ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 567–576
Published online 14 February 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12608

ORIGINAL RESEARCH ARTICLE

Invasive haemodynamics in *de novo* everolimus vs. calcineurin inhibitor heart transplant recipients

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Abstract

Aims Invasive haemodynamic profiles at rest and during exercise after heart transplantation (HTx) have never been described in a randomized trial where *de novo* everolimus (EVR)-based therapy with early calcineurin inhibitor (CNI) withdrawal has been compared with conventional CNI treatment. We report central invasive haemodynamic parameters at rest and exercise during a 3 year follow-up after HTx in a sub-study of the SCandiavian Heart transplant Everolimus De novo stUdy with earLy calcineurin inhibitor avoidancE trial. We hypothesized that the nephroprotective properties, the less development of cardiac allograft vasculopathy (CAV), and the antifibrotic properties of EVR, in comparison with CNI-based immunosuppression, would demonstrate favourable invasive haemodynamic profiles in patients at rest and during exercise.

Methods and results Ninety of 115 HTx recipients randomized to EVR or CNI treatment performed right heart catheterization at rest and 68 performed right heart catheterization at exercise up to 3 years after HTx. Haemodynamic profiles were compared between EVR and CNI treatment groups. Resting haemodynamics improved in both groups from pre-HTx to the first follow-up at 7–11 weeks post-HTx and thereafter remained unchanged up to 3 years of follow-up. During follow-up, cardiac reserve during exercise increased with higher levels of maximum heart rate (118 to 148 b.p.m., $P < 0.001$), mean arterial pressure (103 to 128 mmHg, $P < 0.001$), and cardiac output (10.3 to 12.2 l/min, $P < 0.001$). No significant differences in haemodynamic parameters were observed between the EVR and CNI groups at rest or exercise. Isolated post-capillary pulmonary hypertension (mean pulmonary arterial pressure > 20 mmHg, pulmonary arterial wedge pressure ≥ 15 mmHg, and pulmonary vascular resistance <3) were measured in 11% of the patients at 7–11 weeks, 5% at 12 months, and 6% at 36 months after HTx. The EVR group had significantly better kidney function (76 mL/min/1 vs. 60 mL/min/1, $P < 0.001$) and reduced CAV ($P < 0.01$) but an increased rate of early biopsy-proven treated rejections (21.2% vs 5.7%, $P < 0.01$) compared with the CNI group at any time point. The differences in renal function, CAV, or early biopsy-proven treated acute rejections were not associated with altered haemodynamics.

Conclusions *De novo* EVR treatment with early CNI withdrawal compared with conventional CNI therapy did not result in differences in haemodynamics at rest or during exercise up to 3 years after HTx despite significant differences in renal function, reduced CAV, and number of early biopsy-proven treated rejections.

Keywords Heart transplantation; Everolimus; Haemodynamics; Calcineurin inhibitor; Exercise

Received: 23 May 2019; Revised: 25 November 2019; Accepted: 9 December 2019
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Introduction

Long-term follow-up of invasive haemodynamics at rest and during exercise after heart transplantation (HTx) has rarely been studied, and exercise reports are mostly from the biatrial surgical era before the bicaval technique was introduced.[1–3] Haemodynamic exercise studies have reported elevated pulmonary pressures in heart transplant recipients as compared with healthy individuals.[4] However, the pulmonary pressures are similar to those in healthy individuals of advanced age but lower than those described in a population of patients with heart failure with preserved ejection fraction.[5–7]

Limited data have supported the mechanism of the unfavourable haemodynamics after HTx, and the effect of immunosuppression agents is unknown. Calcineurin inhibitor (CNI) treatment has been a cornerstone in achieving improved survival after HTx but is associated with arterial hypertension, nephrotoxicity, and cardiac allograft vasculopathy (CAV).[8,9] The mammalian target of rapamycin (mTOR) inhibitor everolimus (EVR) is an alternative drug to reduce the early development of CAV and nephrotoxic burden of CNI as shown by several randomized trials in HTx patients receiving mTOR inhibitors as a substitute for CNI.[10–12] However, mTORs do not have the same immunosuppressive potency as CNIs and may increase the incidence of early graft rejections.[11,13] An EVR-based treatment with early withdrawal of CNI vs. traditional CNI immunosuppression in the SCandiavian Heart transplant Everolimus De novo stUdy with earLy calcineurin inhibitor avoidancE (SCHEDULE) trial demonstrated a favourable outcome on renal function and the development of CAV.[11] However, in the EVR group, an increased number of rejections were observed, which has so far limited the clinical impact of the SCHEDULE protocol internationally.[14]

Invasive exercise haemodynamics describes graft function in a *de novo* manner and gives additional information compared with echocardiography and biomarkers. Exercise-induced pulmonary hypertension (PH) is not clearly defined, and central haemodynamics after HTx is highly dependent on high blood volume, ischaemic reperfusion injury, inadequate increase in heart rate (HR) response, development of arterial hypertension, and diastolic dysfunction. Repeated rejection episodes, immunosuppressive therapy, CAV, and fibrosis have been referred to as late causes of restrictive graft function,[15–17] but long-term follow-up is still lacking. The previous definition of exercise-induced PH was removed in 2008 owing to difficulties defining a clear cut-off value given that PH varies by age, gender, body size, and increase in cardiac output (CO).[18]

No invasive exercise haemodynamic studies have previously been reported in a randomized immunosuppressive trial. We sought to assess the impact of two immunosuppressive regimens on invasive haemodynamics at rest and during exercise. The hypothesis was that the nephroprotective reduced CAV and antifibrotic properties of EVR, as compared with a CNI-based immunosuppression, would demonstrate a favourable invasive haemodynamic profile at rest and during exercise up to 3 years after HTx. We explored possible mechanisms of unfavourable haemodynamics with background variables, renal function, CAV, and rejections.

Methods

Study design, population, and conduct

This study was a predefined sub-study of the SCHEDULE trial. The SCHEDULE trial was a prospective, multicentre, randomized, controlled, open-label trial. In the study, adult *de novo* HTx recipients (n = 115) were randomized (1:1 ratio) to an EVR group [low-dose EVR, low-dose cyclosporine (CNI), mycophenolate mofetil (MMF), and corticosteroids (CSs) with withdrawal of CNI and step up to full dose EVR after 7–11 weeks] or a CNI group (conventional treatment with cyclosporine, MMF, and CS). The study design has previously been described.[19]

The study was approved by the ethics committee for each centre and was registered with clinicalTrials.gov (NCT01266148). It was conducted in compliance with Good Clinical Practice and in accordance with the 2000 Declaration of Helsinki and 2008 Declaration of Istanbul. Written informed consent was obtained from all study participants before inclusion.

Study population

Of the initial 115 recruited participants, 102 from all five study centres completed a 3 year follow-up. Of these 102 patients, 90 performed a right heart catheterization (RHC) at rest at 7–11 weeks and 12 and 36 months post-HTx and then entered the sub-study. Prespecified in the study protocol, patients from two centres (Gothenburg and Oslo) also performed an RHC at exercise at 7–11 weeks and 12 and 36 months after HTx. For the exercise evaluation, 68 of 68 potential patients had 3 year invasive exercise haemodynamic data.

Right heart catheterization

Right heart catheterization (RHC) was predominantly performed through the right internal jugular vein using a Swan Ganz catheter (Baxter Health Care Corp). If patients had more than one RHC before HTx, the one closest to the HTx or a ventricular assist device implantation as a bridge-to-heart HTx was used. Pulmonary artery pressure (mPAP, $PAP_{diastolic}$, and $PAP_{systolic}$), pulmonary artery wedge pressure (PAWP), mean right atrial pressure (mRAP), and mean arterial pressure (MAP) were measured. HR was recorded from

electrocardiogram. CO was measured by the thermodilution technique at the pulmonary artery position, and an average was calculated using at least three injections. The following formulas were used to calculate cardiac index (CI) = CO/body surface area; stroke volume index = CI/HR × 1000; right ventricular stroke work index = stroke volume index × (mPAP-mRAP) × 0.0136; transpulmonary gradient (TPG) = MPAP-PAWP; pulmonary vascular resistance (PVR) = TPG/CO; diastolic pressure gradient (DPG) = $PAP_{diastolic}$ − PAWP; and pulmonary artery pulsatility index (PAPi) = (PAP-$_{systolic}$ − $PAP_{diastolic}$)/mRAP.

Data collection and analysis

Right heart catheterization (RHC) was performed at rest before HTx and at rest at 7–11 weeks and 12 and 36 months after HTx. In all patients capable of exercise RHC, measurements were performed during supine bicycle exercise. The steady-state workload (in watts) selected for each patient was predefined as 50% of the maximal workload achieved by the patient during a cardiopulmonary exercise test the day before RHC (which represents a maximum workload when supine on the RHC bench). Haemodynamic measurements were obtained 4 min after supine exercise.

Intravascular ultrasound imaging

Intravascular ultrasound (IVUS) was performed at 7–11 weeks and 12 and 36 months post-HTx using a 20 MHz, 2.9F monorail, electronic Eagle Eye Gold IVUS catheter (Volcano Therapeutics, Corporation Inc, CA). IVUS examination was performed at different time points on the same major epicardial coronary artery (preferentially the left anterior descending coronary artery).[20]

Grayscale intravascular ultrasound analysis

A predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities in HTx recipients is maximal intimal thickness (MIT) as assessed by IVUS.[21] Changes in MIT between matching segments at 7–11 weeks and 12 and 36 months post-HTx were used as the primary grayscale IVUS efficacy variable. Secondary IVUS variables were percent atheroma volume (PAV), total atheroma volume, and CAV. PAV expresses the summation of atheroma areas in proportion to the external elastic membrane area using the equation PAV = ∑(external elastic membrane$_{area}$ − Lumen$_{area}$)/∑(external elastic membrane$_{area}$) × 100. CAV was defined as a ≥0.5 mm increase in mean MIT over the entire matched segment.

Immunosuppression

All patients received induction treatment with a regimen composed of antithymocyte globulin (ATG, Thymoglobulin ®Genzyme Corporation, Cambridge, MA) within 12 h before HTx and continued for up to 3 days. Patients were randomized within 5 days to either the EVR or the CNI group. The EVR group was treated with low-exposure EVR (Certican; Novartis Pharma AG, Basel, Switzerland), low-exposure cyclosporine (Sandimmun Neoral; Novartis Pharma AG), MMF, and CSs with cyclosporine withdrawal between 7 and 11 weeks post-HTx. The CNI group was treated with cyclosporine, MMF, and CSs. Target trough levels and target doses of the treatment have been previously reported.[19]

Statistics

Patient characteristics and haemodynamic variables are presented as mean ± SD. Comparisons were made between treatment groups at rest and after 4 min of exercise at 7–11 weeks and 12 and 36 months; differences between the treatment groups were tested using two-tailed paired *t*-tests. An analysis of variance was performed to investigate the relationship between individual haemodynamic variables and background variables, clinical outcome, recipient and donor characteristics, cardiovascular risk factors, and laboratory values. Continuous background variables were treated as linear covariates and categorical background variables as factors. An analysis of covariance was used to compare changes in IVUS endpoints between treatment groups. The baseline IVUS value was included as a covariate and treatment group as a fixed factor. Analysis of covariance *P*-values represent between-group contrast. Linear regression analysis was conducted to evaluate the relationship between CAV and haemodynamic parameters at rest and during exercise.

All analyses were performed both as intention to treat and as per-protocol-treated patients. Statistical significance was set to $P < 0.05$ (two tailed).

Results

Study population

In all, 90 patients performed an RHC at rest during 7–11 weeks and then at 12 and 36 months post-HTx, and 68 patients performed RHC during exercise at corresponding time points. The pre-transplant characteristics of patients in the SCHEDULE population and the exercise subgroups were similar (*Table 1*).

In accordance with the main study,[11] there was a renal benefit for the EVR group vs. the CNI group in measured glomerular filtration rate (mGFR) (36 month data: 76 ± 23

Table 1 Patient characteristics

	All (n = 90)	EVR exercise (n = 33)	CNI exercise (n = 35)
Age (years)	50.6 ± 12.8	50.6 ± 14.4	49.9 ± 12.6
Male	74 (72%)	24 (73%)	26 (74%)
BMI (kg/m^2)	24.4 ± 3.5	23.6 ± 3.5	25.0 ± 3.5
Medical history			
Hypertension	13 (13%)	6 (18%)	5 (14%)
Diabetes	16 (16%)	3 (9%)	7 (20%)
Chronic obstructive pulmonary disease	5 (5%)	1 (3.%)	1 (3%)
Previous smoker	52 (51.%)	16 (49%)	20 (57%)
Primary reason for HTx			
Hypertrophic cardiomyopathy	4 (3.9%)	2 (6.1%)	2 (6%)
Idiopathic dilated cardiomyopathy	52 (51%)	16 (49%)	23 (66%)
Congenital heart disease	2 (2%)	2 (6%)	0
Ischaemic heart disease	26 (27%)	9 (27%)	7 (20%)
Myocarditis	2 (2%)	0	1 (3%)
Postpartum	2 (2%)	0	1 (3%)
Restrictive cardiomyopathy	3 (3%)	1 (3%)	0
Other	11 (11%)	3 (9%)	1 (3%)
Renal function pre-HTx			
Serum creatinine (umol/L)	105 ± 38	103. ± 38	103 ± 26
mGFR	62 ± 16	62 ± 16	63 ± 14
HTx from LVAD	23 (24%)	8 (24%)	9 (26%)
Donor characteristics			
Age	44.5 ± 13.5	41.0 ± 15.3	44.4 ± 12.7
Male sex	66 (65%)	21 (64%)	25 (71%)
Cold ischaemia time (min)	193 ± 73	185 ± 77	195 ± 77
Lab			
HBA1c (mmol/mol)	6.0 ± 0.9	5.7 ± 0.7	6.2 ± 0.9
Sodium (mmol/L)	139 ± 3.8	139 ± 4.2	139. ± 3.4
Potassium (mmol/L)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5
NT-proBNP (ng/L)	436 ± 356	454 ± 330	489 ± 385
Hgb (g/L)	12.8 ± 1.9	12.6 ± 1.6	13.0 ± 1.8
Acute rejection episodes			
Number of patients with rejection ≥2R	17 (17%)	7 (21%)	2 (6%)
Renal function 36 months post-HTx			
Serum creatinine (umol/L)	—	86 ± 22	113 ± 36
mGFR	—	76 ± 23	60 ± 36

BMI, body mass index; CNI, calcineurin inhibitor; EVR, everolimus; HBA1c, haemoglobin A1c; HTx, heart transplantation; LVAD, left ventricular assist device; mGFR, measured glomerular filtration rate.
Pre-transplant patient characteristics for all patients that performed an RHC at rest at the 3 year follow-up and patient characteristics divided into the subgroups EVR (n = 33) and CNI (n = 35) for patients that performed RHC at rest and during exercise at the 3 year follow-up (n = 68).

mL/min/1.73 m^2 vs. 60 ± 36 mL/min/1.73 m^2, $P < 0.001$) and a favourable outcome for CAV parameters at 12 and 36 months (Ps < 0.01). The proportion of patients treated for rejection (ISHLT ≥2R) during the first year was 5.7% in the CNI group and 21.2% in the EVR group ($P < 0.01$). Graft function, as assessed by echocardiography, N-terminal prohormone brain natriuretic peptide (NT-proBNP), and troponin T, demonstrated no differences between the two treatment groups at 12 and 36 month follow-ups. There was no difference between the two groups for the rate of pulmonary adverse events. The survival rate at the 36 month follow-up was 88% in the CNI and 95% in the EVR group.

Immunosuppression and concomitant medications

At the 36 month follow-up, 94% of the patients in the EVR group were still prescribed EVR, and within this group, 24% had returned to combination therapy with low-dose CNI and low-dose EVR. In the CNI group, only 6% of the patients were treated in combination with a CNI and EVR regimens. All patients continued to receive MMF, and 52% received steroids (equally in both groups). Beta-blockers, angiotensin-converting-enzyme inhibitor/angiotensin II receptor inhibitor (ARB)/MRA, and diuretics were primarily prescribed for hypertension and not heart failure. In the EVR vs. CNI groups, the use of beta-blockers was 30 and 45%, ACE/ARB 58 and 80%, and diuretics 24 and 9%, respectively. Statins were prescribed to 88% of the patients in the EVR group and 97% in the CNI group.

Haemodynamics before heart transplantation

Baseline haemodynamics at rest before HTx or ventricular assist implantation as a bridge to HTx was similar in the EVR and CNI groups (Supporting Information, *Table S1*). In our cohort,

53% of the patients had PH before transplantation (mPAP ≥25 mmHg) and one third had PVR ≥ 3 wood units. Exercise RHC before HTx was not performed in very few patients that were able to perform a supine stress test.

Resting haemodynamics after heart transplantation

At 7–11 weeks post-HTx, haemodynamics at rest was significantly improved compared with pre-HTx values and remained unchanged during the 36 month follow-up, except for the mPAP that decreased with time (*Figure 1*). mPAP ≥25 mmHg was measured in 14% of the patients at 7–11 weeks, 5% at 12 months, and 9% at 36 months post-HTx. Precapillary PH (mPAP ≥25 mmHg, PVR ≥3, and PAWP ≤15) was observed in 3% of the patients at 7–11 weeks and 0% at both 12 and 36 months post-HTx. With the new criteria of precapillary PH (mPAP >20 mmHg, PVR ≥ 3 wood units, and PAWP ≤15), PH was observed in 1.5% of the patients at 7–11 weeks and 0% at both 12 and 36 months after HTx. Isolated postcapillary PH (mPAP >20 mmHg, PAWP ≥15 mmHg, and PVR < 3) was observed in 11% of the patients at 7–11 weeks, 5% at 12 months, and 6% at 36 months.

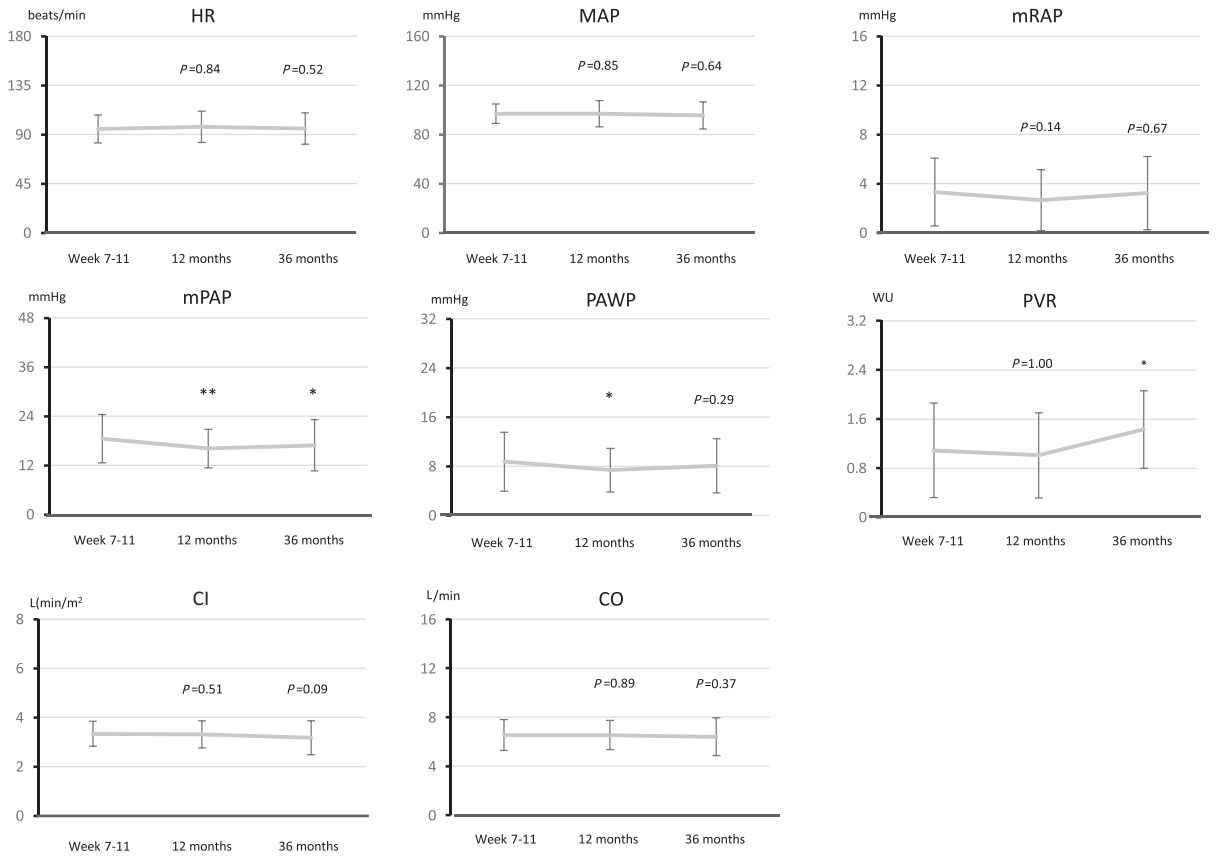
Right ventricular stroke work index for the whole population was 8.3 ± 2.9 at 7–11 weeks, 7.1 ± 2.7 at 12 months, and 6.8 ± 3.1 at 36 months. The reduction was statistically significant between 7–11 weeks and 12 months (P = 0.009) and 36 months (P = 0.003) but not between 12 and 36 months (P = 0.46). There were no statistical differences in DPG or PAPi at the three time points.

Haemodynamics at rest between the EVR and CNI groups is shown in Supporting Information, *Table S2a*. There were no differences in invasive resting haemodynamic parameters between the two treatment groups. The primary endpoint at rest was not met.

Exercise haemodynamics after heart transplantation

None of the patients developed ischaemic signs on electrocardiogram or symptoms during the cardiopulmonary exercise test the day before RHC. There was a trend towards

Figure 1 Haemodynamic characteristics at rest for heart rate (HR), mean arterial pressure (MAP), mean right atrial pressure (mRAP), mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), pulmonary vascular resistance (PVR), cardiac index (CI), and cardiac output (CO). Statistical testing with analysis of covariance and *P*-value represents changes from baseline. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.



improved performance during exercise from 7–11 weeks to 36 months. The workload during supine bicycle exercise increased gradually from 50 W at 7–11 weeks to 68 W at 36 months ($P < 0.001$). Throughout the follow-up period cardiac reserve, maximum MAP and CO/CI increased during exercise ($P < 0.001$) (*Figure 2*). There were no differences in invasive haemodynamic profile during exercise between the EVR and CNI groups in the predefined endpoint. The primary endpoint during exercise was not achieved.

After 4 min of exercise, 78% of the patients had a mPAP ≥30 mmHg and 42% had a mPAP ≥35 mmHg at 36 months. The proportion of patients with PAWP ≥25 mmHg during exercise was 20% at 7–11 weeks, 21% at 12 months, and 26% at 36 months; the proportion of patients with PAWP ≥30 mmHg during exercise was 4% at 7–11 weeks, 8% at 12 months, and 16% at 36 months.

There was no statistical difference in DPG or PAPi at any of the time points.

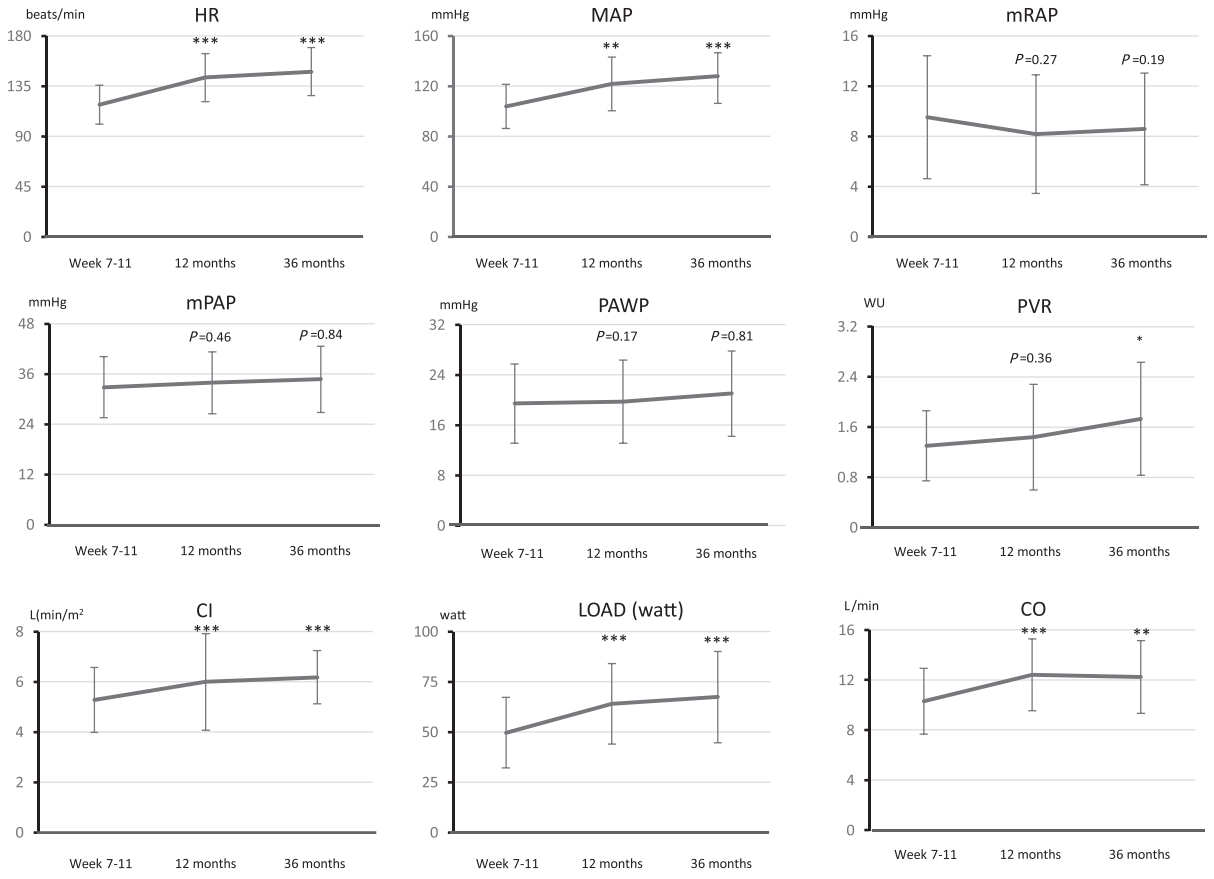
Haemodynamics during exercise in the EVR and CNI groups is shown in Supporting Information, *Table S2b*.

We analysed the relationship between peak exercise for mRAP, mPAP, PAWP, CO, CI, TPG, and PVR and the following variables: age, body mass index, mGFR, pre-HTx, haemoglobin, cold ischaemia time, donor age, NT-proBNP, number of rejections (ISHLT ≥2R), sex, diabetes, hypertension, primary reason for HTx, CAV, and EVR treatment. None of the background variables significantly influenced the haemodynamic parameters at rest or during exercise. Detailed analysis of patients with treated rejections vs. no treated rejections (independent of the two study groups) did not reveal any differences for rest or exercise haemodynamics.

The relationship between an increase in HR, CO, and CI from rest to exercise at 7–11 weeks and at 12 and 36 months post-HTx and the background variables age, body mass index, mGFR before HTx, mGFR after HTx, haemoglobin, cold ischaemia time, donor age, NT-proBNP, sex, diabetes, hypertension, CAV, and EVR treatment was analysed. None of the background variables were predictors of change in HR, CO, or CI.

An increase in HR, CO, and CI from rest to exercise at 36 months post-HTx did not differ between patients on beta-

Figure 2 Haemodynamic characteristics at exercise for heart rate (HR), mean arterial pressure (MAP), mean right arterial pressure (mRAP), mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), pulmonary vascular resistance (PVR), cardiac index (CI), workload (watt), and cardiac output (CO). Statistical testing with analysis of covariance and *P*-value represents changes from baseline. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.



blockers (independent of immunosuppressive regimen) at 7–11 weeks ($P = 0.71$), 12 months ($P = 0.77$), and 36 months ($P = 0.57$), respectively, on ACE/ARB at 7–11 weeks ($P = 0.22$), 12 months ($P = 0.55$), and 36 months ($P = 0.64$), respectively, or on diuretics at 7–11 weeks ($P = 0.45$), 12 months ($P = 0.33$), and 36 months ($P = 0.43$), respectively. An increase in HR during exercise for patients on beta-blockers was 55 ± 20 and 67 ± 20 without beta-blockers ($P = 0.59$).

No correlation was noted between the extent of MIT, total atheroma volume, PAV, and haemodynamic variables at rest or during exercise at 12 or 36 months.

Discussion

This sub-study of the SCHEDULE trial is the first to describe haemodynamic profiles at rest and during exercise throughout a 3 year follow-up in heart transplant recipients randomized to two immunosuppressive regimens. Moreover, it is the largest exercise RHC study performed after the bicaval approach was introduced. Our results show that both immunosuppressive groups displayed improved haemodynamics 7–11 weeks post-HTx compared with pre-HTx values. During the subsequent 36 months of follow-up, there were no substantial changes in resting haemodynamics. However, during exercise, there was a trend towards an increase in HR, MAP, and CO/CI across the 36 month follow-up. We did not observe any significant difference in predefined haemodynamic variables at rest or exercise between HTx recipients treated with EVR and an early CNI-free regimen and patients treated with traditional CNI-based immunosuppression.

Blood pressure at rest and during exercise did not differ between the treatment groups despite a trend toward higher consumption of angiotensin-converting-enzyme inhibitor/ARB and beta-blockers in the CNI group. This effect may have been balanced by the higher use of diuretics in the EVR group, probably because of peripheral oedema, a recognized side effect of EVR.

Only a few reports have investigated invasive haemodynamics during exercise after HTx.[3,22–24] These studies have consistently shown that exercise haemodynamics improves significantly compared with the pre-transplant level but remains lower than those observed in healthy individuals.[25–27] In a study by Pflugfelder et al.[24] superior haemodynamics was observed during exercise with a CO of 12 l/min, which is slightly above our finding. In contrast, Lundgren et al.[3] reported a CO of 6.5 l/min, but with an HR of approximately 20 b.p.m. less than our data and those of Pflugfelder et al. Otherwise, haemodynamic profiles during exercise demonstrate similar patterns, except for the elevated PAWP of 20 mmHg in our study and close to 30 mmHg in the two other studies.

Three years after HTx, 78% of our patients developed mPAP $\geq$30 mmHg, but only 26% developed PAWP $\geq$25 mmHg during exercise. The upper limits of normal exercise (PAWP or mPAP) in the supine position are not established as they tend to differ with age, sex, and body size. The definition of exercise-induced PH was removed in 2008.[18] DPG decreased to a negative value from rest to exercise, unmasking the presence of a post-capillary cause of PH. Herve et al.[28]described the importance of PAWP (which also indirectly includes DPG) and demonstrated that increases in pulmonary pressures are mainly post-capillary with restrictive graft physiology. Because cardiac systolic function was maintained (EF $>$ 50%),[11] our data support the view that the main reason for increased pulmonary pressure during exercise is secondary to diastolic dysfunction.

A previous report with repeated resting RHC has shown a continuous reduction in PVR during a 5 year follow-up.[2] This finding is in contrast to our finding demonstrating stable values after 7–11 weeks up to 3 years. To our knowledge, data on haemodynamic changes over time during exercise with repeated RHC for up to 36 months have not been reported elsewhere.

Renal dysfunction before and after HTx is an independent risk factor for post-HTx mortality.[29,30] The primary result from the SCHEDULE trial showed a clear renal benefit for the EVR group as compared with the CNI group for up to 3 years.[11] Lower systemic blood pressure and favourable renal function may decrease pressure/volume burden on the left side of the heart, with secondary reduction in pulmonary pressures. Despite the relatively large renal benefit in the EVR group, the haemodynamic parameters measured at rest or during exercise did not differ from the CNI group. Invasive haemodynamics, independent of treatment group, did not correlate with mGFR at any of the time points. Both treatment groups had relatively preserved renal function, potentially obscuring a renal effect on haemodynamic profiles that might become evident if renal dysfunction continues to progress with secondary fluid retention and hypertension.

In the SCHEDULE trial, patients in the EVR group had significantly reduced progression of CAV. There was no association between unfavourable development of CAV and unfavourable haemodynamics. Biopsy-proven acute rejections in total and grade $\geq$ 2R were more common in the EVR group than in the CNI group.[11,12] Of note, the higher number of early rejections in the EVR group did not influence the haemodynamic profile at either the 12 or 36 month follow-up. No relationship was found between rejections and unfavourable haemodynamics independent of treatment group.

Preserved graft function at rest and during exercise, despite a higher frequency of rejections, indicates that *de novo* EVR-based immunosuppression is safe up to 3 years post-HTx. Our findings contest the critics of the SCHEDULE trial who suggest that EVR *de novo* with early CNI withdrawal

could be hazardous.[14] A 3 year follow-up may be too short to unmask an effect of both CAV and repeated rejections on invasive haemodynamics as a substitute for graft function. On the other hand, some studies have shown that CAV shortly after HTx does not correlate with long-term CAV.

Some studies have shown a correlation between myocardial fibrosis and restrictive cardiac physiology.[15,16] Several factors have been proposed for the development of allograft fibrogenesis, including cyclosporine toxicity, which may lead to interstitial fibrosis.[31] While unable to detect any trends for unfavourable physiology (defined by increased mPAP and PAWP and decreased CO) in the CNI group, the relatively limited follow-up could influence differences that otherwise might appear between the two groups.

Limitations

Because this haemodynamic exercise study included only patients from two of the five centres participating in the SCHEDULE trial, the power of the study is limited. Thus, conclusions should be drawn cautiously. During exercise, interpretation of haemodynamic curves has to be performed in light of the knowledge that respiratory variations increase with workload. On the other hand, all invasive exercise studies face the same challenge, and no guidelines are yet available. Twenty-four percent of the patients in the EVR group went back to a combination of low-dose CNI and low-dose EVR, which may have impacted the results.

The 3 year follow-up may be too short to detect the effects of treatment regimen, CAV, renal function, or early rejections. Invasive data up to 3 years should not be used to promote long-term safety of a CNI-free regimen, but they do support the echocardiography and biochemistry data that are similar in both groups at the 3 year follow-up. Further studies, independent of patient groups, are needed to gain insight into the complex physiology during exercise.

Conclusion

This sub-study of the SCHEDULE trial demonstrates for the first time that EVR introduction with early CNI withdrawal or maintenance with traditional CNI treatment had a similar impact on invasive haemodynamics at rest and during exercise despite a different effect on renal function, frequency of early acute rejections, and the development of CAV. The favourable haemodynamics we predicted in the EVR group was not verified. A gradual improvement in exercise performance and exercise haemodynamics up to 3 years following HTx was observed. These results demonstrate that the increased rejection rate in the EVR group does not jeopardize the haemodynamic profile at rest or during exercise up to 3 years post-HTx and that graft function is well maintained with both immunosuppressive regimens. However, longer follow-ups may reveal differences in haemodynamic profiles.

Acknowledgments

The authors are grateful to the SCHEDULE investigators, co-investigators, and study nurses: Copenhagen: Lene Larsen and Charlotte Just; Aarhus: Else Marie Tram and Dorte MØlbak; Göteborg: Nedim Selimovic, Smita Dutta Roy, Helena Rexius, Annie Janssen, and Marita Rosenberg; Lund: Liselotte Persson, Björn Kornhall, Björn Ekmehag, and Øyvind Reitan; Oslo: Wenche Stueflotten, Anne Relbo, Ingelin Grov, and Asgrimur Ragnarsson.

Conflict of interest

None declared.

Funding

The SCHEDULE trial was funded by Novartis Scandinavia. This sub-study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG-774081).

Author Contributions

Niklas Bergh participated in writing of the paper, data analysis, and performance of the research. Einar Gude participated in writing of the paper, data analysis, research design, and performance of the research. Sven-Erik Bartfay and Entela Bollano participated in performance of the research, data analysis, and reviewing of the paper. Arne K. Andreassen, Göran Dellgren, Lars Gullestad, Finn Gustafsson, Kristjan Karasson, Göran Rådegran, and Bert Andersson participated in research design, performance of the research, and reviewing of the paper. Satish Arora and Pia Dahlberg participated in performance of the research, data analysis, and reviewing of the paper.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Hemodynamic characteristics pre-HTx at rest. Values are presented as mean ± SD.

Table S2. (A) Hemodynamic characteristics for the EVR and CNI group at rest and (B) at 4-min exercise at weeks 7-11 and at 12 and 36 months post-HTx. Values are presented as mean. Comparisons were performed between the two treatment groups (EVR and CNI) at the different time points.

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