Interaction of Impaired Coronary Flow Reserve and Cardiomyocyte Injury on Adverse Cardiovascular Outcomes in Patients Without Overt Coronary Artery Disease

Running title: Taqueti et al.; Flow Reserve, Troponin and Cardiovascular Outcomes

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Abstract

Background—Minimally elevated serum cardiac troponin (Tn) reflects myocardial injury and is associated with increased mortality, even absent coronary artery disease (CAD). We sought to investigate the relationship between low-level Tn elevation and impaired coronary flow reserve (CFR), an integrated measure of coronary vasomotor function, and assess their contributions to adverse outcomes in patients without overt CAD.

Methods and Results—Consecutive patients (N=761) undergoing evaluation for suspected CAD with Tn before stress myocardial perfusion positron emission tomography (PET), were followed (median 2.8 years) for major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction or late revascularization. Patients with flow-limiting CAD, left ventricular ejection fraction (LVEF) <40%, and/or revascularization within 60 days of imaging were excluded. CFR was quantified from stress/rest myocardial blood flow using PET. Compared to patients with negative Tn, those with at least one positive Tn (n=97) had higher pretest clinical scores, more renal dysfunction, and lower LVEF and CFR. In adjusted analysis, impaired CFR remained independently associated with positive Tn (odds ratio 2.18, 95%CI 1.37-3.47, P=0.001), and both impaired CFR and positive Tn independently associated with MACE (hazard ratio 2.25; 95%CI 1.31-3.86; P=0.003 and 2.42; 95%CI 1.34-4.40; P=0.004, respectively). Impaired CFR and positive Tn identified patients at highest risk of MACE (log-rank P<0.0001), with a significant interaction (P<0.007) seen between CFR and Tn.

Conclusions—In patients without overt CAD, impaired CFR independently associated with minimally elevated Tn and MACE. Impaired CFR, here reflecting microvascular dysfunction, modified the effect of a positive Tn on adverse outcomes.

Key words: coronary artery disease, troponin, coronary flow reserve, microvascular dysfunction
Minimally elevated levels of serum cardiac troponin are associated with increased mortality, even among subjects without acute coronary syndromes (ACS)\(^1\text{–}^3\) or overt coronary artery disease.\(^4\) Increasing evidence from screening of large epidemiologic cohorts, primarily using high-sensitivity cardiac troponin assays, suggests that subclinical cardiac structural abnormalities may contribute to excess risk,\(^5\text{–}^6\) especially of incident heart failure,\(^7\text{–}^8\) in patients with low but detectable levels of troponin. These cardiac troponin values have been associated with the presence of left ventricular hypertrophy, diabetes mellitus and chronic kidney disease.\(^9\text{,}^10\)

Although impaired hemodynamics, endothelial dysfunction and coronary vasomotor stiffness, all of which may lead to chronic myocardial ischemia and injury, have been invoked as potential mechanisms of mild elevations in cardiac troponin,\(^9\text{,}^11\) the pathophysiology of this process in non-ACS settings remains unclear.

Coronary vascular dysfunction, as assessed by a reduced coronary flow reserve (CFR, calculated as the ratio of hyperemic to rest absolute myocardial blood flow), is highly prevalent among patients with known or suspected coronary artery disease (CAD), and identifies patients at high risk for major adverse cardiac events, including cardiac death.\(^12\text{–}^15\) These associations are seen even in the absence of obstructive epicardial CAD\(^16\) or defects in relative myocardial perfusion imaging,\(^14\text{,}^15\) and are especially evident across heterogeneous-risk cohorts, such as those with diabetes,\(^17\) older age,\(^18\text{,}^19\) or chronic kidney disease,\(^20\) in whom diffuse atherosclerosis and/or microvascular dysfunction likely contribute to adverse outcomes. Because CFR provides a quantitative assessment of the integrated effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction,\(^21\) its role as a sensitive marker of myocardial tissue perfusion warrants further investigation.

We sought to explore the mechanistic relationship between biomarkers of coronary
vasomotor function and low-level myocardial injury, and their contributions to cardiovascular outcomes in patients without overt CAD. We hypothesized that impaired CFR, as quantified noninvasively by positron emission tomography (PET), associates independently with low, but positive levels of cardiac troponin, and that both impaired CFR and elevated troponin associate independently with adverse cardiovascular outcomes.

Methods

Study Population

Study participants were consecutive patients referred for serial serum cardiac troponin testing within 14 days prior to stress testing with myocardial perfusion PET for evaluation of suspected CAD at Brigham and Women’s Hospital (BWH) between January 1, 2006 and July 31, 2011. The most common indications for testing included evaluation of chest pain, dyspnea or their combination. Patient history, medication use and select laboratory values were ascertained at time of PET imaging. From 1975 patients, a final cohort of 761 was established after excluding those with known CAD (including prior revascularization and/or myocardial infarction), known severe valvular disease, PET evidence of flow-limiting CAD (semi-quantitative perfusion summed stress score >2) or left ventricular ejection fraction (LVEF) <40%, and/or coronary revascularization within 60 days of imaging. Thus, no patients with positive troponin demonstrated a rise and fall of troponin values in concert with electrocardiographic changes or symptoms to prompt an early invasive clinical strategy of angiography and revascularization for ACS. The study population therefore included patients who “ruled out” for significant disease using conventional clinical diagnostics. A pretest clinical score integrating age, sex, type of chest pain, presence of hypertension, diabetes, hyperlipidemia, current smoking, family history
of premature CAD, body mass index (BMI) > 27 kg/m², and estrogen status into a pretest probability of finding ≥50% stenosis in ≥1 major coronary artery on angiography was calculated as previously described, with values 0-8, 9-15, and 16-24 indicating low, intermediate, and high pre-test probability scores, respectively. The estimated glomerular filtration rate (eGFR) was determined using the abbreviated Modification of Diet in Renal Disease formula, with values over 60 ml/min/1.73m² reported as >60 by local laboratory convention. The study was approved by the Partners Healthcare Institutional Review Board, and conducted in accordance with institutional guidelines.

**Serum Cardiac Troponins**

All patients underwent serial assessment of serum cardiac troponin using the clinically-available local assay within 14 days prior to PET imaging. Serial assessment involved three consecutive blood draws approximately every 8 hours over a 24-hour period. From 2006 to 2011, 3 different troponin assays were sequentially utilized at BWH: cTnl (Siemens Healthcare Diagnostics, initially introduced by Bayer HealthCare LLC, Diagnostics Division) with reference range <0.10 μg/L reflecting a 99th-percentile cutoff point of 0.16 μg/L; Tnl-Ultra (Siemens Healthcare Diagnostics) with reference range <0.04 μg/L reflecting a 99th-percentile cutoff point of 0.04 μg/L; and cTnT fourth-generation Elecsys (Roche Diagnostics) with reference range <0.01 μg/L reflecting a 99th-percentile cutoff point of less than 0.01 μg/L. Values above the reference range indicate a positive troponin. The peak value from serial assessment for each patient was used.

**PET Imaging**

Patients were imaged with a whole-body PET–computed tomography scanner (Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, WI) using ⁸²Rubidium (1480-2200 MBq) as the
flow tracer at rest and pharmacologic stress, as previously described.\textsuperscript{26} Computed tomography was used for attenuation correction only. For semi-quantitative assessment of myocardial scarring and ischemia, 17-segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard five-point scoring system.\textsuperscript{27} Summed rest, stress, and difference (stress – rest) scores, with higher scores reflecting larger areas of myocardial scar, scar plus ischemia, or ischemia, respectively, were computed; summed stress scores \( \leq 2 \) were considered normal.\textsuperscript{28} Rest LVEFs were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM; Ann Arbor, Michigan), and LV mass was indexed to body surface area.

Absolute global myocardial blood flow (MBF, in mL/min/g) was quantified at rest and at peak hyperemia using automated factor analysis and a validated two-compartment kinetic model, as previously described.\textsuperscript{26} Hyperemia was achieved predominantly through vasodilation with regadenoson or dipyridamole. Per-patient global CFR was calculated as the ratio of stress to rest absolute MBF for the whole left ventricle. Rest MBF and CFR were corrected for rest rate pressure product (heart rate x systolic blood pressure), an index of baseline cardiac work. Stress coronary vascular resistance was calculated by dividing stress mean arterial pressure by myocardial blood flow. MBF and CFR values were not clinically available to referring physicians. Radiation exposure per study was \( \leq 4.6 \) mSv. Quantitative measures of CFR were obtained in patients undergoing PET myocardial perfusion at no additional clinical cost, imaging time or radiation exposure.

**Outcomes**

Subjects were followed for the occurrence of a first major adverse cardiovascular event (MACE). The pre-specified primary endpoint was a composite of cardiovascular death, nonfatal
myocardial infarction or late coronary revascularization (occurring after 60 days from PET imaging). Ascertainment of clinical endpoints was determined by blinded adjudication of the longitudinal medical record, Partners Healthcare Research Patient Data Registry, the Social Security Death Index, and the National Death Index. Only events meeting the 2012 Third Universal Definition of Myocardial Infarction\(^29\) were classified as such; all myocardial infarctions occurred \(>30\) days following initial Tn assessment. The date of the last consultation was used to determine follow-up. Over 90\% of patients had \(>30\) days of follow-up.

**Statistical Analysis**

Baseline characteristics are reported as rates with percentages (%) for categorical variables and medians with first and third quartiles (Q1-Q3) for continuous variables. We used Fisher's-exact test and the Wilcoxon rank-sum test to assess differences in categorical and continuous baseline characteristics. A positive peak troponin value (e.g., above the reference range for the specific assay) was used as a pre-specified dichotomous variable in order to accommodate the three different assays with varying detection thresholds in clinical use throughout the study period. For clinical convenience, we display CFR primarily as a dichotomous variable using \(<2\) as a cutpoint for an impaired ratio. CFR \(<2\) is associated with worse cardiovascular outcomes in a general referral population,\(^{13-15}\) and approximately serves as a median value in our patient population. Where indicated, we also report analyses performed using CFR as a continuous variable (in increments of \(-1\) absolute units).

Logistic regression was used to assess the independent relationship between CFR and positive troponin. Candidate variables tested included demographic characteristics, medical history and medication use, and noninvasive imaging parameters, with the most clinically important covariates and/or significant univariable associations included in the multivariable
model. To avoid overfitting, demographic and medical history variables (age, sex, chest pain, type, hypertension, diabetes, hyperlipidemia, smoking history, family history of premature CAD, BMI, and estrogen status) were incorporated into a validated, aforementioned pretest clinical score\(^2\) in the final model.

Cumulative event-free survival curves for the primary MACE endpoint of cardiovascular death, nonfatal myocardial infarction or late revascularization were compared across dichotomous categories of positive troponin and impaired CFR using the log-rank test. Cox proportional-hazards models were used to examine the association between troponin, CFR and outcome events after controlling for effects of clinically important covariates. Data were censored at the time of the last visit. Univariate associations were tested, and Cox models sequentially added pretest clinical score and laboratory and imaging variables, with collinearity index used to check for linear combinations among covariates, and the Akaike information criterion assessed to avoid overfitting. The proportional hazards assumption was evaluated using martingale residuals,\(^3\) and time-dependent variables included as necessary. An interaction term for troponin and CFR was tested for significance in the adjusted model. The final model with troponin and CFR was, in addition, adjusted for pretest clinical score, LVEF, and estimated GFR. A P-value of <0.05 was considered to indicate statistical significance, and all tests were two-sided. No adjustment for multiple comparisons was performed. The SAS analysis system, version 9.3, was used for all analyses (SAS Institute).

**Results**

**Baseline Characteristics and Distribution of Positive Cardiac Troponins**

Distribution of baseline characteristics is shown between categories of troponin status (**Table 1**).
The median (Q1-Q3) age of patients in the overall cohort was 62 (53-73) years, 71.0% were women, 58.0% were white, and median pretest clinical score was 12 (8-14), consistent with intermediate risk of coronary artery disease. Over three-quarters of patients had history of hypertension, over half had dyslipidemia, and nearly one-third had diabetes mellitus. Compared to patients with negative troponin (n=664), those with positive troponin (n=97) were older, with more renal dysfunction, higher use of cardiovascular medications, lower LVEF and lower CFR. Lower CFR was driven by reduced myocardial blood flow at peak stress, not differences in myocardial blood flow at rest.

Distribution of peak serum cardiac troponin values is shown (Figure 1) by clinically-available assay (reference range): cTnT (<0.01 μg/L), 32.5%; cTnI-Ultra (<0.04 μg/L) 63.6%, cTnI (0.1 μg/L), 3.9%. Ninety-seven patients (12.7%) had a peak troponin value above the assay reference range on serial testing prior to PET imaging. Of these positive troponin values, most were minimally elevated above the reference range. Median (Q1-Q3) values for troponin by assay (reference range) were: cTnT (<0.01 μg/L), 0.03 (0.02-0.06); cTnI-Ultra (<0.04 μg/L), 0.08 (0.05-0.14); and cTnI (0.1 μg/L), 0.13 (0.11-0.14).

Association Between Positive Troponin and Impaired Coronary Flow Reserve

In univariable analysis, there was a significant association between impaired CFR and a positive troponin (odds ratio for CFR<2 relative to ≥2 was 2.45, 95% confidence interval (CI) 1.57-3.82, P<0.0001). This association remained significant in a multivariable logistic regression model incorporating pretest clinical score, LVEF, eGFR, atrial fibrillation and use of aspirin, statins, beta-blockers, and/or angiotensin inhibitors (Figure 2, adjusted odds ratio for CFR was 2.18, 95%CI 1.37-3.47, P=0.001). When CFR was analyzed as a continuous variable, consistent results were seen for univariable and multivariable associations between CFR and a positive...
troponin (odds ratio and adjusted odds ratio per 1 unit decrease in CFR, 1.80, 95%CI 1.34-2.43, P=0.0001 and 1.62, 95% CI 1.19-2.20, P=0.002, respectively) (Table 2). Impaired CFR thus associated independently with low, but positive levels of cardiac troponin in a population of patients without flow-limiting CAD.

**Coronary Flow Reserve, Positive Troponin and Incident Cardiovascular Events**

During follow-up over a median of 2.8 years (Q1-Q3 1.6-4.0), 60 (7.9%) subjects met the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction or late revascularization, including 23 deaths (Table 3). There were 377 patients with negative troponin and preserved CFR, 35 patients with positive troponin and preserved CFR, 287 patients with negative troponin and impaired CFR, and 62 patients with positive troponin and impaired CFR. This latter subgroup demonstrated the highest risk of MACE (log-rank P<0.0001) (Figure 3A).

In univariable modeling, cumulative incidence of MACE was significantly associated with impaired CFR (hazard ratio 2.48, 95% CI 1.45-4.24, P=0.001), as well as a positive troponin (hazard ratio 3.31, 95% CI 1.89-5.82, P<0.001). The addition of clinically important covariates into a multivariable model, including pretest clinical score, LVEF, and eGFR category led to significant associations for impaired CFR or positive troponin (adjusted hazard ratio for impaired CFR 2.25, 95% CI 1.31-3.86, P=0.003; and for positive troponin 2.42, 95% CI 1.34-4.40, P=0.004, respectively) (Table 4). These associations remained significant after including both CFR and troponin status into the model adjusting for pretest clinical score, LVEF and eGFR (adjusted hazard ratio for impaired CFR 2.05, 95% CI 1.19-3.56, P=0.01; and for positive troponin 2.10, 95% CI 1.15-3.85, P=0.02, respectively). Consistent results were seen across models for hazard ratios using CFR as a continuous variable. In addition, there was a significant interaction between troponin status and CFR as a continuous variable, with P<0.007 in the final
adjusted model. In adjusted analysis, only those patients with positive troponin and impaired CFR experienced the highest cumulative incidence of events (P<0.0001) (Figure 3B). This is further illustrated in Figure 4, which shows that patients with low CFR and positive troponin had significantly higher adjusted event rates than any other subgroups. In contrast, patients with high CFR and positive troponin showed event rates that were not statistically different from those with high CFR and negative troponin.

Coronary flow reserve thus associated with incident cardiovascular events independently of troponin status, and impaired coronary flow reserve and positive troponin together identified patients at highest risk of events. These data demonstrate that presence of impaired coronary flow reserve modified the effect of cardiac troponin elevation on risk of MACE, such that only troponin-positive patients with concomitant impairment in coronary flow reserve experienced worse cardiovascular outcomes.

Discussion

We demonstrate for the first time that impaired global CFR independently associated with positive cardiac troponin, and that both positive troponin and impaired CFR independently associated with adverse cardiovascular outcomes, in patients without overt (flow-limiting) CAD. Furthermore, we provide evidence, via a highly significant interaction, for effect modification of the association between troponin status and the primary endpoint of cardiovascular death, nonfatal MI and late revascularization, by CFR.

In the setting of increased oxygen demand, impaired CFR reflects an upset supply-demand relationship, which may, in turn, exacerbate myocardial ischemia and injury, and worsen global ventricular mechanics and dysfunction. In patients without evidence of flow-limiting...
CAD and relatively preserved LVEF, this supply-demand mismatch may occur at the level of the microcirculation,\textsuperscript{32} increasing coronary vascular resistance and cardiomyocyte workload,\textsuperscript{33} and triggering maladaptive responses that may further exacerbate existing endothelial dysfunction and subendocardial ischemia,\textsuperscript{34} resulting in low-level myocyte injury and extracellular matrix remodeling. It is this complex interplay of insults, exactly in the comorbid population of hypertensive, diabetic, older, often female patients with chronic kidney disease, as represented in this study, that may synergize to propagate the ventricular-vascular stiffening which may be central to the emerging epidemic of heart failure with preserved ejection fraction (HF-PEF).\textsuperscript{35, 36}

Indeed, recent data reframe HF-PEF as a disorder of “cardiovascular reserve function,” in which low-level inflammation in the coronary microvasculature may serve as a potential driver of myocardial dysfunction and remodeling,\textsuperscript{35, 37} and possibly also coronary vasomotor dysfunction.\textsuperscript{38, 39} The observation that chronic circulating levels of high-sensitivity troponins are associated with increased incidence of cardiovascular death or heart failure (but not ACS) in patients with stable CAD and preserved LVEF,\textsuperscript{7, 40, 41} underscores the likely interplay of chronic microvascular dysfunction and subclinical myocardial injury in the pathway to diastolic dysfunction and heart failure outcomes. Additional studies are warranted to explore further a mechanistic relationship between distal coronary ischemia, low-level cardiomyocyte injury and adverse structural remodeling, which may ultimately lead to cardiovascular outcomes, including HFpEF.

This study must be interpreted in the context of its single-center observational design, in which subjects were patients clinically referred for serial cardiac troponin assessment and subsequent PET myocardial perfusion imaging. CFR results were not available to referring clinicians, and thus did not affect downstream management decisions regarding additional testing
or therapies. At our institution, PET myocardial perfusion imaging is routinely available and used in patients with a high prevalence of risk factors who are unable to exercise optimally, as it provides additional sensitivity for detection of perfusion abnormalities while exposing patients to less radiation and shorter testing duration. Also, the locally-available troponin assays varied over the course of the study period, and high-sensitivity troponins assays were not available. Nonetheless, a recent small study of patients with nonischemic cardiomyopathy demonstrated that release of high-sensitivity cardiac troponin T (cTnT) correlated with elevated LV end-diastolic pressure measured invasively, and that 18 patients manifesting impaired coronary flow reserve (<2, by Doppler flow velocity in the left anterior descending artery) showed higher levels of cTnT.\textsuperscript{42} That we see the described associations and a significant interaction between less sensitive troponin assays and coronary flow reserve in the current study suggests that these relationships are robust. Thus, we expect that even stronger associations may be present between measures of CFR and cardiac troponin values measured using newer high-sensitivity assays in a similar patient population, and future work should test this hypothesis. Our relatively modest sample size limits extensive subgroup analysis for outcomes. That very few patients demonstrated both a preserved CFR and a positive Tn may indicate a shared pathway underlying low-level injury and ischemia, although this cannot be discerned from the present data.

This study cohort was specifically defined so as to exclude overt CAD, by excluding patients with prior myocardial infarction, coronary revascularization by CABG or PCI, and abnormal semi-quantitative perfusion (using a stringent cutoff of SSS >2) on index PET imaging. To minimize overt structural abnormalities, we also excluded patients with known severe valvular disease and LVEF \textless 40\%. Although it is conceivable that some patients in this intermediate pretest-risk cohort harbored severe, flow-limiting multi-vessel CAD without
perfusion abnormalities, our clinical experience with PET suggests this to be unlikely (i.e. in a
much higher pretest-risk population referred for invasive catheterization, of a minority of 52
patients with SSS ≤3, 4 were found to have obstructive multi-vessel disease, with noninvasive
imaging also showing accompanying high-risk features such as abnormal LVEF or transient
ischemic dilation16).

Despite inherent limitations and the inability to draw temporal or causal inferences, this
work is the first to link the associations of functional biomarkers of coronary flow reserve and
positive troponin with clinically-meaningful cardiovascular outcomes in a real-world population
of patients without flow-limiting CAD. Prospective studies are warranted to investigate the role
of impaired coronary flow reserve as a target for intervention in disorders of chronic ischemia
and inflammation.

Conclusions
In patients without overt CAD, impaired coronary flow reserve independently associated with
mildly elevated cardiac troponin, and remained independently associated with adverse
cardiovascular events. CFR modified the effect of a positive troponin on cardiovascular
outcomes, such that only those patients with detectable troponin and impaired CFR were at
highest risk of events.

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Table 1. Baseline Characteristics of Patients by Troponin Status

<table>
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<tr>
<th>Characteristic</th>
<th>Overall (N = 761)</th>
<th>Cardiac Troponin†</th>
<th>P†</th>
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<tr>
<td></td>
<td></td>
<td>Negative (n = 664)</td>
<td>Positive (n = 97)</td>
</tr>
<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Age‡, y (Q1-Q3)</td>
<td>62 (53-73)</td>
<td>62 (53-72)</td>
<td>67 (59-82)</td>
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<tr>
<td>Female sex (%)</td>
<td>540 (71.0)</td>
<td>479 (72.1)</td>
<td>61 (62.9)</td>
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<tr>
<td>White race (%)</td>
<td>441 (58.0)</td>
<td>397 (59.8)</td>
<td>44 (45.4)</td>
</tr>
<tr>
<td>Body mass index‡, kg/m²</td>
<td>29.9 (25.4-35.7)</td>
<td>30.1 (25.7-35.8)</td>
<td>27.4 (23.0-34.4)</td>
</tr>
<tr>
<td>Pretest clinical score‡§ (0-24)</td>
<td>12 (8-14)</td>
<td>11 (8-14)</td>
<td>12 (9-15)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension (%)</td>
<td>581 (76.4)</td>
<td>501 (75.5)</td>
<td>80 (82.5)</td>
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<tr>
<td>Dyslipidemia (%)</td>
<td>408 (53.6)</td>
<td>354 (53.3)</td>
<td>54 (55.7)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>244 (32.0)</td>
<td>208 (31.3)</td>
<td>36 (37.1)</td>
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<td>Current smoker (%)</td>
<td>73 (9.6)</td>
<td>64 (9.6)</td>
<td>9 (9.3)</td>
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<td>Family history of CAD (%)</td>
<td>176 (23.1)</td>
<td>161 (24.3)</td>
<td>15 (15.5)</td>
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<tr>
<td>Atrial fibrillation (%)</td>
<td>34 (4.5)</td>
<td>27 (4.1)</td>
<td>7 (7.2)</td>
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<tr>
<td>eGFR &lt;60 ml/min/1.73m² (%)</td>
<td>172 (22.6)</td>
<td>126 (19.0)</td>
<td>46 (47.4)</td>
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<tr>
<td>Renal hemodialysis (%)</td>
<td>14 (1.8)</td>
<td>2 (0.3)</td>
<td>12 (12.4)</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Aspirin (%)</td>
<td>439 (57.7)</td>
<td>369 (55.6)</td>
<td>70 (72.2)</td>
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<td>Statin (%)</td>
<td>353 (46.4)</td>
<td>293 (44.1)</td>
<td>60 (61.9)</td>
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<td>Beta-blocker (%)</td>
<td>371 (48.8)</td>
<td>310 (46.7)</td>
<td>61 (62.9)</td>
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<tr>
<td>Nitrate (%)</td>
<td>50 (6.6)</td>
<td>45 (6.8)</td>
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<td>Angiotensin inhibitor (%)</td>
<td>232 (30.5)</td>
<td>193 (29.1)</td>
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<td>Diuretic (%)</td>
<td>236 (31.0)</td>
<td>201 (30.3)</td>
<td>35 (36.1)</td>
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<td>Insulin (%)</td>
<td>102 (13.4)</td>
<td>86 (13.0)</td>
<td>16 (16.5)</td>
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<tr>
<td>Noninvasive imaging parameters</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left ventricular ejection fraction‡, %</td>
<td>62 (56-68)</td>
<td>63 (57-68)</td>
<td>58 (51-65)</td>
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<td>Left ventricular mass index‡, g/m²</td>
<td>63.4 (56.2-69.9)</td>
<td>62.9 (56.1-69.5)</td>
<td>66.6 (58.4-74.3)</td>
</tr>
<tr>
<td>Rest Heart Rate‡, bpm</td>
<td>68 (61-78)</td>
<td>69 (61-78)</td>
<td>67 (61-77)</td>
</tr>
<tr>
<td>Rest Systolic Blood Pressure‡, mm Hg</td>
<td>150 (132-169)</td>
<td>150 (132-169)</td>
<td>153 (131-167)</td>
</tr>
<tr>
<td>Rest myocardial blood flow‡, ml/min/g</td>
<td>1.1 (0.8-1.4)</td>
<td>1.1 (0.8-1.4)</td>
<td>1.1 (0.8-1.4)</td>
</tr>
<tr>
<td>Stress global myocardial blood flow‡, ml/min/g</td>
<td>2.3 (1.7-2.9)</td>
<td>2.3 (1.7-2.9)</td>
<td>1.9 (1.5-2.5)</td>
</tr>
<tr>
<td>Stress coronary vascular resistance‡, mm Hg/ml/min/g</td>
<td>40.4 (31.1-56.5)</td>
<td>39.8 (30.7-55.5)</td>
<td>48.3 (34.2-63.7)</td>
</tr>
<tr>
<td>Coronary flow reserve‡, %</td>
<td>2.1 (1.6-2.7)</td>
<td>2.1 (1.6-2.7)</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td>Follow Up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up ≥30 days (%)</td>
<td>690 (90.7)</td>
<td>602 (90.7)</td>
<td>88 (90.7)</td>
</tr>
</tbody>
</table>

*Cardiac troponin T or I, as determined by clinically-available local assay; †The P-value is for the comparison between groups, and is based on the Fisher’s-exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables; ‡Continuous variables are presented as medians with first and third quartiles (Q1-Q3); §Pretest clinical score integrates age, sex, presence of hypertension, dyslipidemia, diabetes, BMI >27, estrogen status, smoking, history, family history, and angina history into a pretest probability of coronary artery disease in patients presenting for stress imaging with symptoms of suspected coronary artery disease. Risk: low (0-8), intermediate (9-15), high (>15); †The P-value is for the comparison of noninvasive imaging parameters of patients with positive and negative troponin status; ‖Stress coronary vascular resistance is calculated by dividing stress mean arterial pressure by coronary flow reserve.
Table 2. Association between Coronary Flow Reserve and Troponin Status.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable Model</th>
<th>Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;binary&lt;/sub&gt; †</td>
<td>2.45 (1.57-3.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;continuous&lt;/sub&gt; §</td>
<td>1.80 (1.34-2.43)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for pretest clinical score, left ventricular ejection fraction, estimated glomerular filtration rate <60, presence of atrial fibrillation, and use of aspirin, beta-blocker, statin, and angiotensin inhibitor.

†Coronary flow reserve <2 relative to ≥2.

§per 1 unit decrease in coronary flow reserve.

Table 3. Patients Meeting Clinical Endpoint.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients (Cumulative Event %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, nonfatal myocardial infarction or late revascularization§</td>
<td>60 (15.7)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>23 (6.7)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>29 (7.3)</td>
</tr>
<tr>
<td>Late revascularization§</td>
<td>14 (2.8)</td>
</tr>
</tbody>
</table>

*Median (Q1-Q3) of follow-up time was 2.8 (1.6-4.0) years; †Denotes cumulative event rate (%) from Kaplan-Meier estimates; §Late revascularization denotes revascularization >60 (median 576) days following noninvasive imaging. Six of the 14 late revascularization events occurred in the context of treatment for nonfatal myocardial infarction.

Table 4. Association between Coronary Flow Reserve, Troponin Status and Major Cardiovascular Events.*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable Model</th>
<th>Multivariable Model 1#</th>
<th>Multivariable Model 2##</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>Tn&lt;sub&gt;positive&lt;/sub&gt; ‡</td>
<td>3.31 (1.89-5.82)</td>
<td>&lt;0.001</td>
<td>2.42 (1.34-4.40)</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;binary&lt;/sub&gt; †</td>
<td>2.48 (1.45-4.24)</td>
<td>0.001</td>
<td>2.25 (1.31-3.86)</td>
</tr>
<tr>
<td>CFR&lt;sub&gt;continuous&lt;/sub&gt; §</td>
<td>1.75 (1.22-2.50)</td>
<td>0.002</td>
<td>1.61 (1.14-2.33)</td>
</tr>
</tbody>
</table>

*Major cardiovascular events denotes composite of cardiovascular death, nonfatal myocardial infarction and late revascularization (>60 days after imaging); †Tn denotes positive relative to negative serum cardiac troponin; ‡Coronary flow reserve <2 relative to ≥2; †per 1 unit decrease in coronary flow reserve; §Adjusted for pretest clinical score, left ventricular ejection fraction, and estimated glomerular filtration rate < 60; ##Adjusted for pretest clinical score, left ventricular ejection fraction, estimated glomerular filtration rate < 60, troponin status and coronary flow reserve. There is a significant interaction between troponin status and coronary flow reserve (as a continuous variable), P < 0.007.
Figure Legends:

Figure 1. Distribution of peak serum cardiac troponin values by clinically-available assay. A, Troponin (Tn) T, reference range <0.01 μg/L (Elecsys cTnT fourth-generation, Roche Diagnostics). B, Troponin I, reference range <0.04 μg/L (TnI-Ultra, Siemens Healthcare Diagnostics). C, Troponin I, reference range <0.10 μg/L, (cTnI, Siemens Healthcare Diagnostics). Values above the reference range indicate positive troponin. The peak value from serial assessment for each patient is shown.

Figure 2. Multivariable-adjusted associations for positive troponin. Model for positive troponin (Tn+) in patients without overt coronary artery disease (CAD) is shown, adjusted for all variables listed. Odds ratios (OR) with 95% confidence intervals (95% CI) are presented for a 10-unit decrease in left ventricular (LV) ejection fraction and a 1-unit increase in pretest clinical score, as well as for binary covariates. Pretest clinical score incorporates age, gender, presence of hypertension, dyslipidemia, diabetes, tobacco use, family history of premature CAD, body mass index ≥27 kg/m², estrogen status, and anginal history into a risk score of finding angiographic disease (≥50% lesion in ≥1 vessel) in a population of patients presenting for stress testing with symptoms of suspected CAD: low (0-8), intermediate (9-15), high (>15).²³

Figure 3. Freedom from major adverse cardiovascular event (MACE) by coronary flow reserve (CFR) and troponin (Tn) status. MACE includes cardiovascular death, nonfatal myocardial infarction and late revascularization (>60 days after stress testing). A, Kaplan-Meier (unadjusted) analysis of time to first event is shown. B, Event-free survival, adjusted for pretest clinical score, left ventricular ejection fraction and estimated glomerular filtration <60, is shown.
Figure 4. Adjusted annualized rates of MACE among patients by coronary flow reserve (CFR) and troponin (Tn) strata. Patients with low CFR and positive troponin (red) had significantly higher event rates than any other subgroups. Annualized event rates were adjusted for pretest clinical score, left ventricular ejection fraction, and estimated glomerular filtration rate <60.
Figure 2

- Coronary flow reserve <2
  - Adjusted OR (95% CI): 2.18 (1.37-3.47)  P = 0.001

- eGFR <60 ml/min/1.83m²
  - Adjusted OR (95% CI): 3.05 (1.91-4.88)  P < 0.001

- LV ejection fraction (-10%)
  - Adjusted OR (95% CI): 1.50 (1.17-1.92)  P = 0.002

- Pretest clinical score (+1)
  - Adjusted OR (95% CI): 1.59 (0.95-2.68)  P = 0.08

- Atrial fibrillation
  - Adjusted OR (95% CI): 1.21 (0.47-3.11)  P = 0.70

- Aspirin
  - Adjusted OR (95% CI): 1.49 (0.89-2.50)  P = 0.13

- Statin
  - Adjusted OR (95% CI): 1.33 (0.81-2.19)  P = 0.25

- Beta-blocker
  - Adjusted OR (95% CI): 1.31 (0.81-2.11)  P = 0.28

- Angiotensin inhibitor
  - Adjusted OR (95% CI): 1.25 (0.78-2.02)  P = 0.35
Figure 3

A. Unadjusted

B. Adjusted

Freedom from Event (%)

Days

P < 0.0001

Tn (-), CFR ≥ 2
Tn (+), CFR ≥ 2
Tn (-), CFR < 2
Tn (+), CFR < 2
Figure 4
Interaction of Impaired Coronary Flow Reserve and Cardiomyocyte Injury on Adverse Cardiovascular Outcomes in Patients Without Overt Coronary Artery Disease

Viviany R. Taqueti, Brendan M. Everett, Venkatesh L. Murthy, Mariya Gaber, Courtney R. Foster, Jon Hainer, Ron Blankstein, Sharmila Dobrala and Marcelo F. Di Carli

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