ORIGINAL ARTICLE

Role of Quantitative Flow Ratio in Predicting Future Cardiac Allograft Vasculopathy in Heart Transplant Recipients

Giosafat Spitaleri, MD; Salvatore Brugaletta, MD, PhD; Luciano Potena, MD, PhD; Sonia Mirabet, MD, PhD; José González-Costello, MD, PhD; Ottavio Zucchetti, MD; Marco Masetti, MD; Lluis Asmarats, MD; Miquel Gual, MD; Elena Nardi, PhD; Domenico Di Girolamo, MD; Gianluca Campo, MD; Marta Farrero, MD, PhD

BACKGROUND: Coronary angiography is the gold standard for cardiac allograft vasculopathy (CAV) diagnosis, but it usually detects the disease at an advanced stage. We investigated the role of quantitative flow ratio (QFR), a noninvasive tool to identify potentially flow-limiting lesions, in predicting CAV development in heart transplant recipients.

METHODS: Consecutive heart transplant recipients with no evidence of angiographic CAV at baseline coronary angiography were retrospectively included between January 2010 and December 2015, and QFR computation was performed. The relationship between vessel QFR and the occurrence of angiographic vessel-related CAV (≥50% stenosis) was assessed.

RESULTS: One hundred forty-three patients were included and QFR computation was feasible in 241 vessels. The median value of QFR at baseline coronary angiography was 0.98 (interquartile range, 0.94–1.00). During a median follow-up of 6.0 years (interquartile range, 4.6–7.8 years), vessel-related CAV occurred in 25 (10.4%) vessels. Receiver-operating characteristic curve analysis identified a QFR best cutoff of ≤0.95 (area under the curve, 0.81 [95% CI, 0.71–0.90]; $P<0.001$). QFR≤0.95 was associated with an increased risk of vessel-related CAV (adjusted hazard ratio, 20.87 [95% CI, 5.35–81.43]; $P<0.001$). In an exploratory analysis, QFR≤0.95 in at least 2 vessels was associated with higher incidence of cardiovascular death or late graft dysfunction (71.4% in recipients with 2–3 vessels affected versus 5.1% in recipients with 0–1 vessels affected, $P<0.001$).

CONCLUSIONS: In a cohort of heart transplant recipients, QFR computation at baseline coronary angiography may be a safe and reliable tool to predict vessel-related CAV and clinical outcomes at long-term follow-up.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: allograft ■ coronary circulation ■ coronary angiography ■ heart transplantation ■ incidence

Although survival of patients undergoing heart transplantation (HT) has improved over the past decades, cardiac allograft vasculopathy (CAV) still represents the major cause of long-term mortality, accounting for up one-third of deaths after the first year post-HT.[1,2] Annual coronary angiography is considered the imaging modality of choice for CAV surveillance.[3] However, coronary angiography has several shortcomings related to the visual estimation of diffuse vessel disease and to its low sensitivity to detect early CAV. Indeed, almost half of HT recipients without evidence of angiographic CAV at 1 year after HT show meaningful intimal thickening measured by intravascular ultrasound (IVUS),[4] which is associated with an increased risk of subsequent major cardiovascular events.[5] Nevertheless, intracoronary imaging is still underused in the routine practice because it is time and

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- In heart transplant recipients, annual coronary angiography is considered the imaging modality of choice for cardiac allograft vasculopathy surveillance.
- Coronary angiography has several shortcomings related to the visual estimation of diffuse vessel disease.
- Quantitative flow ratio is a noninvasive tool that has been shown to identify potentially flow-limiting coronary lesions.

WHAT THE STUDY ADDS

- In patients without evidence of angiographic cardiac allograft vasculopathy at baseline coronary angiography, quantitative flow ratio might identify heart transplant recipients at high risk for cardiac allograft vasculopathy.
- Quantitative flow ratio may be a safe and cost-effective gatekeeper to detect vessels that are deemed for further intracoronary assessment.

Nonstandard Abbreviations and Acronyms

BCA	baseline coronary angiography
CAV	cardiac allograft vasculopathy
CCTA	coronary computed tomography angiography
FFR	fractional flow reserve
HT	heart transplantation
IVUS	intravascular ultrasound
LGD	late graft dysfunction
MIT	maximal intimal thickness
QFR	quantitative flow ratio

resource-consuming and it is not free of complications related to the use of coronary wires.[6]

Quantitative flow ratio (QFR) is a novel tool to identify potential flow-limiting coronary lesions based on 3-dimensional (3D) quantitative coronary angiography and contrast flow, and it does not require the use of pressure wires or hyperemia induction. QFR has shown good agreement with pressure wire-determined fractional flow reserve (FFR) measurements, and its prognostic significance has been demonstrated in patients with ischemic cardiomyopathy.[7–10] In HT recipients undergoing coronary angiography for CAV surveillance, the advantage of QFR could be the prompt identification of those vessels that need further anatomic assessment with wire-based techniques.

Thus, the aim of this study was to test whether QFR can predict CAV development and clinical outcomes in HT recipients without evidence of angiographic disease.

METHODS

Data Sharing

The data, analytical methods, and study materials will be made available to other researchers for the purposes of reproducing results or replicating procedures. Please contact M.F. with specific requests at mfarrero@clinic.cat.

Study Design

This was a multicenter, retrospective, observational study conducted at 4 centers in 2 countries (Italy and Spain). Consecutive patients ≥18 years old who received HT between January 2010 and December 2015 and underwent follow-up coronary angiography after HT for CAV surveillance were included. The first coronary angiography performed after HT was considered the baseline coronary angiography (BCA). CAV severity was evaluated by the interventional cardiologist performing the angiography and patients with CAV grade >0 at BCA, according to International Society for Heart and Lung Transplantation classification,[11] were excluded. The BCAs of the patients included were reviewed by 2 independent observers, who confirmed the absence of CAV and agreed in 100% of the cases, and QFR analysis was performed. The study protocol was approved by the Medical Ethics Committee in all participating centers and the subjects included gave informed consent. The study was conducted in compliance with the protocol, the Declaration of Helsinki, and applicable local requirements. M.F. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

QFR Computation

Computation of QFR was performed retrospectively, using the software package QAngio XA 3D (Medis Medical Imaging System, Leiden, the Netherlands). In the first step, 2 angiographic projections, at least 25° apart, were selected, and 3D reconstruction of the interrogated vessel without its side branches was performed, as previously described.[7] 3D quantitative coronary analysis data were readily available. Then, the software computed the fixed and contrast vessel QFR.[7] As compared to fixed QFR value, contrast QFR value was obtained integrating the frame count analysis in the computation. Details of computational methods are described in the Supplemental Material. In the present analysis, we used vessel contrast QFR values because it showed a better diagnostic accuracy[7] compared with fixed QFR. QFR was calculated in the left anterior descending, left circumflex, and right coronary artery starting from the most proximal available segment until its diameter became <1.5 mm. QFR computation was performed in the core laboratory of the University Hospital of Ferrara.[10,12,13] Study angiograms were anonymized and submitted to the core lab. Two independent operators, blinded to outcomes, performed the QFR analysis. Both operators were certified for QFR computation. The inter-observer agreement was very high in all cases (k>0.95).

Follow-Up

After BCA, CAV surveillance was performed according to International Society for Heart and Lung Transplantation HT guidelines by coronary angiography or coronary computed

tomography angiography (CCTA).[3] Recipients with evidence of CAV at CCTA underwent coronary angiography to confirm CAV diagnosis. CAV surveillance protocols in each participating center and CCTA imaging procedures are described in detail in the Supplemental Material. For the purpose of this study, follow-up angiograms were evaluated by 2 independent observers, who classified coronary stenoses as mild (<50% diameter) or moderate-severe (≥50% diameter). Discrepancies were resolved by a third reviewer.

Clinical follow-up was performed through medical electronic records available in each participating center. Follow-up was censored at the time of death or at the end of March 2020. Median follow-up duration was 6.0 years (interquartile range [IQR], 4.6–7.8 years).

End Points

We investigated the relationship between vessel QFR measured at BCA and outcomes at the vessel and recipient level. The primary end point was the occurrence of vessel-related CAV, defined as the presence of any >50% coronary stenosis in the interrogated vessel during follow-up. As secondary exploratory end point at the recipient level, we analyzed the incidence of the composite of late graft dysfunction (LGD) and cardiovascular death according to the number of vessels with low QFR values (0−1 vessels versus 2−3 vessels). Because in our cohort no patient underwent retransplantation, we did not include this outcome. LGD was defined as the occurrence of typical HF signs and symptoms together with evidence of a structural or functional abnormality of graft (reduced left ventricular ejection fraction or elevated filling pressures or right ventricular systolic dysfunction) beyond the initial HT hospitalization.[14] In the case of repeated events of the composite end point, the first event was the one considered. All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. All events were adjudicated by an independent clinical event committee blinded to vessel QFR values.

Statistical Analysis

Continuous variables are presented as median and IQR; categorical variables are reported as counts and percentages. Comparisons between continuous variables were performed using the Mann-Whitney test; comparisons between categorical variables were evaluated using Fisher exact tests. Linear association between QFR and maximal intimal thickness (MIT) evaluated by IVUS was determined by Pearson correlation coefficient (r). The optimal cutoff value of vessel QFR for predicting the occurrence of vessel-related CAV was calculated by maximizing the sum of sensitivity and specificity, using receiver-operating characteristic curve analysis. Observations were grouped according to high and low levels of vessel QFR and were used in time-to-event analysis. Time-to-event curves were estimated by Kaplan-Meier method and compared using the log-rank test. Adjusted hazard ratios with 95% CIs of vessel-related CAV were determined using Cox proportional hazard regression. To avoid overfitting, those variables that had a $P<0.05$ at univariate analysis were included in the Cox regression model. A 2-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed by an independent statistician (E.N.) using SPSS (version 25.0, SPSS, Chicago, IL) and Stata (version 13.0; Stata Corp, College Station, TX).

RESULTS

Study flow chart is shown in Figure 1. Out of 441 consecutive patients who underwent HT within the study period, 91 died before BCA was performed, and in 88 recipients, BCA could not be analyzed due to Digital Imaging and Communications in Medicine information missing. Therefore, BCA was available in 262 patients. Of these, 234 had no evidence of angiographic CAV at BCA. Median time to BCA after HT was 365 days (IQR, 140–393 days). QFR computation was not performed in 91 patients (461 [65.7%] vessels), due to lack of at least 2 angiographic projections ≥25° apart. Overall, QFR analysis was performed in 143 patients (241 vessels) that constituted the final study cohort. The median value of QFR at BCA was 0.98 (IQR, 0.94−1.00). To identify any potential selection bias, we compared baseline characteristics of patients included/excluded from the analysis (Table S1): in patients included in the final cohort, history of hypertension and hypercholesterolemia were more common and time to BCA was shorter than in patients that were excluded from the analysis.

Detailed patient and vessel characteristics of the final population included in the analyses are reported in Table 1.

QFR and Vessel-Related CAV

Vessel-related CAV was detected in 25 (10.4%) vessels during follow-up (Figure 2). Figure 3 shows the occurrence of vessel-related CAV by 0.05 strata of QFR values (4 strata from ≤0.85 to 1.00).

Vessel QFR at BCA was significantly lower in vessels that developed CAV during follow-up compared with those that did not (0.93 [IQR, 0.87−0.93] versus 0.98 [IQR, 0.95−1.00], respectively, $P<0.001$). Receiver-operating characteristic curve analysis identified a vessel QFR cutoff of ≤0.95 as having the best predictive accuracy for vessel-related CAV, with 77% sensitivity and 76% specificity (area under the curve, 0.81 [95% CI, 0.71−0.90]; $P<0.001$, Figure S1A). Vessels showing QFR values ≤0.95 had a significantly higher vessel-related CAV rate compared with those with values >0.95 (25.9% versus 2.5%, $P<0.001$, Figure 4). At Cox regression analysis, vessel QFR≤0.95 was associated with an increased risk of vessel-related CAV (adjusted hazard ratio, 20.87 [95% CI, 5.35−81.43]; $P<0.001$; Table 2). QFR showed a good ability to discriminate vessels at risk for CAV in patients undergoing BCA before and after the first year post-HT (Figure S1B).

QFR and Clinical Outcomes at the Recipient Level

At the recipient level, the composite of cardiovascular death and LGD occurred in 8.4% of recipients (Table S2).
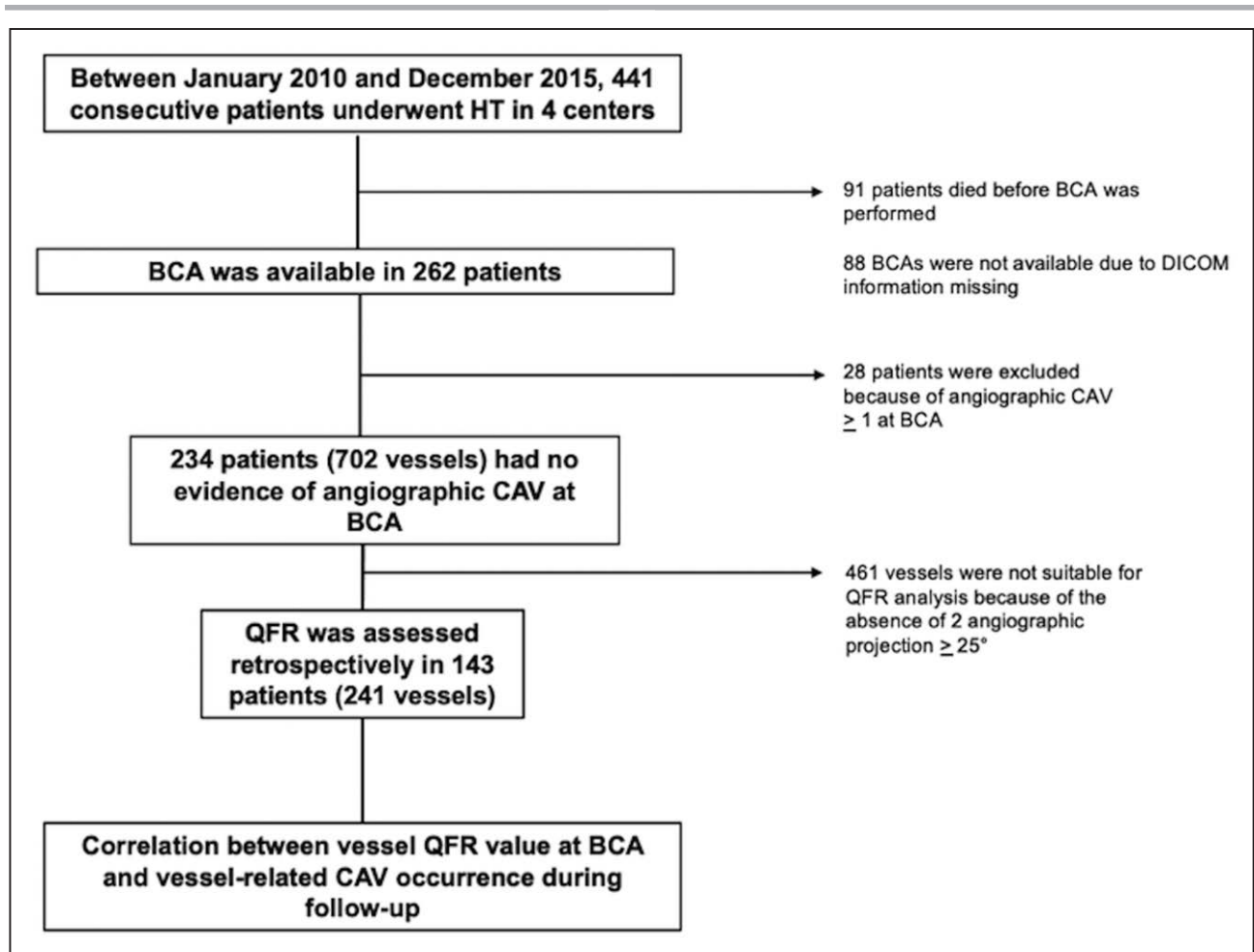
Figure 1. Study flow chart.
BCA indicates baseline coronary angiography; CAV, cardiac allograft vasculopathy; DICOM, Digital Imaging and Communications in Medicine; HT, heart transplantation; and QFR, quantitative flow ratio.

Incidence of cardiovascular death and LGD was higher in HT recipients with 2 to 3 vessels with QFR≤0.95 compared with recipients with 0 to 1 vessel (71.4% versus 5.1%, respectively, P<0.001; Figure 5 and Table S2). A significant association was confirmed for both cardiovascular death (42.9% versus 2.9%, respectively; P<0.001; Table S2) and LGD (42.9% versus 3.7%, respectively; P<0.001; Table S2).

QFR and Maximal Intimal Thickness at BCA

IVUS was performed down the left anterior descending in 27 patients. Median MIT at BCA was 1 mm (IQR, 0–1.5 mm). Out of the 27 vessels analyzed by IVUS, vessel-related CAV occurred in 5 vessels. In univariate analysis, there was no significant association between MIT at BCA and vessel-related CAV (hazard ratio, 1.98 [95% CI, 0.43–9.18]; P=0.38). However, we observed an inverse correlation between vessel QFR values and MIT at BCA, even though it was not significant at an alpha level of 0.05 (r=−0.35, P=0.07).

DISCUSSION

To the best of our knowledge, our study is the first to investigate the prognostic role of QFR in HT recipients. Our main findings are (1) lower vessel QFR at baseline was an independent predictor of angiographic vessel-related CAV at follow-up; (2) a higher number of coronary vessels with a QFR≤0.95 was associated with a higher occurrence of clinical outcomes, such as cardiovascular death and LGD.

It is known that CAV progression is usually silent and patients often present with late manifestations of the disease, such as late graft failure and sudden death. Although HT recipients undergo coronary angiography more often than non-HT patients with equivalent risk profile, CAV diagnosis can be challenging. Indeed, because CAV involves the entire coronary tree with concentric and diffuse disease pattern in contrast to the focal and eccentric epicardial lesions in atherosclerosis, angiography may underestimate vessel narrowing at plaque sites. Therefore, International Society for Heart and Lung Transplantation guidelines recommend the

Table 1. Baseline Characteristics

	Overall cohort (n=143)	Patients with 0–1 vessel with QFR≤0.95 (n=136)	Patients with 2–3 vessels with QFR≤0.95 (n=7)	P value
Recipients				
Age, y	57 [49–64]	57 [49–64]	58 [43–65]	0.96
Male sex	100 (69.9)	96 (70.6)	4 (69.9)	0.43
Donor/recipient sex mismatch	39 (27.3)	35 (25.9)	4 (57.1)	0.09
History of diabetes	35 (24.5)	34 (25.5)	1 (14.3)	1.00
History of hypertension	85 (59.4)	82 (60.3)	3 (42.9)	0.44
History of hypercholesterolemia	79 (55.2)	77 (56.6)	2 (28.6)	0.24
History of ischemic cardiomyopathy	48 (33.6)	48 (35.3)	0 (0.0)	0.1
Cellular rejection >2R*	51 (35.7)	47 (34.6)	4 (57.1)	0.25
AMR*	12 (8.4)	9 (6.6)	1 (14.3)	0.41
CMV IgG positive	115 (80.4)	109 (81.3)	6 (85.7)	1.00
CMV IgG donor+/recipient −	23 (16.1)	22 (16.7)	1 (14.3)	1.00
Time to BCA, d	365 [140–393]	365 [152–397]	276 [53–348]	0.05
Total cholesterol at BCA, mg/dL	181 [154–215]	181 [154–215]	181 [124–208]	0.7
LDL at BCA, mg/dL	103 [78–124]	103 [79–124]	103 [69–121]	0.62
Hb1Ac at BCA, % (n=96)	5.9 [5.5–6.4]	5.9 [5.5–6.4]	5.5 [5.4–6.2]	0.55
Treatment				
Tacrolimus	94 (65.7)	90 (66.2)	4 (57.1)	0.69
Ciclosporin	42 (29.4)	40 (29.6)	2 (28.6)	1.00
Mycophenolate	115 (80.4)	109 (83.2)	7 (100.0)	0.59
Everolimus	25 (17.5)	24 (18.3)	1 (16.7)	1.00
Statins	109 (76.2)	105 (82.0)	5 (83.3)	1.00
Donor age, y	44 [36–54]	44 [36–54]	44 [25–54]	0.86
Ischemic time, min	189 [140–227]	187 [142–227]	211 [135–227]	0.6
Vessels (n=241)				
LAD	138 (57.3)			
LCx	37 (15.4)			
RCA	66 (27.4)			

Data are mean±SD, n (%) or median [interquartile range]. AMR indicates antibody mediated rejection; BCA, baseline coronary angiography; CMV, cytomegalovirus; Hb1Ac, glycated hemoglobin; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; QFR, quantitative flow ratio; and RCA, right coronary artery.

*Before BCA.

use of IVUS in conjunction with coronary angiography to reveal early intimal hyperplasia.[3] However, it seems hard to gain a global penetration of this strategy in the real-world setting due to procedural time increase, radiation exposure, complications, and costs.[6] FFR has emerged as a new tool that may predict adverse outcomes in HT recipients.[15] Nevertheless, besides the use of coronary wires, FFR provides the administration of adenosine, which is associated with transient, although not significant, symptoms.[16] Although papaverine could be used as an alternative to adenosine for FFR measurements,[17] the use of these drugs may result in longer procedural times and higher costs. Conversely, QFR is a safe tool based solely on 3D vessel reconstruction and contrast frame counting which has been shown to be superior to angiography and faster than FFR for the evaluation of intermediate coronary stenosis in patients with ischemic cardiomyopathy.[7–9] In HT recipients, QFR could increase

the diagnostic power of coronary angiography, which, despite being a good screening tool for coronary artery disease, may not be sufficient for detecting early CAV.

First, in an HT setting, we found that lower vessel QFR at BCA was associated with an increased risk of vessel-related CAV during a median follow-up of 6 years (adjusted hazard ratio, 20.87 [95% CI, 5.35–81.43]; P<0.001). This strong relationship might reflect the presence of subtle intimal thickening already at the time of BCA that was not detected by coronary angiography and that could have been identified if a more sensitive diagnostic tool was used. Therefore, one might speculate that QFR could be used in HT recipients without angiographic evidence of coronary disease as a cost-effective gatekeeper to detect vessels at high risk of CAV that are deemed for further intracoronary assessment. In fact, although IVUS was performed only in 27 patients, we found a trending inverse correlation between vessel QFR
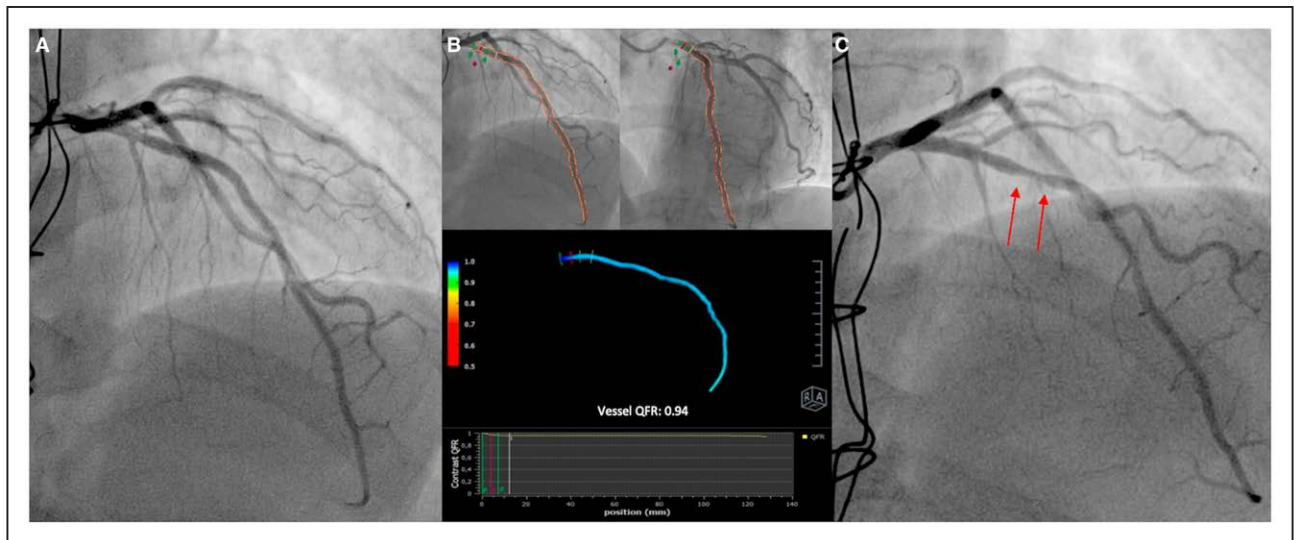
Figure 2. Example of quantitative flow ratio (QFR) assessment in a patient without evidence of angiographic cardiac allograft vasculopathy at baseline coronary angiography (BCA).
A, Left anterior descending (LAD) with no lesions at BCA; (**B**) 2 angiographic projections, at least 25° apart, were selected, and 3-dimensional reconstruction of the interrogated vessel without its side branches was performed. QFR value is ≤0.95; (**C**) evidence of angiographic stenosis in the mid-portion of LAD (red arrows) at 4 y after BCA.

value and MIT. Regarding the cutoff value, in a study by Fearon et al,[15] FFR<0.90 soon after HT, but not FFR measured at 1 year, predicted death and retransplantation at long-term follow-up. The authors postulated that an abnormal FFR (defined as FFR<0.85) at 1 year was not associated with clinical outcomes because during a longer follow-up patients might develop more significant microvascular dysfunction which can increase the FFR

value. Indeed, we found that QFR≤0.95 was the best cutoff to identify vessels at risk for future CAV.

Furthermore, we found that the presence of vessel QFR≤0.95 in >1 vessel was associated with important long-term clinical outcomes. In particular, the overall incidence of cardiovascular death and LGD at 6 years was 8.4% but it rose up to 71.4% in patients with at least 2 vessels with QFR value≤0.95, a proportion similar to that
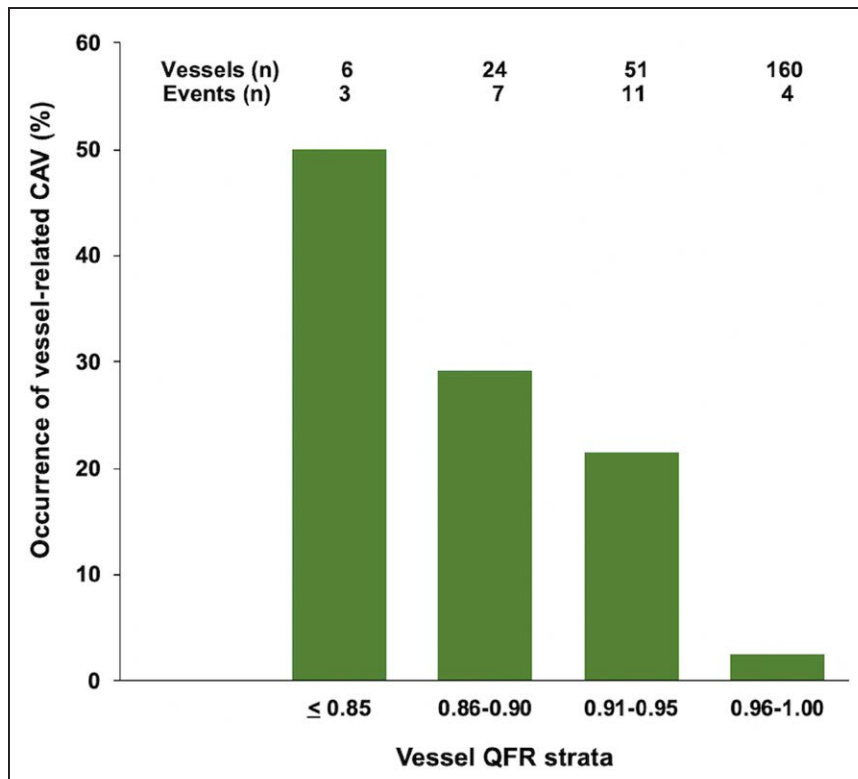

Figure 3. Occurrence of vessel-related cardiac allograft vasculopathy (CAV) according to vessel quantitative flow ratio (QFR) strata.
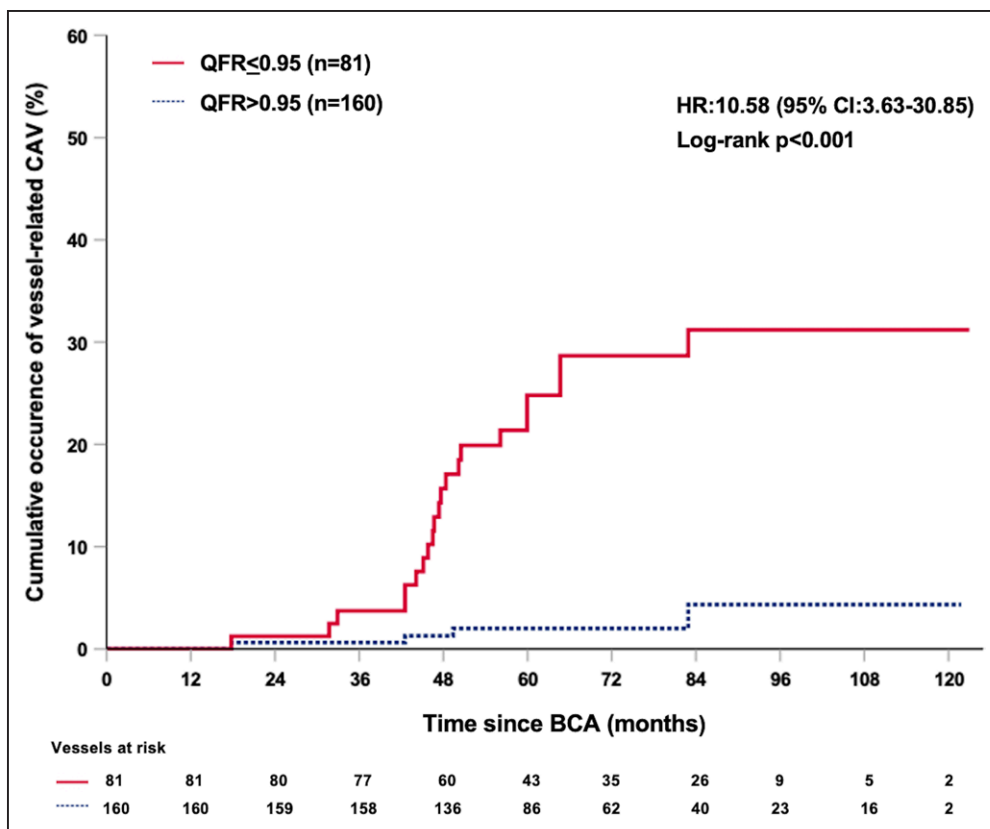
Figure 4. Cumulative occurrence of vessel-related cardiac allograft vasculopathy (CAV) according to the best cutoff.
BCA indicates baseline coronary angiography; HR, hazard ratio; and QFR, quantitative flow ratio.

of patients with angiographic CAV grade 2 to 3.[18] This finding suggests that QFR could be helpful also in risk stratification of HT recipients, although the analysis of hard end points was exploratory and severely limited by the very small number of subjects with QFR≤0.95 in 2 to 3 vessels. Therefore, our results should be interpreted in light of this limitation and considered as background for further investigation. In fact, in a future perspective, QFR assessment might identify those patients who require—beyond the identification of angiographic CAV—a closer follow-up with adoption of potential preventive measures, such as rejection surveillance, changes in immunosuppression, or intense metabolic control, which can eventually improve patient prognosis.[19]

Study Limitations

This study has several limitations related to its retrospective nature. First, because angiogram acquisition at BCA

Table 2. Predictors of Vessel-Related CAV From Cox Regression Model

	HR (95% CI)	P value
Vessel QFR≤0.95 at BCA	20.87 (5.35–81.43)	<0.001
Donor age	1.09 (1.02–1.16)	0.01

BCA indicates baseline coronary angiography; CAV, cardiac allograft vasculopathy; HR, hazard ratio; and QFR, quantitative flow ratio.

was not intended for QFR computation, a significant proportion of vessels (65.7%) was excluded from the study because of the lack of proper angiographic projections. However, QFR analysis was feasible in >90% of vessels with at least 2 angiographic projections ≥25° apart. Prospective acquisition should easily increase the analyzable proportion of vessels. Second, we included HT recipients from 2010 to 2015, to provide a reasonable follow-up for the occurrence of clinical events. The relevance of this diagnostic method at shorter follow-up remains to be established. Third, after BCA, CAV surveillance was performed by CCTA in 12 (8.3%) patients. Since it is not clear whether CCTA is sufficiently sensitive for detecting early disease and coronary angiography is currently considered the gold standard for CAV diagnosis, results should be interpreted in light of this limitation. Fourth, IVUS was not performed routinely in all transplant centers and vessel-related CAV was diagnosed using coronary angiography. Therefore, we are not able to hypothesize what the relationship between QFR and CAV would be if a more sensitive diagnostic method, like IVUS, was extensively used. Fifth, routine FFR measurements were not performed in the HT population included in the study, so we were not able to describe the correlation between QFR and FFR; although this relationship has shown to be very good in the coronary artery disease population, further validation studies comparing FFR and QFR in HT setting
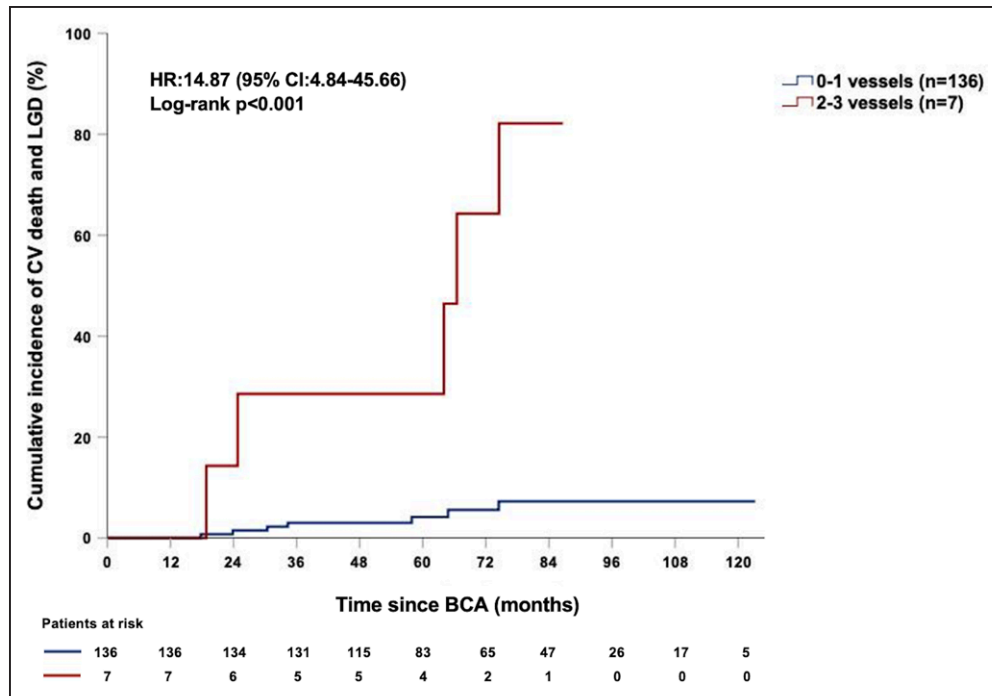
Figure 5. Incidence of cardiovascular (CV) death or late graft dysfunction (LGD) according to the number of vessels with quantitative flow ratio ≤0.95 at baseline coronary angiography (BCA) after heart transplantation.
HR indicates hazard ratio.

are warranted. Sixth, QFR analysis requires the availability of a dedicated software, which could limit its broad application. In addition, the QFR analysis performed by a core lab, although useful for improving accuracy and reproducibility, might limit the generalization of our findings to routine clinical care. Finally, the impact of shear stress on coronary vessels was not evaluated. Interestingly, in a study by Gaudio et al,[20] the calculation of shear stress using angiography-derived FFR has recently been proposed to improve risk prediction in patients with coronary artery disease. Therefore, as future perspective, QFR analysis could be integrated by shear stress data, especially in HT recipients without overt angiographic CAV, to predict adverse events.

Conclusions

In our cohort of HT recipients, lower vessel QFR values at BCA predict the occurrence of angiographic vessel-related CAV and clinical outcomes at long-term follow-up. The role of QFR in the detection of early CAV and its possible application in improving HT patients' outcomes will need to be evaluated in future prospective studies.

Affiliations

Heart Failure Clinic and Cardiology Service, University Hospital Germans Trias i Pujol, Badalona, Spain (G.S.). Hospital Clínic, Cardiovascular Clinic Institute, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain (G.S., S.B., M.F.). Heart Failure and Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy (L.P., M.M.). Cardiology Department, Hospital de la Santa Creu i Sant Pau, IIB-SantPau, CIBERCV, Universidad Autónoma de Barcelona, Spain (S.M., L.A.). Advanced Heart Failure and Heart Transplant Unit, Heart Disease Institute, Bellvitge University Hospital, Bellvitge Biomedical Research Institute, Barcelona, Spain (J.G.-C., M.G.). Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona, Italy (O.Z., G.C.). Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy (E.N.). Cardiologia Interventistica, A.O. Sant'Anna e San Sebastiano, Caserta, Italy (D.D.G.). Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy (G.C.).

Supplemental Material

Supplemental Methods
Tables S1–S2
Figure S1

REFERENCES

1. Khush KK, Potena L, Cherikh WS, Chambers DC, Harhay MO, Hayes D, Jr, Hsich E, Sadavarte A, Singh TP, Zuckermann A, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report-2020; focus on deceased donor characteristics. *J Heart Lung Transplant.* 2020;39:1003–1015. doi: 10.1016/j.healun.2020.07.010

2. Chih S, Chong AY, Mielniczuk LM, Bhatt DL, Beanlands RS. Allograft vasculopathy: the Achilles' heel of heart transplantation. *J Am Coll Cardiol.* 2016;68:80–91. doi: 10.1016/j.jacc.2016.04.033

3. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, et al; 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. doi: 10.1016/j.healun.2010.05.034

4. St Goar FG, Pinto FJ, Alderman EL, Valantine HA, Schroeder JS, Gao SZ, Stinson EB, Popp RL. Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. *Circulation.* 1992;85:979–987. doi: 10.1161/01.cir.85.3.979

5. Rickenbacher PR, Pinto FJ, Lewis NP, Hunt SA, Alderman EL, Schroeder JS, Stinson EB, Brown BW, Valantine HA. Prognostic importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation. *Circulation.* 1995;92:3445–3452. doi: 10.1161/01.cir.92.12.3445

6. Nguyen P, Seto A. Contemporary practices using intravascular imaging guidance with IVUS or OCT to optimize percutaneous coronary intervention. *Expert Rev Cardiovasc Ther.* 2020;18:103–115. doi: 10.1080/14779072.2020.1732207

7. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, et al; FAVOR Pilot Trial Study Group. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the International Multicenter FAVOR Pilot Study. *JACC Cardiovasc Interv.* 2016;9:2024–2035. doi: 10.1016/j.jcin.2016.07.013

8. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan Study. *J Am Heart Assoc.* 2018;7:e009603. doi: 10.1161/JAHA.118.009603

9. Westra J, Tu S, Campo G, Qiao S, Matsuo H, Qu X, Koltowski L, Chang Y, Liu T, Yang J, et al. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. *Catheter Cardiovasc Interv.* 2019;94:693–701. doi: 10.1002/ccd.28283

10. Spitaleri G, Tebaldi M, Biscaglia S, Westra J, Brugaletta S, Erriquez A, Passarini G, Brieda A, Leone AM, Picchi A, et al. Quantitative Flow ratio identifies nonculprit coronary lesions requiring revascularization in patients with ST-Segment-Elevation myocardial infarction and multivessel disease. *Circ Cardiovasc Interv.* 2018;11:e006023. doi: 10.1161/CIRCINTERVENTIONS.117.006023

11. 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. doi: 10.1016/j.healun.2010.05.017

12. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, Ielasi A, Spitaleri G, Di Girolamo D, Mezzapelle G, et al. Prognostic value of QFR measured immediately after successful stent implantation: the international multicenter prospective HAWKEYE Study. *JACC Cardiovasc Interv.* 2019;12:2079–2088. doi: 10.1016/j.jcin.2019.06.003

13. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, Ielasi A, Spitaleri G, Di Girolamo D, Mezzapelle G, et al. Angio-based index of microcirculatory resistance for the assessment of the coronary resistance: a Proof of Concept Study. *J Interv Cardiol.* 2020; 2020:8887369. doi: 10.1155/2020/8887369

14. López-Sainz Á, Barge-Caballero E, Barge-Caballero G, Couto-Mallón D, Paniagua-Martin MJ, Seoane-Quiroga L, Iglesias-Gil C, Herrera-Noreña JM, Cuenca-Castillo JJ, Vázquez-Rodríguez JM, et al. Late graft failure in heart transplant recipients: incidence, risk factors and clinical outcomes. *Eur J Heart Fail.* 2018;20:385–394. doi: 10.1002/ejhf.886

15. 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. doi: 10.1161/CIRCULATIONAHA.115.018741

16. Layland J, Carrick D, Lee M, Oldroyd K, Berry C. Adenosine: physiology, pharmacology, and clinical applications. *JACC Cardiovasc Interv.* 2014;7:581–591. doi: 10.1016/j.jcin.2014.02.009

17. Mizukami T, Sonck J, Gallinoro E, Kodeboina M, Canvedra A, Nagumo S, Bartunek J, Wyffels E, Vanderheyden M, Shinke T, et al. Duration of hyperemia with intracoronary administration of papaverine. *J Am Heart Assoc.* 2021;10:e018562. doi: 10.1161/JAHA.120.018562

18. Prada-Delgado O, Estévez-Loureiro R, Paniagua-Martín MJ, López-Sainz A, Crespo-Leiro MG. Prevalence and prognostic value of cardiac allograft vasculopathy 1 year after heart transplantation according to the ISHLT recommended nomenclature. *J Heart Lung Transplant.* 2012;31:332–333. doi: 10.1016/j.healun.2011.12.006

19. Masetti M, Potena L, Nardozza M, Prestinenzi P, Taglieri N, Saia F, Pece V, Magnani G, Fallani F, Coccolo F, et al. Differential effect of everolimus on progression of early and late cardiac allograft vasculopathy in current clinical practice. *Am J Transplant.* 2013;13:1217–1226. doi: 10.1111/ajt.12208

20. Gaudio LT, Veltri P, De Rosa S, Indolfi C, Fragomeni G. Model and application to support the Coronary Artery Diseases (CAD): development and Testing. *Interdiscip Sci.* 2020;12:50–58. doi: 10.1007/s12539-018-0311-6