European Journal of Preventive Cardiology

ESC European Society of Cardiology

Full research paper

European Journal of Preventive Cardiology
2018, Vol. 25(13) 1360–1370
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DOI: 10.1177/2047487318777435
journals.sagepub.com/home/ejpc

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Endothelial dysfunction as predictor of angina recurrence after successful percutaneous coronary intervention using second generation drug eluting stents

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Abstract

Background: The role of endothelial dysfunction in predicting angina recurrence after percutaneous coronary intervention is unknown.

Design: We assessed the role of peripheral endothelial dysfunction measured by reactive-hyperaemia peripheral-artery tonometry (RH-PAT) in predicting recurrence of angina after percutaneous coronary intervention.

Methods: We enrolled consecutive patients undergoing percutaneous coronary intervention with second-generation drug-eluting stents. RH-PAT was measured at discharge. The endpoint was repeated coronary angiography for angina recurrence and/or evidence of myocardial ischaemia at follow-up. Patients with in-stent restenosis and/or significant de novo stenosis were defined as having angina with obstructed coronary arteries (AOCA); all other patients as having angina with non-obstructed coronary arteries (ANOCA).

Results: Among 100 patients (mean age 66.7 ± 10.4 years, 80 (80.0%) male, median follow-up 16 (3–20) months), AOCA occurred in 14 patients (14%), ANOCA in nine patients (9%). Repeated coronary angiography occurred more frequently among patients in the lower RH-PAT index tertile compared with middle and upper tertiles (14 (41.2%) *vs.* 6 (18.2%) *vs.* 3 (9.1%), $p = 0.006$, respectively). ANOCA was more frequent in the lower RH-PAT index tertile compared with middle and upper tertiles. In the multivariate regression analysis, the RH-PAT index only predicted angina recurrence. The receiver operating characteristic curve of the RH-PAT index to predict the angina recurrence demonstrated an area under the curve of 0.79 (95% confidence interval: 0.69–0.89; $p < 0.001$), with a cut-off value of 1.705, having sensitivity 74% and specificity 70%.

Conclusions: Non-invasive assessment of peripheral endothelial dysfunction using RH-PAT might help in the prediction of recurrent angina after percutaneous coronary intervention, thus identifying patients who may need more intense pharmacological treatment and risk factor control.

Keywords

Endothelial dysfunction, PCI, recurrent angina

Received 26 February 2018; accepted 25 April 2018

Introduction

Persistence or recurrence of angina after successful percutaneous coronary intervention (PCI) represents an important clinical issue involving from one-fifth to

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one-third of patients undergoing myocardial revascularization at one-year follow-up.[1] The pathophysiology of angina persisting or recurring after successful PCI is complex and includes both structural and functional alterations. Structural causes like in-stent restenosis (ISR) or coronary atherosclerosis progression in other segments explain symptom recurrence after successful PCI in some patients, while functional causes such as vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction explain symptoms in the remaining patients.[1]

Endothelial dysfunction is a systemic pathological condition that can be detected from the early phase of atherosclerosis to the advanced atheroma, resulting in obstructive coronary artery disease (CAD).[2] Moreover, functional causes of angina such as coronary epicardial spasm or microvascular dysfunction have been shown to be associated with endothelial dysfunction.[3,4] Previous studies evaluating peripheral endothelial function assessed by forearm flow-mediated dilation (FMD) demonstrated that the presence of endothelial dysfunction predicted the occurrence of cardiovascular events and the progression of coronary atherosclerosis beyond traditional risk factors.[5,6] Moreover, in the bare-metal stent (BMS) era, peripheral endothelial dysfunction assessed by FMD was shown to be a strong predictor of BMS-ISR.[7]

Reactive-hyperaemia peripheral-arterial tonometry (RH-PAT) is a non-invasive technique to assess peripheral microvascular endothelial function by measuring changes in digital pulse volume during reactive hyperaemia.[8] Using this test, the Framingham Heart Study reported that RH-PAT indexes correlated inversely with various cardiovascular risk factors,[9] indicating the clinical utility and predictive value of the RH-PAT test. Moreover, other studies demonstrated that RH-PAT indexes correlated with the presence of coronary microvascular endothelial dysfunction assessed by intracoronary acetylcholine (ACh) administration[10] predicted the presence of ischaemic heart disease in women (with both obstructive and non-obstructive CAD)[11] and the occurrence of ISR in patients treated with first-generation drug-eluting stent (DES) implantation.[12]

In this study, we aimed at assessing whether endothelial dysfunction measured by fingertip RH-PAT can predict the risk of repeated coronary angiography due to recurrence of angina after successful PCI with second generation DES.

Methods

Study population

We prospectively enrolled consecutive patients admitted to the Catheterization laboratory of the Policlinico Gemelli and undergoing PCI with second-generation DES for significant CAD with documented evidence of myocardial ischemia between October 2014 and January 2015. All procedures were performed according to standard practice. Exclusion criteria were balloon angioplasty only without stent deployment or with BMS/first-generation DES ($n=3$); death during hospitalization ($n=1$); comorbidities affecting RH-PAT results, such as haemodialysis ($n=4$), advanced cancer ($n=3$), collagen disease ($n=3$), severe aortic valve stenosis ($n=2$).

The study complied with the Declaration of Helsinki with respect to investigation in humans, was approved by an institutional review committee and was conducted in accordance with the guidelines of the local ethics committee. Written informed consent was obtained from all patients.

Peripheral endothelial function assessment

The RH-PAT index was measured using the RH-PAT system (EndoPAT2000; Itamar Medical, Caesarea, Israel) after PCI, on the day of discharge, in the early morning, with patients in a fasting state (>12 h), before taking any medications and after >3-day discontinuation of vasodilators (nitrates, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers).

The principle of RH-PAT has been described previously.[13] Briefly, a blood pressure cuff was placed on one upper arm, while the contralateral arm served as a control. PAT probes were placed on one finger of each hand. After a 5-min equilibration period, the cuff was inflated to 60 mmHg above the systolic pressure or 200 mmHg for 5 min and then deflated to induce reactive hyperaemia. The RH-PAT data were digitally analysed online (Endo-PAT2000 software version 3.0.4). The RH-PAT index reflects the extent of reactive hyperaemia and was calculated as the ratio of the average amplitude of PAT signal over 1 min starting 1.5 min after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of PAT signal of a 2.5-min time period before cuff inflation (baseline) (control arm, B; occluded arm, D). Thus, the RH-PAT index is $(C/D)/(A/B) \times$ baseline correction.

Clinical follow-up

The incidence of death from any cause, cardiac death, readmission for acute coronary syndrome (ACS), repeated coronary angiography, repeated PCI with or without target lesion revascularization (TLR), and recurrence of angina was assessed at six, 12 and 18 months by telephonic interview and/or clinical check. We collected also Seattle Angina Questionnaires

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(SAQs) at one year.[14] An exercise-stress test (EST) was scheduled for all patients, with the time interval from index PCI to EST left to the physician's discretion. Cardiac death included sudden death or death preceded by typical chest pain; recurrence of ACS was defined as typical chest pain at rest associated with ST-segment and/or T wave abnormalities on the electrocardiogram and/or detection of increased serum troponin T levels. TLR was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent. Major adverse cardiac events (MACEs) were defined as the composite of death from any causes, readmission for ACS or repeated PCI. All planned staged procedures in patients with multivessel disease were performed during the index admission and were not included in the events at follow-up.

All patients with typical angina and/or evidence of ischaemia at EST at follow-up underwent a diagnostic coronary angiogram in order to rule out occurrence of ISR or progression of coronary atherosclerosis in other segments. At EST, ST-segment depression was considered diagnostic for myocardial ischaemia when horizontal or downsloping and $\geq$1 mm at 0.08 s from the J point. Patients presenting with typical angina at follow-up were classified as having angina with obstructed coronary arteries (AOCA) or angina with non-obstructed coronary arteries (ANOCA) according to the underlying mechanism responsible for symptom recurrence. In particular, patients presenting with typical angina and/or evidence of ischaemia at EST and with evidence at coronary angiogram of significant ISR or significant de novo stenosis due to progression of disease in other coronary segments were classified as AOCA; all other patients were classified as ANOCA.

Statistical analysis

RH-PAT index values were divided into tertiles. Data distribution was assessed according to the Kolgormonov–Smirnov test. Continuous variables were compared using a one-way analysis of variance or non-parametric Kruskal–Wallis test, as appropriate, and data were expressed as mean $\pm$ standard deviation (SD) or as median (range). Categorical data were evaluated using the chi-squared test or Fisher exact test as appropriate. Pearson's correlation coefficient was used for evaluation of possible association with the RH-PAT index. All tests were two-sided, and a p-value ≤ 0.05 represented statistically significant differences.

Logistic regression analysis was employed to determine predictors of recurrent angina or repeated PCI. Significant variables ($p < 0.1$ in the univariate analysis) were entered into multivariate analysis. Receiver operating characteristic (ROC) curves were constructed for the RH-PAT index to predict repeated coronary angiography due to recurrence of angina. The area under the curve (AUC), sensitivity and specificity were calculated to predict the ability of the RH-PAT index to detect patients with recurrent angina, with an AUC value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy. We defined optimal thresholds for the RH-PAT index by maximizing the sum of sensitivity and specificity.[15]

Results

Baseline clinical and angiographic characteristics across RH-PAT index tertiles

A total of 100 patients (mean age 66.7 $\pm$ 10.4 years, 80 (80.0%) male) were enrolled in final analysis. Patients in the lower tertile had a RH-PAT $\leq$ 1.68, patients in the upper tertile had a RH-PAT index > 2.12, patients in the middle tertile had a RH-PAT > 1.68 and $\leq$2.12. Patients in the lower RH-PAT index tertile presented a trend for a higher body mass index compared with patients in the middle and higher RH-PAT index tertiles (27.9 $\pm$ 3.5 *vs.* 26.1 $\pm$ 3.6 *vs.* 25.9 $\pm$ 3.9, p = 0.055, respectively). Moreover, RH-PAT index presented an inverse correlation with the body mass index ($r = -0.22$, $p = 0.049$). Other clinical, angiographic and procedural characteristics did not differ across RH-PAT tertiles (Table 1). Similarly, baseline and post-procedural high-sensitivity troponin T levels did not differ across RH-PAT tertiles. Median time from PCI to RH-PAT index assessment was two days (range 1–6 days). No adverse events deriving from vasodilator discontinuation for RH-PAT index assessment were reported.

Clinical outcome according to RH-PAT index tertiles

Clinically-driven repeated coronary angiography at follow-up occurred in 23 patients (23.0%) in the overall population (median follow-up time 16 (range 3–20) months), more frequently in patients in the lower RH-PAT index tertile compared with patients in the middle and upper tertiles (14 (41.2%) *vs.* 6 (18.2%) *vs.* 3 (9.1%), $p = 0.006$, respectively) (Figure 1). Furthermore, patients in the lower RH-PAT tertile, compared with patients in the middle and upper tertiles, had a more frequent positive EST (13 (38.2%) *vs.* 5 (15.1%) *vs.* 2 (6.1%), $p = 0.003$, respectively) and a significantly lower SAQ score at one year (40.5 (11–94) *vs.* 54 (25–95) *vs.* 70 (25–100), $p = 0.008$, respectively) (Table 2).

Among patients undergoing repeated coronary angiography, obstructed coronary arteries were detected in 14 of 23 patients (61%), whereas in nine of 23 patients (39%) coronary arteries and stents were unobstructed.

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Table 1. Clinical, angiographic and procedural characteristics of overall population and according to RH-PAT index tertiles.

Characteristics	Total population $N = 100$	Lower tertile $n = 34$	Middle tertile $n = 33$	Upper tertile $n = 33$	*p*
Clinical characteristics					
Age	66.7 ± 10.4	65.2 ± 9.9	66.2 ± 9.6	68.6 ± 11.8	0.39
Male gender, *n* (%)	80 (80.0)	28 (82.3)	25 (75.8)	27 (81.8)	0.76
BMI	26.8 ± 3.6	27.9 ± 3.5	26.1 ± 3.6	25.9 ± 3.9	0.055
Hypertension, *n* (%)	76 (76.0)	26 (76.5)	28 (84.8)	22 (66.6)	0.23
Smoke, *n* (%)	39 (39.0)	14 (41.2)	15 (45.5)	10 (30.3)	0.43
Hypercholesterolaemia, *n* (%)	79 (79.0)	26 (76.5)	29 (87.9)	24 (72.7)	0.29
Diabetes, *n* (%)	33 (33.0)	10 (29.4)	9 (27.3)	14 (42.4)	0.38
Familial history of cardiovascular diseases, *n* (%)	34 (20.0)	12 (35.3)	10 (30.3)	12 (36.4)	0.86
Previous history of PCI	15 (15.0)	6 (17.6)	5 (15.1)	4 (12.1)	0.82
Previous history of CABG	12 (12.0)	7 (20.6)	2 (6.1)	3 (9.1)	0.22
Previous history of ACS	18 (18.0)	7 (20.6)	6 (18.2)	5 (15.1)	0.84
ACS as clinical presentation, *n* (%)	41 (41.0)	17 (50.0)	14 (42.4)	10 (30.3)	0.26
Baseline hs-TnT, ng/mL	0.04 (<0.01–16.70)	0.04 (0.01–16.70)	0.04 (<0.01–13.20)	0.02 (0.01–10.25)	0.37
Post-procedural hs-TnT (peak), ng/mL	0.44 (0.01–49.20)	0.89 (0.01–21.39)	0.35 (0.01–49.20)	0.14 (0.01–13.20)	0.13
Admission therapy					
Aspirin, *n* (%)	73 (56.0)	28 (82.3)	28 (84.8)	23 (69.7)	0.33
Thienopyridines, *n* (%)	41 (41.0)	16 (47.1)	13 (39.4)	12 (36.4)	0.66
Statins, *n* (%)	67 (67.0)	20 (58.8)	24 (72.7)	23 (69.7)	0.44
Beta-blockers, *n* (%)	53 (53.0)	19 (55.9)	17 (5.5)	17 (51.5)	0.92
ACE-Is and/or ARBs, *n* (%)	60 (60.0)	21 (61.8)	22 (66.7)	17 (51.5)	0.44
CCBs, *n* (%)	13 (13.0)	6 (17.6)	4 (12.1)	3 (9.1)	0.66
Insulin, *n* (%)	7 (7.0)	3 (8.8)	2 (6.1)	2 (6.1)	0.88
Discharge therapy					
Aspirin, *n* (%)	98 (98.0)	34 (100.0)	32 (97.0)	32 (97.0)	1.0
Thienopyridines, *n* (%)	100 (100.0)	34 (100.0)	33 (100.0)	33 (100.0)	1.0
Statins, *n* (%)	88 (88.0)	31 (91.2)	30 (90.9)	27 (81.8)	0.41
Beta-blockers, *n* (%)	70 (70.0)	26 (76.5)	23 (69.7)	21 (63.6)	0.52
ACE-Is and/or ARBs, *n* (%)	72 (72.0)	27 (79.4)	22 (66.7)	23 (69.7)	0.48
CCBs, *n* (%)	14 (14.0)	6 (17.6)	4 (12.1)	4 (12.1)	0.75
Insulin, *n* (%)	8 (8.0)	3 (8.8)	3 (9.1)	2 (6.1)	0.88
Angiographic characteristics					
Multivessel disease, *n* (%)	45 (45.0)	18 (52.9)	16 (48.5)	11 (33.3)	0.24
Syntax score	13.8 ± 8.7	15.7 ± 9.8	11.5 ± 6.5	14.1 ± 9.1	0.14
Stented vessel					0.93
LAD	47 (46.0)	17 (50.0)	16 (48.5)	14 (42.4)	
LCx	22 (23.0)	7 (20.6)	8 (24.2)	7 (21.2)	
RCA	31 (31.0)	10 (29.4)	9 (27.3)	12 (36.4)	
Procedural characteristics					
Number of implanted stents, *n*	1.36 ± 0.70	1.38 ± 0.70	1.30 ± 0.58	1.39 ± 0.83	0.85
Stent length, mm	26 ± 8	27 ± 9	29 ± 6	23 ± 8	0.31
Stent diameter, mm	2.85 ± 0.31	2.88 ± 0.28	2.83 ± 0.34	2.86 ± 0.32	0.76
Stent type					0.80
EES	42 (42.0)	15 (44.1)	13 (39.4)	14 (42.4)	
ZES	37 (37.0)	12 (35.3)	11 (33.3)	14 (42.4)	
Others	21 (21.0)	7 (20.6)	9 (27.3)	5 (15.1)	

ACE-I: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor antagonist; BMI: body mass index; CABG: coronary artery bypass grafting; CCB: calcium-channel blocker; EES: everolimus-eluting stent; hs-TnT: high-sensitivity troponin T; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; RH-PAT: reactive-hyperaemia peripheral-artery tonometry; ZES: zotarolimus-eluting stent.

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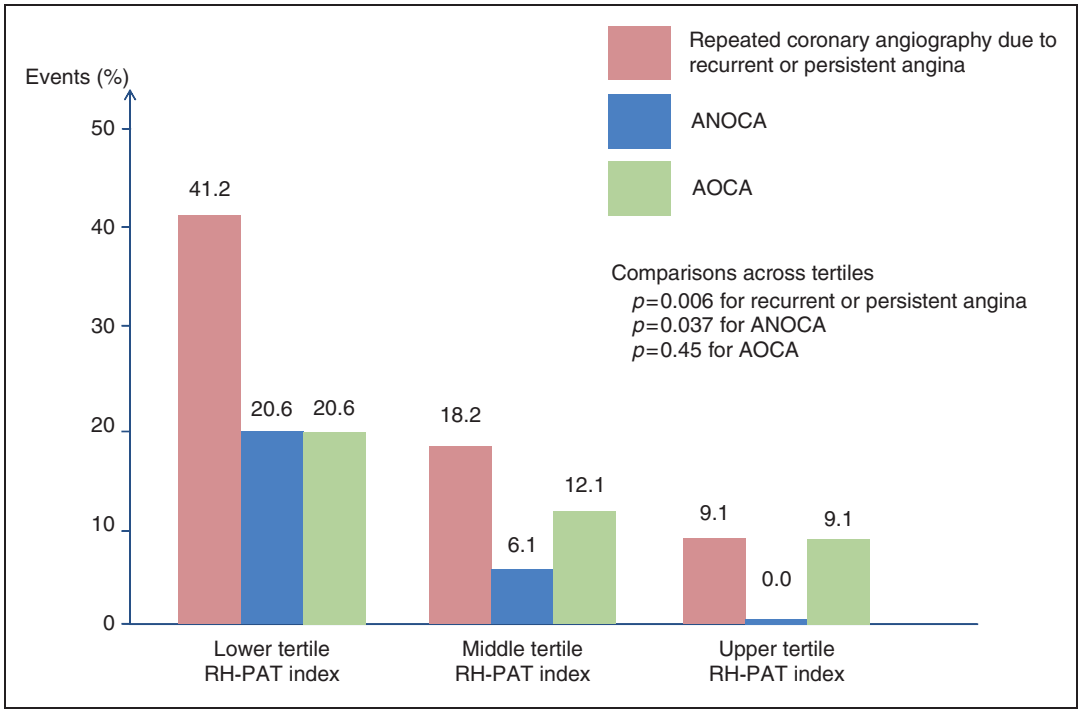

Figure 1. Rates of repeated coronary angiography due to recurrent or persistent angina, ANOCA and AOCA according to RH-PAT index tertiles.
ANOCA: angina with non-obstructed coronary arteries; AOCA: angina with obstructed coronary arteries; RH-PAT: reactive-hyperaemia peripheral-artery tonometry.

Table 2. Clinical outcomes of overall population and according to RH-PAT index tertiles.

Characteristics	Total population $N = 100$	Lower tertile $n = 34$	Middle tertile $n = 33$	Upper tertile $n = 33$	p
Repeated CA due to persistence or recurrence of angina, *n* (%)	23 (23.0)	14 (41.2)	6 (18.2)	3 (9.1)	0.006
AOCA, *n* (%)	14 (14.0)	7 (20.6)	4 (12.1)	3 (9.1)	0.45
TLR, *n* (%)	6 (6.0)	3 (8.8)	2 (6.1)	1 (3.0)	1.0
PCI for atherosclerosis progression, *n* (%)	8 (8.0)	4 (11.8)	2 (6.1)	2 (6.1)	0.61
ANOCA, *n* (%)	9 (9.0)	7 (20.6)	2 (6.1)	0 (0.0)	0.037
Readmission for ACS, *n* (%)	8 (8.0)	3 (8.8)	3 (9.1)	2 (6.1)	1.0
Death from any causes, *n* (%)	8 (8.0)	3 (8.8)	4 (12.1)	1 (3.1)	0.43
Cardiac death, *n* (%)	7 (7.0)	3 (8.8)	3 (9.1)	1 (3.1)	0.69
MACEs, *n* (%)	22 (22.0)	10 (29.4)	8 (24.2)	4 (12.1)	0.23
Positive EST, *n* (%)	20 (20.0)	13 (38.2)	5 (15.1)	2 (6.1)	0.003
Time from index PCI to EST, months, median (range)	12 (2–16)	9 (2–12)	12 (4–14)	12 (9–16)	0.03
SAQ score	50 (11–100)	40.5 (11–94)	54 (25–95)	70 (25–100)	0.008
Mean follow-up time, months	16 (3–20)	16 (3–20)	16 (5–18)	15 (6–18)	1.0

ACS: acute coronary syndrome; ANOCA: angina with non-obstructed coronary arteries; AOCA: angina with obstructed coronary arteries; CA: coronary angiography; EST: exercise-stress test; MACE: major adverse cardiac event; PCI: percutaneous coronary intervention; RH-PAT: reactive-hyperaemia peripheral-artery tonometry; SAQ: Seattle Angina Questionnaire; TLR: target lesion revascularization.

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Among AOCA patients, typical angina occurred in 11 patients, whereas three patients had a positive EST without symptoms. All ANOCA patients had typical angina and a positive EST. Occurrence of AOCA was numerically more frequent in the lower RH-PAT index tertile compared with the middle and upper tertiles (7 (20.6%) *vs.* 4 (12.1%) *vs.* 3 (9.1%), $p = 0.45$, respectively), although this difference did not reach statistical significance. Of note, occurrence of ANOCA was significantly more frequent in the lower tertile compared with the middle and upper tertiles (7 (20.6%) *vs.* 2 (6.1%) *vs.* 0 (0.0%), $p = 0.037$, respectively) (Figure 1).

Finally, rates of MACE, death from any causes, cardiac death and readmission for ACS did not differ across RH-PAT index tertiles (Table 2).

Medical therapy prescribed at discharge and during follow-up visits was not tolerated in 32 (32%) patients. In particular, statins were down-titrated or discontinued in 27 patients, beta-blockers in three patients, calcium-channel blockers in two patients, nitrates in two patients, ranolazine in one patient. Of note, adherence to medical therapy did not differ between patients undergoing repeated coronary angiography and patients not requiring a repeated coronary angiography (Table 3). However, patients undergoing repeated coronary angiography were more frequently treated with anti-ischaemic drugs at follow-up compared with patients not requiring a repeated coronary angiography (Table 3).

At univariate logistic regression analysis, RH-PAT index (ß = 0.14, 95% confidence interval (CI) 0.04–0.56, $p = 0.005$) and hypertension (ß = 4.20, 95% CI 0.91–19.44, $p = 0.066$) were the only variables with a p-value < 0.1 as predictors of repeated coronary angiography due to recurrent or persistent angina at follow-up. In the multivariate regression analysis including both RH-PAT index and hypertension, only RH-PAT index was a significant predictor of repeated coronary angiography due to recurrent or persistent angina at follow-up (ß = 0.13, 95% CI 0.03–0.57, $p = 0.006$) (Table 4). At the same time, at univariate logistic regression analysis, RH-PAT index (ß = 0.31, 95% CI 0.09–1.03, p = 0.057) and diabetes (ß = 3.2, 95% CI 1.006–10.17, $p = 0.049$) were the only variables with a p-value < 0.1 as predictors of any repeated PCI at follow-up (Table 4). We did not perform a multivariate regression analysis for any repeated PCI due to the low event rate.

ROC analysis of the RH-PAT index to predict recurrence of angina

ROC curves were constructed to assess the ability of the RH-PAT index to predict repeated coronary angiography due to recurrent angina. The AUC for detection of repeated coronary angiography was 0.79 (95% CI: 0.69–0.89, $p < 0.001$) of RH-PAT index (Figure 2(a)). Using an RH-PAT index cut-off value of 1.705, the sensitivity and specificity for the detection of repeated coronary angiography were 74% and 70%, respectively. Of note, the RH-PAT index was particularly able to detect recurrence of ANOCA with an AUC

Table 3. Medical therapy at follow-up in the overall population and according to the occurrence of repeated coronary angiography.

Characteristics	Total population $N = 100$	RCA $n = 23$	No RCA $n = 77$	p
Adherence to medical therapy[a], *n* (%)	68 (68.0)	16 (69.6)	52 (67.5)	0.85
Aspirin, *n* (%)	98 (98.0)	22 (95.6)	76 (98.7)	0.36
Thienopyridines, *n* (%)	71 (71.0)	17 (73.9)	54 (70.1)	0.73
Statins, *n* (%)	69 (69.0)	17 (73.9)	52 (67.5)	0.56
Beta-blockers, *n* (%)	65 (65.0)	21 (91.3)	44 (57.1)	0.002
ACE-Is and/or ARBs, *n* (%)	70 (70.0)	16 (69.6)	54 (70.1)	0.96
CCBs, *n* (%)	12 (12.0)	7 (30.4)	5 (6.5)	0.002
Nitrates, *n* (%)	7 (7.0)	7 (30.4)	0 (0.0)	<0.001
Ivabradine, *n* (%)	13 (14.0)	9 (39.1)	4 (5.2)	<0.001
Ranolazine, *n* (%)	10 (21.0)	10 (43.5)	0 (0.0)	<0.001

[a]Adherence to medical therapy refers to adherence to therapy prescribed at discharge and at follow-up visits. Follow-up therapy refers to therapy before coronary angiography for the RCA group and to therapy at last follow-up visit for the no-RCA group. ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor antagonist; CCB: calcium-channel blocker; RCA: repeated coronary angiography.

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Table 4. Univariate and multivariate logistic regression analysis for recurrence or persistence of angina and for any repeated PCI at follow-up.

	Univariate analysis			Multivariate analysis		
	ß	95% CI	*p*	ß	95% CI	*p*
Recurrence or persistence of angina						
RH-PAT index	0.14	0.04–0.56	0.005	0.13	0.03–0.57	0.006
Hypertension	4.20	0.91–19.44	0.066	3.97	0.79–19.86	0.09
Any repeated PCI						
RH-PAT index	0.31	0.09–1.03	0.057			
Diabetes	3.2	1.006–10.17	0.049			

CI: confidence interval; PCI: percutaneous coronary intervention; RH-PAT: reactive-hyperaemia peripheral-artery tonometry.

for detection of 0.81 (95% CI: 0.69–0.92, $p = 0.002$) (Figure 2(b)). Using an RH-PAT index cut-off value of 1.61, the sensitivity and specificity for the detection of recurrence of ANOCA were 77% and 78%, respectively. The AUC for detection of recurrence of AOCA was 0.70 (95% CI: 0.56–0.85, $p = 0.015$) of the RH-PAT index (Figure 2(c)). Using an RH-PAT index cut-off value of 1.725, the sensitivity and specificity for the detection of recurrence of AOCA were 67% and 71%, respectively.

Discussion

Our study investigated the predictive value of the RH-PAT index, a non-invasive technique to assess peripheral microvascular endothelial function, for repeated coronary angiography due to recurrence or persistence of angina after successful PCI with second-generation DES. Pathophysiology of angina persisting or recurring after successful PCI is complex and includes both structural and functional alterations. Structural causes include ISR, stent thrombosis, progression of atherosclerotic disease in other coronary segments and diffuse atherosclerosis without focal stenosis. Functional causes include vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction.[1] The latter are related to both endothelial dysfunction and smooth muscle cell alterations.[1]

The main findings of our study are the following: 1) repeated coronary angiography due to recurrence or persistence of angina at a median follow-up of 16 months occurred in 23% of patients after successful PCI with second-generation DES; 2) ANOCA represented a frequent cause of recurrent angina, being responsible for symptoms in 39% of patients; 3) patients with lower values of RH-PAT index had a higher rate of recurrence of angina and a lower SAQ as compared with patients with higher values and this was observed for both AOCA and ANOCA; 4) RH-PAT was the only independent predictor of repeated coronary angiography due to recurrent angina in the multivariate analysis.

Rate of angina recurrence after successful PCI

In our study 23% of patients undergoing successful PCI with second-generation DES had persistence or recurrence of angina at follow-up, in line with previous studies.[1] In the COURAGE trial, 34% of patients randomized to PCI had persistent angina at one-year follow-up,[16] and in the NHLBI Dynamic Registry enrolling patients undergoing PCI by DES[17] persistent or recurrent angina were reported by 20% of patients. Also the FAME trial[18] reported a similar rate of recurrence of angina both in the fractional flow reserve-guided PCI arm and in the angiography-guided PCI arm. Of note, recurrent angina post-PCI is associated with a significant economic burden, with total healthcare costs in the first year after the index PCI that were 1.8 times greater compared with patients without angina post-PCI.[19]

Functional mechanisms underlying recurrence of angina

In addition to ISR and significant de novo stenosis due to progression of disease in another coronary segment, vasoconstriction of epicardial coronary arteries at the site of stent implantation and/or coronary microvascular dysfunction represent potential functional causes of recurrent angina.[1] Ong et al.[20] documented an enhanced epicardial vasoconstriction, associated with reproduction of patient's symptoms, in response to intracoronary ACh administration in 51 out of 104 patients (49%) undergoing coronary angiography for post-PCI recurrent angina and found to have no significant coronary stenoses, while 18 patients (17%)

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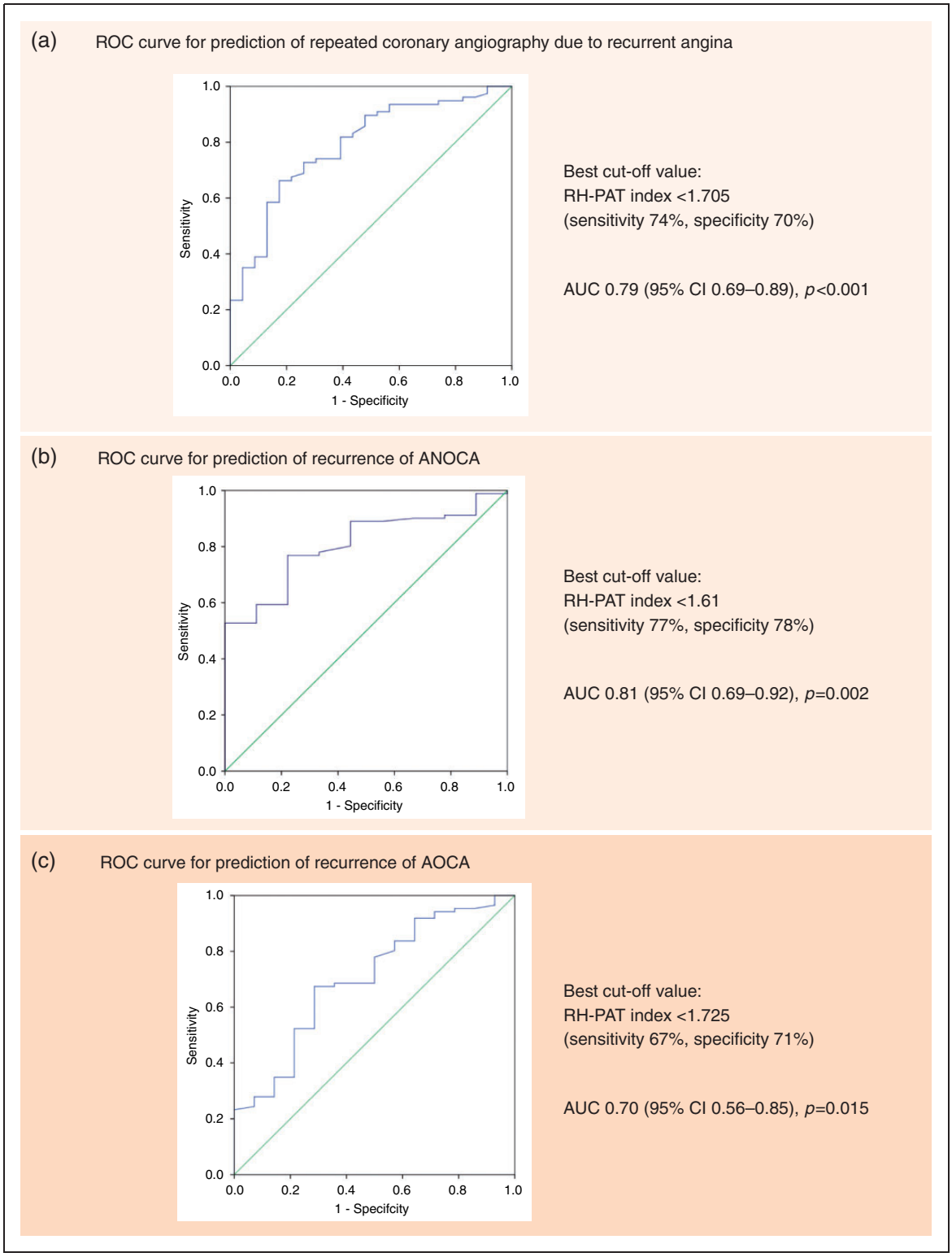

Figure 2. ROC curves of the RH-PAT index to predict repeated coronary angiography due to recurrence of angina (a), ANOCA (b) or AOCA (c).
ANOCA: angina with non-obstructed coronary arteries; AOCA: angina with obstructed coronary arteries; AUC: area under the curve; CI: confidence interval; RH-PAT: reactive-hyperaemia peripheral-artery tonometry; ROC: receiver operating characteristic.

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showed evidence of microvascular, rather than epicardial, vasoconstriction in response to intracoronary ACh. The role of coronary microvascular dysfunction in post-PCI angina has been suggested by several studies. Li et al.,[21] using the intracoronary thermodilution method, recently found a greater reduction of coronary blood flow (CBF) and a greater increase of the index of microvascular resistance in response to intravenous adenosine (140 μg/kg per min) in patients with post-PCI recurrent angina, compared with PCI patients without recurrent angina. These findings are in agreement with those by Milo et al.[22] who, using transthoracic Doppler echocardiography of the left anterior descending (LAD) coronary artery, found reduced CBF response to adenosine (140 μg/kg per min) at three- and six-month follow-up in patients with successful PCI of single-vessel disease of the LAD artery with evidence of myocardial ischaemia on treadmill EST, compared with those with negative EST. Importantly, a similar impairment of CBF response to cold pressor test also was found in this study, suggesting that both endothelium-dependent and endothelium-independent vasodilator function of coronary microcirculation were impaired in these patients.[23]

Previous studies demonstrated that the RH-PAT index on the one hand correlated with the presence of coronary endothelial dysfunction[10] and on the other with the presence of metabolic cardiovascular risk factors.[9] Moreover, a study by Matsuzawa et al.[11] demonstrated that the RH-PAT index significantly correlated with CBF response to intracoronary ACh administration and was significantly reduced in patients presenting with ANOCA who were diagnosed as having myocardial ischaemia by simultaneous measurement of coronary flow and cardiac lactate production. In contrast, a study of Michelsen et al.[24] demonstrated that the RH-PAT index failed to correlate with endothelium-independent coronary flow reserve in women with ANOCA, suggesting that the RH-PAT index may represent a reliable tool to assess endothelial-dependent rather than endothelial-independent vasodilator function of coronary microcirculation.

Taken together these findings suggest that the functional alterations responsible for persistence or recurrence of angina after successful PCI are multiple and complex and include impairment of both endothelium-dependent and endothelium-independent coronary vasodilatory function as well as enhanced susceptibility to vasoconstrictor stimuli, similarly to what has been described in patients with primary microvascular angina.[25] It is likely that these alterations operate in all patients with persistence or recurrence of angina after successful PCI, although their relevance is probably different in different patients. It is also well established that endothelial dysfunction plays an important role in patients with recurrence of angina caused by ISR and/or progression of atherosclerosis in non-treated epicardial segments. Thus, it is not surprising that the RH-PAT index, a simple non-invasive marker of endothelial dysfunction, is able to predict the persistence or recurrence of angina and/or ischaemia after successful PCI. Nevertheless this is the first study, to the best of our knowledge, to suggest that this simple approach might be clinically useful in this clinical setting.

Limitations

Our study has some limitations. First, this is a single-centre study with a relatively small number of enrolled patients. Larger studies are needed in order to evaluate the association of endothelial dysfunction with clinical endpoints in the current DES era. Second, we did not perform during repeated coronary angiography any invasive test in order to demonstrate a reduced coronary flow reserve or the occurrence of epicardial or microvascular spasm. Thus, an extracardiac cause of chest pain cannot be excluded. However, along with recurrence of angina, all ANOCA patients had a positive EST, while AOCA patients had typical angina and/or a positive EST along with significant stenosis at coronary angiogram. Third, we enrolled patients undergoing PCI for both stable angina and ACS. However, clinical presentation did not predict recurrence of angina nor correlate with different RH-PAT index values. Moreover, we performed RH-PAT index assessment at discharge and we cannot exclude any interference of peri-procedural myocardial necrosis in the RH-PAT measurement. However, baseline and post-procedural high-sensitivity troponin T levels did not differ across RH-PAT index tertiles. Finally, we did not perform RH-PAT index assessment at follow-up. Further studies evaluating the RH-PAT index according to changes in medical therapy or in symptoms occurrence are warranted.

Conclusions

In conclusion, our study demonstrates that non-invasive assessment of peripheral endothelial dysfunction using the RH-PAT index might help in predicting the risk of repeated coronary angiography due to recurrent angina after successful PCI, thus suggesting the opportunity of a more intense treatment including high dose statins, potent dual antiplatelet therapy and intense risk factor control in patients with lower RH-PAT index values.[26,27] Moreover, also chronic aerobic exercise demonstrated favourable effects on endothelial function and should be considered in these patients at follow-up.[28,29] Interventional trials are warranted to test these working hypotheses.

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Author contribution

RAM, GN and FC contributed to the conception or design of the work; RAM, GN, FV, VV, MR, FM, FF, IP, AML, FB, DD, CA, CT, GAL and FC contributed to the acquisition, analysis, or interpretation of data for the work; RAM, GN, GAL and FC drafted the manuscript; RAM, GN, FM, IP, AML, DD, CA, CT, GAL and FC critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Study supported by a research grant from Abbott Vascular, Santa Clara, CA.

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