Heart Failure

Ongoing Myocardial Injury in Stable Severe Heart Failure
Value of Cardiac Troponin T Monitoring for High-Risk Patient Identification

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Background—The progression of chronic heart failure (CHF) is related to ongoing myocyte loss, which can be detected by cardiac troponin T (cTnT). We examined the prevalence and prognostic value of increased cTnT concentrations in serial blood specimens from patients with severe CHF.

Methods and Results—Clinical, echocardiographic, and 6-minute walk test data were collected prospectively at baseline and at 1 year in 115 outpatients (mean age, 61±11 years; 75% men; 62% coronary heart disease) with CHF and a left ventricular ejection fraction <40%. Blood samples were collected at baseline and at 3, 6, and 12 months of follow-up. cTnT concentrations ≥0.02 ng/mL were considered abnormal, and a Tn index (highest cTnT measurement/0.02 ng/mL) was calculated. In 62 patients (54%), cTnT was consistently <0.02 ng/mL (group 1); 28 (24%) had a single abnormal cTnT result (group 2); and 25 (22%) had ≥2 abnormal cTnT results (group 3). At 18 months, CHF hospitalization-free survival was 63%, 46%, and 17%, respectively (P=0.0001). In a Cox proportional-hazards model, hospitalization for worsening CHF in the previous year (HR=2.1; 95% CI, 1.1 to 4.1), functional class III–IV (HR=2.3; 95% CI, 1.1 to 4.6), and number of abnormal cTnT samples (HR=1.6; 95% CI, 1.1 to 2.4) were independently associated with prognosis. A cTnT rise of 0.020 ng/mL in any sample was associated with an excess of 9% (95% CI, 1% to 18%) in the incidence of combined end point.

Conclusions—Abnormal cTnT concentrations were detected in >50% of outpatients with advanced CHF. This ongoing myocardial necrosis was a strong predictor of worsening CHF, suggesting a role of cTnT-based monitoring to identify high-risk patients. (Circulation. 2004;110:2376–2382.)

Key Words: heart failure ■ troponin ■ prognosis

Chronic heart failure (CHF) is a widely prevalent, progressive disorder of multiple causes. Progression of CHF manifests clinically as a loss of functional capacity, declining quality of life, deterioration of ventricular function, and high hospitalization and mortality rates, with important consequences for public health.1–3 The risk is highest 2 to 6 months after hospitalization for decompensated CHF, when the readmission rate approaches 60%.4–7 The reported in-hospital mortality ranges between 3.8% and 13.0%,7–8 and ~50% of patients die within 5 years after the diagnosis of CHF, a rate that has remained stable despite therapeutic advances.

Ventricular remodeling is the currently accepted mechanism for the progression and clinical development of CHF.9–10 Although several factors contribute to this remodeling, activation of the sympathetic and neurohormonal systems plays a key role. The final common pathway is the loss of myocytes. Cardiac troponins T (cTnT) and I are markers of myocardial injury. Their introduction into clinical practice has changed the perception and definition of myocardial infarction,11,12 and they are currently the object of extensive research in patients with CHF.13–17

We hypothesized that the leak of cTnT during the stable phase of CHF may be a sign of ongoing subclinical progression of CHF. This study (1) examined the prevalence of increased concentrations of cTnT in serial blood samples collected from ambulatory patients with CHF and (2) tested the hypothesis that persistently increased concentrations of cTnT in these patients are associated with a worse long-term outcome.

Methods
Our Institutional Committee on Human Research approved this study, and all patients granted their written informed consent to participate. Between January 7, 2001, and March 31, 2001, 115 consecutive patients from the heart failure clinic, with a diagnosis of CHF present for ≥30 days and a left ventricular ejection fraction (LVEF) <40%, were prospectively included in the study if they fulfilled at least one of the following criteria.

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1. History of hospitalization because of cardiogenic acute pulmonary edema, including 2 of the 3 following manifestations: (a) dyspnea, tachypnea, and orthopnea, (b) rales audible over ≥2/3 of the lung fields, and (c) diffuse, bilateral, alveolar infiltrates on chest roentgenogram.

2. History of congestion, including signs and symptoms of pulmonary congestion (dyspnea on exertion, nocturnal cough, orthopnea, rales, 3rd sound) and/or systemic venous congestion (edema, ascites, hepatomegaly, or jugular venous distension).

3. History of dyspnea on exertion or paroxysmal nocturnal dyspnea.

4. History of Framingham criteria \(^\text{18}\) at the time of initial evaluation or during a hospitalization.

In addition, all patients had to have remained clinically stable for ≥30 days after a hospital admission for cardiac decompensation. Patients were excluded if they had (1) an acute coronary syndrome in the previous 3 months (unstable angina, acute myocardial infarction, or a percutaneous or surgical revascularization procedure); (2) the presence of a life-limiting malignancy, hepatic or renal disease, or a baseline creatinine concentration >2.5 mg/dL; or (3) refusal to participate in the study.

Study Protocol

On initial evaluation, a clinical examination was performed. The functional class was graded according to number of METS reached during a specific activity, determined by a specific questionnaire,\(^\text{19}\) and classified as class I if the exercise capacity was ≥7 METS, class II if between 5 and 7 METS, class III if between 2 and 5 METS, and class IV if it was <2 METS. A chest roentgenogram and ECG were obtained in all patients.

Baseline therapy included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (95% of patients), \(\beta\)-adrenergic blockers (65%), diuretics (84%), spironolactone (29%), digoxin (63%), amiodarone (41%), antiplatelet agents (65%), and antithrombotics (41%).

Six-Minute Walk Test and 2D Echocardiography

A 6-minute walk test was performed in all groups on admission to the study and at 12 months of follow-up. The patients were instructed to walk at their own pace to cover the longest distance possible in 6 minutes. Symptoms during exercise, heart rate, and blood pressure before and after exercise, and overall distance covered were recorded.

Two-dimensional and M-mode echocardiograms were performed at baseline and at 12 months. An ATL HDI 5000 echograph (Advanced Technologies Laboratories) and a 4- to 2-MHz transducer with second harmonic frequency band were used, and the studies were recorded on videocassette with an MD-830 Panasonic recorder. The measurements were made in both modes, and the ventricular volumes and LVEF were calculated by Simpson’s modified method.\(^\text{20}\)

Laboratory Screening

Fasting blood samples were obtained for measurements of chemistry panel. The serum was stored at −30° until analysis. cTnT was measured by a third-generation electrochemiluminescent immunoassay with an Elecsys 2010 automatic analyzer (Elecsystroponin-T, Roche Diagnostics). The lower detection limit was 0.010 ng/mL, and values ≥0.02 ng/mL were considered abnormal. All blood samples for cTnT measurements were collected during scheduled ambulatory visits. The primary physicians were unaware of the troponin results, and the laboratory was not informed of the patient’s condition.

Follow-Up Schedule

Patients were followed up in our heart failure clinic, with visits scheduled at 3, 6, and 12±3 months. Blood samples were drawn for measurements of cTnT. Functional capacity, LVEF, and distance covered in the 6-minute walk test were measured at baseline in all patients and at 12 months in the survivors. Patients who could not be seen in the clinic were contacted by telephone to obtain clinical data and adverse events.

Definitions and Study End Points

The combined primary end point of the study was all-cause mortality and hospitalization for worsening of CHF at 18 months of follow-up. The development of signs and/or symptoms of cardiac decompensation requiring an increase in doses of diuretics or addition of other drugs was defined as worsening CHF. Visits to the emergency room for decompensated CHF were defined as emergency visits for CHF. Hospitalization for worsening CHF that required the administration of intravenous diuretics, inotropes, and/or vasodilators for >12 hours was defined as hospitalization for CHF.

Statistical Analysis

Patients were included in group 1 if all cTnT measurements were within normal limits, group 2 with a single abnormal sample, and group 3 with ≥2 abnormal ones. It was assumed that ≥95% of patients would have ≥2 samples during the study period, with 100% of baseline measurements available, and that up to 25% of the follow-up samples would be missing. Categorical variables are expressed as percentages, and they were compared by use of the Pearson χ² test; a Fisher exact test correction was used to compare patients with versus without events. Continuous variables are presented as mean±SD and were compared among the 3 groups by 1-way ANOVA using the Bonferroni test as a post hoc contrast analysis. The Mann-Whitney \(t\) or \(U\) tests were used for comparisons of independent samples. Comparisons of variables between baseline and 12 months were made with the Wilcoxon matched-pairs signed-rank test. To establish the optimal cTnT cutoff point for prognostic purposes, the area under the receiver operating characteristic (ROC) curve corresponding to the highest cTnT level ever obtained during follow-up in an individual patient was determined with regard to combined end point. The relation between highest cTnT level/cutoff value of 0.02 ng/mL (Tn index) was calculated. Differences with probability values <5% were considered statistically significant.

Hospitalization-free survival curves were constructed by the Kaplan-Meier method and compared by log-rank test. Two different Cox proportional-hazards models were built using variables significantly associated with the combined study end point in univariate analysis, one of them with degree of myocardial damage and another with Tn index. All statistical analyses were performed with the SPSS 10.0 program.

Results

The mean age was 61.2±10.8 years, and 75% were men. Ischemic heart disease was present in approximately two thirds of patients, one third had been hospitalized for management of CHF in the previous year, and >50% of patients were in CHF functional class III–IV (Table 1).

The results of the cTnT measurements are detailed in Table 2. The median number of samples per patient was 4 (mean, 3.3±0.8), which was similar among groups. Four patients (3.5%) who died within the first 3 months had a single cTnT measurement (cTnT was normal in 3), 96.5% had ≥2, 82% had ≥3, and 51% had ≥4 cTnT specimens.

Grades of Myocardial Injury

There were 62 (54%), 28 (24%), and 25 (22%) patients included in groups 1, 2, and 3, respectively. The baseline characteristics are compared among groups in Table 1. Age increased from group 1 to group 3. Likewise, a higher number of samples with abnormal cTnT corresponded to a higher functional class and a greater number of previous hospitalizations for CHF. The physical findings and baseline labora-
Evolution of Functional Capacity, LVEF, and 6-Minute Walk Distance

Functional class worsened between baseline and 1 year in group 3 and remained unchanged in groups 1 and 2 (Table 4). Baseline LVEFs were lower in groups 2 and 3 compared with group 1. LVEF increased between baseline and 1 year in all groups. However, the increase was not significant in group 3. The distance in the 6-minute walk test was significantly shorter in group 3 than in groups 1 and 2 at both time points.

cTnT and Long-Term Outcomes

Worsening CHF was observed in 27.4%, 64.3%, and 88% of patients in groups 1, 2, and 3, respectively (P<0.0001). Hospitalizations for CHF patients, respectively (P<0.0001), and /H11021 Worsening CHF was observed in 27.4%, 64.3%, and 88% of patients in groups 1, 2, and 3, respectively (P<0.0001), and /H11021 Worsening CHF was observed in 27.4%, 64.3%, and 88% of patients in groups 1, 2, and 3, respectively (P<0.0001), and /H11021 Worsening CHF was observed in 27.4%, 64.3%, and 88% of patients in groups 1, 2, and 3, respectively (P<0.0001), and

Highest Level of cTnT and Outcome: Importance of Tn index

The area under the ROC curve of highest cTnT level was 0.68 (95% CI, 0.58 to 0.79) to predict the combined end point, and a 0.020-ng/mL cutoff showed a sensitivity of 62% and specificity of 71% (Figure 3A). According to the increase of Tn index (≤1 to ≥5), the incidence of combined end point was 29%, 54%, 60%, 80%, and 78%, respectively (P=0.006). In the proportional-hazards model, each level of Tn index was associated with reduced hospitalization-free survival (Figure 3B).

Prognostic Role of cTnT Monitoring

Variables associated with the combined end point in the univariate analysis are shown in Table 5. In the first Cox proportional-hazards model, the variables independently associated with the primary end point were hospitalization for CHF in the previous year (hazard ratio [HR]=2.1), functional class III–IV (HR=2.3), and number of abnormal cTnT results (HR=1.6). In the second model, the variables associated with events were hospitalization in the previous year (HR=2.39), functional class III–IV (HR=2.87), and Tn index (1.09). Thus, for each increment of 0.020 ng/mL in cTnT obtained in any sample, there was an excess of 9% (95% CI, 1% to 18%) in the incidence of death or hospitalization for worsening heart failure.

Discussion

This study demonstrated that leaks of cTnT by monitoring of serial concentrations during the follow-up of optimally

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### Table 1. Baseline Characteristics of Each Study Group

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>62 (54.0)</td>
<td>28 (24.3)</td>
<td>25 (21.7)</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>59.1±11.7</td>
<td>61.3±10.2</td>
<td>66.2±7.7</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>46 (74.2)</td>
<td>21 (75.0)</td>
<td>19 (76.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>36 (58.1)</td>
<td>20 (71.4)</td>
<td>17 (68.0)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>11 (17.7)</td>
<td>7 (25.0)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>30 (48.4)</td>
<td>13 (46.4)</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>38 (61.3)</td>
<td>18 (64.3)</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td>Functional class III–IV, n (%)</td>
<td>31 (50)</td>
<td>19 (68.0)</td>
<td>16 (64.0)</td>
</tr>
<tr>
<td>Hospitalization in last year, n (%)</td>
<td>14 (22.6)</td>
<td>9 (32.1)</td>
<td>14 (56.0)</td>
</tr>
</tbody>
</table>

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### Table 2. Rates of Abnormal cTnT Samples at Baseline and at 3, 6, and 12 Months

<table>
<thead>
<tr>
<th>Months of Follow-Up</th>
<th>Baseline</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with samples available, n (%)*</td>
<td>115 (100)</td>
<td>81 (71)</td>
<td>92 (80)</td>
<td>90 (78)</td>
</tr>
<tr>
<td>cTnT ≥0.02 ng/mL, n (%)†</td>
<td>37 (32)</td>
<td>23 (28)</td>
<td>16 (17)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Mean value±SD, ng/mL</td>
<td>0.039±0.027</td>
<td>0.044±0.020</td>
<td>0.074±0.129</td>
<td>0.072±0.073</td>
</tr>
<tr>
<td>Range, ng/mL</td>
<td>0.020–0.146</td>
<td>0.020–0.085</td>
<td>0.020–0.551</td>
<td>0.020–0.291</td>
</tr>
</tbody>
</table>

*Percentages are relative to the entire patient population.
†Percentages are relative to the total number of patients with samples available.
treated outpatients with CHF is a frequent finding that identifies a high-risk population in the long term and suggests a subclinical ongoing internal process despite an otherwise stable clinical condition. Furthermore, the presence of persistently increased cTnT concentrations is a powerful independent predictor of death or hospitalization for CHF.

Troponins T and I are elements of the troponin-tropomyosin complex in muscle fibers, although a small cytoplasmic fraction of both subunits also exists. The use of these markers in acute coronary syndromes has prompted a revision of the criteria for diagnosis of myocardial infarction by the Joint European Society of Cardiology/American College of Cardiology Committee.11,12

The relationship between troponins and CHF has been studied in various clinical settings. In the outpatient setting with CHF, the prevalence of myocardial injury was 25% to 50%.14,16,17,21,22 Conversely, the presence of troponin in decompensated CHF was also associated with more profound clinical and hemodynamic deterioration, more severe LV remodeling, and worse short- and long-term prognosis.15,23–27 Combining cTnT and brain natriuretic peptide (BNP) offers a new risk-stratifying tool that detects cellular injury as well as ventricular overload.26

In contrast, data pertaining to the monitoring of serial cTnT concentrations are scarce. In a retrospective study of patients with nonischemic dilated cardiomyopathy, Sato et al13 found cTnT values /H11350 0.02 ng/mL in 45% of the population. Three evolutionary patterns were distinguished: persistently normal, high initial concentrations falling during follow-up, and persistently high concentrations. This last pattern was associated with the lowest long-term survival. We describe 2 new and different monitoring methods in a population with ischemic heart disease. One is based on the number of samples with abnormal cTnT concentrations; the other is based on the quantitative level of cTnT in any sample.

| TABLE 3. Baseline Physical Findings, ECG, Biochemistry, Echocardiogram, and 6-Minute Walk Test |
|-----------------------------------------------|----------------|----------------|----------------|----------------|
| Group 1                                      | Group 2         | Group 3         | P              |
| Blood pressure, mm Hg                         |                 |                 |                |
| Systolic                                     | 119.3±20        | 124.1±23.5      | 118.6±20.2     | 0.54           |
| Diastolic                                     | 72.6±10.7       | 77.6±11.7       | 72.0±13.8      | 0.12           |
| Hematocrit, %                                | 42.4±4.4        | 42.8±4.09       | 43.2±5.4       | 0.79           |
| Creatinine, mg/dL                            | 1.16±0.32       | 1.38±0.30       | 1.62±0.62      | <0.001         |
| Sodium, meq/L                                | 141.8±3.0       | 141.6±3.5       | 142.2±3.2      | 0.79           |
| Glycemia, mg/dL                              | 1.07±0.38       | 1.33±0.61       | 1.09±0.32      | 0.035          |
| C-reactive protein, mg/dL                    | 0.48±1.25       | 1.81±7.49       | 0.44±0.61      | 0.27           |
| Sinus rhythm, n (%)                          | 45 (72.6)       | 15 (53.6)       | 15 (60.0)      | 0.18           |
| Left bundle-branch block, n (%)              | 16 (25.8)       | 16 (57.1)       | 7 (28.0)       | 0.011          |
| LV diastolic diameter, mm                    | 59.6±7.9        | 63.2±10.0       | 61.2±7.7       | 0.17           |
| LV systolic diameter, mm                     | 47.6±9.4        | 51.8±10.6       | 50.1±8.8       | 0.15           |

| TABLE 4. Changes in Functional Capacity, LVEF, and Distance Covered in 6 Minutes Between Baseline and 12 Months Among Study Groups |
|-----------------------------------------------|----------------|----------------|----|
| Group                                       | Baseline       | 12 Months      | P  |
| Functional class                            |                |                |    |
| 1                                           | 2.3±0.9        | 2.4±0.7        | NS |
| 2                                           | 2.5±0.7        | 2.7±0.8        | NS |
| 3                                           | 2.5±0.8        | 3.2±0.4        | 0.002 |
| P (among groups)                            | NS             | <0.0001        |    |
| LVEF, %                                      |                |                |    |
| 1                                           | 28.5±7.8       | 36.0±11.5      | <0.0001 |
| 2                                           | 22.3±7.9       | 32.7±12.9      | 0.033 |
| 3                                           | 25.4±7.8       | 30.6±10.6      | NS |
| P (among groups)                            | 0.003          | NS             |    |
| Distance walked in 6 minutes, m             |                |                |    |
| 1                                           | 406±65         | 398±102        | NS |
| 2                                           | 360±81         | 415±80         | NS |
| 3                                           | 339±90         | 321±59         | NS |
| P (among groups)                            | 0.001          | 0.021          |    |

Figure 1. Hospitalization (for CHF)–free survival according to degree of myocardial injury. Group 1: all cTnT samples within normal limits; group 2: a single cTnT sample abnormal; group 3: ≥2 abnormal cTnT measurements.
Clinical Characteristics and Evolutionary Patterns of Myocardial Injury

At baseline, the clinical characteristics of groups 2 and 3 were indicative of higher risk. Furthermore, these 2 groups had larger LV end-diastolic diameters, lower LVEF, and worse functional class, and they were able to cover shorter distances.

Over time, functional class and overall clinical status deteriorated significantly in group 3. Although the distance walked in 6 minutes remained unchanged during the study period, it was distinctly shorter in group 3 than in the other groups. Whereas LVEF increased significantly in groups 1 and 2, the 5% increase measured in group 3 was statistically nonsignificant. Our observations are at variance with previous reports in which LVEF in patients with high cTnT concentrations remained unchanged or decreased, compared with patients with normal cTnT concentrations.13,16 The recording of follow-up echocardiograms limited to surviving patients and the effect of random differences might explain that discrepancy.

Prognostic Role of cTnT Monitoring

The incidence of study end points was consistent with a population at risk followed up in a comprehensive heart failure clinic.6,28,29 cTnT monitoring identified a population with nearly 50% hospitalization (for CHF)–free survival at 18 months among patients with a single abnormal cTnT measurement, versus <20% when several serial samples were abnormal. This difference was a result of both CHF progression and mortality. More importantly, cTnT monitoring was an independent predictor of the primary study end point.30 Previous studies, particularly in patients hospitalized for decompensated CHF, have confirmed the prognostic value of troponins.21–27 In 238 patients with advanced CHF, Horwich et al16 reported the association between detectable levels of cTnI and impaired hemodynamics, elevated BNP levels, progressive LV dysfunction, and poor prognosis. Moreover, the presence of both cTnI and BNP was associated with a 12-fold increased risk of long-term mortality.

A high creatinine concentration may be related to the high rate of rising cTnT.31 However, the third-generation assay is highly specific, and cTnT has emerged as one of the most powerful predictors of mortality in patients with renal impairment, including those treated with hemodialysis.32,33 Moreover, cTnT was associated with poor prognosis in patients with preserved renal function, suggesting that the rise and prognostic role of cTnT are independent of renal function.

From the published experience on troponins in CHF, 2 additive mechanisms of myocardial injury could be hypothesized. First, in the ambulatory setting, up to 50% of patients may have low-grade ongoing cellular injury, either by an increase in cell membrane permeability with release of the cytoplasmic pool or by other phenomena causing apoptosis or minimum necrosis. This identifies high-risk patients with higher myocardial vulnerability. Second, in the event of additional myocardial injury, or because of their greater susceptibility to minor events, such as a diet transgression or fluid overload, these patients rapidly develop decompensated CHF. Under these new conditions, the marker may increase further, as has been described in patients with acute pulmo-
ary edema, in whom it is difficult to distinguish between troponin increases from CHF versus from true myocardial infarction.\textsuperscript{15}

**Limitations of the Study**

Because coronary angiography was not mandated by our protocol, the absence of coronary artery disease may not have been strictly confirmed in some patients. However, the >60% prevalence of ischemic heart disease in the 3 groups is similar to that previously reported in other populations of patients with CHF.\textsuperscript{16} In addition, neither hemodynamic nor neurohormone measurements, including BNP, were made in our patients.

The fact that up to 29% of our patients did not have all 3 cTnT measurements during follow-up may be viewed as another study limitation, because could it be possible that some of the patients who were assigned to group 1 would have been classified in a different group if all samples had been obtained. However, our study objectives could be reached with at least 2 measurements (baseline and 1 during follow-up), which were achieved in more than 96% of the population. In addition, the importance of the highest value of cTnT underscores the role of a single sample.

**Clinical Implications**

Because myocardial injury has been related to the progression of CHF, monitoring of cTnT offers a means of identifying a subgroup of patients with myocardial vulnerability and at increased risk. Patients with CHF might be monitored periodically through cTnT. The association between high levels of cTnT and ventricular remodeling was recently reported, suggesting that titration of β-blockers and ACE inhibitors, drugs with antiremodeling effects, should be recommended.\textsuperscript{27} This contribution should be tested via the efficacy of several drugs on the production or mitigation of myocardial injury and impact on risk or clinical benefit.

In conclusion, the serial detection of increased cTnT concentrations in ambulatory patients with CHF was associated with an unfavorable clinical evolution. Long-term monitoring of myocardial injury was a strong prognosticator, suggesting that this strategy may play a useful role in the detection of high-risk patients.

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**References**

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