Clinical Investigation

Predictors of Elevated Cardiac Enzyme Levels

in Hospitalized Patients with Atrial Fibrillation and No Known Coronary Artery Disease

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We retrospectively studied the predictive capabilities of elevated cardiac enzyme levels in terms of the prognosis of patients who were hospitalized with atrial fibrillation and who had no known coronary artery disease.

Among 321 patients with atrial fibrillation, 60 without known coronary artery disease had their cardiac enzyme concentrations measured during hospitalization and underwent stress testing or cardiac catheterization within 12 months before or after hospitalization. We then compared the clinical and electrocardiographic characteristics of the 20 patients who had elevated cardiac enzyme levels and the 40 patients who had normal levels.

*Age, sex, and comorbidities did not differ between the groups. In the patients with elevated cardiac enzyme levels, the mean concentrations of troponin T and creatine kinase-MB isoenzymes were 0.08 ± 0.08 ng/mL and 6.49 ± 4.94 ng/mL, respectively. In univariate analyses, only peak heart rate during atrial tachyarrhythmia was predictive of elevated enzyme levels (*P *<0.0001). Mean heart rate was higher in the elevated-level patients (146 ± 22 vs 117 ± 29 beats/min;* P=*0.0007). Upon multivariate analysis, heart rate was the only independent predictor of elevated levels. Coronary artery disease was found in only 2 patients who had elevated levels and in one patient who had normal levels (*P=*0.26).*

Increased myocardial demand is probably why the presenting heart rate was predictive of elevated cardiac enzyme levels. Most patients with elevated enzyme levels did not have coronary artery disease, and none died of cardiac causes during the 6-month follow-up period. To validate our findings, larger studies are warranted. ***(Tex Heart Inst J 2016;43(1):38-42)***

Key words: *Atrial fibrillation/blood/physiopathology; biological markers/blood; creatine kinase/blood; heart diseases/diagnosis; hospitalization; predictive value of tests; prognosis; retrospective studies; risk assessment/methods; troponin/blood*

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Patients are frequently hospitalized for new-onset or chronic atrial fibrillation (AF) with symptoms or rapid ventricular response. Cardiac enzyme concentrations—of troponin T, the creatine kinase-myocardial band isoenzyme (CK-MB), or both—are then often obtained. Elevated cardiac enzyme concentrations in these patients raise the possibility of coronary artery disease (CAD), which might influence management and treatment decisions.[1]

Tachycardia is one cause of troponin elevation in noncoronary diseases, and careful interpretation of the laboratory results is necessary. In AF, elevated cardiac enzyme levels confer a risk of future vascular events or death.[2-4] However, the predictors of elevated cardiac enzyme levels in patients hospitalized with AF but without known CAD are not well studied. In addition, outcomes are not well investigated.

In patients without known CAD who were hospitalized with AF, we surmised that the magnitude of heart-rate (HR) elevation determined the rise in cardiac enzyme levels. In addition, we predicted no difference in outcomes between patients with normal versus those with elevated cardiac enzyme levels. We present our findings here.

Patients and Methods

This study was approved by the Mayo Foundation institutional review board. A retrospective cohort study design was used. We reviewed the medical records of 321 patients who had been hospitalized with the diagnosis of AF or atrial flutter during 2006. We identified 60 patients who met our inclusion criteria: confirmed AF or atrial flutter, hospitalization, no known CAD, and measurement of CK-MB and troponin T levels during hospitalization. We excluded patients who had known CAD, patients who had not undergone stress testing or coronary angiography within 12 months before or after the index hospitalization, and patients whose primary diagnosis was ST-segment-ele-

vation myocardial infarction (MI). We defined known CAD as a history of coronary artery bypass grafting, MI, percutaneous coronary intervention, a prior positive stress test, or a prior angiogram that revealed ≥70% stenosis of a coronary artery. The outcomes were analyzed as any CAD detected by means of stress testing or cardiac catheterization within 12 months before or after hospitalization, or as cardiac-related death within 6 months after hospitalization. We used the highest level of troponin T measured during the hospitalization. Patients were considered to have elevated cardiac enzyme levels if at least one CK-MB or troponin T value was above the upper limit of normal range: 6.1 ng/mL for CK-MB, and 0.03 ng/mL for troponin T.

Collection of Clinical Data

We collected the clinical variables of age, sex, height, weight, and comorbidities. Diagnoses of hypertension, diabetes mellitus, and hyperlipidemia had been documented by each treating physician. Smoking status was classified as never, past, or current. Family histories of CAD were positive if a first-degree family member had been affected at a young age (men, <55 yr; women, <65 yr). Statin and rate-control therapies upon presentation were reviewed (β-blocker, diltiazem, verapamil, or digoxin). In patients whose echocardiographic data were available, we calculated left ventricular (LV) mass index (LVMI) by means of 2-dimensional linear LV measurements, as recommended by the American Society of Echocardiography.[5,6] The presence of LV hypertrophy was determined according to the criteria LVMI ≥96 g/m^2 in women and ≥116 g/m^2 in men.[6] We classified AF as new-onset, paroxysmal, or persistent/permanent. Blood pressure was collected from the first reported instance at the time of the patient's hospitalization. We collected clinical data on chest pain, dyspnea, diaphoresis, nausea, vomiting, and palpitations. From the first available 12-lead electrocardiogram (ECG), we collected maximal ST-segment depression in any lead, as well as the fastest HR during AF. Upon presentation and ECG, 58 patients were in AF. In 2 patients who had reverted to sinus rhythm at the time of the ECG, we used the highest HR from the ambulance in one patient and the highest HR on the hospital room monitor during AF in the other.

Statistical Analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentages. The associations between each group and specific clinical or ECG characteristics were evaluated with use of the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. We used univariate and multivariate logistic regression to determine which variables were associated with elevated cardiac enzyme levels. A P value <0.05 was considered statistically significant. Statistical analyses were performed with use of JMP® Pro 10.0 (SAS institute Inc.; Cary, NC).

Results

Twenty patients with AF had elevated cardiac enzyme levels and 40 had normal levels during hospitalization. We found no significant differences between these groups in age, male sex, comorbid conditions, family histories of CAD, smoking status, or relevant medical therapies (Table I). Nor were there differences in LVMI (96 ± 32 vs 92 ± 20 g/m^2; P=0.99) or the prevalence of LV hypertrophy (22% vs 18%; P=0.72).

The groups did not differ in presenting symptoms at the time of hospitalization (Table II). However, the

TABLE I. Baseline Characteristics of the Patients

Variable	Cardiac Enzyme Level		P Value
	Elevated (n=20)	Normal (n=40)	
Age (yr)	70 ± 9	70 ± 11	0.82
Male	9 (45)	24 (60)	0.29
Hypertension	12 (60)	25 (63)	1
Diabetes mellitus	2 (10)	10 (25)	0.3
Family history of CAD	7 (35)	13 (33)	1
Current/former smoker	9 (45)	19 (48)	1
Statin therapy	8 (40)	14 (35)	0.78
Rate-control therapy	14 (70)	24 (60)	0.57

CAD = coronary artery disease

Data are presented as mean ± SD or as number and percentage. P <0.05 was considered statistically significant.

TABLE II. Symptoms and Cardiac Enzyme Levels at Presentation

Variable	Cardiac Enzyme Level		P Value
	Elevated (n=20)	Normal (n=40)	
Chest pain	7 (35)	10 (25)	0.54
Palpitations	14 (70)	23 (58)	0.41
Dyspnea	12 (60)	17 (43)	0.27
Troponin T (ng/mL)	0.08 ± 0.08	0.01 ± 0.002	<0.0001
CK-MB (ng/mL)	6.49 ± 4.94	3.26 ± 1.34	0.0005

CK-MB = creatine kinase-myocardial band

Data are presented as mean ± SD or as number and percentage. P <0.05 was considered statistically significant.

mean troponin T level in the elevated-enzyme group was 0.08 ± 0.08 ng/mL, versus 0.01 ± 0.002 ng/mL in the normal-range group (P <0.0001). The mean CK-MB in the elevated-enzyme group was 6.49 ± 4.94 ng/mL, versus 3.26 ± 1.34 ng/mL in the normal-range group (P=0.0005). The data in Table III indicate no difference between the groups in AF type, recovery to sinus rhythm, or ST-segment depression.

In a univariate model when each cardiac risk factor was tested, only HR was predictive of elevated cardiac enzyme levels (P <0.0001) (Table IV). Heart rate was higher in the patients who had elevated enzyme levels (146 ± 22 vs 117 ± 29 beats/min; P=0.0007) (Fig. 1).

TABLE III. Comparison of AF Type and ECG Values between Groups

Variable	Cardiac Enzyme Level		*P* Value
	Elevated (n=20)	Normal (n=40)	
Type of AF	—	—	0.42
New-onset or paroxysmal	16 (80)	36 (90)	—
Persistent/ permanent	4 (20)	4 (10)	—
Recovery to sinus rhythm	16 (80)	26 (65)	0.37
ST-segment depression (mm)	0.28 ± 0.57	0.45 ± 0.8	0.33

AF = atrial fibrillation; ECG = electrocardiographic

Data are presented as mean ± SD or as number and percentage. P <0.05 was considered statistically significant.

TABLE IV. Univariate Predictors of Elevated Cardiac Enzyme Levels

Variable	Odds Ratio	95% CI	*P* Value
Age	0.99	0.95–1.05	0.96
Male sex	0.55	0.18–1.61	0.27
Hypertension	0.9	0.30–2.77	0.85
Diabetes mellitus	0.33	0.05–1.45	0.15
Smoking	0.9	0.30–2.66	0.85
Chest pain	1.62	0.49–5.19	0.42
ST-segment depression	0.68	0.24–1.49	0.36
LVMI	1.01	0.98–1.03	0.64
Heart rate	1.05	1.02–1.09	<0.0001

CI = confidence interval; LVMI = left ventricular mass index

P <0.05 was considered statistically significant.

After adjustment for age and sex in a multivariate model, HR was the only independent predictor of elevated cardiac enzyme levels: the odds ratio was 1.69 for every 10-beat increase in HR (95% confidence interval, 1.26–2.54; P <0.0001) (Table V).

All 60 patients underwent stress testing or cardiac catheterization during a mean 23 ± 77 days from the time of hospitalization. Most (57 patients, 95%) did not have CAD. Only 2 patients with elevated enzyme levels had CAD, in comparison with 1 patient who had normal levels (P=0.26). In those 2 elevated-level patients, one had a single 70% stenosis in the left circumflex coronary artery (LCx); the other patient had an 80% lesion in the left anterior descending coronary artery (LAD) and a 40% lesion in the right coronary artery (RCA). The patient with normal enzyme levels had a 70% lesion in the posterior descending branch of the RCA and 30%-to-40% lesions in the LAD and LCx.

One study participant with elevated enzyme levels died within 6 months of hospital discharge, of malignant lymphoma.

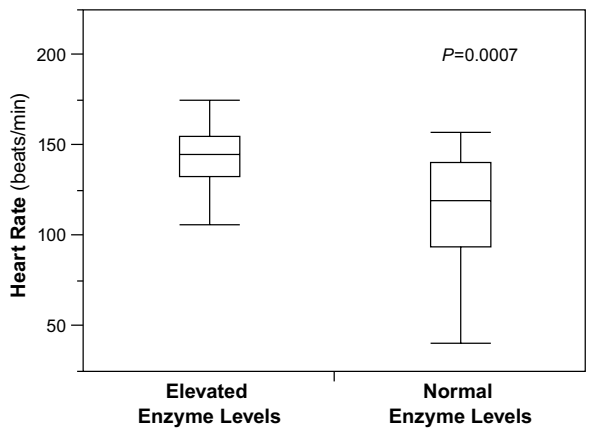

Fig. 1 *Heart rate was higher in patients who had elevated cardiac enzyme levels than in those who had normal levels. The horizontal lines in the boxes represent the median, and the boxes represent the 25th through 75th percentiles.*

P *<0.05 was considered statistically significant.*

TABLE V. Multivariate Predictors of Elevated Cardiac Enzyme Levels

Variable	Odds Ratio	95% CI	*P* Value
Age	1.03	0.96–1.11	0.45
Male sex	0.63	0.18–2.18	0.46
Each 10-beat increase in HR	1.69	1.26–2.54	<0.0001

CI = confidence interval; HR = heart rate

P <0.05 was considered statistically significant.

Discussion

We found that, in patients hospitalized with AF but without known CAD, only the presenting HR during AF was predictive of elevated cardiac enzyme levels during hospitalization. In contrast, neither presenting symptoms such as dyspnea and chest pain nor ECG markers such as ST-segment depression were similarly predictive. Of most importance, more than 90% of patients with normal or elevated cardiac enzyme levels had no CAD during the 6-month follow-up period, and there were no cardiac-related deaths.

Investigators have suggested a link between myocardial ischemia and AF in patients with acute MI and in patients with CAD[7-12] who are at high risk of recurrent acute MI; however, no one apparently has studied the predictors and outcomes of patients with AF, elevated cardiac enzyme concentrations, and no known CAD. To our knowledge, ours is the first comprehensive study to evaluate patients without previous CAD who were hospitalized for AF at a tertiary care center.

Diseases other than MI are associated with troponin elevation[13,14] in the absence of significant CAD, such as sepsis, AF, pulmonary embolism, subarachnoid hemorrhage, and high-dose chemotherapy. However, we know of no investigators who have evaluated the relationship between HR and elevation in cardiac enzyme levels.

Troponin I and troponin T are myocardial regulatory proteins that control the calcium-mediated interaction of actin and myosin.[15] Although both troponins are specific to the heart, troponin T is also expressed to a minor extent in skeletal muscle. It is thought that troponin release during MI is from cytosol, with subsequent release due to the degradation of actin and myosin filaments.

Coronary thrombosis from plaque rupture is the mechanism for type 1 MI, whereas a mismatch between oxygen supply and demand results in type 2 MI.[16] Accordingly, patients with severe anemia, shock, and prolonged respiratory failure are most often expected to have type 2 MI because of decreased supply, and patients with LV hypertrophy in the presence of severe hypertension and prolonged tachycardia from AF (as in our study) or other tachyarrhythmias are expected to have type 2 MI because of increased demand.[16] Patients with faster HRs (>146 beats/min) are more likely to have type 2 MI because of excessive demand, especially if the duration of tachycardia is prolonged in the presence of AF.

Our results also suggest that patients with AF and no known CAD are at low risk for CAD in the short term, because the elevation of cardiac enzyme levels might be related to demand ischemia caused by tachycardia. These results contradict those of a recent study by Gupta and colleagues[12] that showed an increased incidence of MI and CAD in patients with elevated cardiac enzyme concentrations who presented with AF. A possible reason for this conflict is that those investigators did not exclude patients who had existing CAD (prevalence, 36%–46% at baseline).[12] Nevertheless, the long-term (>1-yr) risk of CAD might increase because of risk factors common to AF patients and CAD patients.[17]

Study Limitations

Our study has the limitations typically inherent in retrospective studies. Selection bias might have influenced our results, in that patients without stress-test or coronary angiographic results within 1 year were excluded. Overall, the prevalence of significant CAD was low (5%), and thus extensive multivariable modeling could not be done—perhaps restricting our ability to detect the prognostic significance of some baseline variables. In addition, the mild troponin T and CK-MB elevations cannot be extrapolated to patients who present with large increases in those enzyme levels in the presence of AF.

Conclusions

In patients without known CAD who were hospitalized with AF, only the presenting HR during atrial tachyarrhythmia was predictive of elevated cardiac enzyme levels during hospitalization, probably because of increased myocardial oxygen demand. Of more importance, most patients with elevated cardiac enzyme levels did not have CAD and were not at high risk of cardiac death during short-term follow-up monitoring. Larger studies are needed to validate our findings.

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