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Review

Increases of Cardiac Troponin in Conditions other than Acute Coronary Syndrome and Heart Failure

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BACKGROUND: Although cardiac troponin (cTn) is a cornerstone marker in the assessment and management of patients with acute coronary syndrome (ACS) and heart failure (HF), cTn is not diagnostically specific for any single myocardial disease process. This narrative review discusses increases in cTn that result from acute and chronic diseases, iatrogenic causes, and myocardial injury other than ACS and HF.

CONTENT: Increased cTn concentrations have been reported in cardiac, vascular, and respiratory disease and in association with infectious processes. In cases involving acute aortic dissection, cerebrovascular accident, treatment in an intensive care unit, and upper gastrointestinal bleeding, increased cTn predicts a longer time to diagnosis and treatment, increased length of hospital stay, and increased mortality. cTn increases are diagnostically and prognostically useful in patients with cardiac inflammatory diseases and in patients with respiratory disease; in respiratory disease cTn can help identify patients who would benefit from aggressive management. In chronic renal failure patients the diagnostic sensitivity of cTn for ACS is decreased, but cTn is prognostic for the development of cardiovascular disease. cTn also provides useful information when increases are attributable to various iatrogenic causes and blunt chest trauma.

SUMMARY: Information on the diagnostic and prognostic uses of cTn in conditions other than ACS and heart failure is accumulating. Although increased cTn in settings other than ACS or heart failure is frequently considered a clinical confounder, the astute physician must be able to interpret cTn as a dynamic marker of myocardial damage, using clinical acumen to determine the source and significance of any reported cTn increase.

Cardiovascular disease (CVD)[3] accounts for more than 800 000 deaths and 6 million hospitalizations and has an estimated cost of more than $71 billion annually in the US *(1)*. Most acute cardiovascular events are due to rupture of coronary plaque, which is the root cause of the acute coronary syndromes (ACS), a continuum of ischemic cardiac disease spanning from unstable angina to frank myocardial necrosis. In the US heart failure (HF) affects more than 5.3 million individuals and is responsible for approximately 1 million hospitalizations and 285 000 deaths yearly and an annual cost burden of $29.6 billion *(1)*.

Biomarkers have revolutionized the diagnosis, risk assessment, and management of ACS and HF patients. In 2007 the National Academy of Clinical Biochemistry developed guidelines for the use of biomarkers in the diagnosis and management of ACS *(2)*. Also in 2007, a task force of the European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation formulated an updated redefinition of myocardial infarction (MI) in which biomarkers play a central role *(3)*. Professional groups are united in establishing cardiac troponin (cTn) as the preferred biomarker for diagnosis of MI. In the context of HF, evidence for a role of necrosis markers continues to develop, particularly for use in risk stratification *(4)*.

Clearly cTn assays have gone through several development "generations." Appreciation of the importance of cTn increases in disease will require knowledge of cTn concentrations in the healthy population. This matter has received particular attention recently because the limit of detection for the newest generation of cTn assays is 10- to 100-fold lower than that of currently available commercial assays *(5)*. In fact, test-induced ischemia has been associated with quantifiable cTn increases in proportion to the grade of ischemia,

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[3] Nonstandard abbreviations: CVD, cardiovascular disease; ACS, acute coronary syndrome; HF, heart failure; MI, myocardial infarction; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; AAD, acute aortic dissection; CVA, cerebrovascular accident; ICU, intensive care unit; PE, pulmonary embolism; RI, renal insufficiency; ECG, electrocardiogram; UGI, upper gastrointestinal; ARDS, acute respiratory distress syndrome; ESRD, end-stage renal disease; CRF, chronic renal failure; HTx, heart transplant; CAV, cardiac allograft vasculopathy; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; CV, cardioversion.

i.e., mild or moderate to severe, with an ultrasensitive assay *(6)*. Even with the use of a less sensitive assay, a population-based sample of 3557 individuals demonstrated a prevalence of increased cTnT in the general population of 0.7% *(7)*. With the use of a high-sensitivity commercial assay in a community-based study of 1089 asymptomatic elderly men without significant cardiac pathology, a cTnI $\geq$0.03 μg/L was associated with a hazard ratio of 5.25 for HF *(8)*. Increasing understanding of the prognostic value of circulating cTn concentrations in the population, through the use of newer high-sensitivity assays, may enable physicians to direct therapy that is biologically tailored to avert adverse cardiac outcomes *(9)*. With the advent and implementation of these higher sensitivity assays, the number of etiologies demonstrating abnormal concentrations and patterns of cTn will likely increase.

Cardiac troponin T (cTnT) and I (cTnI) are sensitive *(10, 11)* markers of cardiac injury, particularly when used with the recommended *(3, 4)* diagnostic cutpoint of the 99th percentile of healthy controls. Lower cutpoints, however, may lead to the misinterpretation of increased cTn as ischemia derived, when in fact the source is non-ACS and non-HF in nature. Thus to avoid unnecessary and costly interventions as well as delays in management decisions, laboratory staff and clinicians must have a working knowledge of clinical disorders other than ACS and HF in which cTn may be increased. The list of clinical entities other than ACS and HF that may be associated with increased cTn is extensive, as shown in Table 1. This narrative review discusses cTn increases in non-ACS and non-HF etiologies.

Acute Disease

Acute non-ACS and non-HF conditions in which substantial increases in cTn and other cardiac biomarkers of necrosis may occur are listed in Table 2.

CARDIAC AND VASCULAR

Acute aortic dissection (AAD) is characterized by separation of the layers within the wall of the aorta and is the most common disorder of the aorta requiring urgent surgical intervention. AAD prevalence ranges from 5–30 cases per million per year, with peak occurrence occurring between the sixth and seventh decade of life. The inhospital mortality of AAD is 27%, and there is a 2:1 male-to-female ratio *(12, 13)*. Development of AAD is associated with inherited, familial, and acquired risk factors *(14)*. AAD mimics ACS *(12)*, but treatments for the 2 conditions are radically different. Therefore, correct diagnosis in this setting is critical because of the potentially disastrous results of inappropriate treatments such as administration of thrombolytic therapy to an AAD patient whose condition is misdiagnosed as ACS *(15)* and the risk associated with a delay in diagnosis of AAD, for which a 1% per h mortality is observed in the first 48 h *(16)*. The mechanism of cTn increase in AAD is not well understood.

In AAD, cTn may be increased in up to 18% of patients at presentation and is reportedly associated with a 3- to 4-fold increased risk of delayed inhospital diagnosis *(17)*. In a study of 66 patients with the eventual diagnosis of AAD, increased cTn occurred in 7 patients (11%) and coronary compromise as a consequence of aortic dissection occurred in 4 patients (6%) *(15)*. On the other hand, a review of 151 patients (76 controls and 75 patients with AAD) indicated that cTn was not increased in association with a diagnosis of AAD *(18)*. Nonetheless, given the consequences of misdiagnosis, AAD should be given consideration in suspected ACS patients even if they are cTn positive. It is noteworthy that blood tests for risk stratification in suspected cases of AAD are being actively investigated; some of these tests include D-dimer, matrix metalloproteinases, smooth muscle myosin heavy chain, and soluble elastin fragments *(19)*.

Cerebrovascular accident (CVA) or stroke is defined as the rapid development of neurologic deficit resulting from disruption of the blood supply to the corresponding area of the brain *(20)*. Risk factors associated with stroke are similar to those for CVD *(21)*. Stroke is classified into 2 subtypes, ischemic (88% of all stroke) and hemorrhagic (12%), with further subdivision of hemorrhagic stroke into intracerebral hemorrhage (9%) and subarachnoid hemorrhage (3%) *(21)*.

Increases in cTn have been reported in all types of stroke, even after patients with ischemic cardiac damage have been excluded *(22)*. Although the etiology of increased cTn in the setting of CVA has not been entirely elucidated, current research supports an exaggerated catecholamine release (likely originating in the right insular cortex) leading to excessive release of intracellular calcium ions and subsequent reversible myocyte dysfunction. An alternate explanation is that the catecholamine surge acts as an uncontrolled severe myocardial stress test, which essentially reveals stable coronary plaques *(23)*. The majority of studies relating cTn and stroke demonstrate an association with adverse outcomes *(22, 24, 25)*, whereas only a few reported studies showed no association *(26, 27)*. In a prospective study of 244 patients with acute ischemic stroke without demonstrable ischemic cardiac disease, increased concentrations of cTnT ($>$0.03 μg/L) were observed in 10% of patients and significantly associated with mortality *(28)*. Increased cTn values have been associated with intracerebral hemorrhage and independently associated with inhospital mortality *(29)*. Both retrospective *(30)* and prospective *(31, 33)* stud-

Table 1. Differential diagnosis of increased cTn in patients without ACS or heart failure.

Acute disease	Chronic disease
○ Cardiac and vascular	○ ESRD
● Acute aortic dissection	○ Cardiac infiltrative disorders
● Cerebrovascular accident	● Amyloidosis
– Ischemic stroke	● Sarcoidosis
– Intracerebral hemorrhage	● Hemochromatosis
– Subarachnoid hemorrhage	● Scleroderma
● Medical ICU patients	○ Hypertension
● Gastrointestinal bleeding	○ Diabetes
○ Respiratory	○ Hypothyroidism
● Acute PE	
● ARDS	Iatrogenic disease
○ Cardiac inflammation	○ Invasive procedures
● Endocarditis	● Htx
● Myocarditis	● Congenital defect repair
● Pericarditis	● RFCA
○ Muscular damage	● Lung resection
○ Infectious	● ERCP
● Sepsis	○ Noninvasive procedures
● Viral illness	● Cardioversion
○ Other acute causes of cTn increase	● Lithotripsy
● Kawasaki disease	○ Pharmacologic sources
● Apical ballooning syndrome	● Chemotherapy
● Thrombotic thrombocytopenic purpura	● Other medications
● Rhabdomyolysis	
● Birth complications in infants	Myocardial injury
– Extreme low birth weight	○ Blunt chest injury
– Preterm delivery	○ Endurance athletes
● Acute complications of inherited disorders	○ Envenomation
– Neurofibromatosis	● Snake
– Duchenne muscular dystrophy	● Jellyfish
– Klippel-Feil syndrome	● Spider
● Environmental exposure	● Centipede
– Carbon monoxide	● Scorpion
– Hydrogen sulfide	
– Colchicine	

ies have demonstrated a relationship between cTn increases and adverse outcomes in subarachnoid hemorrhage. Overall, cTn is increased in approximately 10% of stroke patients and is associated with worse outcomes.

Intensive care unit (ICU) patients are prone to a number of clinical conditions that are associated with increased cTn, including hypotension, infection, sepsis, arrhythmias, pulmonary embolism (PE), increased intracranial pressure, and renal insufficiency (RI) *(34)*. Increases in cTn reportedly occur in 43% (interquartile range 21% to 59%) of noncardiac ICU patients in whom no flow-limiting coronary artery disease is detected by stress echo or present at autopsy *(35)*. Increased cTn concentrations are clearly associated with increased risk of inhospital mortality, with an odds ratio of approximately 2.5 (95% CI 1.9–3.4) *(34)*. In non-ACS patients admitted to the ICU, potential etiol-

Table 2. cTn increase in the setting of acute noncoronary diseases.[a]

Disease state	References	Comment
Cardiac and vascular		
AAD	Hansen et al. *(15)*, Rapezzi et al. *(17)*, Rapezzi et al. *(18)*, Mir *(19)*	AAD is frequently confused with ACS, leading to delayed diagnosis and significant bleeding due to inappropriate treatment with antithrombotic agents. cTn positivity, an ACS-like ECG, and dyspnea are clinical confounders. Increased cTn in AAD is associated with long in-hospital diagnosis times. D-dimer and cTn may be useful tests for workup of AAD.
CVA		cTn is increased in 15% to 20% of patients with stroke of ischemic, hemorrhagic, or subarachnoid hemorrhage subtype. Stroke patients with cTn increases generally have poorer outcomes than similar patients without increases.
Ischemic stroke	Sandhu et al. *(22)*, Jensen et al. *(24)*,[R] Apak et al. *(25)*, Ay *(26)*	
Intracerebral hemorrhage	Sandhu et al. *(22)*, Apak et al. *(25)*	
Subarachnoid hemorrhage	Sandhu et al. *(22)*, Horowitz et al. *(30)*, Naidech et al. *(31)*	
Medical ICU	Lim et al. *(34)*,[SR] Lim et al. *(35)*,[R] Klein and van de Leur *(37)*[R]	cTn increases in critically ill patients are associated with increased mortality and ICU length of stay. The underlying cause and clinical significance of increased cTn in this population remains to be elucidated. Increased cTn appears to confer prognostic importance similar to that in ACS patients. Frequency of cTn increases is 43%, ranging from 12% to 85%.
UGI bleeding	Babuin and Jaffe *(11)*, Cook et al. *(38)*, Iser et al. *(39)*, Vasile et al. *(40)*, Wu et al. *(41)*	In the setting of UGI bleeding, increased cTn portends a poor prognosis.
Cardiac inflammation		
Endocarditis	Purcell et al. *(45)*, Kahveci et al. *(46)*, Barton *(123)*	Patients with endocarditis and increased cTn have a increased morbidity and mortality.
Myocarditis	Feldman and McNamara *(47)*,[R] Lauer et al. *(48)*, Cassimatis et al. *(51)*[R]	In all patients with suspected myocarditis, cTn should be measured to assess the presence and extent of myocardial cell damage and to aid in prognosis.
Pericarditis	Bonnefoy et al. *(49)*, Thanjan et al. *(50)*,[R] Oakley *(124)*[R]	Perimyocarditis should be considered if MI has been ruled out in a patient with dyspnea and chest discomfort, especially if the patient has a history of recent viral illness.
Respiratory		
PE	Kline et al. *(52)*, Pruszczyk et al. *(53)*, Ghanima et al. *(56)*, Tapson *(57)*,[R] Fromm *(61)*[R]	In massive acute PE cTn is used most commonly in risk stratification with known PE; the test is not a sensitive diagnostic tool. Brain natriuretic peptide may be increased in congestive HF or other conditions that cause pulmonary hypertension. May help identify patients who will benefit from a more aggressive treatment.
ARDS	Bajwa et al. *(58)*, Snow et al. *(59)*, Christenson *(125)*	Increased cTn may be an important factor in morbidity and mortality in ARDS patients.
Infectious		
Sepsis	Maeder et al. *(60)*,[R] ver Elst et al. *(63)*, Spies et al. *(64)*, Mehta et al. *(65)*, Favory and Neviere *(126)*,[R] Kalla et al. *(127)*	In the setting of sepsis, increased cTn is associated with increased morbidity and mortality.
Acute viral infection	Eisenhut *(128)*[SR]	Increased cTn occurs in respiratory syncytial virus and enterovirus infections, and is an indicator of morbidity (both) and mortality (enterovirus).
Other diseases		
Kawasaki disease	Kanaan and Chiang *(93)*[R]	Although cTn increases have been reported in Kawasaki disease, the role of cTn in diagnosis and monitoring of treatment effectiveness is still under investigation.
Apical ballooning syndrome	Prasad et al. *(129)*[R]	Although the clinical presentation of this syndrome (including increased cTn) often mimics ACS, cardiac dysfunction resolves quickly and long-term prognosis is excellent.
Thrombotic thrombocytopenic purpura (TTP)	Hawkins et al. *(130)*[R]	Screening for cTn increases, at presentation and during the acute course of TTP, is important to document the frequency of cardiac ischemia in patients with TTP.

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Table 2. cTn increase in the setting of acute noncoronary diseases.[a] *(Continued from page 2101)*

Disease state	References	Comment
Rhabdomyolysis	Li et al. *(131)*	Non-ACS–related increases in cTn in the setting of rhabdomyolysis have a prevalence of up to 17% and are associated with increased morbidity but not mortality.
Preterm infants	EL-Khuffash et al. *(132)*	cTn may aid in assessing myocardial function and volume loading in preterm infants
Hereditary syndromes (see Table 1 for a detailed list)	Schoeffler et al. *(133)*	The significance of increased cTn in hereditary syndromes is not well understood.
Environmental exposures (see Table 1 for a detailed list)	Zhu et al. *(134)*, Brvar et al. *(135)*, Teksam et al. *(136)*, Yalamanchili and Smith *(137)*	Although rare instances of cTn increase have been reported in accidental and intentional environmental exposures, the diagnostic and prognostic utility of cTn values has not yet been elucidated.

[a] [R] indicates review article; [SR] indicates systematic review.

ogies for increased cTn include subendocardial injury secondary to increased wall stress (as seen in congestive heart failure), imbalances of supply and demand resulting from left ventricular hypertrophy secondary to hyper- or hypotension, and increased myocardial oxygen consumption (as seen in patients requiring pharmacologic blood pressure support because of septic shock) *(36)*.

Hypotension can cause cardiac damage and cTn release in critically ill patients with noncardiac disease. cTn measurements were increased in 55% (6 of 11) patients with systolic hypotension (<90 mm), whereas only 17% (4 of 25) normotensive patients had cTn increase. Also, the degree of cTn increase seen in hypotensive patients was consistently higher than that of normotensive patients *(37)*. In surgical ICU patients, hypotension was more frequently associated with patients (5 of 6 vs 2 of 11) who had subsequent increases in cTn *(35)*. This myocardial necrosis likely goes undetected on the electrocardiogram (ECG) in many of these patients *(37)*. Severity of hypotension is also related to cTn increase; the incidence of hypotension in patients requiring intravenous vasopressors increased from 21% with cTn concentrations within reference intervals to 40% with an intermediate increase in cTnI, to 55% with a high cTn increase *(34)*. Increases in cTn were consistently associated with worse outcomes in hypotensive patients *(34, 37, 35)*.

Upper gastrointestinal (UGI) bleeding is a clinical feature that contributes substantially to morbidity, mortality, and excess length of stay in the ICU *(38)*. Up to 19% of patients with UGI bleed have an increased cTn, indicating cardiac injury *(39)*. An interesting finding is that in patients for whom UGI bleeding is severe enough to require medical ICU admission, cTnT increases are related to long-term but not short-term mortality *(40)*. Patients with UGI bleeding and increased cTn have longer hospital stays and require transfusion of more units of red blood cells *(41)*. It has been proposed that cTn might be used as a prognostic screening tool in ICU patients, especially in patients who are hemodynamically unstable and elderly *(39)*. Overall, cTn increases occur in a substantial proportion of UGI bleed patients and confer a high risk profile for adverse outcomes.

Not every increased cTn concentration in ICU patients should be diagnosed or treated as an MI *(42)*, and there is need for cardiac diagnostic criteria and establishment of optimal management strategies in critically ill patients with increased cTn concentrations *(43)*. Although one group of investigators reported no increase in mortality for hospitalized patients who were cTnI positive *(44)*, the study population was not predominantly critically ill patients. Overall, increased cTn concentrations in ICU patients are independently associated with short- and long-term mortality even after adjustment for severity of disease *(11)*.

Cardiac Inflammation is associated with increased cTn. Potential causes for increases in cTn in the setting of cardiac inflammation include an oxygen supply/demand mismatch, the direct effect of proinflammatory cytokines (such as tumor necrosis factor α and interleukin 6), bacterial endotoxins, and microvascular thrombosis resulting from a hypercoagulable state *(45)*. Endocarditis, inflammation of the innermost layer of the heart, is associated with a high prevalence (65% *(45)* and 81% *(46)*) of increased cTn values. Additionally, endocarditis patients with increased cTn have worse outcomes, including death, abscess, and central nervous system events *(45)*. A combination of cTn and N-terminal probrain natriuretic peptide measurements offered more prognostic information than either of the biomarkers alone *(46)*.

Myocarditis, inflammation of the myocardium, can lead to coronary artery thrombus, coronary ischemia, dilated cardiomyopathy, cardiac arrhythmias, and sudden death. Patients with myocarditis frequently have increased cTn *(47)*, and in this setting

cTn has a sensitivity of 53%, specificity of 94%, positive predictive value of 93%, and a negative predictive value of 56% *(48)*. Increased cTn concentrations are prognostic in patients with myocarditis and are useful for assessing the presence and extent of myocardial cell damage *(47)*.

Pericarditis, inflammation of the double-walled fibroserous sac that surrounds and supports the heart, has been associated with an increase in cTn, particularly in younger patients and those with recent infection. Increased cTn can be a better indicator of the presence of cardiac damage than other indicators such as the ECG *(49)*. Perimyocarditis should be considered if MI has been ruled out in a patient with dyspnea and chest discomfort, especially with a history of recent viral illness *(50)*.

Pediatricians should be aware of postvaccination myopericarditis and its usually benign clinical course. Smallpox vaccine myopericarditis is a real entity and symptoms after vaccination should be appropriately evaluated, managed, and reported *(51)*. When used in conjunction with clinical suspicion, cTn is fairly specific for myopericarditis. False-negative results occur, however, because 50% of children with histologically proven myopericarditis do not have increased cTn *(49)*.

RESPIRATORY DISEASES

Acute PE is occlusion of the pulmonary artery or one of its branches, usually by a dislodged venous thrombus. Increases in cTn occur in 10% *(52)* to 50% *(53)* of PE patients. These increases are typically modest and appear to reflect the amount of myocardium injured. Recently, PE has been reported as the most common non-ACS cause of increased cTn *(54)*. This release of cTn is attributed to the combination of acute pressure overload within the right ventricle, impaired coronary artery flow, and the hypoxic state caused by the PE *(55)*. Increased cTn is a significant predictor of an adverse hospital course; patients with PE and increased cTn measurements are at significant risk of a complicated hospital course and fatal outcome *(53)*. A PE scoring algorithm that includes cTn has been proposed *(56)*. Increased cTn may be helpful in the management of PE patients by aiding in the identification of high-risk patients who might benefit from aggressive treatment *(57)*.

Acute respiratory distress syndrome (ARDS) is characterized by pulmonary and systemic inflammation and epithelial injury that cause alveolar filling and respiratory failure *(58)*. In this setting, vasoconstriction and thrombosis can occur and cause pulmonary hypertension, resulting in right ventricular strain and myocardial injury *(59)*. Progression of disease worsens this situation; mechanical ventilation may raise intrathoracic pressures and further impact myocardial function *(58)*.

Patients with ARDS have a high prevalence of myocardial injury and increased cTn. In one study, 89 (35%) of 248 ARDS patients had increased cardiac biomarkers. The c-statistic for cTn for predicting mortality was only 0.63, but this result was quite comparable to many more complex scoring methods for predicting outcomes in this setting, and increased cTn values were significantly and independently associated with higher 60-day mortality and increased organ failure. Of note, this effect was most pronounced in lower severity illness. Occult myocardial injury may be an important factor in morbidity and mortality in ARDS patients *(58)*.

INFECTIOUS DISEASES

Sepsis results from the presence of infectious organisms or their toxins in the blood or other tissues and is responsible for more than 200 000 deaths annually. Sepsis is frequently associated with biochemical changes such as high concentrations of tumor necrosis factor α, interleukin 6, and C-reactive protein and systemic symptoms such as fever, chills, malaise, hypotension, and mental status changes. Reports indicate that approximately 50% of patients admitted to ICUs with sepsis, severe sepsis, and septic shock but without ACS have increased cTn that is not due to flow-limiting etiologies *(60)*. Mechanistically, cTn release may result from transient loss in membrane integrity *(61)*, direct cytotoxicity of bacterial endotoxins, microvascular thrombotic dysfunction, and reperfusion injury *(62)*.

Myocardial dysfunction is a common complication in septic patients, and left ventricular dysfunction portends a poor prognosis *(60)*, particularly in elderly patients with underlying cardiac disease *(63)*. Septic patients with increased cTn are at increased risk of in-hospital mortality. Mortality rates of 63% *(64)* and 83% *(65)* have been reported in cTn-positive patients; by contrast, in cTn-negative patients, much lower mortality rates were reported, of 24% *(64)* and 37% *(65)*. Biochemical markers, including cTn, have emerged as possible tools for evaluation and quantification of cardiac dysfunction in septic patients. Other risk factors for increased cTn are severity of underlying infection, RI, and underlying cardiac disease.

National Academy of Clinical Biochemistry guidelines for use of cTn in conditions other than ACS discuss sepsis and septic shock in the context of monitoring critically ill patients for prognosis, need for ionotropic support, and extent of left ventricular dysfunction *(41)*. However, the therapeutic implications of increased cTn in septic patients have not been elucidated and properly designed studies are needed to evaluate the relationship between the diagnostic

Table 3. cTn increases in non-ACS non-HF chronic disease.[a]

Disease	Citations	Comment
ESRD	Bozbas et al. *(66)*, Freda et al. *(67)*, Balamuthusamy et al. *(70)*, Troyanov et al. *(71)*	Consideration must be given to the diminished sensitivity and specificity of increased cTn for the diagnosis of ACS in patients with ARF.
Cardiac infiltrative disease		
Amyloidosis	Selvanayagam et al. *(72)*,[SR] Dispenzieri et al. *(73)*, Shah et al. *(75)*[R]	cTn increase is related to mortality in patients with newly diagnosed amyloidosis.
Other infiltrative/inflammatory diseases	Martorell et al. *(78)*, Yasutake et al. *(79)*, Ranque et al. *(80)*, Almashaleh et al. *(81)*, Badsha et al. *(82)*	The significance of increased cTn in other infiltrative/inflammatory disorders (sarcoidosis, scleroderma, etc) is not known.
Chronic systemic diseases		
Systemic hypertension	Babuin and Jaffe *(11)*, ver Elst et al. *(63)*, Carlson et al. *(83)*	The significance of increased cTn in relation to hypertension is still under investigation.
Pulmonary hypertension	Torbicki and Kurzyna *(84)*, Torbicki et al. *(85)*	In the setting of PH, increased cTn is associated with increased mortality.
Diabetes	Wallace et al. *(7)*	The significance of increased cTn in the setting of diabetes is not yet known.
Hypothyroidism	Babuin and Jaffe *(11)*	No reports of increased cTn related to hypothyroidism have been published.

[a] [R] indicates review article; [SR] indicates systematic review.

use of cTn for assessing cardiac dysfunction and the prognostic use of cTn for guiding the treatment of these patients *(41)*.

Chronic Disease

Chronic conditions in which increased cTn measurements have been reported are listed in Table 3.

RENAL DYSFUNCTION

Chronic kidney disease, with its resulting renal dysfunction, is associated with excessive cardiovascular mortality, especially in those patients receiving renal replacement therapy *(66)*. Prevalence of CVD in patients with chronic renal failure (CRF) is up to 73% and is responsible for approximately half of all CRF-related deaths *(67)*. In patients with a functioning kidney allograft, CVD is the most common cause of death *(66)*. Atypical presentation of ACS (often without angina) and silent ischemia occur with increased frequency in patients with CRF; interpretation of the ECG in these patients can be complicated by the presence of left ventricular hypertrophy, electrolyte derangement, conduction abnormalities, and medications *(67)*. Although the underlying cause of increases in non-ACS cTn in patients with CRF is not well understood, evidence of ongoing myocyte damage *(67)* or of a clinically silent "micro-MI" has been reported *(68, 69)*. Within this context, the correct interpretation of cTn results becomes increasingly important.

Early assays for cTnT showed up to 71% cTn positivity in asymptomatic end stage renal disease (ESRD) patients and were attributed to cross-reactivity with cTnT from skeletal muscle. More recent (and cardiac-specific) assays show cTnT positivity in the 17% range, whereas cTnI has been shown to be positive in approximately 7% of asymptomatic ESRD patients. The discordance of cTnI and cTnT has been attributed to method imprecision and cellular protein distribution, as well as differing interactions with dialysis membranes *(67)*. Retrospective analysis of 108 African-American patients with RI/ESRD and an admitting diagnosis of ACS showed sensitivity (60% RI, 73% ESRD) and specificity (71% RI, 83% ESRD) of increased cTnI for the detection of obstructive coronary artery disease *(70)*. Prospective evaluation of 101 hemodialysis-dependent patients, followed for a total of 3 years, showed that patients with an increased cTnI ($\geq$0.3 μg/L) had an unadjusted increased hazard ratio of 3.37 (95% CI 1.56–7.25, $P = 0.001$) for the development of coronary artery disease compared with patients with an undetectable cTnI concentration. The same study demonstrated equal prognostic utility of cTnI and cTnT *(71)*. Although the diminished diagnostic sensitivity and specificity of cTn for the diagnosis of ACS in CRF necessitates an extra measure of judg-

ment to interpret laboratory findings in these patients, the clinical utility of cTn for the diagnosis of ACS in this situation must not be underappreciated.

CARDIAC INFILTRATIVE DISEASES

Amyloidosis is a clinical disorder caused by extracellular deposition of insoluble abnormal fibrils derived from aggregation of misfolded normally soluble protein *(72)*. Cases with obvious cardiac association have a poor prognosis, with a median survival of 6 months and 6% survival at 3 years *(73)*. Postmortem ultrastructural examination has demonstrated myocardial damage, in the form of direct myocyte compression, as an etiology for the increases in cTn observed in patients with amyloidosis *(74)*. Recent observational studies suggest that the presence of detectable cTn in the serum of affected patients portends an adverse prognosis *(72, 75)*. A retrospective assessment of 261 patients with newly diagnosed systemic amyloidosis showed that median survival for patients with detectable cTnT and cTnI (6 and 8 months, respectively) was worse than for patients with undetectable values (22 and 21 months, respectively) *(73)*. In a series of 50 consecutive patients with light-chain amyloidosis and 15 patients with hereditary amyloidosis, cTnT values in patients with cardiac amyloidosis were increased compared to those in patients with light chain amyloidosis but no cardiac involvement [0.105 (0.030) vs 0.019 (0.010) μg/L; $P < 0.05$] *(76)*. Amyloid infiltration of the myocardium leads to increases in cTn that are not related directly to cardiac hemodynamics or coronary anatomy *(77)*. Other infiltrative diseases, including hemochromatosis, sarcoidosis, scleroderma, and other inflammatory disorders, have been implicated as possible sources of increased cTn *(11, 78)*, but published evidence is limited *(78–82)*.

CHRONIC SYSTEMIC DISEASES

Systemic hypertension has been found to be associated with increases in noncardioischemic cTn *(11)*. Compared with cTnI-negative patients, cTnI-positive individuals tended to have a more frequent history of arterial hypertension *(63)*. However, a retrospective study of 183 patients with a history of systemic hypertension ($P = 0.283$) *(83)* demonstrated no difference in baseline cTn concentrations. In the setting of pulmonary hypertension, cTn release that persists despite therapy is a poor prognostic sign *(84)* and an independent marker of increased mortality risk *(85)*. In multivariable logistic regression analysis diabetes mellitus, left ventricular hypertrophy, HF, and ESRD were independently associated with increased cTnT. In the general population, cTnT increase is rare in individuals with or without ESRD. Even minimally increased cTnT may indicate the presence of subclinical cardiac injury and have important clinical implications, a hypothesis that should be tested in longitudinal outcome studies *(7)*.

Iatrogenic Conditions

INVASIVE PROCEDURES

Heart transplantation. In 2004, 186 heart transplantation centers performed 2016 heart transplantations (HTx) in the US, with survival rates of 84%–86% at 1 year, 76%–78% at 3 years, and 68%–72% at 5 years *(21)*. Cardiac allograft vasculopathy (CAV), commonly referred to as chronic rejection *(86)*, limits the long-term success of HTx. CAV, graft failure, and malignancy are the most important causes of death in patients who survive the first year after undergoing an HTx *(87)*. Mechanisms of nonischemic cTn increases that occur immediately after HTx include incomplete cardioprotection, reperfusion injury, and direct surgical trauma *(88)*. Increases in cTn have been reported up to 3 months after HTx; however, the mechanism of these increases is less well understood *(89)*. In a study of 57 HTx patients evaluated between 1 and 12 months after surgery, cTnT concentrations were significantly higher ($P = 0.008$) in patients with CAV demonstrated by endomyocardial biopsy *(90)*. In the setting of acute allograft rejection following HTx, the sensitivity and specificity of cTn for the detection of significant graft rejection were 80.4% and 61.8%, respectively, and the negative predictive value was 96.2% *(91)*. In a pediatric HTx population (n = 9), the predictive power of a single cTnT measurement was not sufficient to replace biopsy *(92)*. cTn measurement has not shown utility in assessing CAV in pediatric HTx recipients *(93)*.

Repair of congenital heart defect. The reported incidence of congenital heart disease varies widely across studies, from about 4 in 1000 to 50 in 1000 live births, variation that depends largely on the spectrum of defects included in each study; the incidence of moderate and severe forms of CHD appears to be about 6 in 1000 live births *(94)*. Increases in cTn following repair of congenital cardiac defects likely result from direct myocyte damage from surgical incisions and other factors, such as aortic cross-clamping and cardiopulmonary bypass *(95)*. In an investigation of a series of 73 elective corrections of cardiac defects, the prediction of severe postoperative complications during the first 24 h in the ICU showed a positive predictive value of 100% and a negative predictive value of 93% with the use of a cTnI threshold of 35 μg/L *(96)*. Systematic review of data suggests that preoperative increases in cTn preceding congenital heart defect repair are a poor prognostic sign *(93)*.

Radiofrequency catheter ablation. Atrial fibrillation (AF), the most common cause of cardiac tachyarrhyth-

Table 4. Iatrogenic causes of cTn increases.[a]

	Citations	Comment
Invasive Procedures		
Htx	Thom et al. *(21)*,[R] Stoica et al. *(86)*, Schmauss and Weis *(87)*,[R] Balduini et al. *(90)*, Dengler et al. *(91)*, Wåhlander et al. *(92)*, Kanaan and Chiang *(93)*[R]	Increase in circulating cTn in the heart donor prior to donation is predictive of acute allograft rejection in heart transplantation [Potapov et al. *(138)*].
		In the setting of acute allograft rejection, the negative predictive value of cTn was 96.2% [Dengler et al. *(91)*].
		In the setting of CAV (chronic rejection), cTn correlates with both positive and negative endomyocardial biopsy [Balduini et al. *(90)*].
Congenital defect repair	Kanaan and Chiang *(93)*,[R] Hoffman and Kaplan *(94)*, Immer et al. *(96)*	Increased cTn prior to repair of congenital heart anomalies indicates poor prognosis.
		Postoperative increase in cTn correlates with significant complications.
RFCA	Hirose et al. *(99)*, Haegeli et al. *(100)*, Madrid et al. *(101)*, Sbarouni et al. *(139)*	cTn detects and quantifies the size of necrosis associated with RFCA.
Lung resection	Lim et al. *(140)*	Increased cTn following lung resection is an independent risk factor for death.
ERCP	Fisher et al. *(141)*	cTn increases occur in up to 8% of ERCP procedures.
Noninvasive procedures		
CV	Joglar and Kowal *(97)*,[R] Gall and Murgatroyd *(102)*,[R] Kosior et al. *(103)*, Skulec et al. *(104)*, Allan et al. *(105)*	Although a few studies have shown occasional increase in cTn (with rare significant increase) associated with cardioversion, most studies show no increase.
		Substantial increases in cTn after cardioversion suggest the presence of myocardial injury from causes unrelated to CV.
Lithotripsy	Eaton and Erturk *(142)*	No significant increase in cTn (for patients with or without arrhythmia associated with shock wave lithotripsy) was reported.
Pharmacologic sources		
Chemotherapy	Dolci et al. *(106)*,[SR] Pavi and Nahata *(107)*[R]	Increased cTn in the setting of high-dose chemotherapy predicts (up to 3 months in advance) the likelihood and severity of left ventricular dysfunction.
		Persistent increase (>1 month) is associated with an 85% likelihood of a major cardiac event within 1 year.
		A persistently negative cTn has a 99% negative predictive value for any cardiac complication.
		For a detailed list of potentially cardiotoxic chemotherapeutic agents, please see Dolci et al. *(106)*.
Other medications	Wallace et al. *(143)*[R]	cTn is specific and sensitive for drug-related myocardial damage. Any increase in serum cTn above baseline is evidence of possible cardiac damage and warrants further investigation.

[a] [R] indicates review article; [SR] indicates systematic review.

mia, affects 2.2 million individuals in the US (between 8% and 10% of those older than 80 years) *(97)* and is associated with significant morbidity and mortality *(98)*. Radiofrequency catheter ablation (RFCA) is a

commonly used nonpharmacologic approach to treating tachyarrhythmias. However, RFCA causes some myocardial damage at the site where the catheter tip contacts tissue. This damage may include lipid membrane disruption and metabolic and structural protein inactivation and denaturation, as well as nuclear damage *(99)*. In a study of 60 patients undergoing RFCA who had no underlying structural heart disease, all patients were found to have increased postprocedure cardiac cTn, with all measurements exceeding the diagnostic threshold for MI *(100)*. Monitoring of cTnI has been reported to be the best way to detect and quantify the amount of myocardial necrosis from radiofrequency ablation *(101)*.

NONINVASIVE PROCEDURES

Cardioversion. As stated previously, AF is a significant cause of both morbidity and mortality. AF can potentiate structural cardiac remodeling if left untreated; cardioversion (CV) may be important in preventing this remodeling *(102)* and restoring sinus rhythm is considered an important therapeutic goal in patients who are younger or highly symptomatic *(97)*. Concern has been expressed about the possible myocardial damage caused by CV, and studies demonstrating a wide range of cTn values as a result of CV have been published (see Table 4). In a study of 48 patients with persistent AF who underwent CV, all patients who received monophasic procedures (45.2%) showed a significant increase in mean plasma cTnI concentration over 24 h ($P < 0.04$) *(103)*. Conversely, in a randomized trial of 141 patients undergoing monophasic or biphasic CV for supraventricular tachycardia, no increases in cTn were observed *(104)*. A substantial increase in cTn following CV is suggestive of myocardial injury that cannot be attributed to the CV *(105)*.

Pharmacologic Sources

CHEMOTHERAPY

The successful application of chemotherapeutic agents in the treatment of various malignancies has led to their increased use and to subsequent increases in reported cardiotoxicity *(106)*. Chemotherapy-related cardiotoxicity was first described in 1967 and is associated with many classes of drugs and individual therapeutic agents. Cardiotoxicity is often a significant limiting factor in treatment *(107)*. In a cohort of 179 consecutive patients receiving high-dose chemotherapy, increased cTnI was observed in 57 patients (32%) in whom echocardiographic monitoring revealed a mean decrease in ejection fraction of 18%. By comparison, the group of patients without increases in cTnI had a mean decrease in ejection fraction of 2.5% ($P < 0.001$) *(108)*. For patients receiving chemotherapy, increased cTn predicts clinically significant left ventricular dysfunction at least 3 months before onset. Additionally, early increases in cTn concentrations predict the degree and severity of future left ventricular dysfunction. Finally, persistence of an increased cTn in the month after the last chemotherapy administration portends an 85% probability of major cardiac events within the first year of follow-up. However, a persistently negative cTn identifies patients who will likely not encounter cardiac complications, at least within the first year after the end of chemotherapy (negative predictive value 99%) *(106)*.

Myocardial Injury

A summary of reported data on cTn increases in the setting of myocardial injury is given in Table 5.

BLUNT CHEST INJURY

Although thoracic injury accounts for only 5%–12% of the admissions to trauma centers, it is associated with increased mortality *(109)*. The exact incidence of cardiac contusion in patients with blunt chest trauma is unknown, but the reported incidence has ranged from 3% to 56% *(110)*. The sensitivity of cTn for diagnosing cardiac contusion in blunt chest injury ranges from 12% to 23%, whereas specificity ranges from 97% to 100%. In this setting, the positive predictive value ranged from 20% to 100% and the negative predictive value ranged from 74% to 100% *(111)*. No significant complications occurred in patients in whom ECG findings were normal and serial measurements of cTn were within reference intervals *(111)*. It has been suggested that in the setting of blunt chest trauma and an absence of other injuries or hemodynamic instability, patients whose ECG and cTnI findings are unremarkable can be discharged. However, increased cTn may serve to identify patients at increased risk of mortality *(112)*.

Endurance Athletes

Increases in cardiac biomarkers in athletes after exercise can complicate differential diagnosis and may result in inappropriate consequences *(113)*. Of 105 asymptomatic finishers of endurance competitive events lasting several hours, increased blood concentrations of cTn above the 99% upper reference values were found in 23% (cTnT) and 33% (cTnI) of individuals. Within 3 months after the events, 21 cTn-positive participants underwent an extensive cardiac examination in which all but 1 (who had coronary heart disease) revealed no signs of persistent cardiac damage *(114)*. Additionally, in 34 endurance athletes with increased cTn, clinical evaluation found 1 athlete with a diagnosed cardiac abnormality, whereas all others had no

Table 5. Troponin increases in the setting of myocardial injury.[a]

Injury type	Citations	Comment
Blunt chest injury	Kanaan and Chiang *(93)*,[R] Bliss and Silen *(109)*,[R] Sybrandy et al. *(110)*,[R] Schultz and Trunkey *(111)*,[R] Elie *(112)*[R]	In the setting of blunt chest injury and an absence of other injuries or hemodynamic instability, patients with normal ECG and cTn can be discharged.
		With a positive predictive value and sensitivity up to 100% for cardiac contusion, increased cTn in the setting of blunt chest injury necessitates further testing.
Endurance athletes	Scharhag et al. *(113)*,[R] Urhausen et al. *(114)*, Tsai et al. *(116)*[R]	Exercise-related increases in cTn's are only mild and of short duration.
		Significant cTn increases in the setting of exercise warrant additional testing
Envenomation		cTn increases resulting from biologic toxin exposure have been reported. Careful attention to the history and physical exam may elucidate this uncommon cause of increased cTn.
Snake	Tsai et al. *(116)*,[R] Lallo et al. *(117)*, Açikalin et al. *(118)*	
Jellyfish	Huynh et al. *(119)*	
Spider	Sari et al. *(120)*	
Centipede	Yildiz et al. *(121)*	
Scorpion	Tsai et al. *(116)*,[R] Meki et al. *(122)*	

[a] [R] indicates review article; [SR] indicates systematic review.

cardiovascular abnormalities that could explain the exercise-induced increases in cTn. An additional 1 hour of intensive and 3 hours of extensive standardized endurance exercise did not reproduce an increase in cTn in these athletes *(115)*. This observation is consistent with a study in which exercise-induced cTn release was not reproduced in 8 participants of the 2004 and 2005 London marathons *(113)*. Among a population of patients completing the Boston Marathon, concentrations of cTnT were associated with abnormalities of right ventricular size and function on echocardiography. In addition, concentrations of cTnT were inversely proportional to the amount of premarathon training, suggesting that favorable cardiovascular adaptations to exercise may render the heart more resistant to exercise-related injury *(115)*.

Exercise-related increases in cTn appear to be from myocardium; however, studies have not yet conclusively determined the pattern and significance of the necrosis thought to lead to cTn increase in this setting. Given that these increases are usually mild and of short duration, they may reflect a reversible membrane leakage of cardiomyocytes with cTn release from the free cytosolic pool of cTn. The ramifications of this process from a cellular viability perspective remain speculative.

Envenomation

Rare cases of myocardial injury induced by biologic toxins have been reported. MI as a result of snake envenomation has been reported *(116)*, with rare occurrences of non-AMI increases in cTn related to snake envenomation *(117)*. In a prospective study of 45 patients who complained of snake bite, none were found to have increased cTn *(118)*. The mechanisms of myocardial damage resulting from snake envenomation are not known, but vasospasm, coagulation abnormalities, and direct myocardial toxicity have been implicated *(116)*. Envenomation by contact with *Cnidaria* spp. (jellyfish) occasionally results in Irukandji syndrome, characterized by back, chest, and abdominal pain; other nonspecific myalgias; nausea; vomiting; restlessness; localized piloerection and sweating; tachycardia; and hypertension. Increase of cTnI has been reported in 22% of patients with Irukandji syndrome *(119)*. Envenomation by arthropods, including black widow spiders *(120)*, centipedes *(121)*, and scorpions *(122)*, has been reported as a source of cTn increases. In a series of 41 children with scorpion sting, the cTnI showed 100% specificity and sensitivity for diagnosis of myocardial injury compared to echocardiographic findings in the envenomed victims *(122)*.

Conclusion

cTn show excellent tissue specificity and are virtually a sine qua non for myocardial damage *(10)*. MI is a clinical diagnosis, and the pitfall of equating an increased cTn with the exclusive diagnosis of MI must be avoided. As with all aspects of medicine, a broad differential diagnosis must be considered, and appropriate

modalities employed to achieve accurate diagnosis, risk prediction, treatment, and assessment of the effectiveness of treatment. Acute and chronic diseases, iatrogenic causes, and myocardial injury have all been found to be related to increased cTn outside of the context of MI and HF. In some of these situations, cTn may aid in ruling in or out a diagnosis; however, increased cTn in non-ACS, non-HF patients often complicates the decision-making process for clinicians. In addition, evidence is accumulating for cTn as a prognostic marker in many non-ACS and non-HF circumstances. It remains to the astute physician to interpret cTn as a dynamic marker of myocardial damage, using clinical acumen to determine the source and significance of any reported increase in cTn.

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