Reduced Survival in Patients with “Coronary Microvascular Disease”

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Int J Angiol 2012;21:89–94.

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Abstract

The syndrome of chest pain, abnormal stress test, and nonflow limiting coronary artery disease (CAD) is common and is attributed to coronary microvascular disease (μ VD). It is associated with increased hospital admissions and health care costs. But its impact on long-term survival is not known. Of the 9941 consecutive patients who had an exercise stress test for evaluation of chest pain between May 1991 and July 2007, 935 had both a positive stress test and a coronary angiogram within 1 year of their stress test forming the study cohort. Significant angiographic CAD defined as $\geq 70\%$ stenosis of an epicardial coronary artery or $\geq 50\%$ stenosis of the left main coronary artery was present in 324 patients. Rest ($n = 611$) were considered to have coronary μ VD. Compared with patients with significant epicardial CAD, patients with coronary μ VD were younger (63 ± 11 vs. 65 ± 10 years, $p = 0.002$), and had lower left ventricular wall thickness ($p < 0.02$), systolic blood pressure (BP; $p = 0.002$), pulse pressure (0.0008), systolic BP with exercise ($p = 0.0001$), and pulse pressure with exercise ($p < 0.0001$). Those with coronary μ VD had a better survival compared with those with significant epicardial CAD, but worse than that expected for age- and gender-matched population ($p < 0.0001$). Coronary μ VD as a cause of chest pain and positive stress test is common. All-cause mortality in patients with coronary μ VD is worse than in an age- and gender-matched population control, but better than those with significant epicardial CAD.

Keywords

- chest pain
- coronary artery disease
- microvascular disease
- survival
- prognosis

The triad of chest pain, evidence of ischemia, and nonobstructive epicardial coronary arteries is common and is attributed to coronary microvascular dysfunction (μ VD).^{1–5} It results in increased hospital admissions, repeated cardiac testing, and increased health care costs. Smaller studies ($n = 157$ to 163) have suggested an increased risk of adverse short-term outcomes and significant decrease in quality of life and high health care costs.^{6–14} However, its impact on survival is not known. We evaluated survival of this group of patients in comparison to age- and gender-matched population and those with significant epicardial coronary artery disease (CAD).

Patients and Methods

Study Population

This is a retrospective cohort study performed at a large university medical center. The study was approved by our institutional review board which waived the need for informed consent. Our exercise stress test database was queried for patients receiving a stress test for chest pain. This yielded 9941 consecutive patients from May 1991 to July 2007. Of these, 1534 patients had a positive stress test defined as ≥ 1 mm stress induced ST depression in the absence of baseline ST-T changes. Of these patients with a positive stress test, coronary

angiogram was performed on 935 patients within 1 year of the stress test forming the study cohort. Administrative clinical, echocardiographic, and angiographic data were compiled.

Exercise Stress Tests

All patients had exercise treadmill stress testing with either Bruce or Ramp protocol, directly supervised by a cardiologist. Heart rate and blood pressures at rest and stress were recorded. The electrocardiograms were analyzed and entered into the database at the time of the examination. Symptoms during the stress test were recorded and stress level in terms of metabolic equivalents (METs) reached from standard reference tables depending on the stress protocol used.

Coronary Angiograms

These were performed for clinical indications as judged by the treating physicians and interpreted by performing invasive cardiologist visually. The data were entered into a database at the time of study. Patients were considered to have significant epicardial CAD if the coronary angiogram demonstrated $\geq 70\%$ diameter stenosis of a major epicardial coronary artery or $\geq 50\%$ left main stenosis. Those with positive stress tests but nonobstructive CAS were considered to have μ VD. Based on these definitions, 611 patients had coronary μ VD and 324 had significant epicardial CAD.

Echocardiograms

In total, 800 patients had a standard two-dimensional echocardiographic examination with interpretation by a level 3-trained echocardiographer. Of these 800 patients, 505 were diagnosed with μ VD and 295 with significant CAD. The left ventricular (LV) ejection fraction was assessed visually and entered into a database at the time of the examination. Anatomic and Doppler measurements were performed according to American Society of Echocardiography recommendations.¹⁵

Mortality Data

The primary end point of this study was all-cause mortality. Mortality data were collected from the Social Security Death Index.

Statistical Analysis

Data were imported into StatView 5.01 (SAS Institute Inc., Cary, NC) for analysis. Kaplan-Meier survival curves were computed for patients with coronary μ VD and patients with epicardial CAD using log rank test. These were compared with age- and gender-matched U.S. population controls obtained from U.S. census data. Characteristics of patients with microvascular versus epicardial disease were compared using unpaired *t* test, or chi-squared test as appropriate. Cox regression analysis was used for multivariate survival analysis. A *p* value of ≤ 0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline features are summarized in ▶Table 1. For the entire cohort, the age was 63 ± 11 years, 70% were men.

When compared with patients with epicardial CAD, patients with coronary μ VD were younger (63 ± 11 vs. 65 ± 10 years, *p* = 0.002). They also had lower LV free wall thickness (10.7 ± 1.9 vs. 11.1 ± 2.9 mm, *p* = 0.003), systolic blood pressure (BP; *p* = 0.002), pulse pressure (0.0008), systolic BP with stress (*p* = 0.0001), and pulse pressure with stress (*p* < 0.0001). Both groups were similar in terms of gender, LV ejection fraction and MET levels achieved with exercise.

Survival as a Function of Significant CAD

Using Kaplan-Meier analysis, as shown in ▶Fig. 1, the survival in those with coronary μ VD was significantly better compared with those with significant CAD, but worse compared with age- and gender-matched U.S. population (*p* < 0.0001).

Other Predictors of Survival and Multivariate Survival Model

▶Table 2 summarizes both the univariate and multivariate predictors of survival using Cox regression analysis in all the 935 patients with positive exercise stress tests. All the variables from ▶Table 1 were used in the analysis and significant ones are listed. The significant univariate predictors of reduced survival included age (*p* < 0.0001), presence of significant CAD (*p* = 0.005), lower LV ejection fraction (*p* = 0.007), higher LV end-systolic dimension (*p* = 0.0001), greater ventricular wall thickness (*p* = 0.0008), higher pulmonary artery systolic pressure (*p* < 0.0001), higher resting blood pressure (*p* = 0.002), higher resting pulse pressure (*p* < 0.0001), lower METs achieved (*p* < 0.0001), lower stress heart rate (*p* < 0.0001), lower delta systolic blood pressure with exercise (*p* = 0.0001), and lower delta heart rate with exercise (*p* < 0.0001). All these were entered into a multivariate model which showed age (*p* < 0.0001), significant CAD (*p* = 0.001), METs achieved (*p* = 0.02), and stress heart rate (*p* = 0.002) to be independent predictors of survival. Gender was not predictive of survival.

Predictors of Survival in Patients with Coronary μ VD

As in the entire cohort, age (*p* < 0.0001), presence of any CAD (*p* = 0.004), higher resting pulse pressure (*p* = 0.003), and lower exercise tolerance as reflected by METs achieved (*p* = 0.0005) were associated with lower survival. Gender, presence or absence of chest pain on stress test, and LV ejection fraction were not predictive of survival.

Discussion

Our study confirms that coronary μ VD, defined as chest pain, a positive stress test, and nonobstructive CAD, is associated with higher all-cause mortality than age- and gender-matched controls, though lower than those with significant epicardial CAD causing chest pain and an abnormal stress test. Our series is larger than other reported studies, with longer follow-up, additional echocardiographic data, and hard mortality data.

Our data suggest that this syndrome is not benign. Morbidity and cost data have been available from earlier studies. Schächinger et al reported an increased risk of cardiovascular

Table 1 Patient Characteristics

Variables	All Patients	Microvascular (n = 611)	Macrovascular (n = 324)	p Value
Age in years	63 ± 11	63 ± 11	65 ± 10	0.002
Men	70%	69%	70%	0.61
Ejection fraction (%)	58 ± 14	57 ± 15	59 ± 13	0.06
LV end-diastolic diameter (mm)	49 ± 7	49 ± 7	49 ± 7	0.69
LV end-systolic diameter (mm)	33 ± 8	33 ± 8	33 ± 8	0.87
Ventricular septum (mm)	11.8 ± 2	11.6 ± 2.5	12.0 ± 2	0.02
LV posterior wall (cm)	10.8 ± 1.6	10.7 ± 1.9	11.1 ± 2.9	0.003
Pulmonary artery systolic pressures (mm Hg)	33 ± 9	33 ± 9	34 ± 9	0.63
Baseline heart rate (bpm)	73 ± 13	73 ± 13	74 ± 12	0.21
Baseline systolic blood pressure (mm Hg)	131 ± 19	129 ± 18	133 ± 19	0.002
Baseline diastolic blood pressure (mm Hg)	79 ± 10	79 ± 10	79 ± 13	0.96
Baseline pulse pressure (mm Hg)	52 ± 18	51 ± 17	55 ± 18	0.0008
Stress heart rate (bpm)	132 ± 24	131 ± 24	133 ± 23	0.31
Stress systolic blood pressure (mm Hg)	172 ± 27	170 ± 25	176 ± 28	0.0001
Stress diastolic blood pressure (mm Hg)	79 ± 11	79 ± 12	78 ± 10	0.31
Delta systolic blood pressure (mm Hg)	41 ± 21	40 ± 20	42 ± 23	0.21
Stress pulse pressure (mm Hg)	93 ± 25	91 ± 24	98 ± 25	<0.0001
Chest pain on stress	38%	42%	34%	0.009
MET level achieved	8.4 ± 3.4	8.3 ± 3.4	8.3 ± 3	0.98
Follow-up duration (years)	7.4 ± 4.4	7.9 ± 4.3	6.9 ± 4.3	0.002
Number of deaths (%)	210 (20%)	117 (19%)	80 (25%)	0.05

LV, left ventricular; bpm, beats per minute; MET, metabolic equivalent.

events over a median follow-up of 7.7 years in 147 patients with abnormal coronary reactivity to acetylcholine after adjusting for other comorbidities.¹³ Kaski et al, had no deaths in a cohort of 99 patients with coronary syndrome X, with a mean follow-up of 7 ± 4 years.¹⁰ The Women and Ischemia

Syndrome Evaluation (WISE) group reported that impaired coronary vasomotor response to acetylcholine, chest pain, or abnormal myocardial energy metabolism detected with magnetic resonance spectroscopy was associated with an increased risk of coronary events, including angina, myocardial infarction, heart failure, hospital admissions, and increased health care costs.^{6,8,12,14} But there are no mortality data and WISE study is restricted to women.

Our study is consistent with the one by From et al.⁹ The authors reported poor prognosis in patients with “false-positive” stress echocardiograms defined as positive stress with nonflow limiting coronary angiograms in a large series of 1477 patients.⁹ The survival in those with “true” and “false” positive stress echocardiograms was similar. This suggests that some patients with “noncardiac” chest pain or “false-positive” stress echocardiograms may be experiencing μ VD or true myocardial ischemia, and that the long-term prognosis is not entirely benign. Hence, both of these categories of patients need further attention in terms of risk factor modification and understanding of their biology that leads to higher mortality.

Our data and that from From et al suggest that positive stress test itself, irrespective of severity of coronary anatomy, is a strong predictor of higher mortality.⁹ Our data suggest in addition, based on multivariate analysis, that higher grades of

Figure 1 Kaplan-Meier survival curves in patients with significant symptomatic coronary microvascular disease compared with age- and gender-matched U.S. population (control) and those with significant epicardial coronary artery disease (CAD).

Table 2 Predictors of Survival in Patients with Positive Stress Tests

Variables	Univariate p Value	Univariate Hazard Ratio with 95% Confidence Interval	Multivariate p Value	Multivariate Hazard Ratio with 95% Confidence Interval
Age (years)	<0.0001	1.09 (1.07–1.10)	<0.0001	1.08 (1.05–1.11)
Significant CAD	0.005	1.51 (1.15–2)	0.001	1.96 (1.30–2.80)
LV ejection fraction (%)	0.007	0.987 (0.978–0.996)	–	–
LV end-systolic diameter (cm)	0.0001	1.37 (1.17–1.61)	–	–
Ventricular septal thickness (cm)	0.0008	2.0 (1.3–3.1)	–	–
PA systolic pressures (mm Hg)	<0.0001	1.05 (1.04–1.07)	–	–
Resting systolic blood pressures (mm Hg)	0.002	1.011 (1.004–1.019)	–	–
Resting pulse pressure (mm Hg)	<0.0001	1.02 (1.01–1.03)	–	–
Stress heart rate (bpm)	<0.0001	0.98 (0.97–0.99)	0.002	0.98 (0.97–0.99)
MET level reached	<0.0001	0.87 (0.83–0.91)	0.02	0.91 (0.83–0.99)
Delta heart rate (bpm)	<0.0001	0.98 (0.97–0.99)	–	–
Delta systolic blood pressures (mm Hg)	0.0001	0.987 (0.981–0.994)	–	–

CAD, coronary artery disease; LV, left ventricular; PA, pulmonary artery; bpm, beats per minute; MET, metabolic equivalent.

coronary stenosis, age, and stress duration are important prognostic factors in addition to stress positivity. These findings are intuitive, but have practical implications in managing these patients. Significant CAD groups were predictably associated with higher age, higher systolic blood pressure, and pulse pressures at rest as well as stress. All these factors are of greater atherosclerotic burden.

Study Limitations

The major limitation of this study is its retrospective nature using administrative databases and lack of availability of reliable pharmacological data which may potentially affect outcomes. However, our study population is large with additional comprehensive echocardiographic data in addition to exercise and angiographic data.

Conclusions

Coronary μ VD as a cause of chest pain and positive stress test is common. All-cause mortality in patients with coronary μ VD is worse than an age- and gender-matched population, but better than those with significant epicardial CAD.

Funding Sources

None

Disclosures

None

Conflicts of Interest

None

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