Prognostic impact of location and extent of vessel-related ischemia at myocardial perfusion scintigraphy in patients with or at risk for coronary artery disease

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Background. **Myocardial perfusion scintigraphy (MPS) has an established diagnostic and prognostic role in patients with or at risk for coronary artery disease, with ischemia severity and extent having already been identified as key predictors. Whether this is affected by the location of myocardial ischemia is uncertain. We aimed at comparing the prognostic outlook of patients undergoing MPS according to the site of ischemia.**

Methods. **Our institutional database was queried for subjects undergoing MPS, without myocardial necrosis or recent revascularization. We focused on the prognostic impact of location of vessel-related ischemia (VRI) at MPS, distinguishing four mutually exclusive groups: single-VRI involving left anterior descending (LAD), single-VRI not involving LAD, multi-VRI involving LAD, and multi-VRI not involving LAD. The primary outcome was the long-term (>1 year) rate of death or myocardial infarction (D/MI).**

Results. **A total of 13,254 patients were included. Moderate or severe VRI occurred in 2,627 (20%) patients. Clinical outcomes were significantly different among the groups of patients with moderate or severe VRI, including death, cardiac death, non-fatal myocardial infarction or their composites (overall $P < .001$). Specifically, and excluding subjects undergoing revascularization as first follow-up event, D/MI occurred in 8.4% of patients with single-VRI involving LAD, 5.5% of subjects with single-VRI not involving LAD, 16.5% of those with multi-VRI involving LAD, and 7.3% of patients with multi-VRI not involving LAD (overall $P < .001$). Even at incremental multivariable Cox proportional analysis, hierarchical VRI was independently associated with an increased risk of D/MI [hazard ratio = 1.17 (1.04-1.08) for each class increment, $P = .010$].**

Conclusions. **Location and extent of myocardial ischemia at MPS according to the VRI concept have a hierarchical predictive impact, with multi-VRI involving LAD being significantly and independently more prognostically ominous than other types of VRI. (J Nucl Cardiol 2016;23:274–84.)**

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INTRODUCTION

Non-invasive imaging tests are a cornerstone in the diagnostic and prognostic work-up of patients with or at risk for coronary artery disease (CAD).[1] Stress/rest myocardial perfusion scintigraphy (MPS) is particularly useful in this setting, as it can combine exercise testing (or pharmacologic stress) with accompanying ECG analysis to detailed multiparametric imaging aimed at quantifying the severity, location, and extent of reversible (i.e., myocardial ischemia) as well as irreversible deficits (i.e., necrosis), enabling a precise three-dimensional characterization of myocardial pathophysiology.[2] Indeed, the prognostic impact of moderate or severe ischemia at MPS is well established,[2-4] and the same applies to extent of ischemia.[5,6]

Demonstration at coronary angiography of a significant stenosis involving the left anterior descending (LAD) has a key impact on prognosis and ensuing management strategy.[7-9] Yet, there is uncertainty on the precise impact of location of ischemia at MPS, as no study has explicitly compared the risk conferred by myocardial ischemia proven at MPS involving regions with LAD disease.[10]

We thus aimed at comparing the mid- and long-term prognosis of patients with or at risk of CAD and scintigraphic evidence of moderate or severe myocardial ischemia in regions typically associated with coronary artery disease in the LAD.

METHODS

This was a retrospective observational study exploiting prospectively collected data entered into a dedicated administrative database (OPCCardioPro, ETISAN, Rome, Italy).[4] All patients provided written informed consent for imaging test and data collection, and the competent authority was notified in keeping with national regulations.

Patients undergoing MPS for the diagnostic or prognostic work-up of CAD since 2004 at our center were identified, excluding those aged <18 years, ineligible for 1-year clinical follow-up, or having a history of coronary revascularization within the last 6 months before MPS. In addition, we a priori excluded all patients with scintigraphic evidence of myocardial necrosis. Subjects were exercised in a fasting state having discontinued long-acting nitrates and beta-blockers for ≥24 hours. Symptom-limited dynamic stress testing was performed on a bicycle ergometer according to a standard protocol. Subjects unable to exercise underwent pharmacologic stress testing with dipyridamole. ^{201}Tl and ^{99m}Tc-methoxy isobutyl isonitrile were used for peak and rest single photon emission computed tomography (SPECT) according to standard protocols.[4] A dual-head gamma camera (Millennium MG or Millennium MyoSIGHT, GE Healthcare, Milan, Italy), equipped with a low-energy, general-purpose collimator, was used.

Seven regions were graphically obtained to quantify the degree of myocardial perfusion, stemming from the established yet more fragmented segmentation approaches,[11,12] as this method is in keeping with the anatomic distribution of the main coronary vessels[4]: (1) apical (thus including the apical anterior, apical septal, apical inferior, apical lateral, and apex segments), (2) antero-medio-distal (including the mid anterior segment), (3) antero-proximal (including the basal anterior segment), (4) septal (including the basal anteroseptal, basal inferoseptal, mid anteroseptal, and mid inferoseptal segments), (5) postero-lateral (including the basal antero-lateral and mid antero-lateral segments), (6) lateral (including the basal inferolateral and mid inferolateral segments), and (7) inferior (including the basal inferior and mid inferior segments). Specifically, region 5 is labeled postero-lateral to avoid implying its blood flow that is provided by the LAD or its diagonal branches. Location and extent of vessel-related ischemia (VRI) at MPS were categorized as follows: VRI involving LAD when regions 1, 2, 3, or 4 ischemic; VRI involving LCX territory when regions 5 or 6 were ischemic; and VRI involving RCA when only region 7 or both regions 6 and 7 were ischemic. Accordingly, the variable combinations of VRI subtypes were used to define 4 separate groups of patients: single-VRI involving LAD, single-VRI not involving LAD, multi-VRI involving LAD, and multi-VRI not involving LAD (Figures 1 and 2).

Semiquantitative interpretation of stress/rest images was performed based on the above 7-region model by consensus of 2 experienced observers using both visual assessment of the color-coded tomographic images for the 3 axes and the standard deviation (SD) polar map of detectable tracer uptake, finally obtaining for each region a 5-point scoring system (0, normal uptake; 1, minimally reduced uptake; 2, mildly reduced uptake; 3, moderately reduced uptake; and 4, severely reduced or absent uptake). This score directly yielded the 5 classes of maximal ischemia score (MIS): (0) no ischemia; (1) minimal ischemia; (2) mild ischemia; (3) moderate ischemia; and (4) severe ischemia, with the final MIS strictly depending on the worst region of perfusion. For the purpose of this work, we distinguished 3 main groups of regions (and thus patients), those without ischemia (score 0), those with minimal or mild ischemia (scores 1 or 2), and those with moderate or severe ischemia (scores 3 or 4), then focusing explicitly on the latter group for VRI analyses. This approach at MPS, combining in a

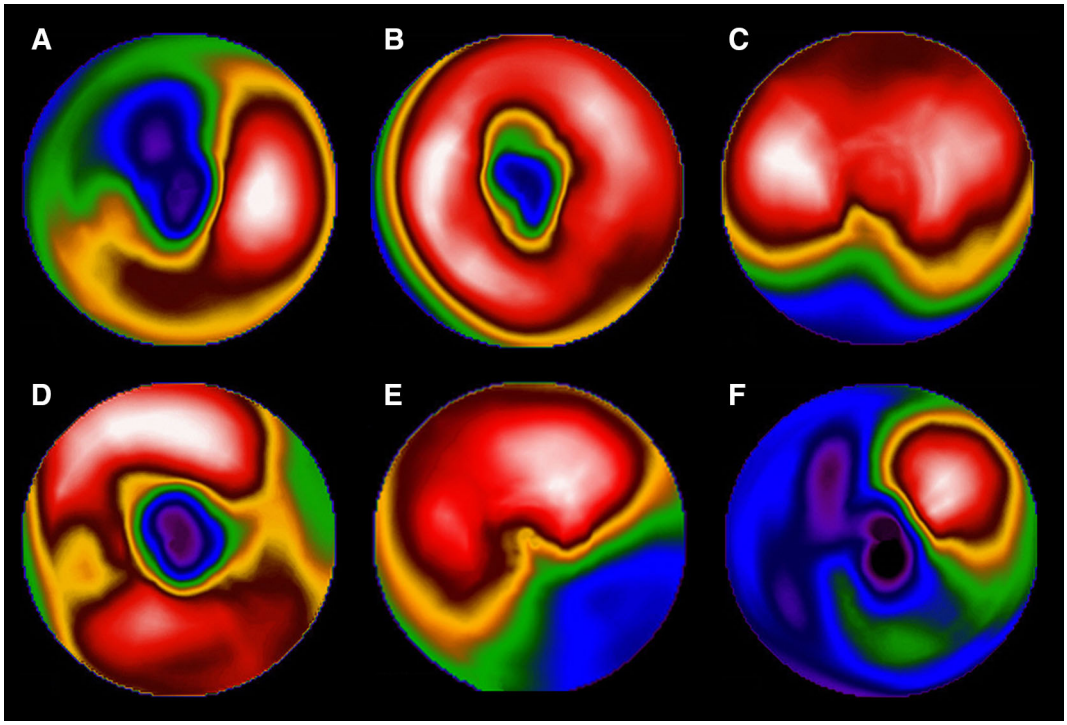


Figure 1. Prototypical cases of vessel-related ischemia (VRI) at myocardial perfusion scintigraphy: single-VRI involving left anterior descending (LAD) [proximal (**A**) vs non-proximal (**B**)], single-VRI not involving LAD (**C**), two-vessel-VRI involving LAD (**D**), two-vessel-VRI not involving LAD (**E**), and three-vessel-VRI (**F**).

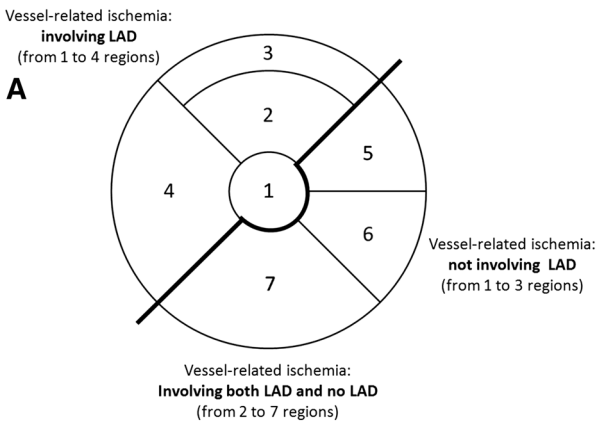
hierarchical and logical fashion regional ischemia quantification with the MIS and VRI concepts, thus provides a comprehensive final score (FS) to synthesize the myocardial perfusion details of any given patient (Figure 2; Online Figure 1).

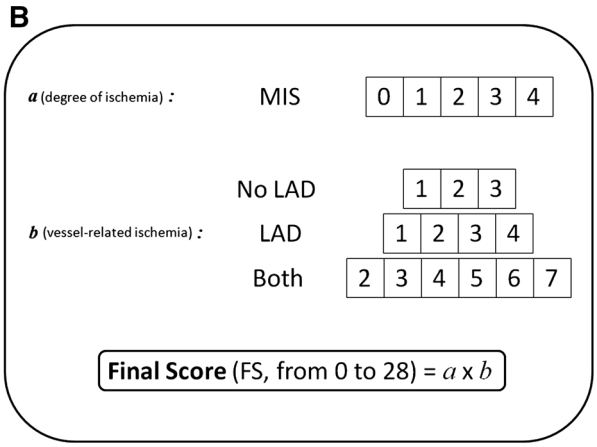
Clinical follow-up was systematically collected after the index MPS, by direct patient visit or phone contact. In case an adverse event was elicited, hard copies of the source documents (e.g., hospitalization records) were retrieved to enable event adjudication and minimize information bias. The primary outcome was the long-term (>1 year) rate of death or myocardial infarction. In addition, we adjudicated rates of death; cardiac death; non-fatal myocardial infarction; percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG); any revascularization; and cardiac death or myocardial infarction. Cardiac death was defined as any death with a specific cardiac cause or without any established non-cardiac cause but occurring suddenly.

Continuous variables are reported as mean ± standard deviation. Categorical variables are reported as n (%). Bivariate analyses were performed using ANOVA for continuous variables and Chi-squared test for categorical variables. Bivariate analyses are provided with overall *P* values and *P*values for subgroup tests. Notably, we chose to provide descriptive and inferential analyses including also patients without moderate or severe VRI to emphasize that ischemia represents a pathophysiologic continuum. Multivariable analyses were performed with Cox proportional hazard analysis to appraise the independent prognostic impact of ischemia location or extent simultaneously adjusting for all covariates significantly ($P < .05$) associated with this parameter, plus summed stress score (SSS), with a backward stepwise selection method (probability of removal .10). Statistical significance was set at the 2-tailed .05 level. *P* values unadjusted for multiplicity were reported throughout. Computations were performed with Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

A total of 13,254 patients were included in the analysis in keeping with our selection criteria. Specifically, 5,436 (41.0%) subjects had no evidence of myocardial ischemia, 5,191 (39.2%) had minimal or mild ischemia, and the remaining 2,627 (19.8%) had moderate or severe ischemia. In the latter set of patients, 4 different and mutually exclusive groups were identified according to VRI subtypes: single-VRI involving LAD [which was present in 749 (5.7%)], single-VRI not involving LAD [878 (6.6%)], multi-VRI involving LAD [428 (3.3%)], and multi-VRI not involving LAD [572 (4.3%)].





C

MIS 1 No LAD	MIS 1 LAD	MIS 1 Both	MIS 2 No LAD	MIS 2 LAD	MIS 2 Both	MIS 3 No LAD	MIS 3 LAD	MIS 3 Both	MIS 4 No LAD	MIS 4 LAD	MIS 4 Both
13	14	15	16	17	18	19	20	21	22-28		
12	13	14	15	16	8	9	10	11	12		
11	12	4	5	6	7	8	9	10	11		
19	20	21	4	5	6	7	8	9	10		
9	10	11	12	13	14	15	16	17	18		
8	9	10	11	12	4	5	6	7	8		
5	6	7	8	9	3	4	5	6	7		
7	8	9	10	11	12	13	14	3	4		
3	4	5	6	7	8	3	4	5	6		
4	5	6	7	2	3	4	5	6	2		
0	1	2	3	1	2	3	4	2	3		

◀**Figure 2.** Myocardial perfusion scintigraphy can be analyzed thoroughly using the maximal ischemia score (MIS) and vessel-related ischemia (VRI) approach, yielding a prognostically relevant final score (FS). After distinguishing the left ventricle in 7 regions [**A**, (1) apical, (2)antero-medio-distal, (3) antero-proximal, (4) septal, (5) postero-lateral, (6) lateral, and (7) inferior], MIS is computed distinguishing patients in 5 separate groups (**B**): absent (0), minimal (1), mild (2), moderate (3), or severe ischemia (4). Then, for VRI appraisal, left anterior descending (LAD) involvement is defined as involvement of at least one of regions 1, 2, 3, or 4, whereas VRI not involving LAD is defined as ischemia in regions 5, 6, or 7. Applying in sequence, MIS and VRI evidently lead to the FS (**B**, **C**). Specifically, patients with no VRI have a FS of 0, those with minimal VRI have a FS ranging between 1 and 7, subjects with mild VRI have a FS ranging between 2 and 14, patients with moderate VRI have a FS ranging between 3 and 21, and those with severe VRI have a FS ranging between 4 and 28. The variability in FS depending on MIS and VRI is clearly highlighted in the comprehensive color-coded table presented in panel C.

Most baseline features were, as expected, significantly different according to this stratification (Table 1). Specifically, age, gender, hypercholesterolemia, hypertriglyceridemia, smoking, diabetes mellitus, and prior revascularization were unevenly distributed in the groups ($P < .05$ for all comparisons). Other differences were evident in procedural features (Table 2): type of stress test, angina pain during stress, workload, maximum heart rate, % of maximum expected heart rate, maximum systolic blood pressure, rate pressure product, ST-segment change, left ventricular ejection fraction, and end-diastolic volume index ($P < .05$ for all comparisons).

Clinical outcomes after 32 ± 21 months were significantly different in the shortlisted groups (Table 3, Figure 3), including death, cardiac death, myocardial infarction, revascularization, or their composites (overall $P < .001$ for all comparisons). Specifically, and excluding subjects undergoing revascularization as first follow-up event, death or myocardial infarction occurred in 8.4% of patients with single-VRI involving LAD, 5.5% of subjects with single-VRI not involving LAD, 16.5% of those with multi-VRI involving LAD, and 7.3% of patients with multi-VRI not involving LAD (overall $P < .001$). Sensitivity analysis including patients undergoing revascularization as first follow-up event confirmed, at both 1-year and long-term follow-up, the overall analyses (Online Table 1).

Multivariable survival analyses, although limited by relatively low event-per-variable ratios due to the multiple subgroups, confirmed the independent prognostic impact of increased severity of VRI (Online Table 2). Even in incremental prognostic models based on a hierarchical VRI score, VRI independently predicted the long-term occurrence of death or myocardial infarction (Online Table 3).

A hypothesis-generating analysis limited to patients undergoing coronary angiography (performed 10.0 ± 17.1 months after MPS in 2,338 [17.6%] subjects) showed a reasonable association between results

Table 1. Baseline features according to location and extent of vessel-related ischemia (VRI) at myocardial perfusion scintigraphy

			Moderate or severe VRI					
			Single-VRI		Multi-VRI			
	No VRI (N = 5,436)	Minimal or mild VRI (N = 5,191)	Involving LAD (N = 749)	Not involving LAD (N = 878)	Involving LAD (N = 428)	Not involving LAD (N = 572)	Overall *P*	Other *P* < .05*
Age (years)	63 ± 10	65 ± 10	66 ± 10	65 ± 10	63 ± 10	66 ± 9	<.001	d
Female gender	2,898 (53.3%)	804 (15.5%)	155 (20.7%)	127 (14.5%)	39 (9.1%)	48 (8.4%)	<.001	a, b, c, d, e
Family history of coronary artery disease	2,404 (44.2%)	2,301 (44.4%)	359 (48.0%)	400 (45.6%)	199 (46.5%)	244 (42.7%)	.340	-
Hypercholesterolemia	3,002 (55.3%)	2,879 (55.5%)	431 (57.5%)	528 (60.1%)	249 (58.3%)	335 (58.8%)	.002	-
Hypertriglyceridemia	837 (15.4%)	878 (16.9%)	143 (19.1%)	169 (19.2%)	86 (20.2%)	138 (24.3%)	<.001	c, e
Hypertension	3,986 (73.3%)	3,813 (73.5%)	544 (72.6%)	650 (74.0%)	321 (75.0%)	405 (70.8%)	.711	-
Current or former smoking	2,675 (49.2%)	3,591 (69.2%)	479 (64.0%)	644 (73.3%)	298 (69.6%)	451 (79.0%)	<.001	a, b, c, e, f
Diabetes mellitus	1,240 (22.8%)	1,494 (28.8%)	258 (34.4%)	295 (33.6%)	200 (46.7%)	217 (37.9%)	<.001	b, d, f
Prior coronary revascularization	1,272 (23.4%)	2,145 (41.3%)	228 (30.4%)	441 (50.2%)	151 (35.3%)	219 (38.3%)	<.001	a, c, d, e

*a = Single-VRI involving LAD vs single-VRI not involving LAD; b = Single-VRI involving LAD vs multi-VRI involving LAD; c = Single-VRI involving LAD vs multi-VRI not involving LAD; d = Single-VRI not involving LAD vs multi-VRI involving LAD; e = Single-VRI not involving LAD vs multi-VRI not involving LAD; f = multi-VRI involving LAD vs multi-VRI not involving LAD; *LAD*, left anterior descending

Table 2. Procedural features according to location and extent of vessel-related ischemia (VRI) at myocardial perfusion scintigraphy

			Moderate or severe VRI					
			Single-VRI		Multi-VRI			
	No VRI (N = 5,436)	Minimal or mild VRI (N = 5,191)	Involving LAD territory (N = 749)	Not involving LAD (N = 878)	Involving LAD (N = 428)	Not involving LAD (N = 572)	Overall *P*	Other *P* < .05*
Exercise stress testing	4,582 (84.3%)	4,486 (86.4%)	657 (87.7%)	742 (84.5%)	361 (84.3%)	510 (89.2%)	<.001	e, f
Anginal pain during stress	387 (7.1%)	436 (8.4%)	76 (10.1%)	82 (9.3%)	37 (8.6%)	55 (9.6%)	.002	-
Workload (Watt)	91 ± 45	105 ± 40	91 ± 38	97 ± 36	85 ± 33	97 ± 36	<.001	a, b, c, d, f
Maximum heart rate (bpm)	145 ± 14	138 ± 14	134 ± 14	136 ± 14	132 ± 14	133 ± 14	<.001	b, d, e
% of maximum expected heart rate	92 ± 7	88 ± 7	87 ± 9	87 ± 8	86 ± 9	86 ± 8	<.001	d, e
Maximum systolic blood pressure (mmHg)	188 ± 18	188 ± 17	184 ± 16	187 ± 17	182 ± 16	185 ± 16	<.001	a, b, d
Rate pressure product (bpm*mmHg)	27,108 ± 3,766	25,816 ± 3,744	24,669 ± 3,689	25,191 ± 3,901	26,635 ± 3,505	24,357 ± 3,316	<.001	a, b, d, e, f
ST-segment deviation ≥ 1.0 mm	240 (6.1%)	755 (21.1%)	300 (55.1%)	373 (57.6%)	219 (51.1%)	253 (57.8%)	<.001	b, d, f
Stress left ventricular ejection fraction (%)	65 ± 10	59 ± 9	52 ± 10	54 ± 9	45 ± 10	52 ± 9	<.001	a, b, d, e, f
Stress end-diastolic volume index ($mL \cdot m^{-2}$)	62 ± 24	76 ± 29	86 ± 34	82 ± 32	110 ± 49	85 ± 34	<.001	a, b, d, f
Summed stress score							<.001	a, b, c, d, e, f
Normal	5,436 (100%)	3,879 (74.7%)	148 (19.8%)	377 (42.9%)	0	0		
Mildly abnormal	0	1,306 (25.2%)	268 (35.8%)	474 (54.0%)	112 (26.2%)	274 (47.9%)		
Moderately abnormal	0	6 (.1%)	237 (31.6%)	26 (3.0%)	176 (41.1%)	285 (49.8%)		
Severely abnormal	0	0	96 (12.8%)	1 (.1%)	140 (32.7%)	13 (2.3%)		

*See legend of Table 1 for explanations; *LAD*, left anterior descending

Table 3. Clinical outcomes according to location and extent of vessel-related ischemia (VRI) at myocardial perfusion scintigraphy, excluding patients undergoing revascularization as first follow-up event

			Moderate or severe VRI					
			Single-VRI		Multi-VRI			
	No VRI (N = 5,340)	Minimal or mild VRI (N = 4,604)	Involving LAD (N = 287)	Not involving LAD (N = 560)	Involving LAD (N = 158)	Not involving LAD (N = 286)	Overall *P*	Other *P* < .05*
Follow-up duration (months)	34 ± 20	30 ± 21	29 ± 21	31 ± 21	31 ± 22	31 ± 21	<.001	-
Death or myocardial infarction	93 (1.7%)	130 (2.8%)	24 (8.4%)	31 (5.5%)	26 (16.5%)	21 (7.3%)	<.001	b, d, f
Cardiac death or myocardial infarction	68 (1.3%)	78 (1.7%)	19 (6.6%)	23 (4.1%)	20 (12.7%)	16 (5.6%)	<.001	b, d, f
Death	41 (.8%)	84 (1.8%)	13 (4.5%)	22 (3.9%)	20 (12.7%)	12 (4.2%)	<.001	b,d,f
Cardiac death	16 (.3%)	32 (.7%)	8 (2.8%)	14 (2.5%)	14 (8.9%)	7 (2.4%)	<.001	b, d, f
Non-fatal myocardial infarction	52 (1.0%)	46 (1.0%)	11 (3.8%)	9 (1.6%)	6 (3.8%)	9 (3.1%)	<.001	a

* See legend of Table 1 for explanations; *LAD*, left anterior descending

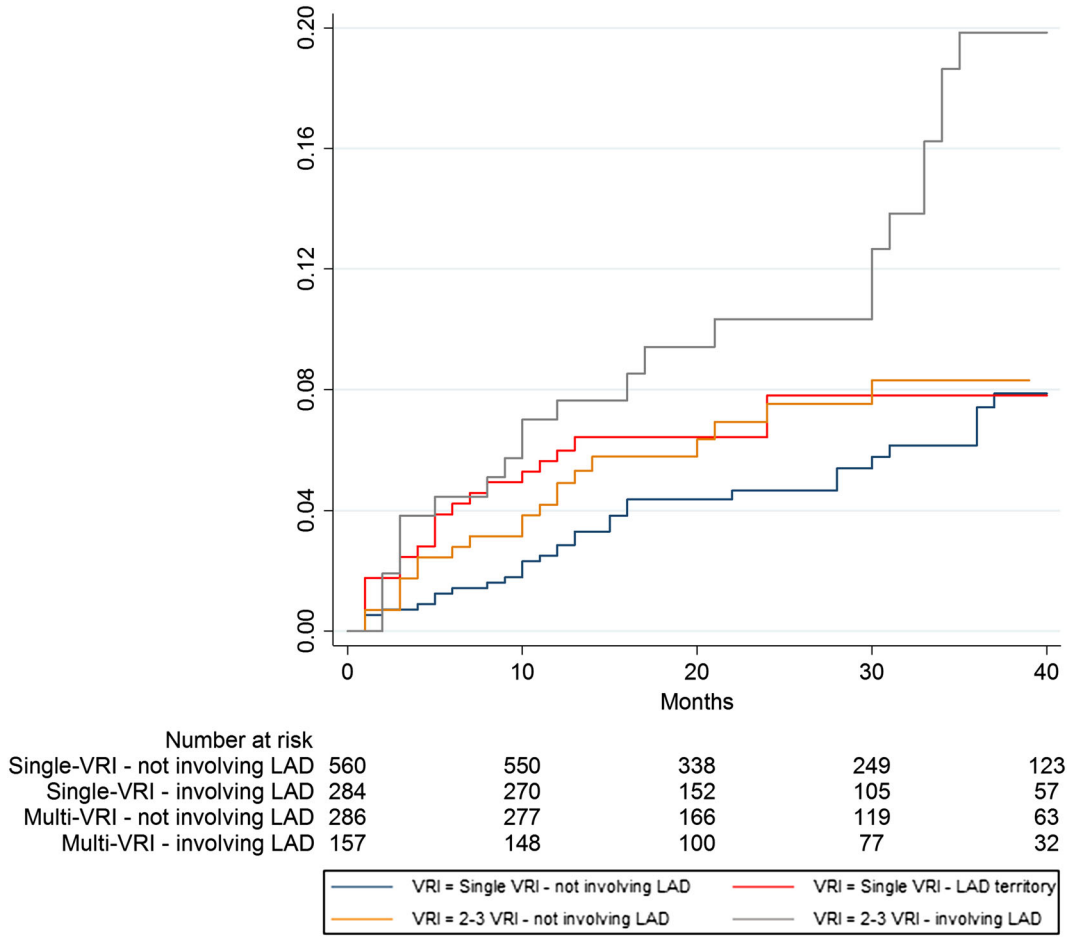


Figure 3. Kaplan–Meier failure curve for the occurrence of death or myocardial infarction, distinguishing patients according to vessel-related ischemia (VRI), and excluding patients undergoing revascularization as first follow-up event [overall log-rank $P < .001$; other log-rank $P < .05$: b, d, f (see legend of Table 1 for explanations)]. Color codes: green, single-VRI involving LAD; dark orange, single-VRI not involving LAD; gray, multi-VRI involving LAD; red, multi-VRI not involving LAD.

of MPS-derived VRI and evidence of significant (≥50% diameter stenosis) coronary artery disease at angiography (Online Table 4).

DISCUSSION

The prognostic role of MPS is well established, irrespective of the means used to interpret or quantify myocardial ischemia.[3-9,13-17] Indeed, a composite of extent and severity of ischemia, such as the SSS, which is used by several institutions worldwide, appear useful and reasonably accurate, despite being altogether oblivious of ischemia location.[3,6,13-17] To date, efforts aiming at a more precise characterization of the impact of ischemia extent on prognosis have been limited.[14-20]

Pivotal randomized trials, meta-analyses, and ensuing guidelines have conversely explicitly clarified the importance of angiographically defined LAD disease and multivessel disease in terms of prognosis, but also in terms of incremental benefits if revascularization is preferred over medical therapy.[7-9,13] Accordingly, guidelines recommend coronary revascularization in patients with the above features,[8,9,13] with CABG favored whenever disease is diffuse or extensive.[21]

We built, upon the above premises, our hypothesis that location and extent of myocardial ischemia, as demonstrated at MPS, are both and independently important to gauge patient risk. As we have recently demonstrated the relevance and reliability of MIS as a user-friendly tool to synthesize the severity of ischemia at MPS,[4] we have then systematically applied the concept of VRI, in terms of both location and extent to our institutional database, in order to identify important correlates but, most importantly, the prognostic

impact of location and extent of myocardial ischemia. Indeed, the combination of the MIS and VRI concepts enables accurate, simple, yet prognostically and clinically relevant decision making as each patient is provided specific guidance on its risk as well as his or her likelihood of benefiting from invasive management and revascularization (Figure 2).

Our findings confirm prior data in support of the importance of severity, and extent of ischemia at MPS.[4-6,14-17,22] However, we provide original data showing that multi-VRI involving LAD at MPS has a unique unfavorable prognostic impact, at odds with multi-VRI not involving LAD. While not reaching nominal statistical significance, even when analysis is limited to subjects with single-VRI, LAD involvement appears detrimental. Moreover, we provide data suggesting that patients with multi-VRI are also at higher risk of adverse events than those with single-VRI. Irrespective of the focus on cardiac death, myocardial infarction, or revascularization as endpoints of interest, a prognostic hierarchy of extent and location of myocardial ischemia appears. While these findings may challenge the pivotal role of monodimensional SSS, similar results have been previously reported for stress echocardiography.[23]

Notably, it must be emphasized that the lower prognostic predictive value of VRI not involving LAD is not necessarily the fault of MPS, but it may be most likely due to the established variability in coronary anatomy, which impedes a correct and consistent characterization of such regional involvement over several cases.[20] In addition, it is conceivable that the very use of the MIS method, with its capability to synthesize the prognostic outlook of a patient undergoing MPS, may have diluted the independent predictive impact of LAD involvement in subjects with single-VRI. Conversely, the higher prognostic predictive value of multi-VRI involving LAD is clearly explained by the stronger and more precise association between LAD ischemia at MPS and LAD disease at coronary angiography.[24,25] Moreover, the fact that the prognostic impact of VRI involving LAD may be worse than VRI not involving LAD is likely due to the fact that LAD (especially when the proximal tract is involved) provides flow to a larger portion of the left ventricle and, specifically, to the anterior portion of the ventricular septum, a key determinant of left and right ventricular performance. Accordingly, LAD disease can translate into substantially variable extents of ischemia, from less than 15% to more than 50% of the left ventricular mass.

The exploratory comparative analysis of angiography and MPS in terms of location and extent of, respectively, disease and ischemia also supports the usefulness of MPS. In particular, it appears evident that MPS can help to characterize each unique patient by defining its prognostic features, thanks to MIS, VRI, and a suitable FS. This assessment is complementary to the information yield stemming from the obviously important baseline features such as age, diabetes mellitus, and exercise tolerance.

These findings may have important clinical implications, as they support the fact that MPS, when correctly and thoroughly interpreted, can provide diagnostic, prognostic, and management guidance. In particular, adequate patient characterization with MPS, including details on severity, location, and extent of myocardial ischemia, may poignantly inform on the incremental risk conferred by a report disclosing moderate or severe ischemia. In addition, it can enable patient triage when considering further invasive assessment and/or revascularization, as well as choosing the most appropriate revascularization means. Thus, it may eventually provide a veritable clinical guideline, with the ultimate goal of maximizing the prognostic benefit and minimizing the procedural risk of PCI or CABG by individualizing their indications.

The risk of underestimating or overestimating coronary artery disease with MPS merits further elaboration.[24,25] First, angiographic severity is by no means the equivalent of functional severity, as clearly shown by studies exploiting fractional flow reserve. In addition, even assuming that patients with three-vessel disease at angiography may have been occasionally assigned to the 2 VRI group with MPS, these subjects are actually still correctly classified at a per-patient level and at a more pragmatic and prognostically relevant level. This provides grounds for our choice to combine patients with 2 VRI involving LAD with patients with 3 VRI. In terms of overestimation, in our series, a small set of patients later showing only single-vessel disease at angiography were categorized as subjects with 2 VRI. However, this finding must be viewed in light of pathophysiologic data demonstrating that indeed myocardial ischemia due to an isolated lesion in a single vessel can still limit the capability to increase blood flow in remote regions without coronary stenoses.[26]

Limitations of this work include the retrospective and observational design and availability of coronary anatomy details in only a subgroup of patients. In particular, no detailed data on type and treatment differences following MPS were available, or how these differences could impact on prognosis. In addition, a specific-type VRI should not consider per se indicative of a precise coronary anatomy, but rather should be used to characterize a patient in terms of prognostic risk and suitability for subsequent invasive assessment. We also

did not define left main VRI, but it appears evident that some other specific VRI groups may have included patients with left main disease or left main equivalent disease. Moreover, we excluded a priori patients with myocardial necrosis as this could have proved a confounding factor in our work focused explicitly on myocardial ischemia. Accordingly, further prospective evaluation is necessary to look at different treatment effects, but this study may prove insightful into further investigation.

NEW KNOWLEDGE GAINED

Among subjects with or at risk for coronary artery disease, location and extent of myocardial ischemia at MPS may have a hierarchical prognostic impact, with multi-VRI involving LAD clearly prognostically more detrimental than other types of VRI. These results have major implications on decision making to choose if and when to opt for invasive angiography and subsequent coronary revascularization.

Disclosures

None.

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