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Profiles of Serial Changes in Cardiac Troponin T Concentrations and Outcome in Ambulatory Patients With Chronic Heart Failure

Wayne L. Miller, MD, PhD,* Karen A. Hartman, BSN,* Mary F. Burritt, PhD,†
Diane E. Grill, MSc,‡ Allan S. Jaffe, MD*†

Rochester, Minnesota

Objectives The purpose of this study was to determine whether different profiles of cardiac troponin T (cTnT) values assessed over time would yield incremental prognostic information on clinically stable outpatients with heart failure (HF).

Background cTnT levels were used to estimate prognosis in HF; however, most studies evaluated hospitalized patients using single measurements.

Methods A cohort of 172 New York Heart Association functional class III to IV outpatients was prospectively studied with serial cTnT measurements collected every 3 months over a 2-year period. The primary end point was death or cardiac transplantation, and secondary end points included HF hospitalization.

Results Of the 172 patients, 22 (13%) died or underwent transplantation during the first year. Therefore, 150 patients were included in the second-year analysis of 3 pre-determined groups: 1) no serial cTnT elevations (defined as $<$0.01 ng/ml); 2) 1 or more, but not all cTnT values elevated $\geq$0.01 ng/ml; and 3) all cTnT values elevated during the first year. During the second year, 30 events occurred: 53 patients had persistently normal cTnT levels ($<$0.01 ng/ml) with 6 primary events (11%); 57 patients had 1 or more but not all cTnT levels elevated with 11 events (19%); 40 patients demonstrated persistently elevated cTnT levels with 13 (33%) primary events (odds ratio: 3.77; 95% confidence interval: 1.28 to 11.07, p = 0.02).

Conclusions Elevations in cTnT, even using a low threshold of 0.01 ng/ml, detected during routine clinical follow-up of ambulatory patients with HF, are highly associated with an increased risk of events, particularly with frequent or persistent cTnT elevations of $\geq$0.01 ng/ml. Therefore, the ability to monitor clinical change through serial cTnT measurements may add to risk assessment in the ambulatory HF population. (J Am Coll Cardiol 2009;54:1715–21) © 2009 by the American College of Cardiology Foundation

Patients with chronic heart failure (HF) manifest progression of disease over time and an adverse prognosis (1,2) even in the absence of overt clinical events (3–5). This risk is attributable in part to intermittent necrosis that we and others have documented based on changes in cardiac troponin T (cTnT) (6–10). Most studies to date have detected these changes in cTnT in acutely decompensated hospitalized patients. We have reported similar results in stable ambulatory outpatients with HF (11). The prognosis after these events, as with acute presentations with elevations in cTnT, is clearly adverse, suggesting that these small HF injuries are analogous to those that lead to acute presentations but are simply less symptomatic and thus less often diagnosed. Our results are consonant with those of other studies, most of which have been of substantially shorter duration (6–9). We reported in ambulatory chronic HF patients that cTnT elevations $\geq$0.01 ng/ml ($\geq$99th percentile of a normal reference population) are associated with increased risks of death/cardiac transplantation and HF-related hospitalizations, both at baseline and during follow-up (11). It is not clear, however, whether specific profiles of cTnT levels over time might provide additional information. Accordingly, we evaluated the profiles of change in serial cTnT measurements every 3 months over a 2-year period in clinically stable outpatients with New York Heart Association (NYHA) functional classes III and IV HF. We sought to assess the hypothesis that specific profiles or the frequency of cTnT elevations emerging from serial

From the *Division of Cardiovascular Diseases, Department of Medicine, †Department of Laboratory Medicine and Pathology, and ‡Division of Biostatistics, Mayo Clinic, Rochester, Minnesota. Supported in part by a grant from Dade-Behring.

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CI = confidence interval
cTnT = cardiac troponin T
HF = heart failure
NYHA = New York Heart Association
OR = odds ratio

measurements would provide incremental risk stratification information in addition to that of single baseline values in predicting adverse cardiac-related events. If so, these findings might lead to an understanding of what types and timing of intervention might be effective in the management of these at-risk patients.

Methods

Patients and study design. A cohort of 200 patients with NYHA functional classes III and IV HF was prospectively enrolled during the period of June 2001 to January 2004 to assess the value of serial monitoring of cTnT and natriuretic peptides in an outpatient HF cohort. These patients were recruited from the Mayo Clinic outpatient HF clinic after initial evaluation and establishment of routine clinical follow-up; every effort was made to coordinate clinical and study-related activities. Informed consent was obtained from all patients after a primary medical evaluation had determined their clinical status. Patients were followed up in the HF clinic with visits scheduled at 3-month intervals (±3 weeks) for a total of 24 months. Patients were excluded if coronary revascularization was anticipated within 6 months, if the patient had been listed for cardiac transplantation, or if they had experienced an episode of acute decompensation within the 30 days before anticipated enrollment. The study was approved by the Mayo Foundation Institutional Review Board and included only those patients who provided written informed consent for clinical research analysis as required by Minnesota Statute 144.335/CFR 21 (Part 50). The average duration of HF at study enrollment was 41.9 ± 44.2 months with a median of 31 months.

Study protocol. Blood for cTnT samples was drawn at study entry (baseline) and at every 3-month follow-up visit thereafter for 2 years. Samples for cTnT were assayed at the time of collection for each patient visit. Clinicians and investigators were blinded to biomarker results. Blood samples were also obtained for plasma electrolytes, serum creatinine, and hemoglobin as clinically indicated. Left ventricular ejection fraction was derived from 2-dimensional echocardiography performed within 3 months of study enrollment and subsequently during routine clinical follow-up as determined by the patient's HF clinic provider. In addition to blood samples obtained for the measurement of biomarkers, an updated patient history was obtained, interim clinical status (such as hospitalizations) was determined, and a physical examination was performed at each follow-up visit. Any change in medications was recorded. Changes in the patients' medical regimens were undertaken by the primary HF cardiologist and not by the study investigator or nurse coordinator. Survival was evaluated during follow-up for each member of the study cohort. The records from all hospitalizations were reviewed. The determination of a hospitalization for decompensated HF required the administration of intravenous diuretics, positive inotropic agents, and/or vasodilators. The mean overall follow-up duration was 18.9 ± 7.8 months (range 0.13 to 26.4 months) and ≥24 months in all survivors.

cTnT measurements and estimated renal function. An elevated cTnT was defined as a value ≥99th percentile of normal reference population corresponding to values ≥0.01 ng/ml. Analyses were done using this recommended European Society of Cardiology/American College of Cardiology guideline cut point (12,13). Analyses were undertaken based on the data during year 1 to assess profiles of cTnT levels, and these profiles were then tested during the second year of follow-up. Renal function was determined at study enrollment (baseline) and at subsequent visits every 3 months by calculation of the estimated glomerular filtration rate (ml/min/1.73 m^2) using the Modification of Diet in Renal Disease equation (14) to allow evaluation of the extent to which cTnT changes were related to alterations in renal function.

Statistical analysis. Analyses were done using SAS software version 9 (SAS Institute Inc., Cary, North Carolina) or using S-Plus software version 7.0 (Insightful Corp., Seattle, Washington). Data for continuous variables are reported as mean ± SD and categorical variables as number and percentage of total cohort. The primary end point was the time until death or cardiac transplantation. The cTnT levels at study enrollment and over the first year of follow-up were grouped into profiles of changes in cTnT, and these groups were used to assess the risk of events occurring during the second year of the study. Patients were only considered at risk in this analysis if they were still alive and enrolled after year 1.

Baseline variables were measured at the start of year 1. Differences between the cTnT profiles were assessed with Pearson's chi-square test for categorical variables or 1-way analysis of variance for continuous variables. Pearson's chi-square test was used to test for differences between the patterns and event rates in year 2. Multivariate logistic regression models were fit for death or cardiac transplantation during year 2 as the dependent variable and the cTnT patterns as the independent variables. Two models were fit, 1 that had separate variables for those with >50% of cTnT normal values (but not all normal) and 1 that had ≥50% elevated values (but not all elevated). In the second model, these 2 groups were combined into 1 variable. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and p values. Due to the limited number of events, we ran separate models for each covariate to assess its impact on the cTnT results. The Kaplan-Meier event curve presented represents the serial measurements of cTnT and accounts for changes that a patient demonstrated during the course of the study (15).

Results

Of the 200 patients enrolled, 10 patients had insufficient data to be included in the study (no study enrollment biomarker data) and 18 patients had only baseline entry measurements without follow-up measurements. Therefore, 172 patients composed the final first-year study cohort. Of these 172 patients, 22 (13%) died or underwent transplantation during the first year. Therefore, 150 patients remained to compose the second-year group for analysis. Three pre-determined patterns of cTnT levels were established: 1) no serial cTnT elevations (defined as <0.01 ng/ml) in follow-up; 2) 1 or more, but not all, cTnT values were elevated (≥0.01 ng/ml); and 3) all serial cTnT values were elevated (≥0.01 ng/ml) during the first year of follow-up. The clinical and demographic characteristics of the surviving patients at the beginning of year 2 of follow-up as a function of the pre-defined cTnT profiles are shown in Table 1. Overall, ischemic and nonischemic etiologies of HF were fairly equally distributed in this patient cohort (80 of 150 [53%] ischemic vs. 70 of 150 [47%] nonischemic).

Primary end point (death or cardiac transplantation) analysis of serial cTnT patterns over time. Figure 1 shows the event rates that occurred during year 2 of follow-up that were associated with the observed year 1 cTnT profiles of change. Overall, 30 events (death or transplantation) occurred during the second year of the study. Of the 150 patients, 53 patients had persistently normal cTnT levels <0.01 ng/ml (Group 1) with an 11% event rate. Of the 57 patients who had 1 or more but not all cTnT levels elevated in year 1 (Group 2), 11 (19%) patients had events during year 2. When this group was subdivided further (Fig. 1), 21 patients had ≥50% normal (but not all normal) cTnT values (i.e., <0.01 ng/ml) and 36 patients had ≥50% elevated (but not all elevated) cTnT ≥0.01 ng/ml. The latter group had a higher event rate in year 2 (10% compared with 25%, $p = 0.038$). Forty patients demonstrated persistently elevated cTnT levels (Group 3), and of these patients, 13 (33%) experienced a primary end point event. These results were significant using the chi-square test ($p = 0.04$), probably because of the influence of those whose cTnT levels were constantly elevated. Those patients with ≥50% of serial cTnT elevated values or all cTnT levels persistently elevated experienced a higher event rate (29%) during the second year. Figure 2 reflects the Kaplan-Meier analyses for primary outcomes in year 2 of follow-up. Multivariate logistic modeling for death versus the proportion of elevated cTnT values with adjustment for covariates of risk was also done. Due to the small number of events, separate models for each of the covariates were run to assess their impact on the cTnT results. This analysis did not affect the overall results (conclusions were unchanged), and cTnT remained the strongest independent risk predictor ($p = 0.01$) of HF-related events (ischemic and nonischemic etiology [$p = 0.11$], renal function [$p = 0.22$], hypertension [$p = 0.86$], NYHA functional class [$p = 0.13$], atrial fibrillation [$p = 0.39$], and sex [$p = 0.03$]).

Because our previous report (11) had suggested that patients with cTnT levels ≥0.03 ng/ml were at even greater risk of events, we assessed the same cTnT groupings using this higher cut-point value (0.03 ng/ml). The results are also shown in Figure 1. Although the same profiles occurred, the event rates were higher in each subgroup, increasing to 45% in those with persistent elevations in cTnT ≥0.03 ng/ml ($p = 0.01$ relative to Groups 1 and 2).

When comparing the cTnT groups (Table 2), logistic regression analysis revealed the same gradient of risk, although not all differences were statistically significant. Patients with all serial cTnT values elevated versus none elevated had the highest risk with an OR of 3.77 and a 95% CI of 1.29 to 11.07 ($p = 0.02$). For those with ≥50% (but not all) elevated serial cTnT levels, the OR was 2.61 (95% CI: 0.84 to 8.13) compared with those without any serial elevations. For those patients with 1 or more elevated cTnT values (but not all) versus no elevated values in follow-up, the OR was 1.87 with a wide 95% CI of 0.64 to 5.49 and was not statistically significant ($p = 0.25$). Patients with ≥50% (but not all) serial normal values had an OR of 0.83 (95% CI: 0.15 to 4.45, $p = 0.82$), which was not different from those with persistently normal cTnT levels throughout the study.

The significance of isolated versus consecutive elevations in cTnT during the first year was also analyzed. Of those with varying levels of cTnT in year 1, 57 patients had 1 or more serial cTnT elevations, and of these, 11 (19%) had events ($p = 0.022$, compared with not having any elevations). A single isolated elevation in cTnT was the most common finding (23 of 57 patients, 40%), and after that, the most common was 2 consecutive elevations (20 of 57 patients, 35%). The highest number of consecutive elevations observed was 4, and this occurred in only 2 patients (4%) with neither of these patients experiencing an event. Thus, we were unable to distinguish differences related to the profile of elevations from the absolute number of elevations.

Hospitalizations for decompensated HF occurred in 60 (40%) patients with an overall total of 150 HF-related hospitalizations during the course of the study. As shown in Table 1, any elevation in cTnT was associated with an approximately 50% incidence of hospitalization, whereas in those patients without any elevations in cTnT during the first year, the occurrence of HF-related hospitalization in year 2 was relatively low at 19%.

Discussion

The results of this study provide novel findings regarding the prognostic significance of serial cTnT measurements observed during clinical follow-up of clinically stable, ambulatory patients with chronic HF. Importantly, frequent elevations (but not necessarily consecutive elevations) in

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Table 1 Baseline Patient Demographic and Clinical Characteristics by cTnT Profiles During Year 1 of Clinical Follow-Up

Variable	No Serial Elevations in cTnT (<0.01 ng/ml) (n = 53)	1 or More But Not All Serial cTnT Elevated (≥0.01 ng/ml) (n = 57)	All Serial cTnT Elevated (≥0.01 ng/ml) (n = 40)	p Value*
Age, yrs	68.4 ± 9.8	73.2 ± 8.2	72.8 ± 10.7	0.018
Sex				0.033
Male	37 (70)	39 (68)	36 (90)	
Female	16 (30)	18 (32)	4 (10)	
Race				0.55
Caucasian	53 (100)	56 (98)	39 (98)	
Native American	0 (0)	1 (2)	1 (3)	
NYHA functional class				0.54
III	51 (96)	53 (93)	39 (98)	
IV	2 (4)	4 (7)	1 (3)	
Diagnosis to enrollment, months	41.2 ± 49.1	46.8 ± 48.4	42.5 ± 41.0	0.81
LVEF, %	28.0 ± 10.8	27.1 ± 12.6	27.9 ± 13.0	0.91
Weight, kg	89.0 ± 23.1	82.1 ± 21.1	92.4 ± 25.5	0.08
Height, cm	172.0 ± 7.0	171.1 ± 9.9	173.3 ± 9.6	0.48
BMI, kg/m^2	29.9 ± 6.9	27.9 ± 5.7	30.9 ± 8.4	0.08
Heart rate, beats/min	70.5 ± 14.2	70.4 ± 11.8	70.2 ± 11.5	0.99
Systolic BP, mm Hg	112.3 ± 18.5	117.7 ± 24.0	113.8 ± 18.9	0.39
Diastolic BP, mm Hg	63.7 ± 11.6	64.3 ± 11.8	61.4 ± 8.8	0.43
Hemoglobin, g/dl	13.0 ± 1.6	12.5 ± 1.9	12.3 ± 1.8	0.29
Creatinine, mg/dl	1.4 ± 0.5	1.6 ± 0.5	1.9 ± 0.7	<0.001
GFR, ml/min/1.73 m^2	53.4 ± 14.9	44.9 ± 14.4	40.9 ± 16.6	<0.001
Potassium, mEq/l	4.5 ± 0.5	4.5 ± 1.4	4.4 ± 0.5	0.64
Sodium, mEq/l	139.8 ± 3.4	138.9 ± 4.6	138.5 ± 4.9	0.32
cTnT, ng/ml	0.0 ± 0.0	0.1 ± 0.9	0.1 ± 0.1	0.42
Primary etiology of HF				0.19
Ischemic	28 (53)	34 (60)	18 (45)	
Valvular	3 (6)	3 (5)	0 (0)	
Idiopathic	19 (36)	15 (26)	13 (33)	
Hypertension	0 (0)	2 (4)	2 (5)	
Other	3 (6)	3 (5)	7 (18)	
Diabetes	13 (25)	15 (26)	17 (43)	0.13
Hypertension	27 (51)	39 (68)	29 (73)	0.06
Hyperlipidemia	34 (64)	35 (61)	26 (65)	0.93
COPD	14 (26)	18 (32)	10 (25)	0.74
CABG	20 (38)	28 (49)	16 (40)	0.45
BiV PPM	2 (4)	4 (7)	2 (5)	0.75
AICD	9 (17)	18 (32)	11 (28)	0.20
Myocardial infarction	22 (42)	30 (53)	18 (45)	0.49
Cerebrovascular disease: stroke	2 (4)	2 (4)	5 (13)	0.13
History of ever smoking	35 (66)	38 (67)	23 (58)	0.61
Atrial fibrillation	15 (28)	32 (56)	21(53)	0.008
Aortic stenosis (moderate to severe)	6 (11)	3 (5)	1 (3)	0.21
Aortic regurgitation	14 (26)	16 (28)	8 (20)	0.65
Mitral regurgitation	37 (70)	42 (74)	26 (65)	0.66
Tricuspid regurgitation (moderate to severe)	10 (19)	16 (28)	7 (18)	0.37
Valve replacement	2 (4)	8 (14)	2 (5)	0.10
ACE inhibitor	39 (74)	44 (77)	33 (83)	0.60
ARB	10 (19)	9 (16)	4 (10)	0.50
Beta-blocker	42 (79)	47 (82)	28 (70)	0.33
Digoxin	27 (51)	37 (65)	24 (60)	0.32
Diuretic agent	43 (81)	53 (93)	38 (95)	0.05
Spironolactone	12 (23)	10 (18)	11 (28)	0.50
Aspirin	32 (60)	33 (58)	22 (55)	0.87
Nitrates	13 (25)	14 (25)	14 (35)	0.45
Antiarrhythmic agents	8 (15)	13 (23)	8 (20)	0.59
Death/cardiac transplant	6 (11)	11 (19)	13 (33)	0.040
Hospitalization for HF	10 (19)	30 (53)	20 (50)	<0.001
Death/transplantation or hospitalization for HF	16 (30)	30 (53)	24 (60)	0.009

Values are presented as mean ± SD or n (%). *p values obtained using Pearson's chi-square test for categorical variables and 1-way analysis of variance for continuous variables.

ACE = angiotensin-converting enzyme; AICD = automatic implantable cardioverter-defibrillator; ARB = angiotensin receptor blocker; BiV PPM = biventricular permanent pacemaker; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; cTnT = cardiac troponin T; GFR = glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

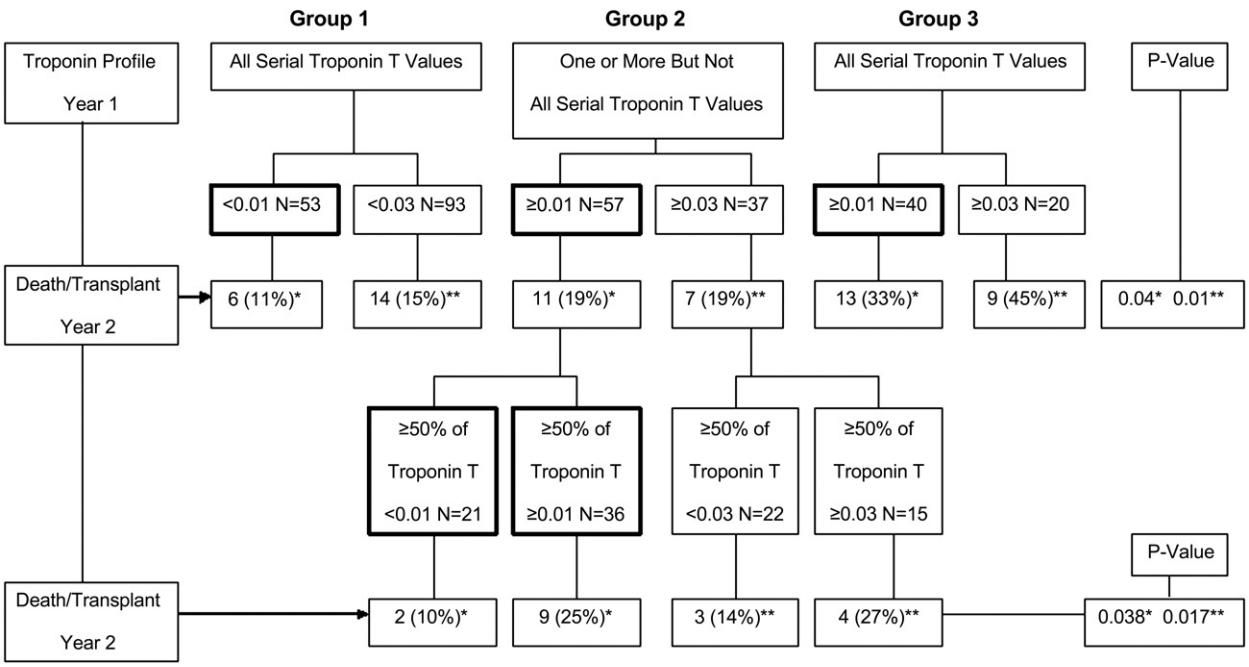

Figure 1 **Cardiac Troponin T Profiles and Outcomes**

Association of year 2 events (death/cardiac transplantation) with profiles of cardiac troponin T during year 1 of clinical follow-up using chi-square analysis.

cTnT during routine clinical follow-up, irrespective of the profile, were a potent predictor of increased mortality or the need for cardiac transplantation. Only a modest number of patients had cTnT elevations at all follow-up visits, and the risk of events was similar to those who manifested >50% but <100% elevations in cTnT values (25% vs. 33%, respectively). Thus, frequent elevations, although intermittent, seem to produce a significant prognostic effect. These findings suggest that the progression of HF is likely related to ongoing necrosis and the magnitude of injury. Such a concept is supported by the data showing that higher values of cTnT elevation (0.03 ng/ml vs. 0.01 ng/ml) were associated with higher event rates. We were unable to discern differences in the timing of these events, which were often intermittent, suggesting that they may occur in a stepwise fashion rather than in a continuous manner. If so, these episodes of elevations in cTnT may be analogous to those that result in hospital admissions and are often associated with an adverse prognosis, but are simply less often detected.

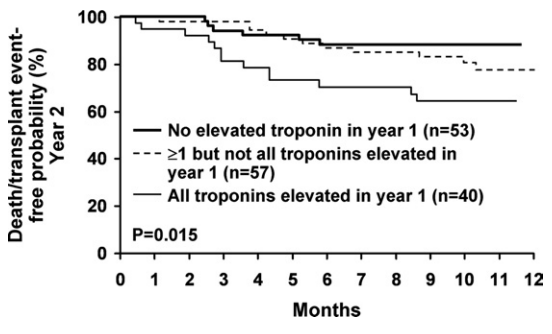

Figure 2 **Cardiac Troponin T Profiles and Risk of Events**

Kaplan-Meier analysis of the risk of death or cardiac transplantation in year 2 based on cardiac troponin T patterns from year 1 of clinical follow-up.

The prognostic value of single-sample baseline elevations in cTnT has been reported by us (11) and others (9,16–19). In our cohort, 103 (54%) patients had baseline elevations of cTnT ≥0.01 ng/ml. Among these, 49 (26%) patients demonstrated elevations >0.03 ng/ml, which is consistent with the frequency seen in other studies (20–23). In addition, we have reported the prognostic significance of the serial measurements of elevations in cTnT occurring at any

Table 2 **Risk of Death/Transplantation in Year 2 Based on cTnT Profiles During Year 1 of Clinical Follow-Up**

cTnT Patterns	Odds Ratio (95% CI)	p Value
All cTnT levels normal (<0.01 ng/ml) vs. ≥50% normal but not all normal	0.83 (0.15–4.45)	0.82
One or more but not all cTnT levels elevated vs. all normal levels	1.87 (0.64–5.49)	0.25
≥50% cTnT levels elevated but not all elevated vs. all normal levels	2.61 (0.84–8.13)	0.10
All cTnT levels elevated vs. all normal levels (<0.01 ng/ml)	3.77 (1.28–11.07)	0.02

CI = confidence interval; cTnT = cardiac troponin T.

time during clinical follow-up (11). Even modest elevations in cTnT were independently associated with an increased short-term risk of death or exacerbation of HF generally occurring within 3 months of the detected change in cTnT level. Changes in cTnT levels occurring during follow-up also modulated the risk with new elevations shifting patients to higher risk and, importantly, reductions in cTnT levels to <0.01 ng/ml reducing risk. This would be consistent with the findings of this study and suggests that not only are baseline and follow-up values of cTnT useful but also that the frequency of cTnT elevations identifies patients at various stages of risk. The data from the current analysis provide the substrate for clinical trials to investigate whether monitoring cTnT levels to mitigate risk will improve outcomes. Treatment trials predicated on biomarker values to guide therapy are topical, and several have been reported to show benefit using B-type natriuretic peptide (BNP) and N-terminal proBNP (24–27). In our study cohort, changes in cTnT levels were shown to be more predictive than BNP levels, likely because only modest decreases in BNP values were observed during treatment (11). We have also reported that large changes in natriuretic peptides are necessary to affect prognosis (28). Thus, even these initial positive results might be improved still further with more aggressive treatment regimens. These results indicate that the differences in cTnT profiles are associated with differences in risk, and, therefore, serial cTnT measurements may provide another means to follow patients and to titrate therapy. These findings also suggest that the impact of cTnT elevations is cumulative and that several recurrent elevations are needed to have a significant impact on prognosis. It is certainly reasonable to hypothesize that mitigating cTnT increases might result in better outcomes. This concept is supported by the fact that those patients with infrequent serial elevations in cTnT, and particularly normalization of cTnT levels, seem to temper the ongoing risk of death and HF-related hospitalizations.

Patients with persistent elevations in cTnT values in the first year clearly had the highest risk of death or transplantation in the second year (OR: 3.77, $p = 0.02$). The magnitudes of the elevations in cTnT were, however, modest compared with those reported for hospitalized patients (19,29). Thus, it may be that larger elevations (>0.03 ng/ml) or third and fourth modest serial elevations result in hospitalization, whereas first and second elevations or those that are very modest in magnitude do not. Such speculation would be consistent with our data. Approximately one-half of the elevations that we observed in cTnT were eventually associated with HF hospitalizations. We did not include values obtained during hospitalizations in this analysis because they were sporadic and used a variety of assays, and sampling was not done in a consistent manner. In the patients with more frequent elevations of cTnT and those patients with more than 1 (but not all) elevated cTnT value, 20 of 40 (50%) and 30 of 57 (53%), respectively, were hospitalized during the second year of follow-up for decompensated HF. Thus, these elevations may presage or at least be similar in prognostic importance to those associated with more severe events (20–22). If so, even modest elevations in cTnT without overt clinical decompensation may reflect similar pathophysiology, but only detectable by the serial monitoring of biomarkers such as cTnT. Our findings suggest that both clinically detectable and, importantly, subclinical myocardial injury may occur. Such events are consistent with myocyte injury/necrosis and/or apoptosis (6–8,17,19) and the concept of small heart failure myocardial infarctions that contribute to progressive deterioration in myocardial function. These events, however, should be clearly distinguished from acute infarctions due to coronary artery abnormalities because we believe that these HF-related events are more likely related to subendocardial demand ischemia/necrosis or apoptosis-induced myocardial stretch and/or toxic cytokines (23,30) than to primary coronary artery events. Abnormal rates of cardiomyocyte apoptosis have been described in patients with heart failure (31), and the intermittent elevations in cTnT may reflect this accelerated process of cell death. Although we cannot absolutely exclude the participation of coronary artery disease in patients whose HF was related to underlying ischemic heart disease and/or endothelial dysfunction, we did analyze for differences in the prognostic effects of cTnT profiles over time based on an ischemic versus nonischemic etiology of the HF and found no differences. An additional important covariate to be considered is renal function, which progressively worsened with myocardial injury, as reflected in the association of decreasing glomerular filtration rate and more frequent elevations in cTnT levels (Table 1). However, in multivariate analysis, cTnT remained the most potent independent predictor of HF-related events.

Study limitations. Eighteen patients elected at various times during follow-up not to continue participation in the study (6 had completed at least 1 year of follow-up) and 8 patients died after the initial enrollment visit and before the first 3-month follow-up visit; therefore, only baseline data were available on these patients. Also, due to the relatively small sample size and limited number of events, we did not fit multiple covariates in our statistical models, so we were unable to control for potential confounding variables simultaneously and chose to report p values.

Clinical implications. It seems that intermittent myocardial injury associated with the progression of HF occurs in apparently clinically stable and ambulatory outpatients. The monitoring over time of cTnT, which is a very sensitive and specific marker of myocardial injury, provides an available means of identifying the subgroup of HF patients at highest risk. An association between elevated cTnT and ventricular remodeling injury has been suggested (17,19), and our findings support a high risk of death or transplantation in patients with persistently elevated cTnT levels, even using a low threshold of 0.01 ng/ml. Our data suggest a stepwise progression of disease, which favors the possibility that targeted intervention at these times, whether with hospital-

ization if clinically overt events or whether detected only by elevations in cTnT, might be beneficial.

Conclusions

The findings show that more frequent elevations in cTnT detected during routine clinical follow-up of ambulatory patients with chronic HF are highly associated with an increased short-term risk of death or cardiac transplantation, as well as the need for HF-related hospitalization. The strategy of serially monitoring cTnT levels, therefore, may have a role in detecting and managing patients with HF who are at higher risk, as advocated by others (32). Even modest elevations (≥0.01 ng/ml) are highly prognostic of poor short-term outcomes. Treatment trials predicated on these findings should be considered.

Reprint requests and correspondence: Dr. Wayne L. Miller, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: miller.wayne@mayo.edu.

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