ORIGINAL RESEARCH

Myocarditis and Early Markers of Cardiac Response Associated with Scorpion Stings in Children

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Introduction—A clinical course ranging from mild local findings to life-threatening systemic findings may occur after scorpion stings. The purpose of this study was to identify priority markers indicating scorpion sting–related cardiac involvement.

Methods—Our study was performed between July 2014, and September 2015 in the Çukurova University medical faculty pediatric emergency department, in Adana, Turkey. Patients admitted with scorpion sting–related cardiac involvement and a control group consisting of patients with no scorpion sting–related cardiac involvement were included in the study. Troponin I at time of presentation and at 6 and 24 h, N-terminal prohormone of brain natriuretic peptide (NTproBNP), ejection fraction as determined by echocardiography at 24 h, and peak and end of T wave (Tp-e) and Tp-e/QTc ratios with echocardiography at 24 h were evaluated.

Results—A patient group consisting of 7 cases of scorpion envenomation–related myocarditis and a control group of 30 cases of scorpion intoxication without myocarditis findings were enrolled. Statistically significantly high glucose, white blood cell values, creatine kinase MB, troponin I, and NTproBNP values were identified in the scorpion sting–related myocarditis group ($P < 0.05$). Ejection fractions determined by echocardiography at time of presentation were significantly lower in the patients with myocarditis compared with the control group ($P < 0.05$). A statistically significant difference was identified between Tp-e/corrected QT interval (QTc) ratios investigated in DI and V2 derivations in patient and control group echocardiograms ($P < 0.05$).

Conclusions—We think that use can be made of NTproBNP in addition to echocardiography and troponin I in the early diagnosis of scorpion sting–related myocarditis and that Tp-e and Tp-e/QTc ratios identified via echocardiography can be used as early markers; however, further studies with larger numbers are needed to confirm this.

Keywords: child, cardiac marker, scorpion envenomation, children, Turkey

Introduction

Scorpion envenomation is a significant health problem, particularly in tropical regions. Children are more susceptible to scorpion stings, and severe intoxication may occur more easily in children than in adults.^{1,2} A clinical course

ranging from mild local findings to life-threatening systemic findings (cardiovascular effects, acute pulmonary edema, and neurotoxic effects) may occur after scorpion stings. Cardiovascular effects and acute pulmonary edema are the most significant life-threatening complications and the most common causes of mortality after scorpion stings.³

Cardiac enzymes are used to determine scorpion sting–related cardiac effects, and electrocardiography (ECG) and echocardiography (ECHO) are used to identify arrhythmias and to assess left ventricular (LV)

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function. Troponin measurement, a biochemical test used to assess cardiac effects in particular, is a reliable marker.⁴

Another biochemical marker used to evaluate cardiac functions in cardiac diseases, especially in adults, is brain natriuretic peptide (BNP), a sensitive and specific marker in the diagnosis of ventricular diseases. Heart muscle cells are the main source of BNP in the circulation.⁵ BNP is first released as a 134-amino acid prehormone and then divides into 108-amino acid proBNP. ProBNP consists of biologically inactive N-terminal proBNP (NTproBNP) and biologically active BNP.⁶ Currently, BNP and NTproBNP measurement is particularly recommended by international guidelines in the diagnosis, prognosis, and assessment of treatment efficacy of heart disease in adults.^{7,8} Serum BNP levels are quite sensitive in determining LV function disorders, and BNP levels rise with the severity of these disorders.⁹ NTproBNP and BNP plasma levels are parallel to one another. However, although NTproBNP is a biologically inactive form, it is less affected by factors such as posture and exercise. Although BNP has a short plasma life of approximately 20 min, the 120-min plasma half-life of NTproBNP makes measurement easier in technical terms.¹⁰ Additionally, BNP remains stable for only 24 h at room temperature, whereas NTproBNP can remain stable for at least 72 h. Therefore, higher NTproBNP levels are identified in circulation and exhibit less diurnal and nocturnal variation.¹¹

The latest adult studies have found that the peak and end of T wave (Tp-e) interval on ECG can be used to determine total (transmural, apical, and global) repolarization dispersal.¹² In addition, an increased Tp-e interval has been described as a potentially useful preliminary marker in ventricular tachyarrhythmia and cardiovascular mortality.^{13,14} At the same time, the Tp-e/QTc ratio is also thought to be a novel marker providing more accurate measurement than other parameters (QT, corrected QT [QTc], and Tp-e interval), independently of heart rate.^{15,16}

The purpose of this study was to determine the relationship between serum troponin, serum NTproBNP, Tp-e, and Tp-e/QTc ratios on ECG and heart ejection fraction, in addition to clinical findings, as early markers of scorpion sting-related cardiac involvement in patients with scorpion stings that are capable of causing severe morbidity and mortality if not treated and to identify a priority marker.

Methods

This study was performed with the approval of the local ethical committee at the Çukurova University medical

faculty pediatric emergency department in Adana, Turkey, between July 2014 and September 2015. Patients admitted to our pediatric emergency department with scorpion sting-related myocarditis and a control group consisting of patients without scorpion sting-related myocarditis were included in the study. Written and verbal permission was obtained from patients' families. Diagnostic criteria for myocarditis were determined as one finding of cardiac insufficiency, such as tachycardia, murmur, gallop rhythm, or muffled heart sounds, and at least one of the following: change on ECG, altered cardiac function at ECHO, or an increase in troponin levels.^{17,18}

The epidemiologic and demographic characteristics, clinical findings, treatments, and results thereof were recorded for all patients in the study. Serum specimens were collected from patients for troponin I and NTproBNP measurement at time of presentation and at 6 and 24 h. Venous specimens from patients presenting to the pediatric emergency department and from the control group for NT-proBNP measurement were placed into 5-mL biochemistry tubes without anticoagulant under standard conditions to minimize sources of preanalytic error. After being kept for 15 to 20 min at room temperature for coagulation, serum samples were separated by centrifugation at 3000 g for 10 min. The serum specimens obtained were transferred to other tubes with no anticoagulant and stored at -80°C until analysis (2 mo). These frozen serum samples were subsequently thawed at room temperature and vortexed.

Serum NTproBNP levels were measured using the electro-chemiluminescence immunoassay (ECLIA) method with in vitro diagnostic standard measurement kits (NT-proBNP Kit catalog No: 04842464190, Roche Diagnostics GmbH, Mannheim, Germany) on a fully automated Cobas e 411 immune-autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). A reference value of $125\text{ pg}\cdot\text{mL}^{-1}$ was adopted. Troponin I was measured in plasma after centrifugation without delay. Serum troponin I levels were measured using the chemiluminescence method with in vitro diagnostic standard measurement kits (troponin kit catalog no. A98143) on a fully automated Access II immune autoanalyzer (Access AccuTnI+3, Beckman Coulter, Brea, CA). Values greater than $0.01\text{ ng}\cdot\text{mL}^{-1}$ were considered abnormal.

ECHO was performed by a pediatric cardiologist using a GE Vivid I portable echocardiography machine (General Electric, Boston, MA). Ejection fraction (EF) and shortening fraction were measured using the Teicholz method with M-mode echocardiography in the first 6 h after presentation and again at 24 h in cases of myocarditis. Because of the absence of a permanent pediatric cardiologist in the emergency department and because it would be unethical to delay treatment in patients

requiring inotropic support, ECHO examination was performed after commencement of inotrope therapy in all patients in the myocarditis group.

Patients' Tp-e and Tp-e/QTc ratios on ECG were calculated. The Tp-e interval was calculated as the interval between the peak and the end of the T wave. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. Tp-e/QTc ratios were determined with the calculation of corrected QT according to Bazett's formula, $QTc = QTd / \sqrt{(R-R \text{ interval})}$.

STATISTICAL ANALYSIS

Statistical analyses were performed on IBM SPSS Statistics Version 20.0 software (IBM Corp, Armonk, NY). Categorical variables were expressed as number and percentage and numerical variables as mean $\pm$ SD (and median, interquartile range [IQR], and minimum – maximum when required). The χ^2 test was used to compare categorical variables between groups. The Shapiro-Wilk test was used to determine whether numerical values were normally distributed. A t test was used to compare normally distributed data, and the Mann-Whitney *U* test was used to compare data without a normal distribution. The statistical significance was set at 0.05 for all analyses.

Results

Thirty-seven patients were included in the study: 7 cases of scorpion sting–related myocarditis representing the patient group and 30 cases of scorpion envenomation without myocarditis findings as the control group. The median age of the patient group was 75 (IQR 12–132) mo, and the median age of the control group was 132 (IQR 60–186) mo. No statistically significant difference was identified between the groups in terms of age or sex ($P>0.05$).

The type of scorpion involved was unknown in 29.7% of cases; 2.7% involved black scorpions, and 67.6% involved yellow scorpions. In terms of timing, 85.7% of participants in the patient group presented because of scorpion stings in the daytime and 14.3% at night, whereas 63.3% of the control group presented in the daytime and 36.7% at night. No significant difference was identified in terms of timing or type of scorpion involved ($P>0.05$).

The patient group presented having vomited at least once, whereas no vomiting was noted in 90% of the control group. The difference between the groups in terms of vomiting episodes was statistically significant ($P<0.001$). Patient and control group demographic, epidemiologic, clinical, and treatment characteristics are summarized in Table 1.

Mean $\pm$ SD troponin I values in the myocarditis group were 1.6 ± 2.7 ng·mL⁻¹ at hour 0, 2.7 ± 4.3 ng·mL⁻¹ at 6 h, and 1.6 ± 2.1 ng·mL⁻¹ at 24 h. In the control group the values were 0.2 ± 0.6 ng·mL⁻¹ at hour 0, 0.01 ± 0.04 ng·mL⁻¹ at 6 h, and 0.0 ± 0.02 ng·mL⁻¹ at 24 h. The NTproBNP values in the myocarditis group were 1523 ± 2419 pg·mL⁻¹ at hour 0, 2184 ± 3214 pg·mL⁻¹ at 6 h, and 4888 ± 4237 pg·mL⁻¹ at 24 h, whereas in the control group the values were 123.2 ± 188.2 pg·mL⁻¹ at hour 0, 233.6 ± 387.8 pg·mL⁻¹ at 6 h, and 144.2 ± 238.6 pg·mL⁻¹ at 24 h. Significant variation was identified between the 2 groups for troponin I and NTproBNP ($P<0.05$). No significant differences were identified between the myocarditis and control groups in terms of leukocyte count and glucose, aspartate aminotransferase, creatine kinase, or creatine kinase MB values ($P<0.05$). Laboratory results and comparisons in the myocarditis and nonmyocarditis groups are summarized in Table 2.

EF values at ECHO performed by a pediatric cardiologist in the first 6 h were $51.6\pm 13.6\%$ in the myocarditis group and $71.3\pm 3.6\%$ in the control group. Statistically significant variation was identified between the 2 groups in EF and SF values in the first 6 h and at 24 h ($P<0.05$). Significant variation was also present in Tp-e/QTc ratios and DI and V2 derivations at ECG ($P<0.05$) (Table 3).

When troponin I and NTproBNP values at hour 0 and 6 h were compared, NTproBNP exhibited higher sensitivity at hour 0, whereas troponin I exhibited greater specificity. At 6 h, sensitivities were similar, whereas troponin I was more specific (Table 4).

Discussion

Scorpion stings are an important health problem, particularly in tropical regions, and affect approximately 1.2 million people every year. More than 3250 cases of scorpion envenomation result in death (0.3%).² The scorpion species found in Turkey are less toxic than other species in the world.¹⁹ However, among the scorpions found in Turkey, *Androctonus crassicauda* (black scorpion) and *Leiurus abdullahbayramii* (yellow scorpion) from the family Buthidae are highly toxic and potentially fatal.^{18,20,21} Although these species are found in our region and we attempted to differentiate black and yellow scorpions in our study, the species involved could not be definitively identified. No statistically significant difference was identified between the myocarditis and control groups in terms of scorpion species by color ($P<0.05$).

Cardiogenic shock or heart failure associated with pulmonary edema, findings of severe scorpion envenomation, occur in approximately 10.3% of cases.^{2,22} Scorpion myocarditis is thought to be associated with myocardial ischemia, increased catecholaminergic activity, and a direct effect of the toxin on myocardial fibrils.

Table 1. Patient and control group demographic, epidemiologic, clinical, and treatment characteristics

<i>Laboratory parameters</i>	<i>Patient n (%)</i>	<i>Control n (%)</i>	<i>P</i>
Sex			
Female	2 (28.6)	15 (50)	0.416
Male	5 (71.4)	15 (50)	
Age, mo	75±55.8	132±66.7	0.094
Time of arrival at hospital			
0–1 h	7 (100)	27 (90)	1.0
1–2 h	0 (0)	3 (10)	
Type of scorpion			
Black	0 (0)	1 (3.3)	0.202
Yellow	3 (42.9)	22 (73.3)	
Unknown	4 (57.1)	7 (23.3)	
Location of sting			
Head/Neck	0 (0)	0 (0)	1.0
Hand	2 (28.6)	9 (30)	
Arm	0 (0)	1 (3.3)	
Body	0 (0)	3 (10)	
Leg	0 (0)	8 (26.7)	
Foot	5 (71.4)	9 (30)	
Time of sting			
Day	6 (85.7)	19 (63.3)	0.389
Night	1 (14.3)	11 (36.7)	
No. of stings			
1	7 (100)	29 (96.7)	1.0
2	0 (0)	1 (3.3)	
District			
Urban	29	2 (6.7)	1.0
Rural	7 (100)	28 (93.3)	
No. of times patient vomited			
0	0 (0)	27 (90)	0.0
1	3 (42.9)	1 (3.3)	
2	3 (42.9)	1 (3.3)	
>3	1 (14.3)	1 (3.3)	
Administration of antivenom	n (%)	n (%)	
Yes	6 (85.7)	9 (30)	<0.05
No	1 (14.3)	21 (70)	
No. of antivenoms			
1	0	9 (30)	
2	5 (71.4)	0 (0)	<0.05
3	1 (14.3)	0 (0)	
Treatment			
Observation	0 (0)	18 (60)	<0.05
Antivenom	0 (0)	1 (3.3)	
Doxazosin	1 (14.3)	5 (16.7)	
Antivenom + doxazosin	0 (0)	6 (20)	
Antivenom + doxazosin + dobutamine (Inotrop)	6 (85.7)	0 (0)	
Hospitalization			
Pediatric emergency	1 (14.3)	18 (60)	<0.05
Pediatric intensive care	6 (85.7)	9 (30)	
Self-discharge	0 (0)	3 (10)	
Result			
Recovery	7 (100)	30 (100)	
Death	0 (100)	0 (0)	

Table 2. Laboratory results and comparisons in the myocarditis and control groups

Laboratory parameters	Patient (n=7) mean±SD	Control (n=30)	P
WBC ($10^3 \mu\text{L}$)	22±6.6	10.25±2.8	<0.05
Hb (g·dL ⁻¹)	12.4±2.4	13±1.4	0.358
Htc (%)	38.1±6.9	39.2±3.8	0.566
MCV (fL)	75.8±8.8	79.8±8.7	0.272
MPV (fL)	9.4±1.4	9.5±1.1	0.903
PCT	0.3±0.1	0.3±0.1	0.295
PDW	13.4±3.1	12.1±2.8	0.138
PLT (10^3 microliters)	349±66.1	289.1±90.8	0.110
GLK (mg·dL ⁻¹)	188.5±71.2	112.9±26.2	<0.05
BUN (mg·dL ⁻¹)	17.5±6.7	11.8±3.2	0.067
Creatinine (mg·dL ⁻¹)	0.6±0.2	0.5±0.2	0.317
SGOT (U·L ⁻¹)	36.7±2.9	26.9±8.2	<0.05
SGPT (U·L ⁻¹)	18.7±4.3	17.2±4.9	0.465
PT (s)	13.1±1.2	12.4±0.8	0.084
PTT (s)	25±3.4	26.2±3.5	0.409
Fibrinogen (mg·dL ⁻¹)	257±71	252.7±55.5	0.872
CK (U·L ⁻¹)			
0 h	264.8±54.3	162.8±100	<0.05
6 h	360.8±75	156.7±160.7	<0.05
24 h	320±234	132.7±144	0.105
CK-MB (ng·mL ⁻¹)			
0 h	36.3±38.3	7±17.4	<0.05
6 h	36.8±38.5	3.1±3.4	<0.05
24 h	21±8.3	2.7±3.8	<0.05
Troponin I (ng·mL ⁻¹)			
0 h	1.6±2.7	0.2±0.6	<0.05
6 h	2.7±4.3	0.01±0.04	<0.05
24 h	1.6±2.1	0.0±0.02	<0.05
NTproBNP (pg·mL ⁻¹)			
0 h	1523±2419	123.2±188.2	<0.05
6 h	2184±3214	233.6±387.8	<0.05
24 h	4888±4237	144.2±238.6	<0.05

BUN, blood urea nitrogen; GLK, glucose; Hb, hemoglobin; Hct, hematocrit; CK, creatine kinase; MCV, mean corpuscular volume; MPV, mean platelet volume; NTproBNP, N-terminal prohormone of brain natriuretic peptide; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelets; PT, prothrombin time; PTT, partial thromboplastin time; SGOT, serum glutamic-oxaloacetic transaminase [aspartate aminotransferase]; SGPT, serum glutamic-pyruvic transaminase [alanine aminotransferase]; WBC, white blood cells.

An increase in LV afterload secondary to vasoconstriction with increased catecholaminergic activity resulting from the toxic effect of scorpion venom causes an increase in right ventricular afterload and pulmonary edema with an increase in LV filling pressure. A decrease in myocardial contractility occurs after the autonomic phase (vascular phase) and a “myocardial phase” in which low cardiac output, hypotension, and shock develop as the body seeks to temporarily increase LV contractility.^{23,24} This condition, known as toxic myocarditis or scorpion sting myocarditis, may develop immediately or hours after scorpion envenomation. Early diagnosis and treatment of scorpion myocarditis will reduce morbidity and mortality. A decrease in LV EFs

and a low fraction time, hypokinesia, and dilatation can be determined at ECHO and can be applied to evaluate cardiac functions in early diagnosis. Sofer et al²⁵ reported that early bedside ECHO has 100% sensitivity and specificity for myocarditis. In their study of 84 patients, Sagarad et al²⁶ identified LV dysfunction in 60 patients with myocarditis and found that EF was less than 50%. No systemic findings developed in 24 patients with normal EF.²⁶ Meki et al⁴ found that EF decreased in moderate and severe intoxications (*Buthus occitanus*, *L. quinquestriatus*). Cupo et al²⁴ found that EF decreased at a level of 16 to 36% in 10 out of 12 patients with severe intoxication findings (*Tityus serrulatus*). Rajashekar et al²⁷ reported no clinical impairment in patients

Table 3. Myocarditis and control group EF, FS, and Tp-e/QT outcomes

<i>ECHO and ECG</i>	<i>Muyocarditis (mean±SD) (min–max)</i>	<i>Control</i>	<i>P</i>
EF			
0–6 h (n=5)	51.6±13.6 (30–63) (n=5)	71.3±3.6 (64–77) (n=18)	0.03
24 h	66.3±10.7 (51–79) (n=6)	72.2±2.2 (69–74) (n=4)	0.241
FS			
0–6 h	26.2±7.9 (14–33)	40.4±3.3 (34–46)	0.014
24 h	41.5±16.8 (25–72)	41.8±2.9 (38–45)	0.978
ECG			
Tp-e DII	0.1±0.02	0.1±0.01	0.402
Tp-e/QTc V1	0.2±0.1	0.2±0.1	0.095
Tp-e/QTc V2	0.3±0.1	0.2±0.1	0.004
Tp-e/QTc V3	0.2±0.1	0.2±0.1	0.384
Tp-e/QTc V4	0.3±0.1	0.2±0.04	0.714
Tp-e/QTc V5	0.3±0.01	0.2±0.04	0.069
Tp-e/QTc V6	0.3±0.01	0.2±0.1	0.059
Tp-e/QTc DI	0.3±0.03	0.2±0.1	0.033
Tp-e/QTc DII	0.3±0.1	0.2±0.04	0.316
Tp-e/QTc DIII	0.2±0.9	0.2±0.1	0.193

ECG, electrocardiography; EF, ejection fraction; FS, shortening fraction; Tp-e, peak–end T wave interval.

Table 4. Comparison Troponin vs NTproBNP in scorpion sting–related myocarditis

<i>Laboratory parameters</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>AUC</i>	<i>95% CI</i>
Troponin I ^a	57.1	96.7	0.760	53–98
0 h				
Troponin I 6 h	71	92.9	0.97	92–100
NTproBNP ^b	80	61.5	0.824	65–99
0 h				
NTproBNP 6 h	71.4	60	0.781	57–99

AUC, area under the curve; NTproBNP, N-terminal prohormone of brain natriuretic peptide.

^a Troponin I cutoff range 0.01 ng·mL⁻¹.

^b NTproBNP cutoff range 125 ng·mL⁻¹.

with normal cardiac functions among cases of scorpion envenomation undergoing ECHO in the first 6 h.²⁷ Similarly, in our study significant variation was found in EF measured in the first 6 h between the cases with myocarditis and the control group ($P<0.05$). One patient with myocarditis had an EF value of 30%. We think that EF values were higher because ECHO could only be performed after inotrope therapy had begun in some cases of myocarditis. EFs at 24 h were greater than 50% and were determined as normal, and all patients were discharged in a healthy condition. Normal EFs were measured in the first 6 h in 18 of the 30 members of the control group, and no clinically significant findings developed. Our low patient number and the fact that

ECHO was performed after inotrope therapy in some cases and could not be applied to all patients for technical reasons prevent us from assessing whether ECHO is a priority marker in determining scorpion myocarditis.

Studies concerning envenomation have found that creatinine phosphatase, troponin, and NTproBNP increase after scorpion stings.^{4,24,28,29} Examination of the literature concerning biochemical markers studied in scorpion envenomations indicates that troponin I levels have high sensitivity and specificity in determining scorpion sting–related cardiac response.^{4,30} Cupo et al³¹ reported that troponin I values did not increase at first presentation in patients with cardiac dysfunction but rose subsequently, reaching maximum levels 24 to 36 h after scorpion sting. Sofer et al²⁵ identified higher troponin values compared with a control group, reported higher troponin values at 24 h, and concluded that troponin values at time of presentation could not be used as a marker in diagnosing cardiac dysfunction.

In a study of NTproBNP, another biochemical marker used to assess cardiac functions, Sagarad et al²⁹ identified significant NTproBNP elevation in patients with scorpion sting–induced myocarditis. Sofer et al²⁵ found NTproBNP elevation at both presentation and 24 h in groups with and without normal ECHO. They concluded that NTproBNP had low sensitivity and specificity.²⁵ In our study we identified statistically significant variations in troponin I and NTproBNP values at time of presentation and at 6 and 24 h between the myocarditis and control groups ($P<0.05$). Troponin I exhibited greater specificity and

NTproBNP greater sensitivity at time of presentation; they exhibited similar sensitivity at 6 h, and troponin I had greater specificity (95% CI).

Findings ranging from sinus tachycardia to severe ventricular arrhythmias can be found at ECG in scorpion intoxication. Ischemia-related ECG findings have been identified in the majority of patients with severe scorpion envenomation.^{25,32–34} Studies have described Tp-e and Tp-e/QTc ratios as markers in ventricular arrhythmias, long QT syndrome, sudden cardiac mortality, hypertrophic cardiomyopathy, and myocardial infarction and as a novel ECG finding indicating mortality.^{15,35,36} Very few studies have been performed with children. No patients in our study developed arrhythmia, and significant differences were present in D1 and D2 derivations between Tp-e/QTc ratios in the ECGs of the patients assessed ($P < 0.05$). We think that Tp-e/QTc ratios can also be a marker of LV dysfunction in children but that further studies involving more cases and a large number of consecutive ECGs are needed on this subject.

There are various limitations to our study. The number of scorpion envenomation patients who developed myocarditis during the study was very low. We were unable to identify the species of scorpion involved in 29.7% of cases. ECHO could not be performed at time of presentation and 24 h in some cases, and for technical reasons the first ECHOs in the group that developed myocarditis were performed after the start of inotrope therapy.

Conclusions

We believe that NTproBNP in addition to ECHO and troponin I and the calculation of Tp-e/QTc ratios at ECG may be useful in the early diagnosis of myocarditis, one of the most fatal complications associated with scorpion sting. However, because of our low patient number, further studies are now needed to be able to recommend a novel cardiac marker.

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