decommissioning Low Flow Investigations:

Baseline Flow Rate (rpm)		2578 ₊₁₄₈
Reduced Flow Rate (rpm)		1822 ₊₆₇
Low flow haemodynamics:	Heart Rate (beats/min)	73 ₊₉
	Systolic Blood Pressure (mm Hg)	101 ₊₁₀
	Diastolic Blood Pressure (mm Hg)	61 ₊₁₂
	Right Atrial Pressure (mm Hg)	4 ₊₃
	Pulmonary Artery Systolic Pressure (mm Hg)	21 ₊₆
	Pulmonary Artery Mean Pressure (mm Hg)	15 ₊₄
	Pulmonary Arterial Wedge Pressure (mm Hg)	9 ₊₃
	Cardiac Index (L/min/m ²)	2.3 _{+0.4}
	Pulmonary Arterial Oxygen Saturation (%)	68 ₊₅
	Peak Exercise Oxygen Consumption (mL/kg/min)	18.0 _{+4.6}
	CT Ejection Fraction (%)	52 ₊₈
	CT End-Diastolic Volume (mL)	154 ₊₆₁

Post Operative VAD Implant

Intact Driveline

Post Operative VAD Decommission

Severed Driveline

Figure 3

Abstract:

To manage myocardial recovery in patients with the HeartWare left ventricular assist device (HVAD), we describe a minimally invasive approach ('decommissioning') that involves disconnecting the driveline and occluding the outflow tract through a small left thoracotomy incision leaving the device in situ, in conjunction with optimal medical therapies and comprehensive assessment of left ventricular recovery. Nine patients (all male, 37 ± 12 years, all non-ischemic dilated cardiomyopathy) had an HVAD implanted for 766 ± 343 days. When left ventricular function improved to mild impairment by echocardiography, patients underwent assessment at reduced flow (2578 ± 148 to 1822 ± 67 rpm) with documentation of compensated right heart hemodynamics and ejection fraction $52 \pm 8\%$. Eight of nine patients underwent decommissioning, and 1 patient had a hybrid procedure of percutaneous occlusion of outflow graft and surgical division of driveline. 2 patients died post operatively at 413 days (sepsis) and 810 days (heart failure). In conclusion, in selected patients with non-ischemic dilated cardiomyopathy a prolonged period of HVAD support in conjunction with heart failure medications can lead to recovery of left ventricular function. Surgical decommissioning is then an option to remove these patients from support. These patients are however not 'cured' and remain at risk for future deterioration in ventricular function and infections.

Key Words: Recovery, left ventricular function, HeartWare left ventricular assist device

Introduction:

~~Whereas~~ myocardial recovery in patients on left ventricular assist devices (LVAD) is well documented^{1,2}, ~~overall it is relatively rare, occurring in 1.3% of implants and in appropriately selected patients can be achieved in 24% of implants~~³. ~~Nevertheless,~~ This potentially offers patients with a history of end-stage heart failure an alternative to long term left ventricular assist device (LVAD) support with its potential complications, or transplantation with its associated risks. ~~Despite this,~~ Two issues with myocardial recovery on LVADs are clear: 1) that patients with recent onset non-ischemic dilated cardiomyopathy are more likely to recover than long standing non-ischemic cardiomyopathy^{2,3,4}, or ischemic patients, and 2) there is a risk of future decline in ventricular function after recovery. For instance, in a recent report on recovery in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) at 1 year post explantation 18 out of 21 patients were alive without further intervention, 1 had died and 2 had undergone transplantation³ Thus, it has been proposed that remission rather than recovery is a more appropriate terminology when there is a risk of relapse in the future⁵. In that context, whether a definitive explant operation is needed initially should be questioned. A simpler operation, ~~leaving the device in-situ, though occluding the outflow graft and severing the driveline using the device as its own apical plug~~ will leave a natural orifice to re-implant a new device at a later date should that be needed.

In response to these issues we have developed a program of myocardial recovery with the HeartWare VAD (HVAD) that involves maximally tolerated standard heart failure therapies, monitoring of recovery for prolonged periods (usually well beyond 1 year), careful assessment of recovery at low HVAD flow rates, and then minimally invasive

‘decommissioning’ surgery which involves leaving the HVAD in-situ, though occludes the outflow graft and cuts the driveline through a small left thoracotomy incision without the need to arrest the heart. In another patient a hybrid procedure of percutaneous outflow graft occlusion and surgical division of driveline was performed. We report the first 9 patients who have undergone this program who had devices implanted over a 7 year period.

Methods:

Between July 2009 and Sept 2016, 170 adult patients underwent implantation of the HVAD at the Freeman Hospital as a bridge to transplant. The strategy as indicated in table 1 was adopted to aid and assess myocardial recovery. In all patients flow rates of the device were set at time of implantation and set in part to allow some degree of aortic valve opening detectable by echocardiography. Patient details of those that were successfully decommissioned are presented in table 2. All patients were male. Eight of the nine patients were on pre-operative inotropes, 2 had intra-aortic balloon pumps, and 2 patients were on arterio-venous extracorporeal membrane oxygenation. Diagnosis was established by a combination of clinical presentation, family history, and myocardial histology. This study adhered to the terms of the United Kingdom Data and Protection Act and Freedom of Information Act, and was approved to obtain confidential information by the local Caldicott Guardian.

Echocardiograms were performed by experienced echocardiographers. Left ventricular dimensions were measured from parasternal long axis views. As left ventricular function is difficult to quantify in patients with the HeartWare device causing difficulty in obtaining apical windows, a scale of left ventricular function was used from 1-4 (1 = normal, 2 = mild, 3 = moderate, and 4 = severe impairment). As this was a semi-quantitative measurement, we also obtained computed tomography (CT) angiograms for measurement of left ventricular end-diastolic volume and ejection fraction for the final assessment pre-decommissioning at low flow. Right ventricular function with the echocardiograms were also measured using a semi-quantitative scale from 1-6 (1 = normal, 2 = mild, 3 = mild-moderate, 4 = moderate, 5 = moderate-severe, and 6 = severe). Right heart catheterization for measurement of right and left heart fillings pressures and thermodilution cardiac output was

performed, and a cardiopulmonary stress test for determination of peak exercise oxygen consumption.

Surgical Decommissioning: In order to keep the surgical trauma to the recovered myocardium to a minimum, a new surgical strategy was introduced⁶, not to remove the pump at all, but rather use the pump as a “plug”. A 5 cm antero-lateral thoracotomy was performed via the sixth intercostal space with the patient in the supine position. This small incision allows exposure of the HVAD pump, and removal of the 3 plastic rings covering the outflow graft. The outflow graft was exposed, encircled and divided. The drive line was then exposed at the lower end of the xiphoid or where it is brought out of the thoracic cavity, and divided (figure 1). In most cases it was feasible to pull out the driveline remnant distally at the exit site. In some cases an additional incision was required to allow removal. In the ninth case, a hybrid procedure was performed with percutaneous closure of the outflow graft and surgical division of the driveline. This was performed because the outflow graft could not be reached through the thoracotomy incision. Anticoagulation with warfarin was continued for an internationalised normalised ratio of 2 – 2.5 following decommissioning, and antiplatelets discontinued.

Data Analysis: Data are presented as mean $\pm$ standard deviation. Survival curves were composed using SPSS (version 22) and groups compared using the Tarone Ware test.

Results:

Nine patients have been surgically decommissioned from this cohort, which represents 5.2 % of the total number, and 10.0 % of those patients with non-ischaemic dilated cardiomyopathy (mean age 37 ± 12 , range 19 – 53 years; all male). Four other patients in the total cohort who are not included in this report had only partial myocardial recovery but serious complications requiring full VAD explantation: 2 with prior myocardial infarction (one with recurrent haemorrhage and one with adverse social conditions precluding discharge from hospital), one patient with idiopathic dilated cardiomyopathy and resistant VAD-related pseudomonas sepsis, and another with idiopathic dilated cardiomyopathy and non compliance-induced device thrombosis. Only one of these partially recovered patients was a long term survivor.

Mean duration of support was 766 ± 343 (range 205 – 1145) days and mean follow up post decommissioning was 695 ± 341 (range 330 – 1359) days. The mean hemodynamics of the successful low flow assessments are presented in table 3. The standard anticoagulation regimen was not changed during the low flow assessments (warfarin target INR 2.7 and aspirin 300 mg daily). On average there were 1.8 ± 1.0 of these assessments for each patient, repeated until patients had acceptable hemodynamics and left and right ventricular function on low flow. Criteria to proceed with surgical decommissioning were after 5 days of low flow investigations: unchanged left and right ventricular function by echocardiogram (with at worst mild left and right ventricular function), left ventricular ejection fraction > 40% on gated cardiac CT, and pulmonary arterial wedge pressure < 15 mm Hg and cardiac index ≥ 1.8 ml/min/m² on low flow. Reasons for not passing the low flow assessments were as follows: low cardiac output N=1, right ventricular function N=2, left ventricular function N=1, and abnormal pulmonary arterial wedge pressure N=3. Of note, all but 1 patient had recent onset heart failure. The mean time from the low flow assessment to the

decommissioning procedure was 94+64 days. Mean post-operative length of stay was 6±1 days.

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One patient died at 413 days post decommissioning due to sepsis. This was a patient with poor mobility due to Becker's muscular dystrophy, obesity and previous methicillin sensitive *staphylococcus aureus* colonisation of his driveline who had been treated with long term suppression with flucloxacillin before the decommissioning. The final admission with sepsis was probably precipitated in part by non-compliance with the antibiotic regimen. Another patient died at 810 days post decommissioning with heart failure. One patient has had a complete VAD explant since the initial decommissioning because of recurrent sepsis. This patient and the remaining 6 patients are well and free from symptoms of heart failure.

Serial Echocardiograms: Results of serial echocardiograms pre and post decommissioning are presented in figure 2. On support, over time there are reductions in left ventricular end-diastolic dimensions, end-systolic dimensions, and improvement in left ventricular function grade. Of note it takes approximately 700 days for left ventricular function to improve to the level of mild impairment. Right ventricular function improves to mild to moderately impaired from between moderate and moderate to severe impairment at the time of implant. Following decommissioning, there is reduction in left ventricular function again, so that after 1 year post decommissioning, left ventricular function on average is between mild and moderate dysfunction. In the 7 survivors, 2 have normal left ventricular function, 3 mild, 1 moderate and 1 severe dysfunction. Left ventricular dimensions do not change, and right ventricular function remains between mild to moderately impaired.

Survival of the decommissioned cohort from the time of VAD implant was compared to all other HVAD patients implanted at this centre. For the non-decommissioned HVAD

cohort an event included death on the device, and death after transplant. Survival was significantly better in the decommissioned group compared to the non-decommissioned patients (figure 3).

Discussion:

We demonstrate in this study that in patients with predominantly recent onset, non ischaemic cardiomyopathy after a significant period of support with the HVAD on maximal medical therapies, careful low flow assessments and minimally invasive surgery leaving the HVAD in-situ but disconnected, that recovered patients can be safely removed from device support. The immediate surgical risk is low, but there are potential problems with long term follow-up with potential sepsis and deteriorating left ventricular function.

Minimally invasive surgery to reduce risk: Surgery to explant the device can carry significant risk. Birks and colleagues reported that 3 of 23 HeartMate II patients explanted died peri-operatively⁷. Frazier and colleagues⁸ have recently reported a modified technique to explant the HeartMate II device that involves leaving the inflow cannula in place and removing the rest of the device. Our technique with the HVAD takes this evolution one step further and retains the device in-situ. An alternative is a percutaneous approach using vascular plugs to close the outflow graft⁹, which we have also used in 1 patient. To-date our approach has not led to any immediate post operative adverse events, though there are potential long term problems. All patients have been left on an empiric dose of warfarin anticoagulation to maintain an INR of 2 – 2.5.

Recovery with the HVAD: The assessment of recovery with the HVAD as described shares a lot of the attributes described with other devices^{7,10,11,12}. There is a period of unloading and when function appears to improve assessments are performed at low flows. Compared to the study from Birks and colleagues with the Heartmate 2 device the development of recovery with increasing function and reduced dimensions in the current

study is significantly slower⁷. In their study the majority of patients achieved normal ejection fractions by 4-5 months. Other groups have shown the same phenomenon. Dandel et al¹⁰ have shown in a group of patients with a variety of LVADs (though not the HVAD) that the mean duration of support to allow explantation was 4.9 ± 2.8 months. Drakos et al¹² have likewise shown that the largest increase in ejection fraction on support was at 270 days. The reasons for this are unclear: there are 2 possibilities – 1) that the HVAD has intrinsic less unloading properties than other VADs, and/or 2) that our setting of aortic valve opening in all patients leads to less unloading. We have previously reported that with the HVAD¹³ at 200 days of support the left ventricular end-diastolic dimension reduces from 7.2 ± 1.0 to 6.9 ± 1.2 cm (at an average of 2522 ± 174 revolutions per minute). In other studies using other continuous flow devices there is apparently greater unloading. For instance, in a comparison of pulsatile and continuous flow unloading with the HeartMate II device, Kato et al¹⁴ have shown that after a median of 100 days support left ventricular end-diastolic dimension reduces from 6.8 ± 1.1 to 5.6 ± 1.5 . Likewise, Maybaum et al¹⁵ have shown greater unloading of the left ventricle in a study involving predominantly the Heartmate 2 device. However, Gupta et al¹⁶ with the HVAD have shown at 100 days that left ventricular end-diastolic dimension reduces from 7.1 ± 1.3 to 6.1 ± 1.4 cm, though at a higher mean pump speed of 2693 ± 139 rpm, specifically set so that the aortic valve was closed. Thus, the issue of slow left ventricular remodelling seems to be an issue of the HVAD settings rather than specifically related to the type of device. We do not know if allowing the aortic valve to open from implantation has benefits in terms of long term recovery. We do however know that an aortic valve that opens is likely to develop aortic regurgitation and thromboembolic events^{17,18}.

Long term outcomes: The long term outcomes of these patients compare favourably to those previously reported with the Heartmate 2 device. Birks et al⁷ have reported an

approximate 50% survival in recovered explanted patients at 750 days, which compares to approximately 50% survival at 2000 days in the current study (figure 3). One patient has died of sepsis and one of heart failure. There is potential for future deterioration in left ventricular function despite the optimal medical treatments, and sepsis, and so these patients cannot be considered cured⁵. Dandel et al have reported a 66% 5 year freedom for heart failure¹⁰. In a group of 27 explanted patients, Frazier et al⁸ have reported 1 transplant, 1 device reimplantation, 3 strokes and 2 deaths for a mean survival time post explant of 1097 ± 926 days. Leaving the device in situ leaves a natural conduit through which to place a new device should that be needed in the future. An alternative is repair of the apical defect, though we do not know if this has a beneficial impact on left ventricular function. Ideally, to minimise long term infection risk those patients who have had systemic infections while the device is operating should probably have a full explant procedure. Our patient who died of sepsis was a high risk patient for both an explant procedure (obesity with Becker's muscular dystrophy) but also at high risk for infection given history of colonisation with methicillin sensitive *Staphylococcus aureus*, so posed a difficult real world dilemma.

Conclusions: In selected patients with end-stage heart failure and non-ischemic dilated cardiomyopathy supported with the HVAD a prolonged period of device support in conjunction with optimal heart failure medications can lead to recovery of left ventricular function. Surgical decommissioning is then a practical option to remove these patients from support without the need for extensive surgery. Nevertheless, there is a risk of deterioration in left ventricular function and recurrence of heart failure in the long term.

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Figure Legends:

Figure 1. Chest X rays of the same patient immediately after VAD implant (left), and then post surgical decommissioning (right). Arrows point to the driveline. Post decommissioning the VAD is in situ, and the arrow indicates where the driveline has been cut. The contrast on the images has been increased so that the driveline is more easily seen.

Figure 2: Serial echocardiograms before decommissioning (left column) and post decommissioning (right). **A. and B.** left ventricular end-diastolic (LVEDD) and end-systolic dimensions (LVESD); **C. and D.** left ventricular function on a graded visual scale from 1-4 with 1 being normal and 4 severe; **D. and E.** right ventricular function on a graded visual scale from 1-6 with 1 being normal and 6 severe. At the bottom of each column is the number of scans available for each time point.

Figure 3: Survival of decommissioned patients (grey line) with all other HVAD patients (black). Survival is significantly better in the decommissioned patients ($P < 0.01$).