

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

Andreas Karydas<sup>a\*</sup>, Maria Koutelou<sup>b</sup>, Athanasios Theodorakos<sup>c</sup>, Athanasios Dritsas<sup>d</sup>  
Gregory Pavlides<sup>1,e</sup>, Demosthenes B. Panagiotakos<sup>f</sup>, Dennis V. Cokkinos<sup>g</sup>

<sup>a\*</sup>Research Associate – 1st Department of Cardiology – Onassis Cardiac Surgery Center (Andreas Syggros Avenue 356, Kallithea 17674, Attiki, Greece.

<sup>b</sup>Director – Laboratory of Nuclear Medicine – Onassis Cardiac Surgery Center, Kallithea Attiki, Greece.

<sup>c</sup>Nuclear Medicine Physician – Laboratory of Nuclear Medicine – Onassis Cardiac Surgery Center, Kallithea Attiki, Greece.

<sup>d</sup>Cardiologist – Director of the Cardiopulmonary Exercise Testing laboratory – 1st Department of Cardiology – Onassis Cardiac Surgery Center, Kallithea Attiki, Greece.

<sup>1</sup>Professor of Medicine and Miscia Chair of Interventional Cardiology, University of Nebraska, <sup>e</sup>Ex Associate Director – Onassis Cardiac Surgery Center, Kallithea Attiki, Greece.

<sup>f</sup>Professor – Dean – School of Health Science and Education – Harokopio University, Athens Greece.

<sup>g</sup>Researcher – Biomedical Research Foundation Academy of Athens, Greece [Ex Director 1st Department of Cardiology – Onassis Cardiac Surgery Center], Emeritus Professor, University of Athens.

\*okaryda1@yahoo.gr

### 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  $2.8 \pm 1.6$  vs  $1.9 \pm 1.3$  ( $p=0.02$ ), CCS  $1.7 \pm 0.8$  vs  $1.3 \pm 0.6$  ( $p<0.05$ ), CCS $\geq 2$  71% vs 41% ( $p<0.03$ ). Five pts from each group reported ETT ANG (17% vs 21% – NS), with Borg scale  $7.7 \pm 3.0$  vs  $7.2 \pm 2.4$  (NS). CCS $\geq 2$  was associated with greater <sup>201</sup>Tl 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 $\geq 2$  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<sup>1¶</sup>

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.<sup>1</sup> In the STICH trial, VIA estimation did not improve outcome;<sup>2,3</sup> however, design limitations are outlined, regarding VIA criteria.<sup>4</sup>

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

Clinically, ANG is considered indicative of VIA. However, neither prospective nor specific studies have been designed to answer accurately this question.<sup>9,10</sup>

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 <sup>201</sup>Tl 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)

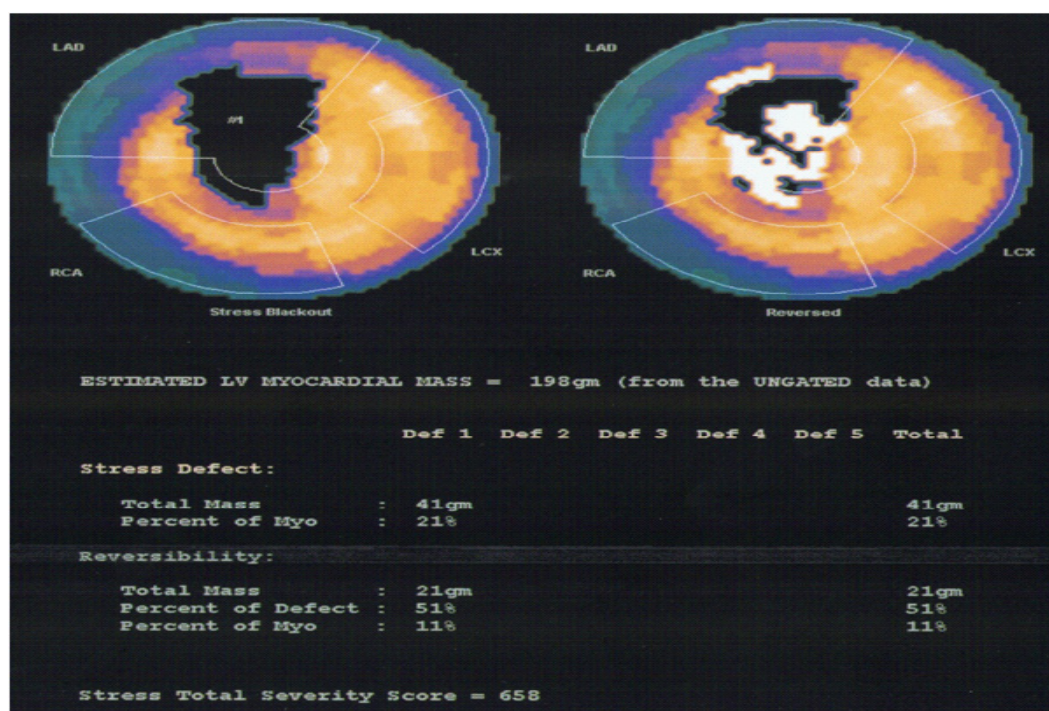
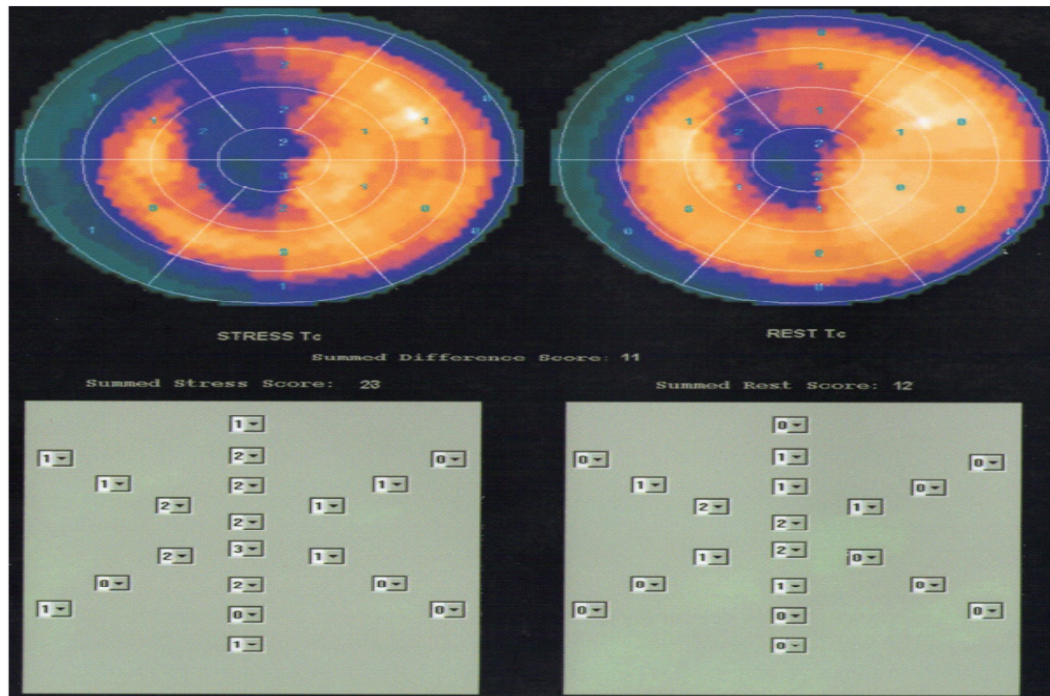


Fig1. 201Tl Reversibility

- 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).<sup>11</sup> Hibernation minimum threshold of 20% of the total LV myocardium was used to classify the heart as viable.<sup>12, 13</sup>



**Fig2.** The same patient as in Fig 1

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

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.<sup>14</sup>

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.<sup>15</sup> 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.<sup>16, 17</sup>

EDD and EF were measured echocardiologically.<sup>18, 19</sup>

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.

**Table1.** Demographic, anthropometric and clinical characteristics of the patricipating to the survey subjects depending on VIA

|   | VIA      |          |         |
|---|----------|----------|---------|
|   | Presence | Absence  | p-value |
| N   | 29       | 26       |         |
| Age (years)   | 66±10    | 63±10    | 0,22    |
| Body Mass Index (kg/m <sup>2</sup> )  | 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 |          |          |         |



**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).

**Table2.** *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 $\pm$ 3,01 | 7,23 $\pm$ 2,39 | 0,52    |
| CCS  | 1,72 $\pm$ 0,80 | 1,31 $\pm$ 0,62 | 0,036   |
| ETT duration (min)   | 6,93 $\pm$ 2,57 | 8,36 $\pm$ 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 $\pm$ 16.23 vs 3.86 $\pm$ 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  $\pm$  8.72 for ANG vs 62.70  $\pm$  8.74 mm,  $p=0.35$  and EF 34.30  $\pm$  9.15% for ANG pts vs 31.38  $\pm$  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  $^{201}\text{Tl}$  initial defect was 15% in ANG group vs 10% ( $p=0.38$ ) and within the entire myocardium 3.13 vs 2.88 ( $p=0.87$ ).

$^{201}\text{Tl}$  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 ( $16 \pm 19\%$  vs  $7 \pm 10\%$ ,  $p=0.04$  and  $5 \pm 5\%$  vs  $2 \pm 2\%$ ,  $p=0.02$ ).

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 ( $2.03 \pm 1.14$  vs  $3.00 \pm 1.82$ ,  $p=0.04$ ) and Gensini score ( $58 \pm 49$  vs  $109 \pm 83$ ,  $p=0.02$ ) and larger EDD ( $64 \pm 9$  vs  $59 \pm 7$  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 1<sup>st</sup> 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  $\geq 2$ ) 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<sup>6,7,20</sup>. Only VIA and ANG prevalence was investigated without need for follow-up.<sup>21, 22, 23</sup>

The evaluation of ANG at ETT was performed by one – the chief – investigator, to ensure homogeneity in assessment of this complaint. We used standard  $^{201}\text{Tl}$  scintigraphy techniques<sup>11</sup>.

VIA classification was based on the minimum general accepted 20% reversibility threshold within the infarct-zone and  $^{201}\text{Tl}$  uptake  $\geq 50\%$  of the maximum count in normal segments.<sup>24,25</sup> At least 20% viable dysfunctional segments are required to result in LVEF improvement<sup>12, 13</sup>. 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.<sup>26,27</sup> 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.<sup>28</sup> Patients classified as everyday-life ANG (CCS  $\geq \text{II}$ ) 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”.<sup>15</sup> 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 segments<sup>29</sup>. 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.<sup>30</sup>

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.<sup>5</sup> 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.<sup>31</sup> 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.<sup>9</sup> 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.<sup>32,33</sup>

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.<sup>34</sup> 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.<sup>35</sup>  $\beta$ -blockers were not routinely stopped before <sup>201</sup>Tl stress testing; no specific recommendations exist as regards their use for ECG, scintigraphic or echocardiographic testing.<sup>36,37,38</sup> 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.<sup>39</sup>

### 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 TI<sup>201</sup> 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.

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| 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 conceceptor 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.

### REFERENCES

1. Schinkel AF, Poldermans D, Elhendy A, Bax JJ. Assessment of myocardial viability in patients with heart failure. J Nucl Med. 2007; 48: 1135-1146.
2. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A et al; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011; 364: 1607-1616.
3. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P et al; STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011; 364: 1617-1625.
4. Perrone-Filardi P, Pinto FJ. Looking for myocardial viability after a STICH trial: not enough to close the door. J Nucl Med 2012; 53: 349-352.

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

5. Gimelli A, Neto JA, Marcassa C, Ferrazzi P, Glauber M, Marzullo P. Beneficial effects of coronary revascularization in patients with ischaemic left ventricular dysfunction with and without anginal symptoms. *Interact Cardiovasc Thorac Surg* 2002; 1: 9-15.
6. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)<sup>1</sup>; European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T et al. Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31: 2501-2555.
7. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011; 124: e574-651. doi: 10.1161/CIR.0b013e31823ba622. Epub 2011 Nov 7.
8. Partington SL, Kwong RY, Dorbala S. Multimodality imaging in the assessment of myocardial viability. *Heart Fail Rev*. 2011 Jul;16(4):381-95. doi: 10.1007/s10741-010-9201-7.
9. Chan RKM, Raman J, Lee KJ, Rosalion A, Hicks RJ, Pornvilawan S et al. Prediction of outcome after revascularization in patients with poor left ventricular function. *Ann Thorac Surg* 1996; 61: 1428-1434.
10. Pagano D, Townend JN, Littler WA, Horton R, Camici PG, Bonser RS. Coronary artery bypass surgery as treatment for ischemic heart failure: the predictive value of viability assessment with quantitative positron emission tomography for symptomatic and functional outcome. *J Thorac Cardiovasc Surg* 1998; 115: 791-799.
11. Holly TA, Abbott BG, Al-Mallah M, Calnon DA, Cohen MC, DiFilippo FP, et al; American Society of Nuclear Cardiology. Single photon-emission computed tomography. *J Nucl Cardiol*. 2010 Oct;17(5):941-73. doi: 10.1007/s12350-010-9246-y.
12. Schinkel AF, Poldermans D, Elhendy A, Bax JJ. Assessment of myocardial viability in patients with heart failure. *J Nucl Med*. 2007 Jul;48(7):1135-46. Epub 2007 Jun 15.
13. Mule JD, Bax JJ, Zingone B, Martinelli F, Burelli C, Stefania A et al. The beneficial effect of revascularization on jeopardized myocardium: reverse remodeling and improved long-term prognosis. *Eur J Cardiothorac Surg*. 2002 Sep;22(3):426-30.
14. Camargo LA, Pereira CA. Dyspnea in COPD: beyond the modified Medical Research Council scale. *J Bras Pneumol* 2010; 36: 571-578.
15. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981; 64: 1227-1234.
16. P. Sellier. Angina pectoris in patients with a history of myocardial infarction. *Eur Heart J* 1996; 17 Suppl G: 25-29.
17. Wang CH, Hsieh IC, Chen SJ, Wang JS, Cherng WJ, Chen CC et al. VE-Cadherin(low) $\alpha$ -smooth muscle actin+ component of vascular progenitor cells correlates with the coronary artery Gensini score. *Circ J* 2012; 76: 477-484.
18. Kaufmann BA, Min SY, Goetschalckx K, Bernheim AM, Buser PT, Pfisterer ME et al. How reliable are left ventricular ejection fraction cut offs assessed by echocardiography for clinical decision making in patients with heart failure? *Int J Cardiovasc Imaging* 2013; 29: 581-588.

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

19. Shahgaldi K, Gudmundsson P, Manouras A, Brodin LA, Winter R. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated with quantitative ejection fraction by real-time three dimensional echocardiography. *Cardiovasc Ultrasound*. 2009 Aug 25;7:41. doi: 10.1186/1476-7120-7-41 .
20. JCS Joint Working Group. Guidelines for Secondary Prevention of Myocardial Infarction (JCS 2011). *Circ J*. 2013;77(1):231-48.
21. Ishihara M, Fujino M, Ogawa H, Yasuda S, Noguchi T et al; J-MINUET investigators. Clinical Presentation, Management and Outcome of Japanese Patients With Acute Myocardial Infarction in the Troponin Era – Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET). *Circ J*. 2015 Apr 24.
22. Kawana A, Takahashi J, Takagi Y, Yasuda S, Sakata Y et al; Japanese Coronary Spasm Association. Gender differences in the clinical characteristics and outcomes of patients with vasospastic angina--a report from the Japanese Coronary Spasm Association. *Circ J*. 2013;77(5):1267-74.
23. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V et al; NRM Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012 Feb 22;307(8):813-22. doi: 10.1001/jama.2012.199.
24. Goel PK, Bhatia T, Kapoor A, Gambhir S, Pradhan PK, Barai S, Tewari S, Garg N, Kumar S, Jain S, Madhusudan P, Murthy S. Left ventricular remodeling after late revascularization correlates with baseline viability. *Tex Heart Inst J*. 2014 Aug 1;41(4):381-8. doi: 10.14503/THIJ-13-3585. eCollection 2014.
25. Haque T, Furukawa T, Takahashi M, Kinoshita M. Identification of hibernating myocardium by dobutamine stress echocardiography: comparison with thallium-201 reinjection imaging. *Am Heart J*. 1995 Sep;130(3 Pt 1):553-63.
26. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995; 25: 333-341.
27. Sirker A, Sohal M, Oldroyd K, Curzen N, Stables R, de Belder A et al. The impact of coronary bifurcation stenting strategy on health-related functional status: a quality-of-life analysis from the BBC One (British Bifurcation Coronary; Old, New, and Evolving Strategies) study. *JACC Cardiovasc Interv* 2013; 6: 139-145.
28. Kaul P, Naylor CD, Armstrong PW, Mark DB, Theroux P, Dagenais GR. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification. *Can J Cardiol*. 2009 Jul;25(7):e225-31. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2723031/pdf/cjc25e225.pdf> Accessed date : 30th Nov 2015
29. Taylor GJ, Humphries JO, Mellits ED, Pitt B, Schulze RA, Griffith LS, Achuff SC. Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation*. 1980 Nov;62(5):960-70.
30. Lamirault G, Susen S, Forest V, Hemont C, Parini A, Le Corvoisier P et al. Difference in mobilization of progenitor cells after myocardial infarction in smoking versus non-smoking patients: insights from the BONAMI trial. *Stem Cell Res Ther*. 2013;4(6):152.
31. Gimelli A1, Glauber M, Giorgetti A, Sambuceti G, L'Abbate A, Marzullo P. Revascularization of dysfunctional myocardium: differential prognostic effects of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in patients with three-vessel disease and mostly viable myocardium. *Interact Cardiovasc Thorac Surg*. 2003 Sep;2(3):301-306.

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

32. Freedland KE, Carney RM, Krone RJ, Smith LJ, Rich MW, Eisenkramer G et al. Psychological factors in silent myocardial ischemia. *Psychosom Med* 1991; 53: 13-24.
33. Trovato GM, Pace P, Tamburino C, Garufi G, Martines GF, Pirri C et al. Elective coronary stent patients: preinterventional functional status and clinical-instrumental assessment. *Heart Vessels*. 2010; 25: 82-86.
34. Dagenais GR, Lu J, Faxon DP, Bogaty P, Adler D, Fuentes F et al; BARI 2D Study Group. Prognostic impact of the presence and absence of angina on mortality and cardiovascular outcomes in patients with type 2 diabetes and stable coronary artery disease: results from the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial. *J Am Coll Cardiol* 2013; 61: 702-711.
35. Notghi A, Low CS. Myocardial perfusion scintigraphy: past, present and future. *Br J Radiol*. 2011 Dec;84 Spec No 3:S229-36. doi: 10.1259/bjr/14625142.
36. Gary J. Balady, Anthony P. Morise. Exercise testing. In: Braunwald's Heart Disease – A Textbook of Cardiovascular Medicine – Tenth Edition: p. 155-174
37. Fallahi B, Beiki D, Akbarpour S, Gholamrezanezhad A, Fard-Esfahani A, Akhzari F. et al. Withholding or continuing beta-blocker treatment before dipyridamole myocardial perfusion imaging for the diagnosis of coronary artery disease? A randomized clinical trial. *Daru*. 2013 Jan 15;21(1):8. doi: 10.1186/2008-2231-21-8.
38. Sicari R. Anti-ischemic therapy and stress testing: pathophysiologic, diagnostic and prognostic implications. *Cardiovasc Ultrasound*. 2004 Aug 20;2:14.
39. Hamby RI, Hamby B, Hoffman I. Symptomatic coronary disease for 20 or more years: clinical aspects, angiographic findings, and therapeutic implications. *Am Heart J*. 1986 Jul;112(1):65-70.

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