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

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

Methods and Results—Consecutive patients (n=761) undergoing evaluation for suspected CAD with troponin before stress myocardial perfusion positron emission tomography were followed up (median, 2.8 years) for major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, or late revascularization. Patients with flow-limiting CAD, left ventricular ejection fraction <40%, or revascularization within 60 days of imaging were excluded. CFR was quantified from stress/rest myocardial blood flow with the use of positron emission tomography. Compared with patients with negative troponin, those with at least 1 positive troponin (n=97) had higher pretest clinical scores, more renal dysfunction, and lower left ventricular ejection fraction and CFR. In adjusted analysis, impaired CFR remained independently associated with positive troponin (odds ratio, 2.18; 95% confidence interval, 1.37–3.47; \( P = 0.001 \)), and both impaired CFR and positive troponin were independently associated with major adverse cardiovascular events (hazard ratio, 2.25; 95% confidence interval, 1.31–3.86; \( P = 0.003 \); and hazard ratio, 2.42; 95% confidence interval, 1.34–4.40; \( P = 0.004 \), respectively). Impaired CFR and positive troponin identified patients at highest risk of major adverse cardiovascular events (log-rank \( P < 0.0001 \)), with a significant interaction (\( P < 0.007 \)) seen between CFR and troponin.

Conclusions—In patients without overt CAD, impaired CFR was independently associated with minimally elevated troponin and major adverse cardiovascular events. Impaired CFR, here reflecting microvascular dysfunction, modified the effect of a positive troponin on adverse outcomes. (Circulation. 2015;131:528-535. DOI: 10.1161/CIRCULATIONAHA.114.009716.)

Key Words: coronary artery disease ■ positron emission tomography ■ microcirculation ■ troponin

Minimally elevated levels of serum cardiac troponin are associated with increased mortality, even among subjects without acute coronary syndromes\(^1\)–\(^3\) or overt coronary artery disease (CAD).\(^4\) Increasing evidence from screening of large epidemiological cohorts, primarily with high-sensitivity cardiac troponin assays, suggests that subclinical cardiac structural abnormalities may contribute to excess risk,\(^5,6\) especially of incident heart failure,\(^7,8\) 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.\(^9,10\) 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,\(^9,11\) the pathophysiology of this process in the absence of acute coronary syndromes remains unclear.

Clinical Perspective on p 535

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 CAD and identifies patients at high risk for major adverse cardiac events, including cardiac death.\(^12\)–\(^15\) These associations are seen even in the absence of obstructive epicardial CAD\(^15\) or defects in relative...
myocardial perfusion imaging,14,15 and they are especially evident across heterogeneous-risk cohorts such as those with diabetes mellitus,17 older age,18,19 or chronic kidney disease20 in whom diffuse atherosclerosis and 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), is associated independently with low but positive levels of cardiac troponin and that both impaired CFR and elevated troponin are associated independently with adverse cardiovascular outcomes.

Methods

Study Population

Study participants were consecutive patients referred for serial cardiac troponin testing within 14 days before stress testing with myocardial perfusion PET for the evaluation of suspected CAD at Brigham and Women’s Hospital between January 1, 2006, and July 31, 2011. The most common indication for testing was evaluation of chest pain, dyspnea, or their combination. Patient history, medication use, and select laboratory values were ascertained at the time of PET imaging. From 1975 patients, a final cohort of 761 was established after the exclusion of those with known CAD (including prior revascularization 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%, 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 ECG changes or symptoms to prompt an early invasive clinical strategy of angiography and revascularization for acute coronary syndromes. The study population therefore included patients in whom significant disease was ruled out with conventional clinical diagnostics.22 A pretest clinical score integrating age, sex, type of chest pain, presence of hypertension, diabetes mellitus, hyperlipidemia, current smoking, family history of premature CAD, body mass index ≥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,23 with values of 0 to 8, 9 to 15, and 16 to 24 indicating low, intermediate, and high pretest probability scores, respectively. The estimated glomerular filtration rate (eGFR) was determined with the abbreviated Modification of Diet in Renal Disease formula. 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 before PET imaging. Serial assessment involved 3 consecutive blood draws approximately every 8 hours over a 24-hour period. From 2006 to 2011, 3 different troponin assays were used sequentially at Brigham and Women’s Hospital: cardiac troponin I (cTnI; Siemens Healthcare Diagnostics, initially introduced by Bayer HealthCare LLC, Diagnostics Division), with a reference range <0.10 µg/L reflecting a 99th-percentile cutoff point of 0.16 µg/L; Tnl-Ultra (Siemens Healthcare Diagnostics), with a reference range <0.04 µg/L reflecting a 99th-percentile cutoff point of 0.04 µg/L; and cardiac troponin T (cTnT) fourth-generation Elecsys (Roche Diagnostics), with a reference range <0.01 µg/L reflecting a 99th-percentile percentile cutoff point of <0.01 µg/L.24,25 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) with rubidium-82 (1480–2200 MBq) as the flow tracer at rest and pharmacological stress, as previously described.26 Computed tomography was used for attenuation correction only. For semiquantitative assessment of myocardial scar and ischemia, 17-segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard 5-point scoring system.27 Summed rest, stress, and difference (stress minus rest) scores, with higher scores reflecting larger areas of myocardial scar, scar plus ischemia, or ischemia, respectively, were computed; summed stress scores ≤2 were considered normal.28 Rest LVEFs were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM; Ann Arbor, MI), and left ventricular mass was indexed to body surface area.

Absolute global myocardial blood flow (in milliliters per minute per gram) was quantified at rest and at peak hyperemia using automated factor analysis and a validated 2-compartment kinetic model, as previously described.29 Hyperemia was achieved predominantly through vasodilation with regadenoson or dipyridamole. Per-patient global CFR was calculated as the ratio of stress to rest absolute myocardial blood flow for the whole left ventricle. Rest myocardial blood flow and CFR were corrected for rest rate-pressure product (heart rate times 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. Myocardial blood flow and CFR values were not clinically available to referring physicians. Radiation exposure per study was ≤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 prespecified primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or late coronary revascularization (occurring >60 days from PET imaging). Ascertainment of clinical end points 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 Infarction29 were classified as such; all myocardial infarctions occurred >30 days after initial troponin assessment. The date of the last consultation was used to determine follow-up. More than 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 quartiles 1 and 3 (Q1 and Q3) for continuous variables. We used the Fisher exact test and the Wilcoxon rank-sum test to assess differences in categorical and continuous baseline characteristics. A positive peak troponin value (eg, above the reference range for the specific assay) was used as a prespecified dichotomous variable to accommodate the 3 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 cut point for an impaired ratio. CFR <2 is associated with worse cardiovascular outcomes in a general referral population30,31 and serves as an approximate median value in our patient population. When 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 or significant univariable associations included in the multivariable model. To avoid overfitting, demographic and medical history variables (age, sex, chest pain, type, hypertension, diabetes mellitus, hyperlipidemia, smoking history, family history of premature CAD, body mass index, and estrogen status) were incorporated into the aforementioned validated pretest clinical score in the final model.

Cumulative event-free survival curves for the primary MACE end point of cardiovascular death, nonfatal myocardial infarction,

### Table 1. Baseline Characteristics of Patients by Cardiac Troponin Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=761)</th>
<th>Troponin* Negative (n=664)</th>
<th>Troponin* Positive (n=97)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age‡ (Q1-Q3), y</td>
<td>62 (53–73)</td>
<td>62 (53–72)</td>
<td>67 (59–82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>540 (71.0)</td>
<td>479 (72.1)</td>
<td>61 (62.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>441 (58.0)</td>
<td>397 (59.8)</td>
<td>44 (45.4)</td>
<td>0.01</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>
<td>&lt;0.01</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>
<td>0.06</td>
</tr>
<tr>
<td><strong>Medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>581 (76.4)</td>
<td>501 (75.5)</td>
<td>80 (82.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>408 (53.6)</td>
<td>354 (53.3)</td>
<td>54 (55.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>244 (32.0)</td>
<td>208 (31.3)</td>
<td>36 (37.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current smoker</td>
<td>73 (9.6)</td>
<td>64 (9.6)</td>
<td>9 (9.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>176 (23.1)</td>
<td>161 (24.3)</td>
<td>15 (15.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (4.5)</td>
<td>27 (4.1)</td>
<td>7 (7.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFR &lt;60 mL·min⁻¹·1.73 m⁻²</td>
<td>172 (22.6)</td>
<td>126 (19.0)</td>
<td>46 (47.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Renal hemodialysis</td>
<td>14 (1.8)</td>
<td>2 (0.3)</td>
<td>12 (12.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Medications, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>439 (57.7)</td>
<td>369 (55.6)</td>
<td>70 (72.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Statin</td>
<td>353 (46.4)</td>
<td>293 (44.1)</td>
<td>60 (61.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>371 (48.8)</td>
<td>310 (46.7)</td>
<td>61 (62.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nitrate</td>
<td>50 (6.6)</td>
<td>45 (6.8)</td>
<td>5 (5.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Angiotensin inhibitor</td>
<td>232 (30.5)</td>
<td>193 (29.1)</td>
<td>39 (40.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diuretic</td>
<td>236 (31.0)</td>
<td>201 (30.3)</td>
<td>35 (36.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Insulin</td>
<td>102 (13.4)</td>
<td>86 (13.0)</td>
<td>16 (16.5)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Noninvasive imaging parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF,‡ n (%)</td>
<td>62 (56–68)</td>
<td>63 (57–68)</td>
<td>58 (51–65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<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>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resting heart rate,‡ bpm</td>
<td>68 (61–78)</td>
<td>69 (61–78)</td>
<td>67 (61–77)</td>
<td>0.63</td>
</tr>
<tr>
<td>Resting systolic blood pressure,‡ mm Hg</td>
<td>150 (132–169)</td>
<td>150 (132–169)</td>
<td>153 (131–167)</td>
<td>0.99</td>
</tr>
<tr>
<td>Resting myocardial blood flow,‡¶ mL·min⁻¹·g⁻¹</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>
<td>0.75</td>
</tr>
<tr>
<td>Stress global myocardial blood flow,‡¶ mL·min⁻¹·g⁻¹</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>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stress coronary vascular resistance,‡¶ mm Hg/(mL·min⁻¹·g⁻¹)</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>
<td>0.01</td>
</tr>
<tr>
<td>CFR,‡¶ %</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>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Follow-up**

| Follow-up >30 d, n (%) | 690 (90.7) | 602 (90.7) | 88 (90.7) | 0.99 |

CAD indicates coronary artery disease; CFR, coronary flow reserve; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and Q, quartile.

*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 exact test for categorical variables and theWilcoxon rank-sum test for continuous variables.

‡Continuous variables are presented as medians (Q1–Q3).

§Pretest clinical score integrates age, sex, presence of hypertension, dyslipidemia, diabetes mellitus, body mass index >27 kg/m², estrogen status, smoking history, family history, and angina history into a pretest probability of CAD in patients presenting for stress imaging with symptoms of suspected CAD. Risk: low (0–8), intermediate (9–15), and high (>15).

¶Rest myocardial blood flow and CFR are corrected for rest rate-pressure product (heart rate times systolic blood pressure).

††Stress coronary vascular resistance is calculated by dividing stress mean arterial pressure by CFR.
or late revascularization were compared across dichotomous categories of positive troponin and impaired CFR by use of 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 by use of Martingale residuals, and time-dependent variables were 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 also adjusted for pretest clinical score, LVEF, and eGFR. A value of \( P < 0.05 \) was considered to indicate statistical significance, and all tests were 2 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

The distribution of baseline characteristics is shown between categories of troponin status (Table 1). The median age of patients in the overall cohort was 62 years (Q1–Q3, 53–73 years); 71.0% were women; 58.0% were white; and median pretest clinical score was 12 (Q1–Q3, 8–14), consistent with intermediate risk of CAD. More than three quarters of patients had history of hypertension; more than half had dyslipidemia; and nearly one third had diabetes mellitus. Compared with 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.

#### Table 2. Association Between CFR and Positive Troponin

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable Model</th>
<th>Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>CFR_{lower}†</td>
<td>2.45 (1.57–3.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CFR_{continuous}‡</td>
<td>1.80 (1.34–2.43)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

 CFR indicates coronary flow reserve; CI, confidence interval; and OR, odds ratio.

*Adjusted for pretest clinical score, left ventricular ejection fraction, estimated glomerular filtration rate <60 mL min\(^{-1}\)·1.73 m\(^{-2}\), history of atrial fibrillation, and use of aspirin, β-blocker, statin, or angiotensin inhibitor.

†CFR <2 relative to ≥2.

‡Per 1-unit decrease in CFR.
for positive troponin by assay were as follows: cTnT (reference range, <0.01 µg/L), 0.03 (Q1–Q3, 0.02–0.06); cTnT-Ultra (reference range, <0.04 µg/L), 0.08 (Q1–Q3, 0.05–0.14); and cTnI (reference range, 0.1 µg/L), 0.13 (Q1–Q3, 0.11–0.14).

### Association Between Impaired CFR and Positive Troponin

In univariable analysis, there was a significant association between impaired CFR and a positive troponin (odds ratio for CFR <2 relative to ≥2, 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, left ventricular ejection fraction, eGFR, LVEF, and the use of aspirin, statins, β-blockers, or angiotensin inhibitors (adjusted odds ratio for CFR, 2.18; 95% CI, 1.37–3.47; P=0.001; Table 2). 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 per 1-unit decrease in CFR, 1.80; 95% CI, 1.34–2.43; P=0.001; adjusted odds ratio per 1-unit decrease in CFR, 1.62; 95% CI, 1.19–2.20; P=0.002, respectively; Table 2). Impaired CFR thus was associated independently with low but positive levels of cardiac troponin in a population of patients without flow-limiting CAD.

### CFR, Positive Troponin, and Incident Cardiovascular Events

During follow-up over a median of 2.8 years (Q1–Q3, 1.6–4.0 years), 60 subjects (7.9%) met the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or late revascularization, including 23 deaths (Table 3). After stratifying by status of troponin and CFR, there were 378 patients with negative troponin and preserved CFR, 34 patients with positive troponin and preserved CFR, 286 patients with negative troponin and impaired CFR, and 63 patients with positive troponin and impaired CFR. The last subgroup demonstrated the highest risk of MACEs (log-rank P<0.0001; Figure 3A).

In univariable modeling, the cumulative incidence of MACEs was significantly associated with impaired CFR (hazard ratio, 2.48; 95% CI, 1.45–4.24; P=0.001) and 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 adjusted hazard ratio for positive troponin, 2.42; 95% CI, 1.34–4.40; P=0.004; Table 4). These associations remained significant after the inclusion of both CFR and troponin status into the model and adjustment for pretest clinical score, LVEF, and eGFR (adjusted hazard ratio for impaired CFR, 2.10; 95% CI, 1.15–3.85; P=0.02). Consistent results were seen across models for hazard ratios with CFR used 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 in patients with high CFR and negative troponin.

CFR thus is associated with incident cardiovascular events independently of troponin status, and impaired CFR and positive troponin together identified patients at the highest risk of events. These data demonstrate that the presence of impaired CFR modified the effect of cardiac troponin elevation on risk of MACEs so that only troponin-positive patients with concomitant impairment in CFR experienced worse cardiovascular outcomes.
myocardial dysfunction and remodeling35,37 and possibly coronary vasomotor dysfunction,38,39 the primary end point of cardiovascular death, nonfatal myocardial infarction, 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.31 In patients without evidence of flow-limiting CAD and relatively preserved LVEF, this supply-demand mismatch may occur at the level of the microcirculation,32 increasing coronary vascular resistance and cardiomyocyte workload31 and triggering maladaptive responses that may further exacerbate existing endothelial dysfunction and subendocardial ischemia,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 that may be central to the emerging epidemic of heart failure with preserved ejection fraction.31 Indeed, recent data reframe heart failure with preserved ejection fraction 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 remodeling35,37 and possibly coronary vasomotor dysfunction.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 acute coronary syndromes) in patients with stable CAD and preserved LVEF 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 further explore a mechanistic relationship among distal coronary ischemia, low-level cardiomyocyte injury, and adverse structural remodeling, which may ultimately lead to cardiovascular outcomes, including heart failure with preserved ejection fraction.

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. At our institution, PET myocardial perfusion imaging is routinely available and is used in patients with a high prevalence of risk factors who are unable to exercise optimally because it provides additional sensitivity for the detection of perfusion abnormalities while exposing patients to less radiation and shorter testing duration. CFR results were not available to referring clinicians and thus did not affect downstream management decisions about additional testing or therapies. A limitation of this study is that the clinically offered troponin assays varied over the course of the study period, and high-sensitivity troponin assays were not available. Nonetheless, a recent small study of patients with nonischemic cardiomyopathy demonstrated that release of high-sensitivity cTnT correlated with elevated left ventricular end-diastolic pressure measured invasively and that 18 patients manifesting impaired CFR (<2 by Doppler flow velocity in the left anterior descending artery) showed higher levels of cTnT.42 That we see the described associations and a significant interaction between less sensitive troponin assays and CFR in the present 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 assessed with 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 troponin may indicate a shared pathway.

Discussion

We demonstrate for the first time that impaired global CFR is independently associated with positive cardiac troponin and that both positive troponin and impaired CFR are 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 end point of cardiovascular death, nonfatal myocardial infarction, 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.31 In patients without evidence of flow-limiting CAD and relatively preserved LVEF, this supply-demand mismatch may occur at the level of the microcirculation,32 increasing coronary vascular resistance and cardiomyocyte workload31 and triggering maladaptive responses that may further exacerbate existing endothelial dysfunction and subendocardial ischemia,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 that may be central to the emerging epidemic of heart failure with preserved ejection fraction.31 Indeed, recent data reframe heart failure with preserved ejection fraction 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 remodeling35,37 and possibly coronary vasomotor dysfunction.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 acute coronary syndromes) in patients with stable CAD and preserved LVEF 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 further explore a mechanistic relationship among distal coronary ischemia, low-level cardiomyocyte injury, and adverse structural remodeling, which may ultimately lead to cardiovascular outcomes, including heart failure with preserved ejection fraction.

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. At our institution, PET myocardial perfusion imaging is routinely available and is used in patients with a high prevalence of risk factors who are unable to exercise optimally because it provides additional sensitivity for the detection of perfusion abnormalities while exposing patients to less radiation and shorter testing duration. CFR results were not available to referring clinicians and thus did not affect downstream management decisions about additional testing or therapies. A limitation of this study is that the clinically offered troponin assays varied over the course of the study period, and high-sensitivity troponin assays were not available. Nonetheless, a recent small study of patients with nonischemic cardiomyopathy demonstrated that release of high-sensitivity cTnT correlated with elevated left ventricular end-diastolic pressure measured invasively and that 18 patients manifesting impaired CFR (<2 by Doppler flow velocity in the left anterior descending artery) showed higher levels of cTnT.42 That we see the described associations and a significant interaction between less sensitive troponin assays and CFR in the present 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 assessed with 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 troponin 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 to exclude overt CAD by excluding patients with prior myocardial infarction, coronary revascularization by coronary artery bypass graft surgery or percutaneous coronary intervention, and abnormal semiquantitative perfusion (using a stringent cutoff of summed stress score >2) on index PET imaging. To minimize overt structural abnormalities, we also excluded patients with known severe valvular disease and LVEF <40%. Although it is conceivable that some patients in this intermediate-pretest-risk cohort harbored severe, flow-limiting multivessel CAD without perfusion abnormalities, our clinical experience with PET suggests this to be unlikely (ie, in a much-higher-pretest-risk population referred for invasive catheterization, of a minority of 52 patients with summed stress score ≤3, 4 were found to have obstructive multivessel disease, with noninvasive imaging also showing accompanying high-risk features such as abnormal LVEF or transient ischemic dilation).36 Despite the inherent limitations and the inability to draw temporal or causal inferences, this work is the first to link the associations of functional biomarkers of CFR 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 CFR as a target for intervention in disorders of chronic ischemia and inflammation.

Conclusions

In patients without overt CAD, impaired CFR was 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 so that only those patients with detectable troponin and impaired CFR were at the highest risk of events.

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Disclosures

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References

CLINICAL PERSPECTIVE

Very low levels of serum cardiac troponin are associated with increased mortality, even among subjects without acute coronary syndromes or overt coronary artery disease. 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, the pathophysiology of this process in the absence of acute coronary syndromes remains unclear. Coronary vascular dysfunction, as assessed by a reduced coronary flow reserve (calculated as the ratio of hyperemic to rest absolute myocardial blood flow), identifies patients at high risk for major adverse cardiac events even in the absence of overt obstructive coronary artery disease. In these patients, diffuse atherosclerosis or microvascular dysfunction likely contributes to adverse outcomes. This study sought to explore the relationship between biomarkers of coronary flow reserve and low-level cardiac injury and their contributions to cardiovascular outcomes in patients without overt coronary artery disease.

These data demonstrated that impaired coronary flow reserve, as quantified noninvasively by positron emission tomography, was associated independently with low-level cardiomyocyte injury and adverse cardiovascular outcomes in patients without flow-limiting coronary artery disease, with a highly significant interaction demonstrated between coronary flow reserve and troponin positivity. Thus, impaired coronary flow reserve, reflecting microvascular dysfunction, modified the effect of a positive troponin on adverse outcomes in an otherwise low-risk population. Investigations of coronary flow reserve may have implications for risk stratification and management of this relatively common clinical scenario.
Interaction of Impaired Coronary Flow Reserve and Cardiomyocyte Injury on Adverse Cardiovascular Outcomes in Patients Without Overt Coronary Artery Disease
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