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FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Prognostic value of comprehensive intracoronary physiology assessment early after heart transplantation

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Aims We evaluated the long-term prognostic value of invasively assessing coronary physiology after heart transplantation in a large multicentre registry.

Methods and results Comprehensive intracoronary physiology assessment measuring fractional flow reserve (FFR), the index of microcirculatory resistance (IMR), and coronary flow reserve (CFR) was performed in 254 patients at baseline (a median of 7.2 weeks) and in 240 patients at 1 year after transplantation (199 patients had both baseline and 1-year measurement). Patients were classified into those with normal physiology, reduced FFR (FFR ≤ 0.80), and microvascular dysfunction (either IMR ≥ 25 or CFR ≤ 2.0 with FFR > 0.80). The primary outcome was the composite of death or re-transplantation at 10 years. At baseline, 5.5% had reduced FFR; 36.6% had microvascular dysfunction. Baseline reduced FFR [adjusted hazard ratio (aHR) 2.33, 95% confidence interval (CI) 0.88–6.15; $P = 0.088$] and microvascular dysfunction (aHR 0.88, 95% CI 0.44–1.79; $P = 0.73$) were not predictors of death and re-transplantation at 10 years. At 1 year, 5.0% had reduced FFR; 23.8% had microvascular dysfunction. One-year reduced FFR (aHR 2.98, 95% CI 1.13–7.87; $P = 0.028$) and microvascular dysfunction (aHR 2.33, 95% CI 1.19–4.59; $P = 0.015$) were associated with significantly increased risk of death or re-transplantation at 10 years. Invasive measures of coronary physiology improved the prognostic performance of clinical variables (χ^2 improvement: 7.41, $P = 0.006$). However, intravascular ultrasound-derived changes in maximal intimal thickness were not predictive of outcomes.

Conclusion Abnormal coronary physiology 1 year after heart transplantation was common and was a significant predictor of death or re-transplantation at 10 years.

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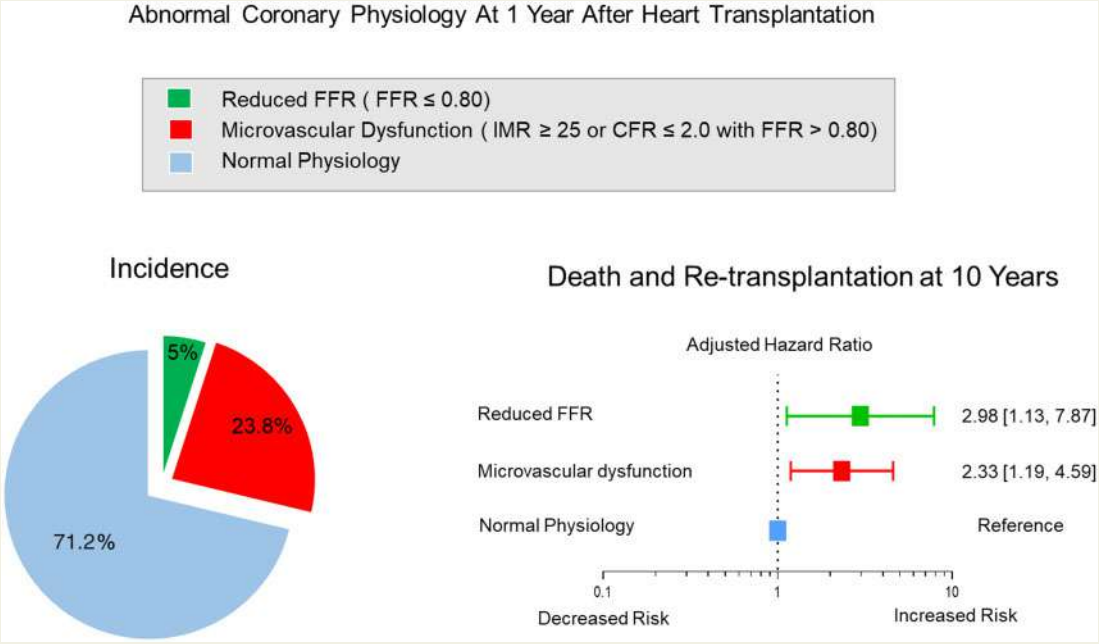
Graphical Abstract



Abnormal coronary physiology at 1 year after heart transplantation. CRF, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance.

Keywords Heart transplantation • Cardiac allograft vasculopathy • Microvascular dysfunction • Coronary stenosis • Prognosis

Introduction

Cardiac allograft vasculopathy (CAV) is the leading cause of late morbidity and mortality (≥1 year) after heart transplantation.[1] Cardiac allograft vasculopathy is a panarterial disease with a progressive and diffuse process involving both the epicardial coronary artery and the microcirculation. Approximately 10% of patients have angiographic coronary artery disease at 1 year, 50% at 5 years, and 80% at 15 years, with long-term mortality increasing with angiographic severity.[2] Cardiac allograft vasculopathy can also manifest as a microvasculopathy, which occurs more frequently than epicardial coronary artery stenosis at 1 year after transplantation and is associated with a higher risk of cardiac events, independent of epicardial coronary artery stenosis.[3]

Clinical guidelines recommend annual or biannual coronary angiography to assess the development of CAV.[4] Intravascular ultrasound (IVUS) is often used to more accurately detect progression of CAV that is not readily apparent with coronary angiography.[5] However, anatomical evaluation is limited to assessing the physiological consequences of epicardial coronary artery disease and is not able to assess microvascular dysfunction. In addition, the presence of epicardial CAV does not necessarily indicate that microvascular dysfunction is present and vice versa.[6,7]

Assessing coronary physiology using a pressure-temperature sensor-tipped guidewire has been well validated in non-transplant patients.[8] The comprehensive physiological assessment of the epicardial coronary artery and microcirculation has helped to characterize the physiological phenotype of patients and to better predict their prognosis.[9,10] Similarly, in transplant patients, fractional flow reserve (FFR) correlates with plaque volume assessed by IVUS, and the index of microcirculatory resistance (IMR) measured after transplantation has been shown to predict the development of CAV, poor graft function, and long-term mortality in single-centre studies.[11,12] The prognostic value of invasively assessing coronary physiology early after heart transplantation has not been adequately validated in a large multicentre study.

This international multicentre registry enrolled heart transplant recipients who underwent a comprehensive intracoronary physiology assessment at baseline and 1 year after transplantation. We then characterized the coronary physiological abnormality into abnormal epicardial coronary physiology and/or microvascular dysfunction and evaluated their long-term prognostic value.

Methods

Study population

Patients were pooled from five prospective cohorts [three prospective randomized trials and two prospective observational studies conducted in four countries (USA, Norway, Sweden, and Korea)].[13–17] The study design, detailed entry criteria of each study, and the key features are summarized in Supplementary material online, *Table S1* and *Figure S1*. For this analysis, only patients evaluated by comprehensive coronary physiological assessment including FFR, IMR, and coronary flow reserve (CFR) at baseline and/or at 1 year after transplantation were included.

Immunosuppressive therapy and surveillance endomyocardial biopsy

All patients received standard immunosuppressive therapy according to the clinical protocol of each participating centre.[13–15,18–20] Briefly, patients received induction therapy with antithymocyte globulin, daclizumab, or basiliximab. Maintenance immunosuppression was based on calcineurin inhibitors (cyclosporin or tacrolimus), antimetabolites (azathioprine or mycophenolate mofetil), and prednisone, which was tapered during the first year at some centres. Calcineurin inhibitors were partially or completely replaced with mammalian target of rapamycin inhibitors (everolimus or sirolimus) in selected patients according to the clinical status or protocol. Therapeutic levels of immunosuppressive agents and associated side effects were carefully monitored and titrated accordingly. Concomitant medications including statins and, in some cases, aspirin were initiated as soon as the patient was able to comply with oral intake. As part of standard clinical care, patients were monitored for the occurrence of acute cellular rejection by endomyocardial biopsies performed at the standard interval according to the clinical protocol of each participating centre and at the time of any suspected episode of rejection. Specimens were graded with respect to rejection by each centre's pathologist according to the criteria of the International Society for Heart and Lung Transplantation (ISHLT) 2004 version.[21]

Intracoronary physiological assessment

At baseline and at 1 year after successful heart transplantation, intracoronary physiological assessment was performed in conjunction with a coronary angiogram and intravascular imaging.[4] After performance of coronary angiography, FFR, IMR, and CFR were measured in the usual fashion with a pressure-temperature sensor-tipped guidewire (Abbott Vascular) placed in the distal two-third of the left anterior descending artery.[12,18] Fractional flow reserve was defined as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperaemia. Index of microcirculatory resistance was calculated as the distal coronary pressure at maximal hyperaemia divided by the inverse of hyperaemic mean transit time.[22] Coronary flow reserve was calculated as resting mean transit time divided by hyperaemic mean transit time. Resting and hyperaemic mean transit time were measured using standard thermodilution techniques.[23] Maximal hyperaemia was induced with intravenous adenosine at 140 μg/kg/min through a central vein or large antecubital vein.

Definition of physiological abnormality

According to intracoronary physiology assessment, the study population was classified into three categories: normal coronary physiology, reduced FFR, and microvascular dysfunction. Patients with reduced FFR were defined as those having an FFR ≤0.80 regardless of IMR and CFR values.[24] Microvascular dysfunction was defined according to standardized COVADIS (Coronary Vasomotion Disorders International Study Group) diagnostic criteria: IMR ≥25 or CFR ≤2.0 in the absence of significant epicardial disease (FFR > 0.80).[25] In addition, sustained abnormal physiology was defined when coronary physiology was abnormal at baseline and at 1 year, and newly developed abnormal physiology was defined when coronary physiology was normal at baseline and abnormal at 1 year.

Coronary angiography and intravascular ultrasound assessment

The angiographic severity of CAV after transplantation was evaluated by ISHLT classification based on 1-year coronary angiography.[5] ISHLT-CAV_0 indicates no detectable angiographic lesion; ISHLT-CAV_1 (mild) indicates angiographic left main <50%, or primary vessel with a maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction; ISHLT-CAV_2 (moderate) indicates angiographic left main <50%, a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of two systems, without allograft dysfunction; and ISHLT-CAV_3 (severe) indicates angiographic left main ≥50%, or two or more primary vessels with ≥70% stenosis, or isolated branch stenosis ≥70% in all three systems, or ISHLT-CAV_1 or ISHLT-CAV_2 with allograft dysfunction.

Intravascular ultrasound was performed in the left anterior descending artery with a 20 MHz (Volcano Corporation Inc., San Diego, CA, USA) or 40 MHz IVUS catheter (Boston Scientific, Natick, MA, USA) and an automatic pullback at 0.5 mm/s. Offline IVUS analyses (EchoPlaque, Indec Systems, Santa Clara, CA, USA) were performed in the IVUS core laboratory of individual participating centres according to the American College of Cardiology clinical expert consensus document.[26] Maximal intimal thickness (MIT) at baseline and at 1 year and the change in MIT was measured. An increase of ≥0.5 mm in MIT within 1 year after transplantation was considered as the rapid progression group.[27,28]

Outcomes

The primary outcome of this study was the composite of death from any cause or re-heart transplantation. A major secondary outcome was the rate of major adverse cardiac events (MACE), the composite of death from any cause, re-heart transplantation, myocardial infarction defined by ischaemic symptoms and signs with cardiac enzyme elevation more than the upper reference limit, coronary revascularization including percutaneous coronary intervention or coronary bypass surgery, stroke, graft dysfunction defined by newly developed left ventricular dysfunction (ejection fraction ≤45%), or readmission due to a cardiac cause. Patients were censored at 10 years or when an event occurred.

Data collection and follow-up

Individual patient data from each study were sent to the study coordinating committee at Stanford University and merged for analysis. The pooled database was checked for completeness and consistency. Patients were followed until May of 2020. The independent ethics committee for each centre/country approved each study protocol.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range; categorical variables are shown as counts and percentages. Continuous variables were compared using one-way analysis of variance; categorical variables were compared using χ^2 statistics or Fisher's exact test. Paired samples were compared using Wilcoxon test or McNemar test. Time-to-event data are presented as Kaplan–Meier estimates. The multivariable Cox regression model was used to identify statistically significant predictors and potential confounders for the primary outcome. In addition, the treatment effect was

estimated separately for each study, and the estimates were combined to provide an overall estimate of the treatment effect using a stratified Cox regression analysis. Variables listed in *Table 1* were selected by the backward elimination methods and those with a significant association with death from any cause and MACE were entered into the final model. To evaluate the prognostic value of physiology study at 1 year, patients who experienced clinical events before the physiology study at 1 year were censored in the multivariable model. In addition, a time-varying Cox proportional model using the physiology study at 1 year as time-varying covariate was performed. The proportional hazards assumption was tested using Schoenfeld residuals. A nested Cox proportional hazard regression analysis was used to investigate the incremental prognostic value of physiology abnormality. The cut-off value of coronary physiology indices was additionally assessed by time-dependent receiver operating characteristic curve analyses. Statistical analyses were performed using the SPSS version 21.0 software (IBM, Chicago, IL, USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All applicable *P*-values were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Comprehensive intracoronary physiological evaluation for epicardial coronary artery and coronary microcirculation using FFR, IMR, and CFR were performed in 254 patients at baseline [7.2 weeks (Q1–Q3, 4.1–10.3) after transplantation] and in 240 patients at 1 year [1.0 year (Q1–Q3, 0.99–1.01)]. Of those, 199 patients had both baseline and 1-year measurement (*Figure 1* and Supplementary material online, *Figure S1*). Overall, the recipient mean age was 50.3 ± 12.7 years with 72.5% male sex. The donor mean age was 36.8 ± 13.8 years with 70.8% male sex. Most patients were Caucasian (86.3%), with 3.3% Asian and 6.3% Black. Sex, blood type, and cytomegalovirus IgG mismatch occurred in 29.2%, 2.1%, and 20.8%, respectively. All patients received standard induction and maintenance immunosuppressive therapy. Patient characteristics are summarized in *Table 1*.

Changes in coronary physiology

Supplementary material online, *Figure S2* depicts the changes in individual physiology indices from baseline to 1 year after transplantation. Fractional flow reserve value did not change significantly [0.92 (Q1–Q3, 0.88–0.94) at baseline to 0.91 (Q1–Q3, 0.86–0.95) at 1 year, $P = 0.45$]. However, IMR decreased significantly from a median of 16.0 (Q1–Q3, 11.3–22.8) to a median of 13.7 (Q1–Q3, 10.1–19.6) ($P = 0.001$) and CFR increased significantly from a median of 3.1 (Q1–Q3, 2.0–4.1) to a median of 3.7 (Q1–Q3, 2.5–5.2) ($P < 0.001$).

Regarding the physiology phenotype, 5.5% of patients had reduced FFR and 36.6% of patients had microvascular dysfunction at baseline; 5.0% of patients had reduced FFR and 23.8% of patients had microvascular dysfunction at 1 year (*Figure 1*). The incidence of patients with reduced FFR was not significantly changed ($P = 0.79$) from baseline to 1 year after transplantation while the incidence of those with microvascular dysfunction was significantly decreased ($P = 0.002$) (*Figure 1*). Smoking status and donor age were significantly associated with microvascular dysfunction (Supplementary material online, *Table S2*).

Clinical outcomes and coronary physiology

At 10 years, the primary outcome of the composite of death from any cause or re-transplantation occurred in 44 patients (40 deaths from any cause, and 4 re-transplantations). In addition, coronary revascularization occurred in 8 patients, stroke in 6 patients, graft dysfunction in 25 patients and readmission in 54 patients among the cohort with physiology evaluation at 1 year (Supplementary material online, *Table S3*).

At baseline physiological assessment, reduced FFR was not associated with a higher risk of death or re-transplantation [adjusted hazard ratio (aHR) 2.33, 95% confidence interval (CI) 0.88–6.15; $P = 0.088$] and MACE (aHR 1.69, 95% CI 0.77–3.71; $P = 0.19$) at 10 years. In addition, microvascular dysfunction at baseline was not associated with the higher risk of death or re-transplantation (aHR 0.88, 95% CI 0.44–1.79; $P = 0.73$) and MACE (aHR 0.88, 95% CI 0.54–1.41; $P = 0.58$) at 10 years (*Table 2*, *Figure 2*, and Supplementary material online, *Table S4*).

At 1-year assessment, reduced FFR was significantly associated with an increased risk of death or re-transplantation (aHR 2.98, 95% CI 1.13–7.87; $P = 0.028$) but was not associated with the risk of MACE (aHR 1.90, 95% CI 0.68–5.34; $P = 0.22$). Microvascular dysfunction was significantly associated with both the risk of death or re-transplantation (aHR 2.33, 95% CI 1.19–4.59; $P = 0.015$) and the risk of MACE (aHR 2.52, 95% CI 1.45–4.35; $P < 0.001$) (*Table 2*, *Figure 2*, and Supplementary material online, *Table S4*). Additional analysis using time-varying Cox proportional model using physiology study at 1 year as time-varying covariate showed consistent results (Supplementary material online, *Table S5*). Sustained abnormal epicardial coronary physiology (reduced FFR) between baseline and 1 year (aHR 11.4, 95% CI 1.68–77.4; $P = 0.013$), and newly developed microvascular dysfunction after baseline assessment (aHR, 7.12, 95% CI 2.53–20.0; $P < 0.001$) (*Table 2* and *Figure 3*) contributed significantly to the prognostic value of the coronary physiological assessment. Adding comprehensive invasive measures of coronary physiology into the model including only clinical variables improved the prognostic performance to predict death and re-transplantation and MACE at 10 years (*Table 3* and Supplementary material online, *Table S6*).

Supplementary material online, *Table S7* demonstrates the prognostic value of individual physiology indices. Coronary flow reserve ≤2.0 at 1 year (aHR 2.32, 95% CI 1.10–4.89; $P = 0.027$) was significantly associated with the risk of death and re-transplantation at 10 years while IMR ≥25 at 1 year was significantly associated with the risk of MACE at 10 years (aHR 2.13, 95% CI 1.20–3.76; $P = 0.009$). FFR ≤0.80 did not show a significant worse outcome compare with FFR >0.80 which included normal physiology and microvascular dysfunction.

Prognostic value of coronary angiography and intravascular ultrasound parameter

In our cohort ($N = 240$) who underwent coronary physiology measurement at 1 year, angiographically detected ISHLT-CAV occurred in 35 patients (14.6%): 29 (12.1%) had ISHLT-CAV_1, and 6 (2.5%) had ISHLT-CAV_2, while most patients ($N = 203$, 84.6%) had no angiographic evidence of CAV and no patients had ISHLT-CAV_3. The

Table 1 Baseline characteristics

	Physiological dysfunction at 1 year			*P*-value
	Normal physiology (*N* = 171)	**Microvascular dysfunction (*N* = 57)**	**Reduced FFR (*N* = 12)**	
Recipient profile				
Age (years)	50.3 ± 12.0	50.2 ± 14.7	50.2 ± 13.0	>0.99
Male sex	119 (69.6%)	44 (77.2%)	11 (91.7%)	0.17
Race—white	148 (86.5%)	50 (87.7%)	9 (75.0%)	0.50
Hypertension	43 (25.1%)	14 (24.6%)	2 (16.7%)	0.81
Diabetes	23 (13.5%)	6 (10.5%)	3 (25.0%)	0.41
Smoking	53 (31.0%)	20 (35.1%)	4 (33.3%)	0.85
CMV IgG positive	114 (66.7%)	40 (70.2%)	11 (91.7%)	0.19
Aetiology				
Ischaemic cardiomyopathy	93 (54.4%)	27 (47.4%)	5 (41.7%)	0.50
Dilated cardiomyopathy	42 (24.6%)	19 (33.3%)	4 (33.3%)	0.38
Donor profile				
Age (years)	36.1 ± 13.7	38.6 ± 14.3	37.6 ± 12.9	0.48
Male sex	118 (69.0%)	43 (75.4%)	9 (75.0%)	0.62
CMV IgG positive	115 (67.3%)	37 (64.9%)	9 (75.0%)	0.79
Cold ischaemic time (min)	200.5 ± 66.0	208.0 ± 66.0	225.4 ± 57.2	0.38
Sex mismatch	55 (32.2%)	13 (22.8%)	2 (16.7%)	0.25
ABO mismatch	3 (1.8%)	2 (3.5%)	0	0.63
Ejection fraction at baseline (%)	58.9 ± 7.76	59.4 ± 6.4	59.2 ± 10.5	0.92
Medication at baseline				
Statins	159 (93.0%)	55 (96.5%)	12 (100%)	0.42
Induction therapy	169 (98.8%)	54 (94.7%)	12 (100%)	0.15
Maintenance therapy				
Tacrolimus	56 (32.7%)	11 (19.3%)	3 (25.0%)	0.15
Cyclosporine	114 (66.7%)	46 (80.7%)	10 (83.3%)	0.081
Mycophenolate	155 (90.6%)	53 (93.0%)	11 (91.7%)	0.86
mTOR inhibitor	52 (30.4%)	21 (36.8%)	3 (25.0%)	0.58
ISHLT CAV classification at 1 year				0.40
CAV 0 (non-significant)	150 (87.7%)	45 (78.9%)	10 (83.3%)	
CAV 1 (mild)	18 (10.5%)	9 (15.8%)	2 (16.7%)	
CAV 2 (moderate)	3 (1.8%)	3 (5.3%)	0	
CAV 3 (severe)	0	0	0	
Physiological measurement at 1 year				
FFR	0.90 ± 0.05	0.92 ± 0.05	0.77 ± 0.03	<0.001
IMR	13.9 ± 4.7	28.3 ± 20.2	15.8 ± 9.6	<0.001
CFR	4.7 ± 2.4	2.2 ± 1.0	3.1 ± 1.3	<0.001
Cardiac events within 1 year				
Overall	47 (27.5%)	15 (26.3%)	3 (25.0%)	0.97
Acute cellular rejection (≥grade 2)	35 (20.5%)	14 (24.6%)	3 (25.0%)	0.78
Myocardial infarction	0	0	0	
Coronary revascularization	1 (0.6%)	0	0	0.82
Stroke	4 (2.3%)	0	0	0.44
Graft dysfunction (ejection fraction ≤45%)	1 (0.6%)	0	0	0.82
Readmission due to cardiac causes	13 (7.6%)	3 (5.3%)	1 (8.3%)	0.83

CAV, cardiac allograft vasculopathy; CFR, coronary flow reserve; CMV, cytomegalovirus; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; ISHLT, International Society for Heart and Lung Transplantation; mTOR, mammalian target of rapamycin.

presence of any ISHLT-CAV (≥ISHLT-CAV$_1$) was significantly associated with a higher risk of the composite of death or re-transplantation (aHR 4.34, 95% CI 1.29–14.6; $P = 0.018$) and MACE (aHR 2.58, 95% CI 1.05–6.31; $P = 0.039$) at 10 years. Nevertheless, the presence of microvascular dysfunction at 1 year was significantly associated with the composite of death or re-transplantation (aHR 2.16, 95% CI 1.09–4.30; $P = 0.028$) and MACE (aHR 2.10, 95% CI 1.12–3.34; $P = 0.008$) even after adjusting for angiographic severity of CAV. In addition, adding coronary physiology assessment improved the prognostic performance of the model including clinical variables plus angiographic severity of CAV (Supplementary material online, *Table S8*).

In our cohort, 206 patients underwent serial IVUS analysis at baseline and at 1 year. An increase of ≥0.5 mm in MIT from baseline to 1 year after transplantation was observed in 10 (4.9%) patients and was not associated with long-term risk of death and re-transplantation [hazard ratio (HR) 1.09, 95% CI 0.26–4.55; $P = 0.91$]. The prognostic significance of reduced FFR (HR 2.53, 95% CI 1.24–5.18; $P = 0.011$) and microvascular dysfunction (HR 4.43, 95% CI 1.52–13.0; $P = 0.007$) compared with normal physiology was maintained even after putting an increase of ≥0.5 mm in MIT into the multivariable model.

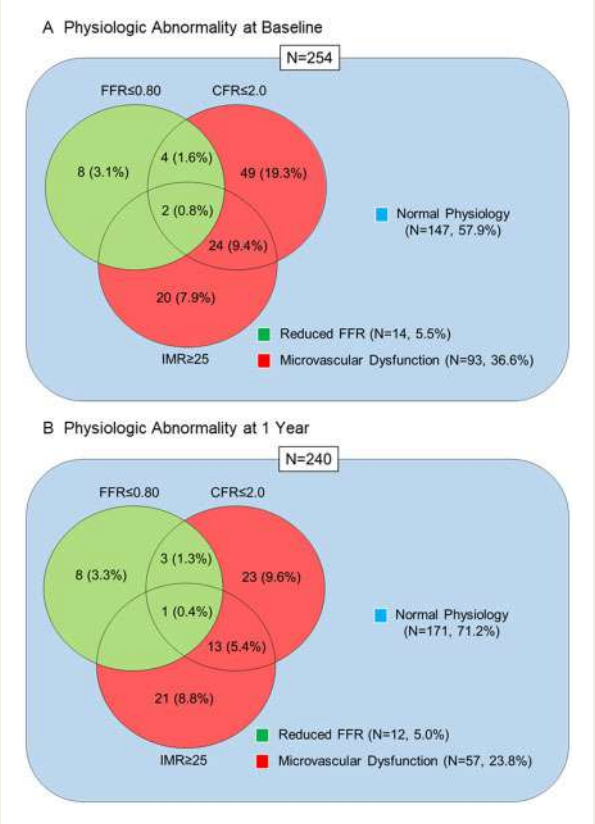


Figure 1 Distribution of coronary physiological abnormality at baseline (A) and 1 year (B). CRF, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance.

Discussion

This is the largest cohort to date studying the prognostic value of intracoronary physiology assessment in cardiac transplant recipients. The primary finding of this international multicentre registry is that either abnormal epicardial coronary physiology or microvascular dysfunction is common, occurring in 42.1% at baseline and 28.8% at 1 year after cardiac transplantation and both abnormal epicardial coronary physiology and microvascular dysfunction at 1 year were significant predictors of the composite of death or re-transplantation at 10-year follow-up (*Graphial Abstract*). This study suggests that for the management of the heart transplant recipient, a comprehensive intracoronary physiology assessment has an important clinical role in characterizing the patient's physiological phenotype and predicting long-term outcomes and, thus, should be considered as a routine monitoring strategy for CAV. Key questions that remain are how a clinician should respond to these abnormal phenotypes and whether adjunctive therapy will prevent future adverse events.

This study confirms a previous pathological study on the prognostic value of microvascular dysfunction using comprehensive physiological assessment in a larger multicentre population.[3,10] Microvascular dysfunction occurred more frequently than abnormal epicardial coronary physiology and had contrasting temporal trends in its incidence and prognostic value. Early after transplantation, 39.2% of patients had microvascular dysfunction, which decreased significantly by 1 year to 29.2% of patients. The prognostic value of microvascular dysfunction at baseline was not significant while microvascular dysfunction at 1 year was strongly associated with the 10-year risk of death or re-transplantation; this was mostly a result of newly developed microvascular dysfunction. These findings suggest different underlying mechanisms of microvascular dysfunction according to the post-transplantation period. Early after transplantation, microvascular dysfunction is likely to be associated with post-operative changes, reperfusion injury, or an early immunological or inflammatory reaction, which are presumed to be temporary and reversible, and, thus, unlikely to mediate long-term outcomes. Microvascular dysfunction at 1 year is likely due to structural changes or overt functional deterioration.[3,18] The incidence of pathological microvasculopathy significantly increased during the 1-year post-transplantation period[3] and microvascular dysfunction at 1 year has been shown to be associated with impaired ventricular function, a decrease in cardiac index and stroke volume index, and more haemodynamically compromising rejection.[18] Therefore, microvascular dysfunction at 1 year could be considered as a clinically relevant surrogate marker for long-term survival after heart transplantation and a potential therapeutic target for medical management, although this needs to be validated in further studies.[14,29]

Currently, there are no standard criteria for detecting microvascular dysfunction after heart transplantation although CFR and IMR measured with a coronary wire in the catheterization laboratory are the best studied. In this study, we defined microvascular dysfunction as either IMR ≥25 or CFR ≤2.0 in the absence of significant epicardial coronary stenosis (FFR > 0.80) according to COVADIS diagnostic criteria.[25] Coronary flow reserve is a dynamic test to evaluate the coronary vasodilatory capacity, defined as hyperaemic coronary blood flow divided by resting flow, and represents the ability of the

Table 2 Physiological abnormality at baseline and 1 year and long-term outcome of death and re-transplantation at 10 years

	Event rate[a] at 10 years, *n* (%)	Unadjusted HR (95% CI)	*P*-value	Adjusted HR[b] (95% CI)	*P*-value
At baseline (*N* = 254)					
Reduced FFR (*N* = 14)	6 (45.0)	2.27 (0.89–5.77)	0.086	2.33 (0.88–6.15)	0.088
Microvascular dysfunction (*N* = 93)	16 (19.9)	0.78 (0.40–1.50)	0.45	0.88 (0.44–1.79)	0.73
Normal coronary physiology (*N* = 147)	23 (21.8)	1 (reference)		1 (reference)	
At 1 year (*N* = 240)					
Reduced FFR (*N* = 12)	6 (55.6)	2.55 (1.00–6.47)	0.050	2.98 (1.13–7.87)	0.028
Microvascular dysfunction (*N* = 57)	17 (33.1)	2.28 (1.18–4.42)	0.015	2.33 (1.19–4.59)	0.015
Normal coronary physiology (*N* = 171)	21 (17.6)	1 (reference)		1 (reference)	
Changes between baseline and 1 year (*N* = 199)					
Reduced FFR (at baseline—at 1 year)					
Abnormal—abnormal physiology (*N* = 2)	2 (100)	14.9 (2.96–75.1)	0.001	11.4 (1.68–77.4)	0.013
Normal—abnormal physiology (*N* = 6)	2 (40.0)	1.33 (0.31–5.75)	0.70	1.85 (0.39–8.82)	0.44
Abnormal—normal physiology (*N* = 8)	2 (27.1)	1.80 (0.41–7.88)	0.44	1.29 (0.26–6.61)	0.76
Normal—normal physiology (*N* = 183)	25 (19.5)	1 (reference)		1 (reference)	
Microvascular dysfunction (at baseline—at 1 year)					
Abnormal—abnormal physiology (*N* = 22)	2 (9.8)	0.36 (0.05–2.83)	0.33	0.38 (0.05–3.14)	0.37
Normal—abnormal physiology (*N* = 21)	8 (46.1)	7.04 (2.63–18.8)	<0.001	7.12 (2.53–20.0)	<0.001
Abnormal—normal physiology (*N* = 47)	10 (25.4)	1.21 (0.51–2.91)	0.66	1.47 (0.56–3.87)	0.44
Normal—normal physiology (*N* = 109)	11 (17.6)	1 (reference)		1 (reference)	

CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio.
[a]Event rates were derived from Kaplan–Meier estimates.
[b]Adjusted by recipient age, recipient race—white, aetiology—ischaemic cardiomyopathy, aetiology—dilated cardiomyopathy, donor sex, induction therapy, maintenance therapy—mycophenolate.

microcirculation to appropriately increase myocardial blood flow. It is important to recognize that CFR interrogates the entire coronary circulation, both the epicardial vessel and the microvasculature, so an abnormal value can be indicative of abnormal physiology in either location. In addition, an abnormal CFR may occur due to increased resting flow, with a normal hyperaemic flow. This has been suggested as a specific endotype of microvascular dysfunction, which cannot be detected by measuring IMR alone. Index of microcirculatory resistance measures the minimum achievable coronary microvascular resistance during hyperaemia. Because it is measured during hyperaemia, it is less dependent on haemodynamic changes and more reproducible than CFR,[30] which incorporates resting flow into its equation. Previous studies showed that both IMR[11,12] and CFR[31,32] were associated with the progression of CAV and decreased long-term survival after transplantation, although there were conflicting results.[33,34] In this study, CFR ≤2.0 was associated with a higher risk of death and re-transplantation at 10 years and IMR ≥25 at baseline and at 1 year were associated with a higher risk of MACE at 10 years.

Abnormal epicardial coronary physiology assessed by FFR ≤0.80 was associated with 10-year mortality or re-transplantation in this study. However, an increase of ≥0.5 mm in MIT based on serial IVUS was not. This could be explained by the low incidence of rapid progression of MIT: 4.9% in our study compared with 29.1% in previous studies,[27,28] probably due to more extensive use of statin therapy and advances in immunosuppressive therapy. In addition, the diffuse nature of CAV can lead to a significant decline in myocardial perfusion pressure without a remarkable increase in MIT in a single plane measurement.[35] Finally, negative vascular remodelling, without intimal thickening can lead to a decrease in FFR.[36] Physicians should be aware that microvascular dysfunction after transplantation can attenuate hyperaemia, resulting in higher FFR values. Nevertheless, FFR continues to provide information about the impact of an epicardial stenosis on the percentage of maximum achievable myocardial flow. A previous study found that microvascular dysfunction improved during the first year after transplantation, and worsened again thereafter.[35] In addition, simultaneous evaluation with microvascular function using IMR and CFR helps to interpret FFR more appropriately in heart transplant recipients.

There is some controversy about the prognostic significance of donor transmitted atherosclerosis. A previous study suggested that donor lesions do not accelerate plaque progression early after transplantation.[37] However, volumetric IVUS analysis demonstrated a significant association between donor transmitted atherosclerosis and worsening of CAV.[38,39] Similarly, this study shows the prognostic value of donor transmitted atherosclerosis based on functional significance for predicting the risk of death or re-transplantation at 10 years, particularly when it is sustained during the first year after transplantation.

This study has several limitations. First, this is a *post hoc* analysis of prospectively collected data. Second, given the wide CIs for the estimate of effect, the findings do not allow for a conclusive

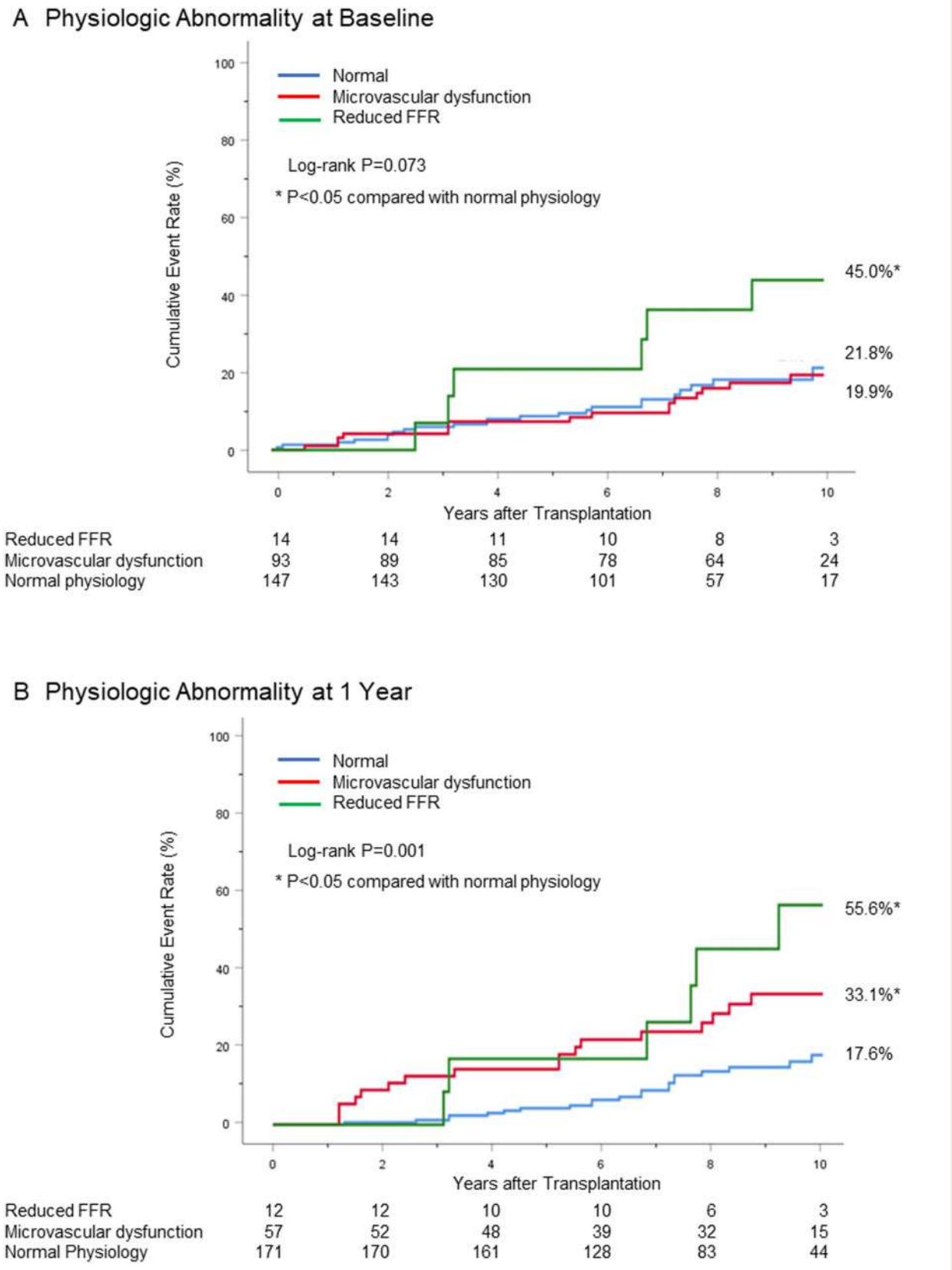


Figure 2 Physiological abnormality at baseline (A) and 1 year (B) and the risk of death and re-transplantation at 10 years. Event rates were derived from Kaplan–Meier estimates and were compared by log-rank test. FFR, fractional flow reserve.

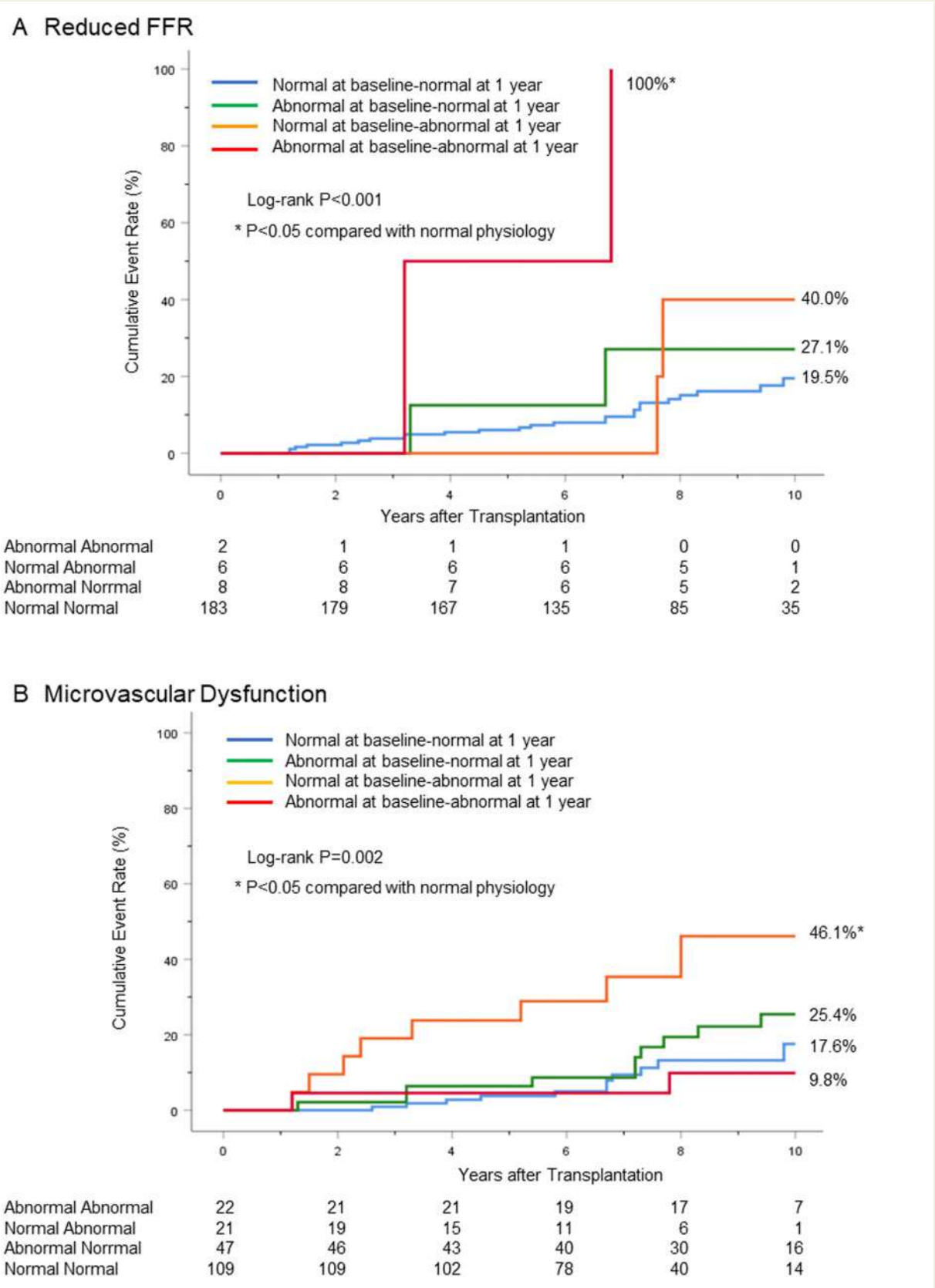


Figure 3 Changes in physiological abnormality of Reduced FFR (A) and Microvascular dysfunction (B) between baseline and 1 year and the risk of death and re-transplantation at 10 years. Event rates were derived from Kaplan–Meier estimates and were compared by log-rank test. FFR, fractional flow reserve.

Table 3 Significant predictors of death and re-transplantation at 10 years

	HR (95% CI)	*P*-value	χ^2 improvement	*P*-value
Model 1—Baseline characteristics[a]				
Recipient age	0.98 (0.95–1.00)	0.037		
Aetiology—ischaemic cardiomyopathy	2.43 (1.02–5.79)	0.044		
Induction therapy	0.27 (0.08–0.85)	0.026		
Model 2—Baseline characteristics + physiology abnormality at baseline			1.01	0.32
Abnormal epicardial physiology at baseline	2.33 (0.88–6.15)	0.088		
Microvascular dysfunction at baseline	0.88 (0.43–1.79)	0.73		
Model 3—Baseline characteristics + physiology abnormality at 1 year			7.41	0.006
Recipient race—white	0.50 (0.22–1.12)	0.092		
Aetiology—ischaemic cardiomyopathy	2.53 (0.94–6.84)	0.067		
Abnormal epicardial physiology at 1 year	2.98 (1.18–4.59)	0.015		
Microvascular dysfunction at 1 year	2.33 (1.18–4.59)	0.028		
Model 4—Baseline characteristics + changes in physiology between baseline and 1 year			14.0	<0.001
Recipient race—white	0.38 (0.13–1.08)	0.068		
Newly developed abnormal epicardial physiology	2.17 (0.45–10.4)	0.33		
Newly developed microvascular dysfunction	7.28 (2.76–19.2)	<0.001		

CI, confidence interval.
[a]Final model included recipient age, recipient race—white, aetiology—ischaemic cardiomyopathy, aetiology—dilated cardiomyopathy, donor sex, induction therapy, maintenance therapy—mycophenolate.

interpretation, although this is the largest study to evaluate the prognostic value of coronary physiology measurements in heart transplant recipients. Third, coronary physiology and IVUS evaluations were performed only in the left anterior descending artery from a selected population. Fourth, the lack of a uniform immunosuppressive regimen partially due to long enrolment period could have affected the results. Fifth, endothelium-dependent epicardial and microvascular dysfunction was not evaluated and may also be an important physiological predictor of outcomes.[11] Sixth, because of the invasive study protocol performing intracoronary physiology assessment both at baseline and at 1 year, unstable patients were not included. Seventh, we had few patients with very low FFR compared with some earlier studies. It may be that more recent improvements in medical management after heart transplantation have led to less CAV and higher FFR values. Finally, this study included three randomized clinical trials. Study randomization may have affected our results.

In conclusion, coronary physiological abnormalities at 1 year after heart transplantation are common and are significant predictors of death and re-transplantation at 10 years. Therefore, invasively assessing coronary physiology may help identify heart transplant recipients at high risk for future adverse events who may benefit from close follow-up and individualized medical therapy. However, it should be taken into consideration that the diagnostic criteria for physiology abnormalities used in this study were derived from patients with non-transplant heart disease and further study to determine the optimal cut-off values of each physiology index in the heart transplantation population will be necessary.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: O.A. has received research grant, and lecture fee from Abbott Vascular. M.R. has received institutional research grant from Stiftelsen DAM. N.H.J.P. has received consulting fees, and outside submitted work from Abbott Vascular, outside submitted work from Hexacath, consulting fees from Opsens, and minor equity from Philips, ASML, Heartflow, and GE. W.F.F. has received institutional research grants from Boston Scientific, Abbott Vascular, and Medtronic Inc., minor stock options from Heart flow, and salary support from the NIH related to grants (5R01HL093475 and R33HL139929). All other authors declared no conflict of interest.

Data availability

Data will be made available upon request in adherence with transparency conventions in medical research and through reasonable requests to the corresponding author.

References

1. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, Meiser B, Rossano JW, Chambers DC, Yusen RD, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: allograft ischemic time. *J Heart Lung Transplant* 2017; **36**:1037–1046.
2. Agarwal S, Parashar A, Kapadia SR, Tuzcu EM, Modi D, Starling RC, Oliveira GH. Long-term mortality after cardiac allograft vasculopathy: implications of percutaneous intervention. *JACC Heart Fail* 2014;**2**:281–288.
3. Hiemann NE, Wellnhofer E, Knosalla C, Lehmkuhl HB, Stein J, Hetzer R, Meyer R. Prognostic impact of microvasculopathy on survival after heart transplantation: evidence from 9713 endomyocardial biopsies. *Circulation* 2007;**116**: 1274–1282.
4. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro

M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J; International Society of Heart and Lung Transplantation Guidelines. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;**29**:914–956.
5. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, Madsen J, Parameshwar J, Starling RC, Uber PA. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010;**29**:717–727.
6. Caracciolo EA, Wolford TL, Underwood RD, Donohue TJ, Bach RG, Miller LW, Kern MJ. Influence of intimal thickening on coronary blood flow responses in orthotopic heart transplant recipients. A combined intravascular Doppler and ultrasound imaging study. *Circulation* 1995;**92**:182–190.
7. Klauss V, Ackermann K, Henneke KH, Spes C, Zeitlmann T, Werner F, Regar E, Rieber J, Uberfuhr P, Reichart B, Theisen K, Mudra H. Epicardial intimal thickening in transplant coronary artery disease and resistance vessel response to adenosine: a combined intravascular ultrasound and Doppler study. *Circulation* 1997;**96**:II159–II164.
8. Kogame N, Ono M, Kawashima H, Tomaniak M, Hara H, Leipsic J, Andreini D, Collet C, Patel MR, Tu S, Xu B, Bourantas CV, Lerman A, Piek JJ, Davies JE, Escaned J, Wijns W, Onuma Y, Serruys PW. The impact of coronary physiology on contemporary clinical decision making. *JACC Cardiovasc Interv* 2020;**13**:1617–1638.
9. Lee JM, Choi KH, Doh JH, Nam CW, Shin ES, Hoshino M, Murai T, Yonetsu T, Mejía-Rentería H, Kakuta T, Escaned J, Koo BK. Long-term patient prognostication by coronary flow reserve and index of microcirculatory resistance: international registry of comprehensive physiologic assessment. *Korean Circ J* 2020;**50**:890–903.
10. Broyd CJ, Hernández-Pérez F, Segovia J, Echavarría-Pinto M, Quirós-Carretero A, Salas C, Gonzalo N, Jiménez-Quevedo P, Nombela-Franco L, Salinas P, Núñez-Gil I, Del Trigo M, Goicolea J, Alonso-Pulpón L, Fernández-Ortiz A, Parker K, Hughes A, Mayet J, Davies J, Escaned J. Identification of capillary rarefaction using intracoronary wave intensity analysis with resultant prognostic implications for cardiac allograft patients. *Eur Heart J* 2018;**39**:1807–1814.
11. Lee JH, Okada K, Khush K, Kobayashi Y, Sinha S, Luikart H, Valantine H, Yeung AC, Honda Y, Fearon WF. Coronary endothelial dysfunction and the index of microcirculatory resistance as a marker of subsequent development of cardiac allograft vasculopathy. *Circulation* 2017;**135**:1093–1095.
12. Yang HM, Khush K, Luikart H, Okada K, Lim HS, Kobayashi Y, Honda Y, Yeung AC, Valantine H, Fearon WF. Invasive assessment of coronary physiology predicts late mortality after heart transplantation. *Circulation* 2016;**133**:1945–1950.
13. Tu W, Potena L, Stepick-Biek P, Liu L, Dionis KY, Luikart H, Fearon WF, Holmes TH, Chin C, Cooke JP, Valantine HA, Mocarski ES, Lewis DB. T-cell immunity to subclinical cytomegalovirus infection reduces cardiac allograft disease. *Circulation* 2006;**114**:1608–1615.
14. Fearon WF, Okada K, Kobashigawa JA, Kobayashi Y, Luikart H, Sana S, Daun T, Chmura SA, Sinha S, Cohen G, Honda Y, Pham M, Lewis DB, Bernstein D, Yeung AC, Valantine HA, Khush K. Angiotensin-converting enzyme inhibition early after heart transplantation. *J Am Coll Cardiol* 2017;**69**:2832–2841.
15. Nytroen K, Rolid K, Andreassen AK, Yardley M, Gude E, Dahle DO, Bjorkelund E, Relbo Authen A, Grov I, Philip Wigh J, Have Dall C, Gustafsson F, Karason K, Gullestad L. Effect of high-intensity interval training in de novo heart transplant recipients in Scandinavia. *Circulation* 2019;**139**:2198–2211.
16. Arora S, Andreassen AK, Karason K, Gustafsson F, Eiskjaer H, Botker HE, Radegran G, Gude E, Ioanes D, Solbu D, Dellgren G, Ueland T, Aukrust P, Gullestad L; SCHEDULE (Scandinavian Heart Transplant Everolimus De Novo Study With Early Calcineurin Inhibitors Avoidance) Investigators. Effect of everolimus initiation and calcineurin inhibitor elimination on cardiac allograft vasculopathy in de novo heart transplant recipients. *Circ Heart Fail* 2018;**11**:e004050.
17. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, Kim JH, Chae IH, Yoon JH, Her SH, Seung KB, Chung WY, Yoo SY, Lee JB, Choi SW, Park K, Hong TJ, Lee SY, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017;**135**:2241–2251.
18. Haddad F, Khazanie P, Deuse T, Weisshaar D, Zhou J, Nam CW, Vu TA, Gomari FA, Skhiri M, Simos A, Schnittger I, Vrotvec B, Hunt SA, Fearon WF. Clinical and functional correlates of early microvascular dysfunction after heart transplantation. *Circ Heart Fail* 2012;**5**:759–768.
19. Jung SH, Kim JJ, Choo SJ, Yun TJ, Chung CH, Lee JW. Long-term mortality in adult orthotopic heart transplant recipients. *J Korean Med Sci* 2011;**26**:599–603.
20. Kim IC, Youn JC, Kobashigawa JA. The past, present and future of heart transplantation. *Korean Circ J* 2018;**48**:565–590.
21. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Burke MM, Demetris AJ, Hammond E, Itescu S, Marboe CC, McManus B, Reed EF, Reinsmoen NL, Rodriguez ER, Rose AG, Rose M, Suciu-Focia N, Zeevi A, Billingham ME. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005;**24**:1710–1720.
22. Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, Yock PG, Yeung AC. Novel index for invasively assessing the coronary microcirculation. *Circulation* 2003;**107**:3129–3132.
23. Pijls NH, De Bruyne B, Smith L, Aarnoudse W, Barbato E, Bartunek J, Bech GJ, Van De Vosse F. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation* 2002;**105**:2482–2486.
24. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van 't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.
25. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN; Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;**250**:16–20.
26. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG, O'Rourke RA, Abrams J, Bates ER, Brodie BR, Douglas PS, Gregoratos G, Hlatky MA, Hochman JS, Kaul S, Tracy CM, Waters DD, Winters WL. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on clinical expert consensus documents. *J Am Coll Cardiol* 2001;**37**:1478–1492.
27. Kobashigawa JA, Tobis JM, Starling RC, Tuzcu EM, Smith AL, Valantine HA, Yeung AC, Mehra MR, Anzai H, Oeser BT, Abeywickrama KH, Murphy J, Cretin N. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol* 2005;**45**:1532–1537.
28. Tuzcu EM, Kapadia SR, Sachar R, Ziada KM, Crowe TD, Feng J, Magyar WA, Hobbs RE, Starling RC, Young JB, McCarthy P, Nissen SE. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. *J Am Coll Cardiol* 2005;**45**:1538–1542.
29. Solberg OG, Stavem K, Ragnarsson A, Ioanes D, Arora S, Endresen K, Benth J, Gullestad L, Gude E, Andreassen AK, Aaberge L. Index of microvascular resistance after early conversion from calcineurin inhibitor to everolimus in heart transplantation: a sub-study to a 1-year randomized trial. *J Heart Lung Transplant* 2016;**35**:1010–1017.
30. Fearon WF, Kobayashi Y. Invasive assessment of the coronary microvasculature: the index of microcirculatory resistance. *Circ Cardiovasc Interv* 2017;**10**:e005361.
31. Tona F, Caforio AL, Montisci R, Gambino A, Angelini A, Ruscazio M, Toscano G, Feltrin G, Ramondo A, Gerosa G, Iliceto S. Coronary flow velocity pattern and coronary flow reserve by contrast-enhanced transthoracic echocardiography predict long-term outcome in heart transplantation. *Circulation* 2006;**114**:I-49–I-55.
32. Tona F, Osto E, Famoso G, Previato M, Fedrigo M, Vecchiati A, Perazzolo Marra M, Tellatin S, Bellu R, Tarantini G, Feltrin G, Angelini A, Thiene G, Gerosa G, Iliceto S. Coronary microvascular dysfunction correlates with the new onset of cardiac allograft vasculopathy in heart transplant patients with normal coronary angiography. *Am J Transplant* 2015;**15**:1400–1406.
33. Escaned J, Flores A, García-Pavía P, Segovia J, Jimenez J, Aragoncillo P, Salas C, Alfonso F, Hernández R, Angiolillo DJ, Jiménez-Quevedo P, Bañuelos C, Alonso-Pulpón L, Macaya C. Assessment of microcirculatory remodeling with intracoronary flow velocity and pressure measurements: validation with endomyocardial sampling in cardiac allografts. *Circulation* 2009;**120**:1561–1568.
34. König A, Spes CH, Schiele TM, Rieber J, Stempfle HU, Meiser B, Theisen K, Mudra H, Reichart B, Klauss V. Coronary Doppler measurements do not predict progression of cardiac allograft vasculopathy: analysis by serial intracoronary Doppler, dobutamine stress echocardiography, and intracoronary ultrasound. *J Heart Lung Transplant* 2002;**21**:902–905.
35. Fearon WF, Nakamura M, Lee DP, Rezaee M, Vagelos RH, Hunt SA, Fitzgerald PJ, Yock PG, Yeung AC. Simultaneous assessment of fractional and coronary flow reserves in cardiac transplant recipients: physiologic Investigation for Transplant Arteriopathy (PITA Study). *Circulation* 2003;**108**:1605–1610.
36. Fearon WF, Felix R, Hirohata A, Sakurai R, Jose PO, Yamasaki M, Nakamura M, Fitzgerald PJ, Valantine HA, Yock PG, Yeung AC. The effect of negative remodeling on fractional flow reserve after cardiac transplantation. *Int J Cardiol* 2017;**241**:283–287.
37. Li H, Tanaka K, Anzai H, Oeser B, Lai D, Kobashigawa JA, Tobis JM. Influence of pre-existing donor atherosclerosis on the development of cardiac allograft

vasculopathy and outcomes in heart transplant recipients. *J Am Coll Cardiol* 2006; **47**:2470–2476.
38. Yamasaki M, Sakurai R, Hirohata A, Honda Y, Bonneau HN, Luikart H, Yock PG, Fitzgerald PJ, Yeung AC, Valantine HA, Fearon WF. Impact of donor-transmitted atherosclerosis on early cardiac allograft vasculopathy: new findings by three-dimensional intravascular ultrasound analysis. *Transplantation* 2011;**91**:1406–1411.
39. Watanabe T, Seguchi O, Yanase M, Fujita T, Murata Y, Sato T, Sunami H, Nakajima S, Kataoka Y, Nishimura K, Hisamatsu E, Kuroda K, Okada N, Hori Y, Wada K, Hata H, Ishibashi-Ueda H, Miyamoto Y, Fukushima N, Kobayashi J, Nakatani T. Donor-transmitted atherosclerosis associated with worsening cardiac allograft vasculopathy after heart transplantation: serial volumetric intravascular ultrasound analysis. *Transplantation* 2017;**101**:1310–1319.