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Assessment of the area at risk after acute myocardial infarction using ^{123}I -MIBG SPECT: Comparison with the angiographic APPROACH-score

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Background. Assessment of the area at risk (AAR) associated with an acute myocardial infarction is crucial for evaluating prevention and revascularization strategies. The aim of this study was to evaluate whether ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) single-photon emission computed tomography (SPECT) provides a more widely available assessment of anatomical AAR than the established anatomical angiographic methods.

Methods. Seventy patients with ST-segment elevation acute myocardial infarction (STEMI) underwent coronary angiography with percutaneous coronary intervention and subsequent ^{123}I -MIBG myocardial scintigraphy with left myocardial relative radiotracer uptake evaluation 12 \pm 10 days after STEMI. Patients were divided into two groups depending on whether the culprit artery was occluded (50 patients) or sub-occluded (20 patients). Two scores were calculated as a percentage of the left ventricular myocardium surface, the first using a standard 17-segment summed rest score derived from the relative quantitative evaluation of ^{123}I -MIBG myocardial uptake (MAR) and the second using the modified APPROACH-score (ApAR).

Results. For the patients with occluded artery, this study showed a high correlation between MAR and the angiographic score (Pearson $r = .762$ and $P < .0001$). For the patients with sub-occluded artery, for which the ApAR is not reliable, this study showed no correlation between MAR and the angiographic score (Pearson $r = .18$ and $P = 0.45$).

Conclusions. ^{123}I -MIBG myocardial scintigraphy provides ARR assessment similar to that of ApAR in patients with a single occluded coronary artery. However, MAR differs from ApAR when angiographic scores are known to be inaccurate (sub-occluded culprit artery) or impossible to use. Further studies are needed to evaluate the potential clinical interest of ^{123}I -MIBG SPECT as an alternative for area at risk assessment after STEMI even when the culprit artery is sub-occluded or when the angiographic scores cannot be used.

Key Words: Myocardial infarction • area at risk • ^{123}I -MIBG SPECT • coronary angiography

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Abbreviations

AAR	Area at risk
ApAR	Modified APPROACH-score evaluation of the area at risk
MAR	¹²³ I-MIBG evaluation of the area at risk
LV	Left ventricle
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation acute myocardial infarction
¹²³ I-MIBG	¹²³ I-metaiodobenzylguanidine
SPECT	Single-photon emission computed tomography
CZT	Cadmium-zinc-telluride
MSA	Mean segmental activity
MRI	Magnetic resonance imaging

See related editorial, pp. 581–585

INTRODUCTION

Acute occlusion of an epicardial coronary artery leads to a transmural progression of cell death (i.e., infarct zone),¹ spreading from the subendocardium to the subepicardial layers, within the ischemic myocardium supplied by the culprit artery (i.e., area at risk).^{2,3}

The area at risk (AAR) is defined as the physiological area with ischemic stress induced by the acute occlusion of a coronary artery. Duration of ischemia and collateral flow are the major determinants of infarct size. An accurate assessment of AAR is crucial to study the reduction in the infarct size (i.e., myocardial salvage) provided by cardioprotective interventions in patients with ST-segment elevation myocardial infarction (STEMI).^{4,5} Importantly, the benefits of protective interventions increase with the size of the patient's AAR.⁶⁻⁹ Up to now, injection of perfusion radioactive tracers prior to reopening the occluded coronary artery by primary percutaneous coronary intervention (PCI) has remained the gold standard for assessing AAR in animal studies.¹⁰ However, this approach is not applicable in the routine clinical settings of an emergency department receiving patients with STEMI, as it requires radioactive tracer injection prior to reperfusion. Cardiac magnetic resonance that visualizes infarct-related edema,^{11,12} angiographic BARI, and APPROACH scores¹³⁻¹⁸ have thus been proposed as alternatives to estimate AAR.

The modified APPROACH-score (ApAR) is based on a score developed at Green Lane Hospital, Auckland, New Zealand.¹³⁻¹⁸ This anatomical approach estimates the myocardial area suffering from ischemia during an

acute myocardial infarction using a semi-automatic quantification method. It assumes that the proportion of left myocardium jeopardized during an acute myocardial infarction is dependent on the length and size of the branches of the culprit coronary artery only. This method has the advantage of allowing for a retrospective analysis of AAR based on clinical angiographic results. The ApAR score provides independent prognostic information for patients with STEMI treated with percutaneous intervention¹⁶ and is correlated with MRI when the artery responsible for the STEMI is the left anterior descending artery, the left circumflex artery, or the right coronary artery.¹⁷ Thus, it is used in clinical research when physicians need to evaluate a new drug or PCI procedure aimed at decreasing the jeopardized myocardium surface or the infarct size.¹⁸ However, although modified APPROACH-score takes into account the culprit coronary artery, it does not take into account the other coronary lesions, collateral flow, residual flow in the culprit artery (sub-occluded artery), or metabolic factors that may modulate the perfusion of AAR. Therefore, the APPROACH-score is likely to overestimate AAR in these usual situations. Moreover, the algorithm described in Ref¹⁴ to calculate the modified APPROACH-score provides neither models nor quantified data to evaluate the area at risk for culprit lesions on diagonal, obtuse marginal, posterior descending or posterolateral arteries. For these reasons, most studies using the ApAR to evaluate the area at risk after myocardial infarction concern only culprit lesions on the left anterior descending, left circumflex or right coronary arteries, and exclude culprit lesions on diagonal, marginal, posterior descending or posterolateral arteries, and patients with evidence of collateral flow (Rentrop grade > 1) supplying the area at risk.^{17,18}

The sympathetic nervous system has great influence on cardiovascular physiology. The norepinephrine analog metaiodobenzylguanidine (MIBG) labeled with ¹²³I is widely used and validated as a marker of adrenergic neuronal function.^{19,20} Alterations in myocardial sympathetic activity can be assessed by ¹²³I-MIBG imaging to predict the prognosis in heart failure,²¹⁻²³ in particular as an independent predictive value for arrhythmic events^{24,25} and cardiac death.^{21,26,27} Moreover, as neuronal tissue is more sensitive to ischemia than myocardial cells,²⁸⁻³⁰ single-photon emission computed tomography (SPECT) using ¹²³I-MIBG after STEMI is also a valuable tool for identifying AAR or at least a myocardial area consistently and reliably included in AAR (appearing as relative uptake defects). Thus, cardiac ¹²³I-MIBG SPECT performed soon after treatment of STEMI in a cardiologic intensive care unit can be used to assess AAR based on the sensitivity of neuronal cells to ischemia only, without assuming any coronary model or hypotheses on the

location of the coronary lesions.³¹ This may provide a physiological measurement that incorporates not only an evaluation of the surface of the jeopardized myocardium, but also a measurement of the severity of the ischemia affecting this surface.

The present study aimed to evaluate the AAR quantification given by ¹²³I-MIBG myocardial scintigraphy compared to that provided by the APPROACH-score in patients with a single left anterior descending, left circumflex, or right coronary-occluded artery and without collateral flow. A secondary objective was to test whether ¹²³I-MIBG myocardial SPECT and the APPROACH-score differed in AAR assessment in a subgroup of patients for whom angiographic scores are known to be inaccurate (sub-occluded culprit artery).

MATERIAL AND METHODS

Between January 2014 and May 2015, all patients with STEMI referred to the intensive care unit of the Department of Cardiology of Montpellier University Hospital for primary coronary intervention were prospectively considered for the study. STEMI was defined as a new ST elevation in two contiguous leads of >0.1 mV in all leads other than leads V2-V3, and for leads V2-V3 ≥ 0.15 mV in women and ≥ 0.2 mV and 0.25 mV in men ≥ 40 years and < 40 years, respectively.

Exclusion criteria included previous history of myocardial infarction, heart failure, dilated or hypertrophic cardiomyopathy, ventricular arrhythmias, Parkinson's disease, psychiatric disease, and any medication with a known potential effect on MIBG uptake before admission to the Department of Cardiology. Among the 96 patients without exclusion criteria considered for the study, 20 were excluded because of the incompatibility of their culprit lesion topography with the assessment of the APPROACH-score (culprit lesions on the diagonal, obtuse marginal, posterior descending artery, and posterolateral artery). Three additional patients were excluded because of a major collateral flow, which would have made irrelevant the angiographic estimation of AAR related to the culprit lesion. Three additional patients refused to undergo the SPECT study. Finally, after appropriate therapy (coronary revascularization and medical treatment), 70 patients were prospectively enrolled and underwent myocardial sympathetic innervation SPECT. The clinical characteristics of the population are described in Table 1. The 70 patients without collateral flow for whom the modified APPROACH-score could be calculated were divided into two categories: the first group included 50 patients with a completely occluded artery at the time of PCI, and the second group included 20 patients with a sub-occluded artery at the time of PCI (TIMI flow >0). For all patients, the modified APPROACH-score was calculated, with investigators blinded to the ¹²³I-MIBG scintigraphic results.

All procedures were in accordance with institutional guidelines. The study was approved by the local ethics committee and the requirement for individual informed consent was waived.

Table 1. Characteristics of the population (number (%), standard deviation)

Age (years)	59 \pm 12
Male (%)	51 (73)
Smokers (%)	34 (49)
Diabetes mellitus (%)	9 (13)
Dyslipidemia (%)	20 (29)
Family history (%)	10 (14)
Height (cm)	169 \pm 14
Weight (kg)	79 \pm 18
BMI (kg/m ²)	26.1 \pm 3.5
Left ventricular ejection fraction (%)	40.1 \pm 12.0
MIBG heart-to-mediastinum ratio	1.58 \pm 0.17

Coronary Angiography

All subjects underwent coronary angiography following a standard catheterization procedure with multiple selective contrast injection into the right and left coronary artery system and a PCI on the culprit lesion. The mean delay between the onset of the symptoms and the PCI was 11 hours and was under 3 hours for 38 patients (54%) and under 24 hours for 62 (89%).

All subjects received at least one stent. Anterograde flow in the infarct-related artery before and after PCI was characterized using the TIMI system. None of the patients included was eligible for coronary artery bypass grafting. All angiographies were reviewed by a single angiographer in order to evaluate the size of the arteries involved in the modified APPROACH-score and to derive this score for all the patients included in the study. This score evaluates the percentage of jeopardized left ventricular myocardium volume and depends on the culprit lesion location, dominance, and major side-branch size of the infarct-related artery, according to the modified APPROACH-score as explained in Ref.¹⁴

¹²³I-MIBG Scintigraphy

The mean delay between ¹²³I-MIBG scintigraphy and PCI was 13 \pm 7 days. All ¹²³I-MIBG SPECT studies were performed in the first month following PCI, with patients in the supine position with arms over the head and using a cardiac-dedicated multi-pinhole cadmium-zinc-telluride (CZT) camera (Discovery NM 530c, GE Healthcare, Tirat Camel, Israel). Tomographic myocardial sympathetic innervation scintigraphy was performed with the following acquisition parameters: list mode, 32 \times 32 matrix size, pixel size—4 mm. No scatter or attenuation correction was performed. All patients underwent a rest intravenous administration of 185 MBq of ¹²³I-MIBG 3 hours before myocardial SPECT.³¹ An additional planar acquisition using an INFINIA Hawkeye gamma camera (GE Healthcare, Tirat Camel, Israel) was performed to quantify the late heart-to-mediastinum ratio.

Myocardial ^{123}I -MIBG bull's eye images were divided into 17 segmental regions.³² Each segment was scored independently using a five-point model depending on the mean segmental activity (MSA) expressed as a ratio of the maximal myocardial activity (0: $\text{MSA} \geq 70\%$; 1: $50 \leq \text{MSA} < 70\%$; 2: $30 \leq \text{MSA} < 50\%$; 3: $10 \leq \text{MSA} < 30\%$; 4: $\text{MSA} < 10\%$).³² The 17 segmental scores were summed and the ^{123}I -MIBG area at risk (MAR) was defined as this summed score *S* expressed as a percentage of the maximum possible score: $\text{MAR}(\%) = 100.S/68$.

Statistical Analysis

The agreement between angiographic estimates of anatomical AAR using the modified APPROACH-score (ApAR) and the ^{123}I -MIBG area at risk (MAR) was assessed in two groups: patients with occluded and patients with sub-occluded arteries. Agreements were assessed using Pearson's correlation, the standard error of the estimate, and Bland-Altman analysis.^{33,34} A two-tailed *P* value $<.05$ was considered statistically significant.

RESULTS

According to coronary angiography, 19 patients had 3-vessel disease (27.1%), 26 had 2-vessel disease (37.2%), and 25 had 1-vessel disease (35.7%). Left ventricular ejection fraction was $40.1\% \pm 12.0\%$ (range 17%-66%) at the time of PCI. The late heart-to-mediastinum ratio was 1.58 ± 0.17 (range 1.25-2.01). All patients included in the study had at least three myocardial segments (18% of the myocardial surface) with an ^{123}I -MIBG uptake significantly higher than that in the mediastinum.

Table 2 shows the anatomic angiographic characteristics of the population in relation to the culprit lesion.

A culprit lesion in the left anterior descending artery was found in 40 patients (57% of the population), with 29 occlusions and 11 sub-occlusions (72% and 28%). A culprit lesion in the left circumflex artery was found in 7 patients (10% of the population), with 4 occlusions and 3 sub-occlusions (57% and 43%). A culprit lesion in the right coronary artery was found in 23 patients (33% of the population), with 17 occlusions and 6 sub-occlusions (74% and 26%). The average MAR was calculated for the global population with occluded and sub-occluded patients according to the occlusion site.

Area at risk assessed with ApAR and MAR in patients with an occluded artery

Fifty of the 70 patients included in the study had an occluded culprit artery with no TIMI flow. MAR was highly correlated with ApAR in these patients: Pearson $r = .76$, $P < .0001$ (Figure 1). Bland-Altman analysis showed no correlation between the average and the difference of ApAR and MAR (Pearson correlation $r = .19$, $P = 0.18$). A mean difference ApAR-MAR of -3.5% of jeopardized left ventricular myocardial volume was found with a 95% confidence interval: $[-11.1\%; 4.2\%]$. The standard error of measurement (SEM) was 1.1%. The Bland-Altman analysis showed good agreement between the two AAR measurement methods. The same good correlations (Figure 2) were found in the subgroups of patients with 1-vessel disease (17 patients, Pearson $r = .64$, $P < .01$), 2-vessel disease (18 patients, Pearson $r = .80$, $P < .01$), and 3-vessel disease (15 patients, Pearson $r = .68$, $P < .01$). ApAR and MAR identified the same myocardial walls as areas at risk for all 50 patients with an occluded culprit artery.

Table 2. Angiographic anatomical culprit lesion localization and ^{123}I -MIBG evaluation of the area at risk (MAR) defined by a ^{123}I -MIBG defect (mean \pm SD)

Culprit lesion localization	Occlusion	Occluded group: MAR (%)	Sub-occlusion	Sub-occluded group: MAR (%)
LAD (n = 40)	29	39 \pm 8	11	24 \pm 12
Proximal (n = 22)	14	43 \pm 7	8	21 \pm 9
Mid (n = 17)	14	35 \pm 9	3	27 \pm 18
Distal (n = 1)	1	34 \pm 0	0	
LCX (n = 7)	4	31 \pm 5	3	30 \pm 14
Proximal (n = 6)	4	24 \pm 6	2	35 \pm 18
Mid (n = 1)	0		1	22 \pm 0
RCA (n = 23)	17	26 \pm 6	6	31 \pm 16
Proximal (n = 10)	9	24 \pm 7	1	31 \pm 0
Mid (n = 8)	6	28 \pm 5	2	14 \pm 16
Distal (n = 5)	2	29 \pm 3	3	26 \pm 16

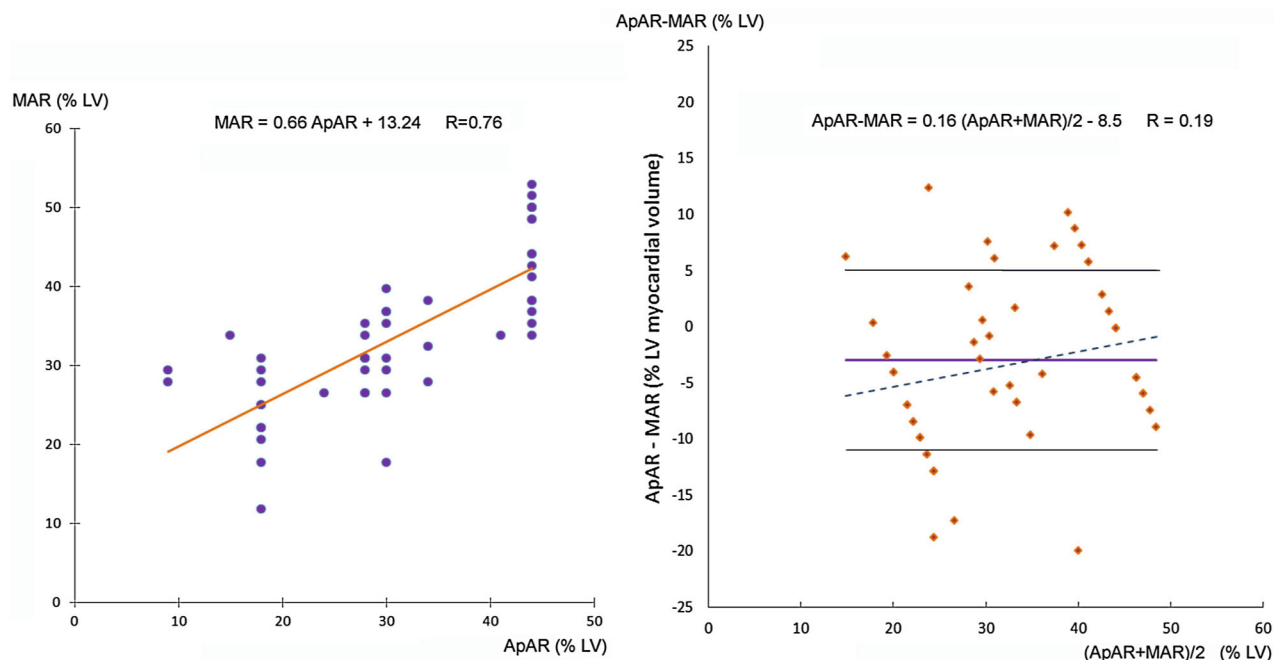


Figure 1. ^{123}I -MIBG defect area vs APPROACH-score for occluded culprit artery (with MAR, ^{123}I -MIBG area at risk; ApAR, anatomical area at risk with modified APPROACH-score; LV, left ventricle). In the Bland-Altman analysis, the *central purple continuous line* represents the mean difference between the two techniques (ApAR and MAR,) and the limits of agreement are given by the mean difference ± 2 standard deviations of the difference (*black lines*). The *dotted line* represents the linear regression line between the difference and the arithmetic mean of the two measures.

Patients were analyzed in subgroups according to echocardiographic left ventricular ejection fraction (EF) and culprit lesion location. MAR and ApAR correlated fairly well for patients with $\text{EF} \leq 30\%$ (10 patients, $r = .62$, $P < .05$), $30\% < \text{EF} < 50\%$ (30 patients, $r = 0.73$, $P < .05$), and $\text{EF} \geq 50\%$ (10 patients, $r = .73$, $P < .05$). In the subgroup of 29 patients with an occluded left anterior descending artery, MAR and ApAR correlated well ($r = .57$, $P < .05$). This correlation analysis was not done for the patients with right or left circumflex coronary artery occlusions as all of them had medium posterior descending and posterolateral arteries and thus identical ApAR.

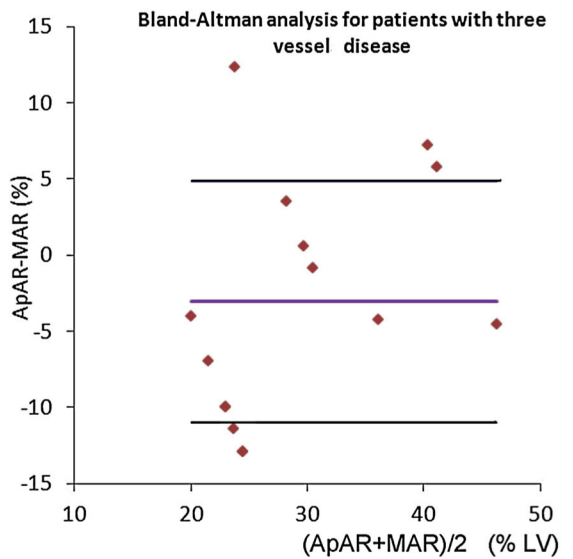
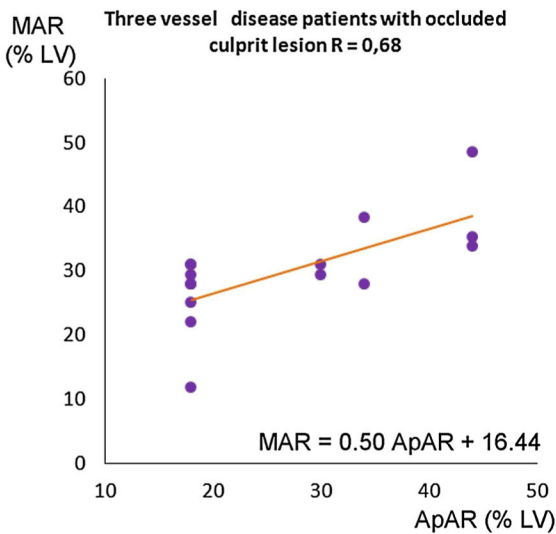
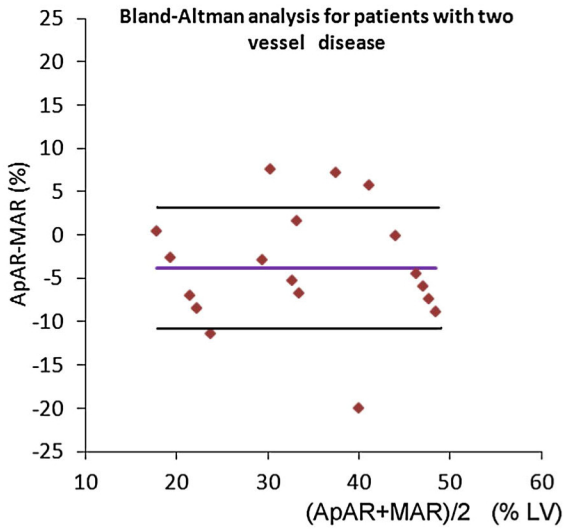
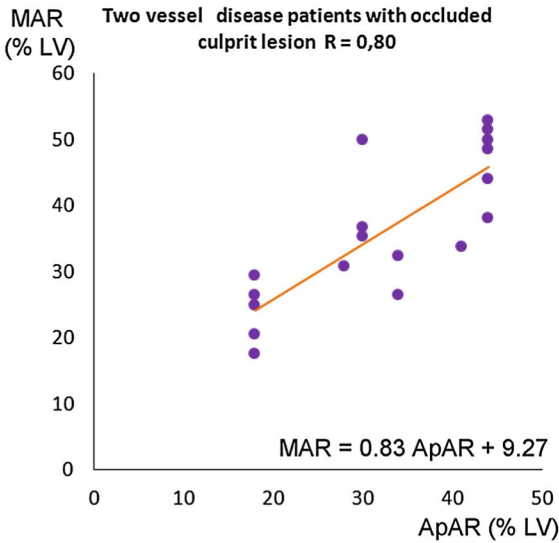
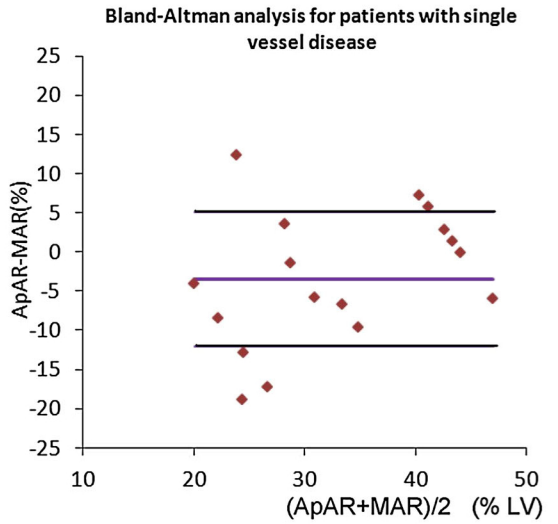
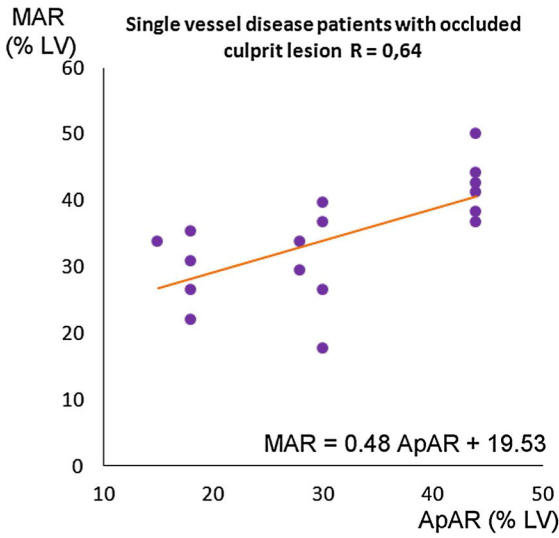
Area at risk assessed with ApAR and MAR in patients with a sub-occluded artery

In the twenty patients with a sub-occluded culprit artery (TIMI flow > 0), MAR did not correlate with ApAR (Pearson $r = .18$, $P = .45$; Figure 3). In this subgroup of patients, Bland-Altman analysis showed a lack of agreement between the two AAR measurement methods and a significant correlation between the average and the difference of the two AAR evaluations ($r = 0.84$ and $P < .0001$). A mean difference ApAR-

MAR of 4.5% of jeopardized left ventricular myocardial volume was found with a 95% confidence interval: $[-18.9\%; 27.9\%]$. The standard error of measurement was 5.2%. ApAR and MAR identified the same myocardial walls as areas at risk for all but one of the 20 patients with a sub-occluded culprit artery. This single patient for whom the location of the AAR differed had a sub-occlusion of the proximal left anterior descending artery with a normal MIBG SPECT, and thus no significant AAR using MIBG, whereas the APPROACH-score was 44.5% in the anterior wall.

Follow-up

None of the patients included in the study died nor had any severe cardiovascular event, including new rhythmic events, during a follow-up of 2 years ± 4 months. Thirty-five of the 70 patients included in the study (50%) agreed to a second MIBG SPECT evaluation after an average follow-up of 1 year and 5 months (SD = 4 months). The mean difference between the area at risk evaluated from the first (MAR₁) and second MIBG SPECT (MAR₂) was $\text{MAR}_2 - \text{MAR}_1 = 5.2\%$ (SD = 9.4%) of the left ventricular surface—that is, less than the surface of 1 segment in the usual



◀ **Figure 2.** ^{123}I -MIBG defect area vs APPROACH-score for patients with occluded culprit artery. (With MAR, ^{123}I -MIBG area at risk; ApAR, anatomical area at risk with modified APPROACH-score; LV, left ventricle). In the Bland-Altman analyses, the *central purple continuous line* represents the mean difference between the two techniques (ApAR and MAR), and the limits of agreement are given by the mean difference ± 2 standard deviations of the difference (*black lines*). The *dotted line* represents the linear regression line between the difference and the arithmetic mean of the two measures.

17-segment analysis. The difference was below 1 segment (6% of the ventricular surface) for 17 patients (49%), between 1 and 2 segments (6-12% of the ventricular surface) for 8 patients (23%), and between 1 and 2 segments (12-18% of the ventricular surface) for 10 patients (29%). Among the 18 patients whose MAR differed by more than one segment, the MAR score decreased for 3 patients (-11%, -12% and -18%) and increased for 15 (mean = $+13.4\% \pm 5.7\%$).

DISCUSSION

In patients with an occluded culprit artery, this study shows high correlation between ApAR and MAR. In this situation where the APPROACH hypotheses are

fulfilled, ^{123}I -MIBG scintigraphy can be used reliably to estimate AAR in the month following an acute myocardial infarction. The analysis of the subgroups of patients with multi-vessel disease (1-vessel disease compared with 2-vessel or with 3-vessel disease) but a single occluded culprit artery showed similar correlation coefficients and similar slopes. Thus, in the population studied, the ^{123}I -MIBG scintigraphy did not overestimate AAR compared with the angiographic score, even when sub-occluded arteries were found by coronary angiography in addition to the culprit lesion.

It is important to note that these results were obtained using SPECT data acquired in the month following PCI and the assessment of the APPROACH-score, indicating that MAR evaluation is possible in routine clinical settings where the patient has to recover from an acute myocardial infarction sufficiently to leave the intensive care unit in order to undergo a scintigraphic examination. This relative stability of MAR over time was confirmed by the relatively small mean modification of the MAR ($+5.2\%$ of the ventricular surface) observed during an average follow-up of 1 year and 5 months.

On the other hand, the lack of correlation between ApAR and MAR in the 20 patients with sub-occluded arteries indicates that MAR provides results that differ from the angiographic scores when these are inadequate

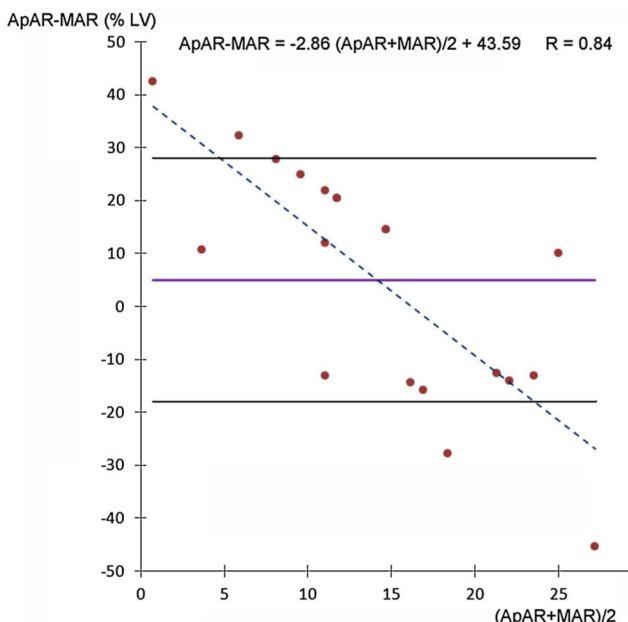
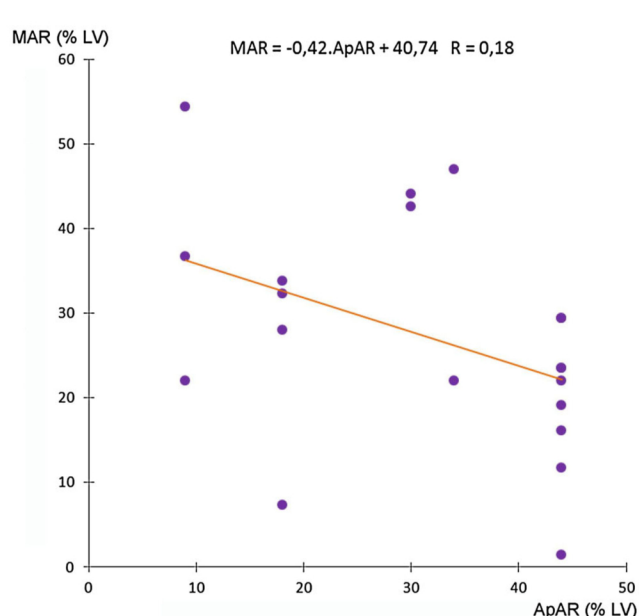


Figure 3. ^{123}I -MIBG defect area vs APPROACH-score for sub-occluded culprit artery (with MAR, ^{123}I -MIBG area at risk; ApAR, anatomical area at risk with modified APPROACH-score; LV, left ventricle). In the Bland-Altman analysis, the *central purple continuous line* represents the mean difference between the two techniques (ApAR and MAR) and the limits of agreement are given by the mean difference ± 2 standard deviations of the difference (*black lines*). The *dotted line* represents the linear regression line between the difference and the arithmetic mean of the two measures.

because of residual flow in the culprit artery. For 12 of these patients, ApAR was higher than MAR, indicating that the myocardial area supplied by the sub-occluded culprit coronary artery was larger than the effective ischemic area detected using ^{123}I -MIBG SPECT. In contrast, 8 patients had a MAR estimation that was higher than ApAR. For 7 of these patients, the angiographic study indicated additional coronary arterial lesions that were not related to the infarct area (2- or 3-vessel disease). In these cases, the loss of integrity of the presynaptic neurons might have been induced by the global ischemic stress associated with several sub-occluded coronary arteries, including the acute culprit lesion.

The specific insight into AAR provided by ^{123}I -MIBG SPECT could help cardiologists in their revascularization strategies, which is currently a bone of contention in the interventional field,³⁵⁻³⁷ especially when ApAR is inappropriate or inaccurate. In the population of the present study, this situation occurred for 43 patients (20 patients with culprit lesion topography incompatible with ApAR, 20 patients with sub-occluded culprit lesions, and 3 patients with major collateral flow) among the 96 patients considered at inclusion (43%).

Moreover, the potentially inadequate angiographic estimation of AAR using ApAR in studies investigating cardioprotective strategies in patients with non-occluded arteries could explain some of the negative results.³⁸

In addition, the possibility of associating ^{123}I -MIBG and ^{201}Tl viability SPECT in routine clinical settings using a one-shot dual-isotope examination³¹ provides a direct comparative analysis of AAR and the necrotic area that may be useful in assessing the myocardial salvage provided by protective interventions in patients with STEMI.

Thus, the physiological uptake of ^{123}I -MIBG in ischemic adrenergic neurons may allow AAR assessment that does not depend on the restrictive hypotheses assumed by ApAR.

LIMITATIONS

The main limitation of this study was the lack of cardiac magnetic resonance imaging (MRI), due to its limited availability in the emergency situations of the study protocol. The preliminary results of this paper should encourage further studies with several typologies of coronary lesions in association with cardiac MRI studies to confirm the interest of ^{123}I -MIBG in the evaluation of AAR after STEMI, especially in the situations where angiographic scores are inappropriate. Moreover, further studies with a larger population and longer follow-up are needed to discriminate the potential

incremental value of APPROACH or MAR scores beyond traditional cardiovascular risk factors.

NEW KNOWLEDGE GAINED

This study found that ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) myocardial SPECT provides results similar to the angiographic APPROACH-score in the limited clinical situations where this score is reliable, and it can thus be regarded as a valuable tool for area-at-risk evaluation in patients with a single occluded coronary artery.

CONCLUSIONS

Besides the usefulness of ^{123}I -MIBG SPECT in assessing AAR in patients with a single occluded coronary artery, the physiology of MIBG uptake after STEMI suggests that further studies including MRI assessment and follow-up of patients after STEMI are needed to evaluate the potential interest of ^{123}I -MIBG SPECT as an alternative for the area-at-risk assessment after STEMI even when the culprit artery is sub-occluded or when the angiographic scores cannot be used. These studies are necessary to provide the physicians with valuable tools for the clinical evaluation of new myocardial salvage procedures during PCI.

Disclosures

There is no conflict of interest to declare.

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