Effect of the Presence and Type of Angina on Cardiovascular Events in Patients Without Known Coronary Artery Disease Referred for Elective Coronary Angiography

Angina pectoris remains one of the most common symptoms in the general population that leads to seeking medical attention.\(^1\)\(^-\)\(^5\) The associations between angina symptoms, noninvasive ischemic testing results, and subsequent adverse events are complex and largely unexplored.

We identified patients without known coronary artery disease (CAD) who were referred for elective coronary angiography. Our objectives were to (1) describe the characteristics of patients referred for typical, atypical, or no angina and (2) examine the associations between angina type, pre-cardiac catheterization stress test results, and burden of coronary atherosclerosis identified on coronary angiography.

Methods | We identified patients in the Duke Databank for Cardiovascular Disease (at Duke University Medical Center) without a history of CAD referred electively between January 1, 1996, and December 31, 2010, to the cardiac catheterization laboratory. The statistical analysis was performed in March 2014. Ischemic chest pain (CP) symptoms at presentation were characterized as typical, atypical, or absent. Pre-cardiac catheterization stress test results were characterized as positive, negative, or not performed. Coronary angiography results were characterized as obstructive CAD, nonobstructive CAD, or no CAD.

For the interrelationship between angina type, pre-cardiac catheterization stress test results, and CAD, a \(\chi^2\) test was conducted for each stress test result category to determine whether the distribution of individuals in each CAD category was dependent upon the type of angina symptom. \(P < .05\) was considered statistically significant.

This study was approved by the Duke University Institutional Review Board. A waiver of informed consent was granted.

Results | A total of 15,888 patients were included in this analysis. Their mean (SD) age was 59.5 (12.2) years, 44.2\% were female, and almost three-quarters were of white race/ethnicity. Angina symptoms among patients included 6163 (38.8\%) with atypical angina, 5867 (36.9\%) with typical angina, and 3858 (24.3\%) with no angina. Among 4994 patients who had a stress test before cardiac catheterization, 3812 (76.3\%) had negative test results demonstrating no ischemia, while 1182 (23.7\%) had positive test results. There were 122 patients who were missing CAD severity information. Among 15,766 patients, findings at cardiac catheterization included 7564 (48.0\%) with obstructive CAD, 5142 (32.6\%) with nonobstructive CAD, and 3060 (19.4\%) with no CAD.

Patients with atypical angina were younger, more commonly female, and less often of white race/ethnicity. They also had the highest rate (66.0\%) of no obstructive CAD (ie, the sum of patients with nonobstructive CAD and those with no CAD). Patients with typical angina had the highest rates of single-vessel (33.6\%), double-vessel (17.5\%), and triple-vessel (18.8\%) disease. Patients with no CP were most likely (63.8\%) to have no obstructive CAD.

Figure 1 shows the interrelationship between angina type, pre-cardiac catheterization stress test results, and degree of CAD. The highest rate of obstructive CAD was found in the typical angina group. Specifically, patients with typical angina and a negative stress test result were most likely (74.3\%) to have...
obstructive CAD. Among the atypical angina group, patients with a positive stress test result were least likely (24.6%) to have obstructive CAD.

Cumulative incidence curves for myocardial infarction by angina type and stress test result are shown in Figure 2. Patients with typical angina had the highest rate of myocardial infarction, with a cumulative 10-year unadjusted Kaplan-Meier incidence rate of 6.7%. Rates of myocardial infarction did not differ significantly across groups based on pre-cardiac catheterization stress test results ($P = .10$). Higher rates of revascularization were found in patients with typical angina (64.0%) compared with those with atypical angina (30.0%) or no CP (26.9%), while lower rates of revascularization were found in patients with positive stress test results (35.2%) compared with those with negative stress test results (47.9%) or no stress test (40.3%).

Discussion | The modern medical era is defined by contemporary diagnostic studies and noninvasive testing. However, our data demonstrate the critical importance of the art of clinical medicine in understanding the type of CP and analyzing symptom characteristics to accurately stratify patient risk.

Despite the large numbers of patients included in this study and long duration of follow-up, this study is limited by the fact that it is a single-center observational study that is subject to the biases inherent in that. By the nature of this study, the diagnoses that led to the cardiac catheterization were determined by the ICD-9 codes listed as the primary indication and the secondary indications for the catheterization. Thus, it is possible that we did not capture nuances of clinical presentation, such as symptom severity and frequency, that may critically affect a physician's evaluation and decision making. Lastly, the causes of death for patients included in this study are not known, which limits our ability to discriminate cardiovascular from non-cardiovascular deaths.

Our study is one of the largest to date to examine the associations between angina type, pre–cardiac catheterization stress test results, and coronary angiography findings. We believe that this study highlights the importance of clinical judgment and a detailed understanding of patients' clinical symptoms in identifying those at highest risk for obstructive CAD.

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Drafting of the manuscript: Vavalle, Shen.

Critical revision of the manuscript for important intellectual content: Shen, Broderick, Shaw, Douglas.

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Recovery of Cardiac Function in Cardiomyopathy Caused by Titin Truncation

Dilated cardiomyopathy (DCM) is a frequent cause of heart failure and a common indication for heart transplantation. Dilated cardiomyopathy has a strong genetic basis, and the most common disease-causing mutations are variants that truncate the sarcomeric protein titin (TTN-truncating variants [TTNtv]) are prevalent in 25% of familial DCM cases and 13% of idiopathic DCM cases. The prognosis of DCM is poor, but functional recovery from end-stage failure has been reported following both optimal medical therapy and left ventricular assist device (LVAD) support, although the underlying cause is irreversible, whereas recovery may be more likely when DCM is caused by reversible, nongenetic factors (eg, myocarditis). To address this directly, we sequenced TTN in 29 patients recovered cardiac function during LVAD support and had their LVAD explanted. The other 41 patients did not recover cardiac function and underwent transplant or died while on LVAD support. A pharmacological regimen designed to promote recovery (combination therapy) was used in 45 of 70 patients and continued after explantation. The study was approved by the National Research Ethics Service Committee South Central, Hampshire B, with written informed consent from participants.

Targeted next-generation sequencing was performed using an assay designed to assess all known coding exons in TTN. Genetic variants in next-generation sequencing data were identified as previously described and were confirmed independently. Statistical comparisons between groups were tested using the Fisher exact test, analysis of variance, and unpaired t test as appropriate. Differences in survival rates were tested using the Mantel-Cox test. Statistical significance was defined as a P value of less than .05.

Table. TTNtv Status and Clinical Features of Patients With LVAD-Supported, End-Stage DCM Who Either Recovered Cardiac Function and Had Successful Explantation (Recovered), or Who Had Transplantation or Died With the Device In Situ (Not Recovered)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TTNtv* (n = 10)</th>
<th>No TTNtv (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recovered†</td>
<td>Not Recovered‡</td>
<td>Recovered</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>6 (100)</td>
<td>4 (100)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Clinical comments</td>
<td>None</td>
<td>1 Postchemotherapy</td>
<td>2 PPCM</td>
</tr>
<tr>
<td>Family history, No. (%)</td>
<td>2 (33)</td>
<td>0 (0)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Survived &gt;30 d post-LVAD implant, No. (%)</td>
<td>6 (100)</td>
<td>2 (50)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Received combination therapy, No. (%)</td>
<td>6 (100)</td>
<td>2 (50)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>31.7 (10.8)</td>
<td>37.3 (15.6)</td>
<td>31.6 (12.5)</td>
</tr>
<tr>
<td>At diagnosis</td>
<td>31.0 (12.2)</td>
<td>38.6 (17.3)</td>
<td>35.5 (12.8)</td>
</tr>
<tr>
<td>Implant, mean (SD)</td>
<td>214 (125)</td>
<td>212 (313)</td>
<td>317 (151)</td>
</tr>
<tr>
<td>LVAD, mean (SD)</td>
<td>64.0 (4.2)</td>
<td>NA</td>
<td>65.9 (9.5)</td>
</tr>
<tr>
<td>FS, %</td>
<td>29.5 (3.3)</td>
<td>NA</td>
<td>31.7 (7.3)</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>44.5 (6.4)</td>
<td>NA</td>
<td>54.3 (8.9)</td>
</tr>
</tbody>
</table>

Abbreviations: DCM, dilated cardiomyopathy; FS, fractional shortening; LVAD, left ventricular assist device; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NA, not applicable; PPCM, peripartum cardiomyopathy; TTNtv, titin truncating variant.

* TTNtv position is given according to locus reference genomic (LRG) sequence 391_t1. A detailed overview of TTN gene structure, including the isoforms and protein domains affected by the TTNtv described here, can be found at http://cardiodb.org/titin.

† TTNtv in cohort who recovered: c.7624C>A; c.76383_76386delTAAT; c.86782C>A; c.87624C>A; c.49346-1G>A; c.58172delA (variants reported in Roberts et al2); c.67495C>T 58172delA; c.69976G>T; and c.71326G>T.

‡ TTNtv in cohort who did not recover: c.7624C>A; c.76383_76386delTAAT; c.86782C>A; c.87624C>A; c.49346-1G>A; c.58172delA (variants reported in Roberts et al2); and c.71326G>T.

δ P values calculated with Fisher exact test.

Value calculated with analysis of variance.

δ P values calculated with unpaired t test.