Feasibility of Quantitative Flow Ratio in Adult Patients With Anomalous Aortic Origin of the Coronary Artery With 5 Years of Clinical Follow-up

Julien Adjedj, MD, PhD[1,2*]; Fabien Hyafil, MD[3*]; Farhang Aminfar, MD[2*]; Xavier Halna du Fretay, MD[4,5]; Fabien Picard, MD, MSc[6]; Patrick Dupouy, MD[7]; Jean-Michel Juliard, MD[5]; Olivier Muller, MD, PhD[2]; William Wijns, MD, PhD[8]; Pierre Aubry, MD[5]; on behalf of the ANOCOR Investigators

Abstract

Objectives. Anomalous origin of the right coronary artery (ARCA) represents the most common form of abnormal coronary origin and may potentially increase the risk for sudden cardiac death. Morphological and functional evaluation of ARCA in adult patients referred for invasive coronary angiogram (ICA) is challenging. Quantitative flow ratio (QFR) is an available method able to virtually calculate fractional flow reserve using 3-dimensional quantitative coronary angiography (3D-QCA) based on ICA. We aimed to evaluate the feasibility of QFR analysis in patients with ARCA and its clinical impact. **Methods.** Using the registry of proximal anomalous connections of coronary arteries (ANOCOR registry), a multicenter observational registry including 472 adult patients with ANOCOR between 2010 and 2013, we retrospectively performed QFR analysis from ICA and evaluated the rate of death, myocardial infarction, and unplanned revascularization at 5 years. **Results.** Among 128 patients with ARCA, 41 (32%) could have QFR analysis with median clinical follow-up of 8.3 years. The mean QFR value was 0.90 ± 0.10, and 3D-QCA analysis showed preserved lumen area despite the elliptical shape of the proximal part of the ARCA, which in the worst cases appeared on ICA as a significant narrowing. The event rate was 12.2% (n = 5), including 3 deaths (1 due to cancer, 1 due to stroke, and 1 cause unknown) and 2 unplanned revascularizations at 5 years. No myocardial infarctions were reported. **Conclusions.** When QFR analysis of ARCA is feasible, non-significant QFR values are associated with good clinical outcome at 5 years.

J INVASIVE CARDIOL 2021;33(4):E269-E274. Epub 2021 March 8.

Key words: anomalous coronary artery, cardiac imaging, fractional flow reserve

Several anomalous aortic origins of a coronary artery have been described, and include connections of the coronary artery above the coronary sinus, from another Valsalva sinus, or from the pulmonary artery. The most frequent anomalous aortic origin of a coronary artery connection detected with invasive coronary angiogram (ICA) concerns the anomalous right coronary artery (ARCA), with an estimated prevalence of 0.07% of ICAs.[1] Guidelines strongly recommend (IA) surgical revascularization in patients with abnormal coronary origin with symptoms or diagnostic evidence consistent with coronary ischemia attributable to the anomalous coronary artery.[2,3] Furthermore, guidelines support that surgery or continued observation may be reasonable for asymptomatic patients with an anomalous left coronary artery (ALCA) arising from the right sinus, or ARCA arising from the left sinus without ischemia, or anatomic or physiological evaluation suggesting the potential for compromise of coronary perfusion (eg, intramural course, fish-mouth-shaped orifice, acute angle) (class IIb). Due to the low prevalence and the frightening potential clinical impact of abnormal coronary origin, little is known about functional evaluation of abnormal coronary origin and clinical outcome. While ARCA detected with ICA showed ostial narrowing, intravascular ultrasound (IVUS) showed a preserved lumen but morphology modification with an elliptically shaped (rather than round) lumen.[4,5] In most cases, fractional flow reserve (FFR) values are ≥0.80, suggesting no significant ischemia induced

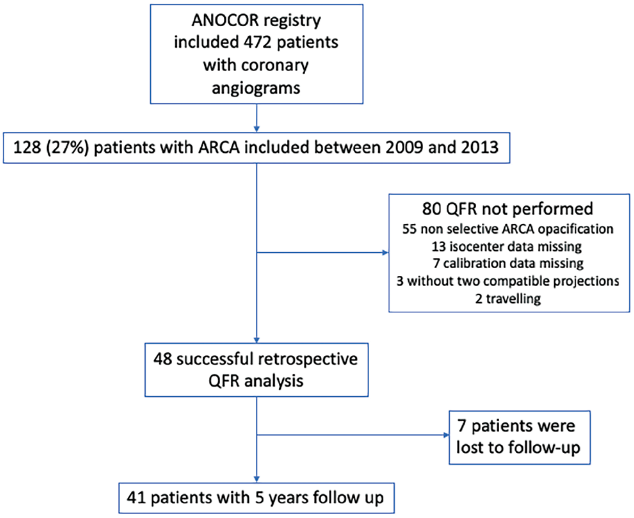

FIGURE 1. Flow chart.

by ARCA.[4,5] However, FFR measurement is invasive, sometimes challenging to perform, associated with a risk of complications, and cost/time consuming. Quantitative flow ratio (QFR) is an FFR calculation derived from coronary angiography and is available in clinical practice. Briefly, QFR calculation is based on 3-dimensional quantitative coronary angiography (3D-QCA) and computational fluid dynamics using contrast medium progression in the coronary artery as a boundary condition, with Thrombolysis in Myocardial Infarction (TIMI) frame count analysis. 3D-QCA has a good correlation with intracoronary imaging for the prediction of intracoronary dimensions.[6] QFR also has a good correlation with FFR.[7] We sought to blindly calculate QFR from retrospective analysis of the coronary angiograms of adult patients with ARCA and 5 years of clinical follow-up included in the registry of anomalous connections of coronary arteries (ANOCOR registry).

Methods

ANOCOR registry. The ANOCOR registry is a multicenter, observational study of adult patients with documented anomalous aortic origin of a coronary artery, validated by an independent committee of cardiologists. The role of the committee is to classify anomalous aortic origin of coronary arteries and help determine the best therapeutic strategy based on the patient's medical file, and invasive coronary angiography or cardiac computed tomography (CT) imaging. This registry included 496 coronary arteries with anomalous aortic origin in 472 patients from 71 centers in France between January 2010 and January 2013. Follow-up was performed by contacting the patient by phone or letter, or, in the case of no answer, by contacting the referring physician. Evaluation follow-up criteria consisted of death, myocardial infarction, or unplanned revascularization. Clinical follow-up was performed at 5 years. We evaluated the clinical presentation, non-invasive stress tests performed, and coronary angiograms with intracoronary imaging, when performed.

3D-QCA and QFR analysis. All angiographic data were sent from the database to an independent core laboratory. Experienced operators certified in QFR analysis performed all measurements using the QFR software Medis Suite 3.1.16.8 QAngio XA (Medis). QFR analysis consisted of the automatically delineated detection of the lumen contour with manual correction if needed. Contrast QFR used a frame count method to derive contrast flow velocity from coronary angiography. 3D-QCA analysis consisted of the overall vessel measurement. Two subgroups were defined: proximal of the ARCA, which represents the abnormal course segment of the vessel starting from the coronary ostium, and distal of the ARCA, corresponding to the overall vessel without the proximal part. We evaluated the following 3D-QCA parameters in the overall vessel group: the proximal and the distal parts of the ARCA, including percentage diameter stenosis, area stenosis, minimum lumen diameter (MLD), lesion length (LL), reference diameter, area at MLD, reference area, reference volume divided by lesion length, and the ellipticity index corresponding to the maximum diameter divided by the minimum diameter in the proximal and distal parts of the study vessel.

Statistical analysis. The summary of descriptive statistics is reported as mean ± standard deviation, median with interquartile range (IQR), or count with percentage of the total, as appropriate. Normal distribution was tested with the Shapiro-Wilk test. Comparisons between groups were performed by Mann-Whitney or unpaired t-test as appropriate. Kaplan-Meier curves were generated to evaluate the cumulative rate of the clinical endpoint (composite of death, myocardial infarction, and unplanned revascularization). *P*-values were considered statistically significant if <.05. All analyses were performed with Prism GraphPad 7.0 (GraphPad Software) and SPSS 21.0 (IBM).

Results

Study population. During the study period, a total of 472 adult patients with anomalous aortic origin of a coronary artery were diagnosed during ICA or CT investigation. Among them, 128 patients (27%) had ARCA with ICA. QFR analysis could not be performed in 80 patients. Forty-one patients had successful QFR analysis and 5 years of clinical follow-up. Details are provided in Figure 1. Mean age of the study population was 61 ± 12 years and 32 (78%) were men. Baseline characteristics of the study population are detailed in Table 1. Clinical presentation of included patients was angina pectoris in 12 patients (29%), acute coronary syndrome (defined as chest pain with troponin elevation) in 8 patients (20%), resuscitated cardiac arrest in 2 patients, palpitations in 2 patients, and syncope in 1 patient.

TABLE 1. Baseline characteristics.

	Patients (n = 41)
Age (years)	61 ± 12
Male sex	32 (78%)
Body mass index (kg/m²)	29.3 ± 20.9
Hypertension	25 (61%)
Dyslipidemia	20 (49%)
Diabetes	10 (24%)
Current smoker	16 (39%)
Family history of cardiac event	4 (10%)
Family history of ANOCOR	0 (0%)
Physical activity	33 (80%)
<20 minutes/week	14 (34%)
20-60 minutes/week	1 (2%)
>60 minutes/week	10 (24%)
Practice sport in competition	1 (2%)
Sport professional	4 (10%)
Previous myocardial infarction	2 (5%)
Cardiomyopathy	4 (10%)
Heart valve disease	3 (7%)

Data presented as mean ± standard deviation or number (%).

TABLE 2. Clinical presentation.

	Patients (n = 41)
Asymptomatic	10 (24%)
Atypical angina	4 (10%)
Angina	8 (20%)
Dyspnea	9 (22%)
Palpitations	2 (5%)
Acute coronary syndrome	8 (20%)
Syncope	1 (2%)
Resuscitated cardiac arrest	2 (5%)
Abnormal resting electrocardiogram	18 (44%)
Non-invasive stress test	22 (54%)
Silent ischemia	11 (27%)
Positive exercise test	7 (17%)
Positive myocardial scintigraphy	4 (10%)

Data presented as mean ± standard deviation or number (%).

Eight patients had dyspnea and 10 patients were asymptomatic, with silent ischemia detected by non-invasive stress tests indicating the ICA. Finally, 18 patients (44%) had an abnormal resting electrocardiogram (ECG) (Table 2).

Invasive coronary angiography. ICA was performed in all patients; nitrate administration and dosage was left to operator discretion. Visual estimation of ARCA detected no coronary artery disease (CAD) in 17 patients (41%); stenosis <50% was detected in 10 patients (24%), and "significant" stenosis >50% in 14 patients (34%). Six patients (15%) had IVUS imaging of the ARCA and 2 patients (5%) had FFR evaluation. An example is provided in Figure 2.

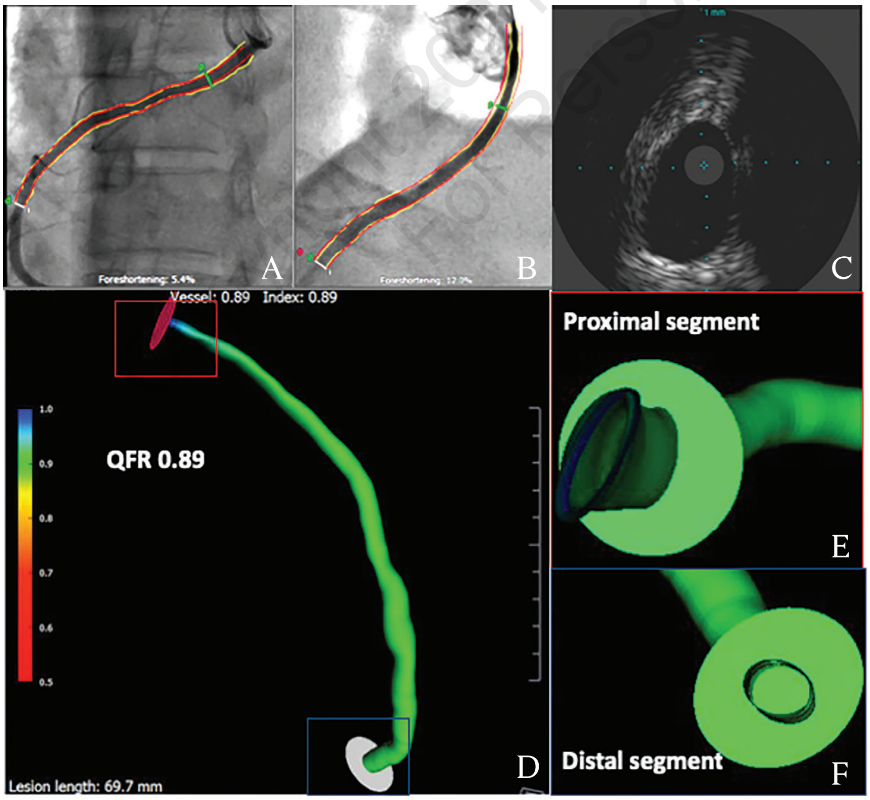

FIGURE 2. Illustration of quantitative flow ratio (QFR) analysis with intravascular ultrasound (IVUS). (A, B) Two angiographic incidences of anomalous origin of the right coronary artery (RCA). (C) The upper right panel shows the IVUS image of the proximal segment of the RCA. (D) The lower left panel shows the 3D reconstruction of the study vessel with QFR colored-coded value. (E, F) Proximal and distal segments of the coronary vessel are shown in sagittal view in the lower right part of the panel.

Table 3. Three-dimensional quantitative coronary angiography and quantitative flow ratio analysis.

	Overall (n = 41)	Proximal (n = 41)	Distal (n = 41)	*P*-Value
3D-QCA lesion length (mm)	83.63 ± 19.70	12.21 ± 3.36	71.02 ± 17.81	<.001
3D-QCA reference diameter (mm)	3.10 ± 0.65	3.68 ± 0.64	2.82 ± 0.53	<.001
3D-QCA diameter stenosis (%)	17.84 ± 16.31	18.67 ± 19.91	17.11 ± 11.23	.72
3D-QCA area stenosis (%)	16.58 ± 19.53	16.77 ± 22.10	16.09 ± 15.99	.67
3D-QCA minimum lumen diameter (mm)	1.72 ± 0.46	2.90 ± 1.13	2.34 ± 0.54	<.01
Area at minimum lumen diameter (mm^2)	4.13 ± 1.95	9.13 ± 5.63	5.44 ± 2.25	<.001
Reference area (mm^2)	7.80 ± 3.32	9.21 ± 3.57	6.47 ± 2.47	<.001
3D-QCA reference volume (mm^3)	625.29 ± 265.19	112.53 ± 60.20	508.41 ± 213.36	<.001
3D-QCA reference volume/lesion length (mm^3)	7.50 ± 2.57	9.02 ± 3.33	7.24 ± 2.56	<.001
Minimum diameter (mm)	—	3.08 ± 1.20	3.05 ± 0.53	.92
Maximum diameter (mm)	—	3.87 ± 1.06	3.18 ± 0.53	<.001
Ellipticity index	—	1.37 ± 0.46	1.05 ± 0.10	<.001
Quantitative flow ratio	0.90 ± 0.10	0.97 ± 0.06	0.90 ± 0.10	<.001

Data presented as mean ± standard deviation or number (%). 3D-QCA = three-dimensional quantitative coronary angiography.

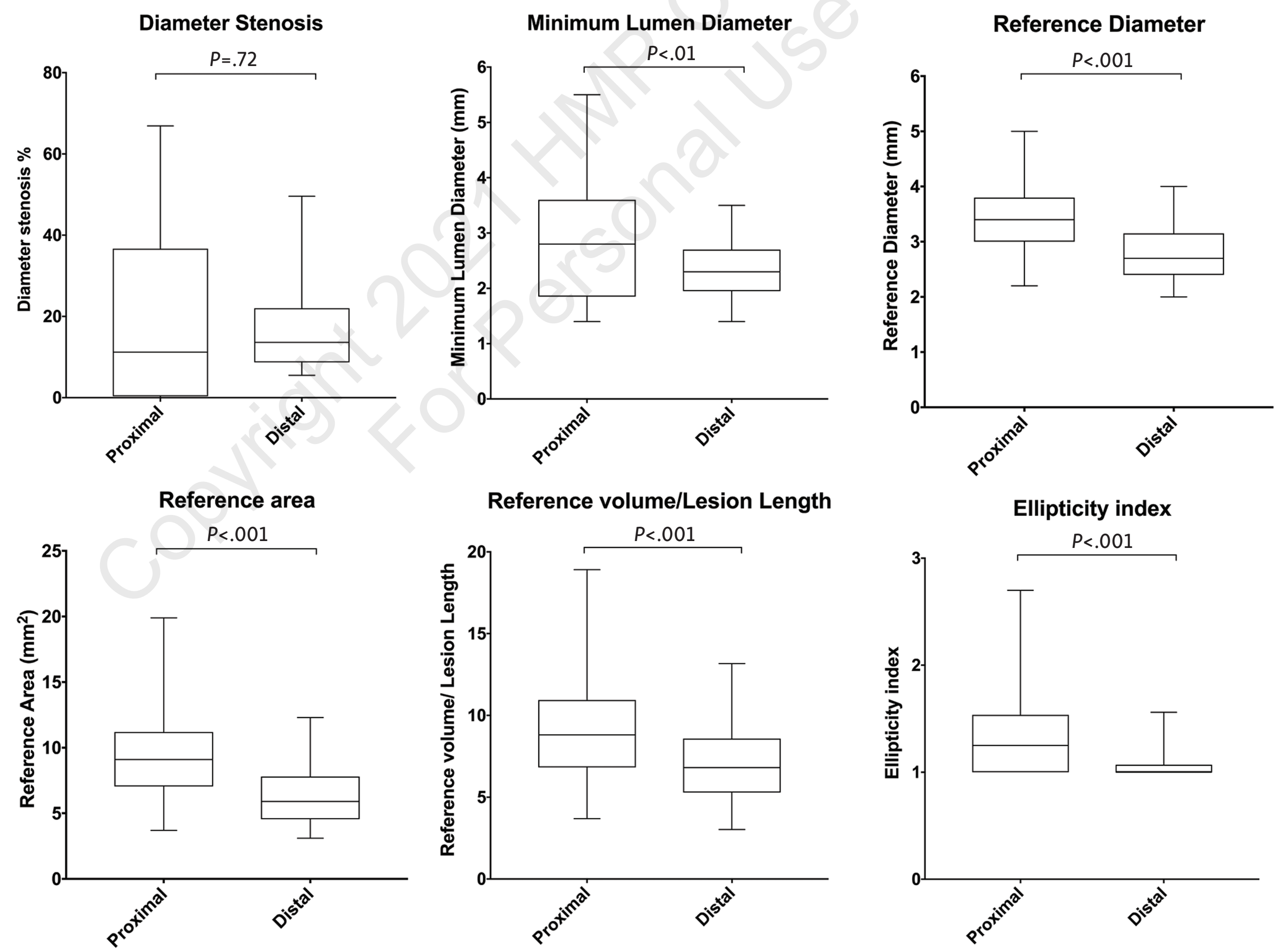

FIGURE 3. Comparison of 3D quantitative coronary angiography (QCA) indices between proximal and distal parts of the study vessel.

TABLE 4. Visual estimation, non-invasive stress tests, and quantitative flow ratio analysis.

	Proximal Stenosis <50%	Proximal Stenosis >50%	*P*-Value	Ischemia -	Ischemia +	*P*-Value
Number of patients	30	11	—	30	11	—
Quantitative flow ratio	0.90 ± 0.10	0.88 ± 0.09	.27	0.89 ± 0.11	0.90 ± 0.10	.46

Data presented as mean ± standard deviation or number.

3D-QCA analysis. Forty-one ARCAs were analyzed with 3D-QCA; details are provided in Table 3 and Figure 3. In summary, study vessels were analyzed from the ostium to the distal part of the vessel, with analyzed segment vessel length of 83.63 ± 19.70 mm. Mean reference diameter was 3.10 ± 0.65 mm with mean stenosis percentage of 17.84 ± 16.31%. The main differences observed between the proximal and distal parts of ARCAs were larger diameter and reference area in the proximal part compared with the distal part (3.68 ± 0.64 mm vs 2.82 ± 0.53 mm and 9.21 ± 3.57 mm^2 vs 6.47 ± 2.47 mm^2, respectively; *P*<.001 for all). Lumen volume divided by lesion length was significantly larger in the proximal part compared with the distal part of the vessel (9.02 ± 3.33 mm^3 vs 7.24 ± 2.56 mm^3, respectively; *P*<.001). The proximal part of the vessel had an ellipticity index significantly higher than the distal part (1.37 ± 0.46 vs 1.05 ± 0.10, respectively; *P*<.001).

QFR analysis. Mean QFR value was 0.90 ± 0.10. Larger QFR drop was observed in the distal part compared with the proximal part (mean QFR values, 0.90 ± 0.10 vs 0.97 ± 0.06, respectively; *P*<.001). Subgroup analysis of QFR mean value according to the proximal stenosis assessed by visual estimation as not significant (<50% of stenosis) or significant (>50% of stenosis) was 0.90 ± 0.10 and 0.88 ± 0.09, respectively (*P*=.27). Subgroup analysis of QFR mean value according to presence or absence of silent ischemia was 0.89 ± 0.11 and 0.90 ±0.10, respectively; *P*=.46) (Figure 4 and Table 4).

Clinical follow-up. Among 48 patients included, 7 were lost to follow-up just after inclusion, and therefore were excluded from the follow-up analysis. All patients were initially treated conservatively. The median follow-up period was 8.3 years. At 5 years of follow-up, 5 events (12.2%) were reported, ie, 3 patients (7%) died (1 due to cancer, 1 due to a stroke, and 1 with unknown cause of death) and 2 patients (5%) underwent unplanned percutaneous coronary intervention (1 patient had intervention in the ARCA) (Figure 5).

Discussion

ARCA is the most frequent anomalous aortic origin of a coronary artery detected with ICA. In adult patients referred for ICA to rule out CAD, ARCA evaluation is challenging. In our study population, from angiography, the ARCA seemed narrowed at

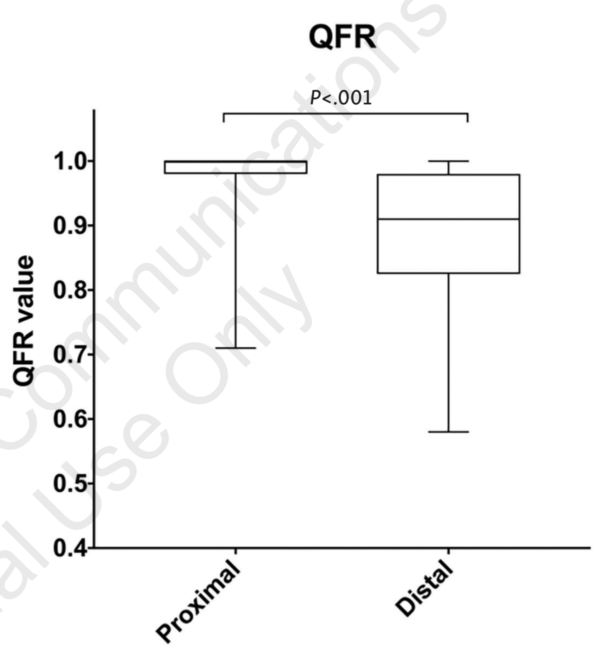

FIGURE 4. Comparison of quantitative flow ratio values between proximal and distal parts of the study vessel.

the proximal part in 24 patients (58%), while 3D-QCA showed a mean diameter stenosis of 17.84 ± 16.31%. This diameter stenosis mismatch between 2-dimensional angiography assessment with visual estimation and 3D-QCA might be due to the oval shape of the proximal part of the ARCA that is not a functionally significant lumen narrowing, as previously described with IVUS and FFR.[5] However, performing FFR or IVUS in an ARCA is challenging, time consuming, and costly. QFR is a novel technology that is available in clinical practice, based on coronary angiography, and can be performed using a diagnostic catheter. QFR analysis is simple and fast to perform in an ARCA. QFR analysis confirms the oval shape of the proximal part of the ARCA with 3D-QCA. Our study showed that most patients had cardiac symptoms and/or positive non-invasive stress tests (27%) or resting ECG modifications (54%) suggested ischemia while QFR results and clinical impact were reassuring (Table 2). Therefore, current non-invasive tests seem not optimal to rule in patients with ARCA and indicate surgical revascularization. Our follow-up showed 1 death with unknown cause and 1 death due to stroke, no

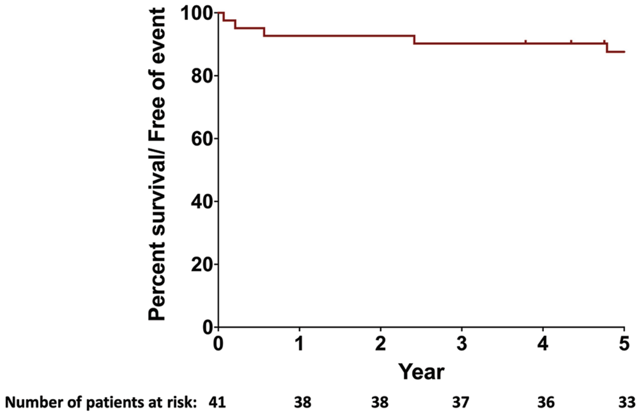

FIGURE 5. Kaplan-Meier survival curve representing the percentage of the population free of events during a period of 5 years of clinical follow-up. The lower part of the panel shows the number of patients at risk.

myocardial infarction, and 2 unplanned percutaneous coronary revascularizations. Based on our study results, QFR seems to be an appropriate and straightforward method to detect ischemia due to ARCA when applicable.

Study limitations. Several limitations that are mainly due to the retrospective nature of this study, which limited our ability to perform QFR analysis, need to be acknowledged. First, ICA was performed between 2010 and 2013, before the validation of virtual FFR calculation based on coronary angiograms. Second, ARCAs are sometimes difficult to catheterize properly in order to obtain vessel opacification. Finally, it is difficult to evaluate the very ostial part of the vessel with ICA. However, to our knowledge, we have collected the largest study population with ARCA, functional evaluation, and long-term outcome reported to date. Our results are consistent with existing literature, and the authors believe that QFR is able to help in the evaluation of ARCA in clinical practice.

Conclusion

Evaluation of anomalous aortic origin of right coronary artery with QFR demonstrated that non-significant QFR values were associated with good long-term outcomes after conservative treatment. When feasible, QFR could be the evaluation method of choice to interrogate the functional impact of ARCA during ICA and could be helpful for clinical decision making.

References

1. Cheezum MK, Liberthson RR, Shah NR, et al. Anomalous aortic origin of a coronary artery from the inappropriate sinus of Valsalva. *J Am Coll Cardiol.* 2017;69:1592-1608.
2. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2011;58:e123-e210.
3. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019;73:1494-1563. Epub 2018 Aug 16.
4. Lee SE, Yu CW, Park K, et al. Physiological and clinical relevance of anomalous right coronary artery originating from left sinus of Valsalva in adults. *Heart.* 2016;102:114-119.
5. Driesen BW, Warmerdam EG, Sieswerda GT, et al. Anomalous coronary artery originating from the opposite sinus of Valsalva (ACAOS), fractional flow reserve- and intravascular ultrasound-guided management in adult patients. *Catheter Cardiovasc Interv*. 2018;92:68-75. Epub 2018 Mar 9.
6. Tu S, Xu L, Ligthart J, et al. *In vivo* comparison of arterial lumen dimensions assessed by co-registered three-dimensional (3D) quantitative coronary angiography, intravascular ultrasound and optical coherence tomography. *Int J Cardiovasc Imaging.* 2012;28:1315-1327.
7. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077-3087.

*Joint first authors.

From the [1]Cardiology Department, Arnault Tzanck Institute, Saint Laurent Du Var, France; [2]Cardiology Department, Lausanne University Hospital, Lausanne, Switzerland; [3]Department of Nuclear Medicine, DMU IMAGINA, European Hospital Georges-Pompidou, Assistance Publique - Hôpitaux de Paris, University of Paris, Paris, France; [4]Cardiology Unit, Oréliance, Saran, France; [5]Cardiology Department, Bichat - Claude-Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [6]Cardiology Department, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [7]Interventional Imaging Cardiovascular Unit, Antony Private Hospital, Antony, France; and [8]the Lambe Institute for Translational Medicine and Curam, National University of Ireland, Galway and Saolta University Healthcare Group, Galway, Ireland.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

Manuscript accepted July 27, 2020.

Address for correspondence: Julien Adjedj, MD, PhD, Cardiology Department, Arnault Tzanck Institute, Saint Laurent Du Var, France. Email: julienadjedj@hotmail.com