

Post-Infarction Myocardial Viability and Angina at Everyday Life Activities versus Treadmill Exercise Test

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Abstract

Background: Myocardial viability (VIA) prevalence in post myocardial infarction (MI) patients (pts) in association with angina (ANG) or not has not been prospectively evaluated.

Methods and Findings: Fifty-five post-MI pts with reduced ejection fraction ($EF \leq 40\%$) underwent stress thallium-201 scintigraphy (Tl-201) viability (VIA) evaluation. ANG at exercise-treadmill-test (ETT) (Borg scale) and at everyday-life (Canadian Cardiovascular Society – CCS) classification was recorded. Groups VIA (29 pts – 53%) vs non-VIA respectively had similar EF ($31 \pm 7\%$ vs $33 \pm 8\%$) (NS), higher diseased vessels number 2.8 ± 1.6 vs 1.9 ± 1.3 ($p=0.02$), CCS 1.7 ± 0.8 vs 1.3 ± 0.6 ($p<0.05$), CCS ≥ 2 71% vs 41% ($p<0.03$). Five pts from each group reported ETT ANG (17% vs 21% – NS), with Borg scale 7.7 ± 3.0 vs 7.2 ± 2.4 (NS). CCS ≥ 2 was associated with greater ²⁰¹Tl reversibility indices within stress defect ($p<0.04$) or total myocardial mass reversibility ($p<0.02$). Binary logistics analysis associated VIA positively with number of diseased vessels and negatively with smoking, while CCS ≥ 2 ANG positively with number of diseased vessels. The main limitation is the relatively small number of pts.

Conclusions: Viability, while not significantly correlated to ETT angina, was positively associated only with more frequent everyday-life (CCS) angina. Clinically, in ischemic cardiomyopathy VIA evaluation is indicated, regardless of ANG.

Keywords: Angina pectoris; exercise test; myocardial perfusion imaging; myocardial hibernation

INTRODUCTION^{1†}

Viability (VIA) in post MI pts with systolic dysfunction is used to evaluate outcomes and determine medical treatment or revascularization (REV). Viable myocardium REV vs medical treatment improves cardiac function

† ANG – angina, CAD – Coronary artery disease, CCS – Canadian Cardiovascular Society, EDD – End-diastolic Diameter, EF – Ejection fraction, ETT – exercise-testing, MI – Myocardial infarction, NPV – Negative predictive value, PPV – Positive predictive value, pts – patients, REV – Revascularization, SDS – Summed Difference Scores, SRS – Summed Rest Scores, SSS – Summed Stress Scores, VIA – viability

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and heart failure symptoms and reduces recurrent MI and mortality.¹ In the STICH trial, VIA estimation did not improve outcome;^{2,3} however, design limitations are outlined, regarding VIA criteria.⁴

Recent European and American Guidelines recommend REV both for angina (ANG) alleviation and prognosis improvement in ischemic cardiomyopathy.^{5,6,7} Scintigraphy, echocardiography, cardiac magnetic imaging or multidetector computed tomography imaging are used to detect VIA.^{1,8}

Clinically, ANG is considered indicative of VIA. However, neither prospective nor specific studies have been designed to answer accurately this question.^{9,10}

Our study is intended to prospectively address ANG accuracy at ETT or everyday-life in predicting VIA.

MATERIAL AND METHODS

Fifty-five post-MI (EF≤40%) ambulatory pts, informed about study aim, were prospectively included and signed informed consent. Fifty two were male (66 ± 10 vs 50 ± 3 years old females). Study protocol conformed to the 1975 Declaration of Helsinki ethical guidelines and was approved by hospital ethics committee.

Mean index-MI-study interval was 12 ± 10 years.

1. Myocardial VIA was assessed by ²⁰¹Tl myocardial SPECT in two ways:
 - 1.1 Qualitative, based on the official nuclear medicine laboratory assay.
 - 1.2 Quantitative, based on special 3-dimensional perfusion polar maps
 - 1.2.1 Reversible defective proportion of the initial defect (%)
 - 1.2.2 Reversible defective proportion of total myocardial mass (Fig 1)

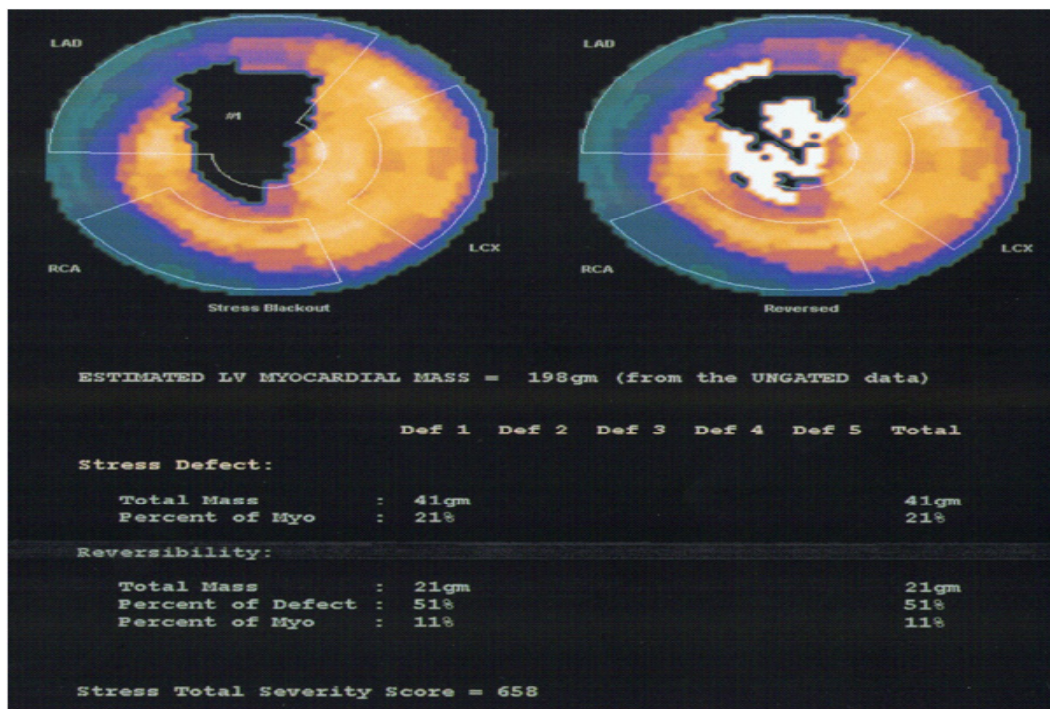


Fig1. 201Tl Reversibility

- a. Defect reversibility 51%
- a. Myocardial mass reversibility 11%

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1.2.3 Objective semiquantitative scores of reversibility (which signifies VIA): Scores SSS (stress-uptake), (SRS) (rest-uptake) and (SDS) between the 2 states for total and individual myocardial segments were calculated using 0 (normal) to 4 (complete) defect grading scale in 20 myocardial segments (Fig 2).¹¹ Hibernation minimum threshold of 20% of the total LV myocardium was used to classify the heart as viable.^{12,13}

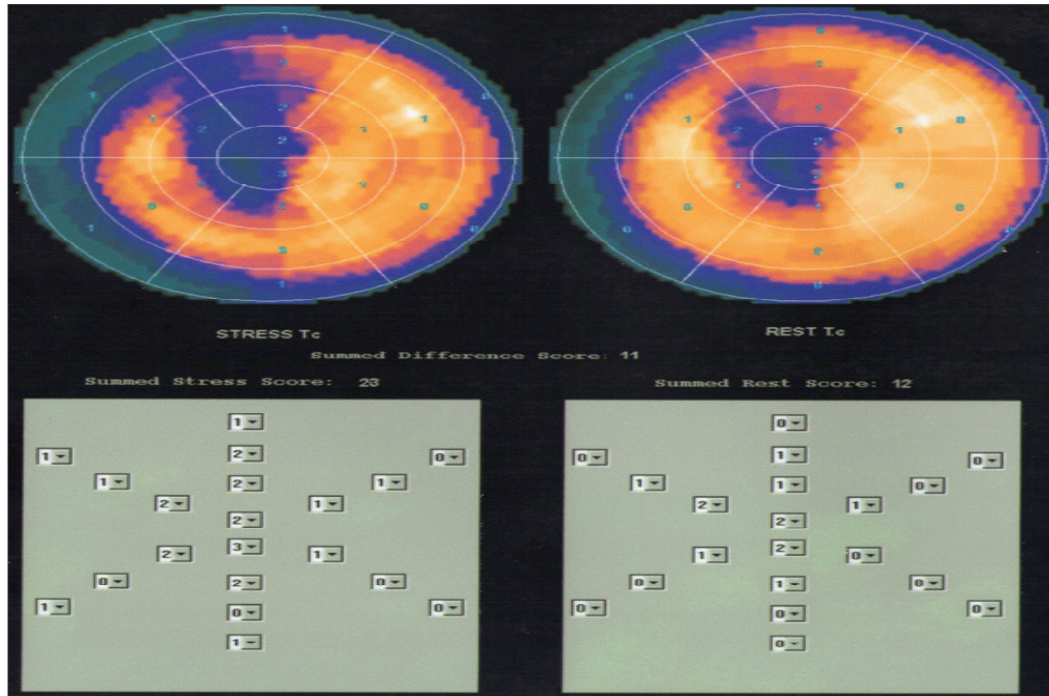


Fig2. The same patient as in Fig 1

Summed Stress Score (SSS) 23, Summed Rest Score (SRS) 12, Summed Difference Score (SDS) 11, Reversibility % = $SDS/SSS \times 100 = 48\%$

2 ANG was evaluated:

2.1 During *ETT*

2.1.1 Qualitatively, on the basis of ANG presence or absence and

2.1.2 Quantitatively, using the specific Borg-RPE (Borg) ANG grading scale.¹⁴

2.2 In *everyday life*

At the time of study-registration, ANG during the last three months was evaluated.

The specific CCS ANG classification was used with ANG-threshold value of II.¹⁵ Thus, pts who reported only intense-effort-ANG (scale I) were considered non-ANG in everyday life.

A timely performed coronary angiogram was evaluated and diseased vessels number (diameter stenosis $\geq 70\%$), Gensini CAD severity index, as well as REV techniques were recorded.^{16,17}

EDD and EF were measured echocardiologically.^{18,19}

Positive family history, smoking, diabetes, hypertension and dyslipidemia and beta-blockers, nitrates, antihypertensive, antiplatelet, antidiabetic, statin, antiarrhythmic and anticoagulant drugs were all recorded.

Quantitative variables are presented as mean (\pm standard deviation). Categorical variables are presented in

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form of frequencies. Comparison between quantitative variables for the presence or absence of ANG or VIA was carried-out using t-test. Correlations between quantitative variables were investigated using Pearson analysis, while the dependence between categorical variables was examined using the Chi-square (X^2). Statistical significance was set at $p < 0.05$.

RESULTS

General Population Data

Anthropometric and epidemiological data, infarct location, REV-technique, CAD-severity and ECHO-estimate of left ventricular function are shown in *Table 1*; only 20% percent of our pts had not undergone any REV.

Table 1. Demographic, anthropometric and clinical characteristics of the participating to the survey subjects depending on VIA

	VIA		p-value
	Presence	Absence	
N	29	26	
Age (years)	66±10	63±10	0,22
Body Mass Index (kg/m ²)	27±3	27±3	0,56
MI location, n (%)			
Anterior	21 (72%)	22 (85%)	
Inferior-posterior	6 (21%)	2 (8%)	
MI location combination	2 (7%)	2 (8%)	0,39
REV technique			
No REV	6 (21%)	5 (19%)	
Only PCI	13 (41%)	9 (35%)	
Only CABG	7 (24%)	7 (26%)	
REV at least twice	3 (10%)	5 (19%)	0,76
Diseased vessels (n - mean value)	2,8±1,6	1,9±1,3	0,02
Gensini score	91±78	63±53	0,13
Coronary grafts			
Without lesion	6 (67%)	7 (58%)	
Stenosis (>70%)	3 (33%)	5 (42%)	0,7
LVEDD (mm)	63±9	62±9	0,74
EF (%)	31±7	33±8	0,34
Hypertension	22 (76%)	19 (73%)	0,81
DM	6 (21%)	8 (31%)	0,39
Dyslipidemia	24 (83%)	23 (88%)	0,55
CAD FH	9 (31%)	9 (35%)	0,78
Active smokers	3 (10%)	11 (42%)	
Ex smokers	13 (45%)	9 (35%)	
Non-smokers	13 (45%)	6 (23%)	0,02
N or n: number, CABG: Coronary Artery Bypass Grafting, CAD FH: Positive Family History for Coronary Artery Disease, DM: Diabetes Mellitus, EF: Ejection Fraction, LVEDD: Left Ventricular End-Diastolic Diameter, MI: Myocardial Infarction, PCI: Percutaneous Coronary Intervention, REV: Revascularization, VIA Viability			

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Results According to the Presence or Absence of VIA

ETT results

VIA emerged in 29 pts (52.7%), five (17.2%) reporting ANG during ETT; 5 non-VIA pts (19.2%) reported such complaints (NS).

VIA-group ETT duration was shorter ($p=0.038$). However, Borg scale was similar (Table 2).

Table 2. Correlation of ANG incidence perception and VIA

	VIA	Lack of VIA	p-value
Total	29	26	
ETT ANG	5	5	0,85
Borg Scale	7,72±3,01	7,23±2,39	0,52
CCS	1,72±0,80	1,31±0,62	0,036
ETT duration (min)	6,93±2,57	8,36±2,42	0,038

Abbreviations: ANG = Angina, CCS = Canadian Cardiovascular Society, ETT = Exercise treadmill test, VIA = Viability

Everyday life ANG (CCS)

Non-VIA group average CCS ANG-scale was significantly lower ($p=0,036$) (Table 2).

Anthropometric, Demographic and Angiographic Data

No statistically significant difference was found as regards age, body mass index, EDD and EF among VIA vs non-VIA as well as baseline and maximum heart rate during ETT. Diseased vessels number was greater in VIA group ($p = 0.02$); however, Gensini score did not differ. Stress defect reversibility was significantly higher in VIA group ($16.52±16.23$ vs $3.86±8.23$, $p=0.002$), as expected. Antiplatelet therapy was more common in non-VIA pts ($p=0.01$); otherwise, drug therapy was comparable (data not shown).

Binary logistics analysis with VIA as dependent variable and the contents of table 1 as covariates derived diseased vessels number (OR 1.927/ 95% CI 1.188 – 3.125, $p=0.008$) and Gensini score (OR 1.029/ 95% CI 1.003 – 1.055, $p=0.030$) as positive and smoking (OR 0.388/ 95% CI 0.175 – 0.861, $p=0.020$) as negative predictors.

Results Concerning ANG Presence

ETT results

Ten pts reported ANG and discontinued exercise. The remaining stopped exercise because of muscle fatigue. There were no differences between the 2 groups as regards VIA ($X^2=0.036$, $p=0.85$) and myocardial function (EDD $59.67 ± 8.72$ for ANG vs $62.70 ± 8.74$ mm, $p=0.35$ and EF $34.30 ± 9.15\%$ for ANG pts vs $31.38 ± 7.22\%$, $p=0.28$).

There was no difference concerning stenosis of the coronary arteries (other than left main), diseased vessels number, Gensini score, risk factors, age, sex and medication as well as baseline and maximum heart rate during ETT. However, left main coronary artery disease was more prevalent in ANG group (0.2 vs 0.02 , $p<0.02$). Reversible proportion of ^{201}Tl initial defect was 15% in ANG group vs 10% ($p=0.38$) and within the entire myocardium 3.13 vs 2.88 ($p=0.87$).

^{201}Tl SSS, SRS and reversibility (dividing SDS/SSS) for the whole myocardium and particular myocardial segments (anterior, septal, inferior[-posterior], lateral and apex) according to ANG at ETT and everyday life (see below) are displayed on Table 3.

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Table3. *Tl-201 scintigraphy Viability Scores vs Treadmill and everyday (by CCS) Angina*

		Anterior	Septal	Inferior	Lateral	Apex	Total
SSS	Angina	2,71±1,89	3,71±1,98	4,14±2,41	5,00±3,70	5,00±1,53	24,13±4,79
	No Angina	3,06±1,76	6,19±2,57	4,19±2,49	5,78±3,46	4,97±1,99	23,83±6,96
	P-value	0,70	0,02	0,96	0,62	0,97	0,88
	CCS≤1	2,94±1,08	5,73±2,82	4,03±2,44	5,88±3,58	4,85±1,96	25,13±7,46
	CCS>1	3,09±1,70	6,00±2,05	4,64±2,54	5,00±3,19	5,36±1,80	21,89±4,51
	P-value	0,80	0,73	0,50	0,45	0,43	0,06
SRS	Angina	2,29±1,80	2,71±1,80	2,71±1,11	3,57±3,10	4,00±1,53	19,38±6,78
	No Angina	2,76±1,74	5,43±3,05	3,41±2,47	4,03±3,35	4,38±2,00	19,32±7,19
	P-value	0,54	0,01	0,25	0,73	0,58	0,98
	CCS≤1	2,70±1,83	5,21±3,18	3,27±2,56	3,85±3,52	4,21±1,93	20,83±7,34
	CCS>1	2,64±1,50	4,36±2,62	3,36±1,36	4,27±2,53	4,64±1,96	16,95±6,01
	P-value	0,91	0,39	0,88	0,67	0,54	0,05
SDS	Angina	0,57±0,98	1,00±1,63	1,43±1,99	1,43±1,27	1,00±1,00	4,75±4,83
	No Angina	0,27±1,24	0,76±2,05	0,78±1,25	1,76±2,19	0,59±0,93	4,55±3,81
	P-value	0,49	0,74	0,44	0,59	0,35	0,92
	CCS≤1	0,27±1,33	0,52±1,77	0,76±1,17	2,03±2,13	0,64±0,93	4,17±3,18
	CCS>1	0,45±1,69	1,64±2,38	1,27±1,90	0,73±1,56	0,73±1,01	5,28±4,98
	P-value	0,56	0,17	0,41	0,04	0,80	0,40
Reversibility %	Angina	12,86±29,21	26,14±30,56	24,43±38,06	27,57±36,30	20,71±19,12	23,43±18,88
	No Angina	9,08±33,93	11,01±42,05	18,27±37,93	28,59±41,65	17,56±25,81	19,33±19,12
	P-value	0,77	0,28	0,70	0,95	0,72	0,61
	CCS≤1	9,13±36,97	8,91±41,35	20,82±39,54	34,85±40,85	18,84±26,08	20,56±20,00
	CCS>1	11,36±17,56	26,95±36,34	14,55±32,18	9,18±33,93	15,82±20,99	18,36±16,06
	P-value	0,79	0,18	0,60	0,05	0,70	0,72

Abbreviations: CCS: Canadian Cardiovascular Society, SDS: Summed difference Score, SRS: Summed Rest Score, SSS: Summed Stress Score; Reversibility (definition)= SDS/SSS x 100%

Sensitivity, specificity, PPV and NPV of ETT-ANG to detect VIA was estimated at 17%, 81%, 50% and 47%, respectively.

Everyday life ANG

Twenty-one pts reported limitation in daily activities due to ANG (Grades II-IV).

Pts with everyday life ANG displayed more often VIA (15/21, 71% vs 14/34, 41%, p=0.03). Thus, there was higher stress defect and total mass reversibility percentage (16 ± 19% vs 7 ± 10%, p=0.04 and 5 ± 5% vs 2 ± 2%, p=0.02).

Everyday life ANG sensitivity, specificity, PPV and PPV to detect VIA was estimated at 52%, 77%, 71% and 59%, respectively. The emergence of ANG in everyday life (CCS II-IV) is statistically significantly associated with the

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presence of VIA vs no ANG (CCS I), $p=0,029$. A weak significant ($r\ 0.28$, $p=0.04$) between Borg-RPE and CCS was observed.

Pts with no ANG in everyday life revealed lower number of diseased vessels (2.03 ± 1.14 vs 3.00 ± 1.82 , $p=0.04$) and Gensini score (58 ± 49 vs 109 ± 83 , $p=0.02$) and larger EDD (64 ± 9 vs 59 ± 7 mm, $p=0.04$). Diabetes and medication were similar.

Table 2 shows higher CCS among VIA pts.

Pearson analysis revealed a non-significant negative correlation between stress defect and both CCS and Borg scores (r value -0.228 and -0.208 , p value 0.115 and 0.151 respectively). Stress defect reversibility either as a percentage of stress defect or as a percentage of the total myocardial mass was non-significantly positively correlated with Borg scale ($r= 0.197$ and 0.093 , $p=0.176$ and 0.526 for stress defect and total myocardial mass respectively), while CCS angina classification was significantly correlated ($r= 0.406$ and 0.458 , $p= 0.004$ and 0.001 for stress defect and total myocardial mass reversibility respectively). After controlling for number of diseased vessels as a confounding factor, stress defect reversibility either as a percentage of stress defect or as a percentage of the total myocardial mass was still positively correlated with CCS angina classification ($r=0.355$ and 0.420 , $p=0.013$ and 0.003 for stress defect and total myocardial mass respectively). These results confirm quantitative evaluation and correlation.

Binary logistics analysis with everyday ANG as dependent variable and the elements of table 1 as covariates revealed number of diseased vessels as negative prognostic factor (OR 1.660/ 95% CI 1.066 – 2.586, $p=0.025$).

Diabetes was associated with 1st diagonal disease ($p=0.039$) and weight ($p=0.033$).

Binary logistics analysis using factors of table 1 as covariates and VIA as dependent variable revealed positive correlation of diseased vessels (OR 1.927/ 95% CI 1.188 – 3.125, $p= 0.008$) and Gensini score (OR 1.029/ 95% CI 1.003 – 1.055, $p= 0.030$) and negative correlation of smoking (OR 0.388/ 95% CI 0.175 – 0.861, $p= 0.020$) with VIA.

Binary logistics analysis using factors of table 1 as covariates and everyday ANG (CCS ≥ 2) as dependent variable revealed positive correlation of diseased vessels with ANG (OR 1.660/ 95% CI 1.066 – 2.586, $p= 0.025$).

DISCUSSION

We tried to clarify specifically and prospectively whether ANG is associated with VIA.

Ambulatory post-MI pts with $EF \leq 40\%$ were consecutively included in accordance with current recommendations about VIA detection^{6,7,20}. Only VIA and ANG prevalence was investigated without need for follow-up.^{21, 22, 23}

The evaluation of ANG at ETT was performed by one – the chief – investigator, to ensure homogeneity in assessment of this complaint. We used standard ²⁰¹Tl scintigraphy techniques¹¹.

VIA classification was based on the minimum general accepted 20% reversibility threshold within the infarct-zone and ²⁰¹Tl uptake $\geq 50\%$ of the maximum count in normal segments.^{24,25} At least 20% viable dysfunctional segments are required to result in LVEF improvement^{12, 13} Both qualitative and quantitative measures of VIA, such as the degree of reversibility of the defect and the total myocardial mass reversibility involved, were used to detect statistically significant correlation between VIA and ANG during everyday life or ETT. We believe that our results would not change with a larger number of pts clinically.

We used the older CCS scoring system for ANG estimation. However, this has been recently found to correlate well with the more contemporary Seattle ANG Questionnaire.^{26,27} We believe that the former and simpler CCS questionnaire can better differentiate between absence or presence of ANG in everyday life, and has shown good correlation with survival.²⁸ Patients classified as everyday-life ANG (CCS \geq II) complained for typical ANG

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or just chest discomfort. Goldman et al already in 1981 demonstrated greater validity for class I status to signify ANG absence than “the unofficial but occasionally used class 0”.¹⁵ We used the same criteria.

Notably, 80% of our pts had undergone at least once either CABG or PCI, resembling in real-life situation, as most post-infarct pts undergoing VIA studies have already undergone REV. Taylor et al showed that post-infarct angina was associated with proximal LAD disease and presence of “risk” i.e viable LV segments²⁹. These data correspond to our findings.

Smoking emerged as a negative factor for VIA according to aforementioned binary logistics analysis. Interestingly Lamirault et al showed that active smoking resulted in decreased blood endothelial progenitor cells and that these alterations may participate in the impairment of cardiac function recovery in smokers after AMI.³⁰

While the ETT ANG frequency and severity was not related in any extent to VIA, everyday life ANG assessed by CCS score was significantly associated with VIA. Correlation was still preserved after control for diabetes mellitus, number of diseased vessels which was statistically significantly correlated with both everyday-life ANG and stress defect reversibility.

Sensitivity, specificity, PPV and NPV for CCS although statistically significant were still rather low from a clinical perspective. Similar results were reported by Gimelli et al who, however, started their evaluation from the presence or not of everyday ANG in pts with EF below 35% without differences emerging between CAD severity, viable segments and wall motion index, between pts with and without everyday life ANG.⁵ Moreover, 68% of pts with and 76% of pts without ANG had mostly viable myocardium. Furthermore, Gimelli et al few months later published an institutional review in which 177 post-MI three-vessel disease pts underwent CABG or PTCA and it was observed that 95 out of 114 CABG pts showed mostly viable myocardium and 95 mentioned everyday life ANG, whereas 51 and 48 out of 63 PTCA pts showed or mentioned viable myocardium or ANG, respectively, thus, VIA or ANG group size are similar.³¹ However, these two variables were neither directly nor prospectively compared, as in our study. Chan et al indirectly corroborate our findings: Everyday life ANG did not influence post coronary REV favorable response in low EF pts.⁹ Again, this study was not designed to correlate ANG and VIA.

Treadmill-test is performed under well-regulated conditions, while variations in environment temperature, speed of gait, incline or emotional state influence everyday-life ANG, thus, everyday-life ANG vs ETT results can be discordant. Anginal perception can be well associated with each individual’s personal characteristics which explains the Borg and CCS significant though weak association.^{32,33}

Everyday-life ANG absence could be explained by fewer diseased vessels and lower Gensini score. Moreover, worse ventricular function and larger left ventricular end-diastolic diameter, signifying remodeling, could be compatible with VIA absence. As numerous variables influence EF, its non-difference seems predictable. Interestingly, diabetes mellitus did not influence any ANG index. Despite diabetic neuropathy predisposition to silent ischemia, recently 61% of studied diabetics mentioned typical ANG.³⁴ Most subjects had REV, which explains the higher number of diseased vessels in the VIA group.

Similarly, drugs, especially b-blockers, did not influence ANG under any set-up. However, antiplatelet high prevalence in pts without VIA cannot readily be explained. In view of our small numbers this can be a spurious finding.

Viability was measured by SPECT, which is suggested to have equivalent long-term survival prognostic value to F-18 fluorodeoxyglucose metabolic imaging or dobutamine echocardiography.³⁵ β -blockers were not routinely stopped before ²⁰¹Tl stress testing; no specific recommendations exist as regards their use for ECG, scintigraphic or echocardiographic testing.^{36,37,38} Also, gated SPECT was not performed, not routinely being used for VIA determination.

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Notably, LM disease was twice more frequent in ETT ANG pts than those without ANG, as in the Hamby et al study, stating more common left main and/or triple vessel disease in coronary artery disease and ANG pts.³⁹

Limitations

Patients number was admittedly low. However, it is difficult to perform such a detailed set of investigations as we did in our sample. The evaluation of ANG at ETT was performed by one – the chief – investigator, to ensure homogeneity in assessment of this complaint. The chosen TI²⁰¹ scintigraphy as a technique to assess VIA is offered for both qualitative and quantitative evaluation.

Concluding, ANG at ETT is not correlated with VIA, while everyday life ANG indicates VIA, justifying the widely held belief. Clinically, however, this association is weak and cannot obviate the use of widely accepted VIA assessment imaging techniques.

What is Already Known?
Angina is considered empirically a marker of myocardial viability.
What this Study Adds?
Everyday life angina may signify myocardial viability.

Funding

All pts underwent the special medical examinations of our study following the recommendation of their physicians. There was no additional financial support to the study.

Author Contribution Statement

Andreas Karydas was the chief investigator in this research and the main author in publication articles.

Maria Koutelou as well as Athanasios Theodorakos, as nuclear physicians estimated myocardial viability from SPECT myocardial perfusion images.

Professor Gregory Pavlides (physician-cardiologist) as director of the coronary catheterization lab performed coronary angiograms on pts who participated in the study.

Athanasios Dritsas (physician cardiologist) supervised exercise treadmill-testing of the pts.

Professor Demosthenes Panagiotakos performed statistical analysis of our data.

Professor Dennis Cokkinos (physician-cardiologist) was the main conceptualizer of the subject of our study and the main coordinator and supporter at all stages of the survey.

All physicians helped to integrate pts in the study.

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