Emerging Role of Cardiac Troponin Testing in Non-Acute Coronary Syndrome-Related Myocardial Injury

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Measurements of cardiac troponin concentration have been proved to be sensitive and specific methods for the detection of myocardial cell damage as well as for risk stratification and prognostication in patients with acute coronary syndromes. A large body of evidence also indicates that cardiac troponin T and troponin I may be useful as markers of cardiac damage in patients with disorders other than acute coronary syndromes including heart failure, myocarditis, pulmonary embolism, sepsis, thermal injury and subarachnoid hemorrhage. More importantly, in several of these clinical conditions, levels of the troponins seem to be able to provide prognostic information and thus, may have an influence on decision-making in the management of these diseases. The present review will summarize the results from recent animal studies and clinical trials and discuss the possible pathophysiologic mechanisms of myocardial injury arising from these critical illness.

INTRODUCTION

Over the past decade, results from several large clinical trials have demonstrated that measurements of cardiac troponin concentrations represent sensitive and specific biochemical methods for detecting myocardial cell necrosis in patients presenting with acute coronary syndromes.[1-3] Measurements of cardiac troponin T (cTnT) and troponin I (cTnI) are currently accepted and recommended as the new standard method for diagnosis of myocardial infarction (MI), replacing CK-MB measurement.[4,5] The troponins have also assumed a central role in risk stratification and therapeutic decision-making in the management of patients with unstable coronary artery disease (unstable angina, non-Q wave MI).[6-10] According to the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines[11] and the European Society of Cardiology (ESC) task force report,[12] patients with chest discomfort and elevated troponin concentrations are at high risk of developing cardiac events (nonfatal MI, death) during the short and long terms.

Data from animal and clinical studies have also indicated that the troponins may be useful as markers of myocardial cell damage in several clinical conditions other than the acute coronary syndromes.[13] A wide range of critical illness has been reported to be associated with chest discomfort and transient electrocardiographic changes, accompanied by release of cardiac marker proteins into the circulation.[14,15] These include acute and chronic heart failures, myocarditis/pericarditis, sepsis and septic shock, acute pulmonary diseases, thermal burns and acute neurologic diseases. The aim of the present review is to summarize the results from recent experimental and clinical studies on the role of cardiac troponin testing in critically ill patients and to discuss the potential pathophysiologic mechanism of cardiac myocyte injury arising in these clinical settings.

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Heart failure

The current concept of the pathophysiology of heart failure is largely based on the hypothesis of neuroendocrine activation, leading to excessive production of hormones of the sympathetic nervous system and renin-angiotensin-aldosterone axis.[16-18] The role of cytokines in the pathogenesis of heart failure has also been increasingly recognized.[18,19] Previous studies have demonstrated the presence of increased concentrations of norepinephrine in the circulation, which can be observed even in patients in the early stage of ventricular dysfunction.[20,21] Experimental evidence linking catecholamines to myocardial cell injury has been reported in rats, rabbits and dogs.[22] In these animals, multifocal myocardial necrosis predominantly distributed in the left ventricular subendocardial areas was found after catecholamine infusion.

The cardiotoxic effect of catecholamines has been demonstrated in an experimental animal model of cardiac injury reported by Mann et al.[23,24] In this study, norepinephrine treatment of cardiac myocyte cultures resulted in a significant release of the enzyme creatine kinase (CK) into the medium. A similar effect of catecholamines was observed in pigs after administration of isoproterenol. Moderate increases in CK and aspartate aminotransferase (AST) activity were present.[22] However, since these enzymes lack specificity for myocardial injury, they should no longer be used to evaluate cardiac disease. Instead, the more cardio-specific troponins (T or I) currently represent the preferred markers for the diagnosis of myocardial injury.[25] Recently, isoprenaline-induced cardiac damage using cardiac troponins as biochemical parameters has been demonstrated in an experimental model in rats.[26] It has been found in this study that elevations of cTnT and cTnI are related to the severity of histologic changes after cardiac injury.

Table 1. Frequency of increased cardiac troponin levels in 8 clinical trials of heart failure.

		NYHA	Cut-off	Increased cardiac troponins (%)	
	n	class	(ng/ml)	cTnT	cTnI
Missov et al.[27]	11	-	0.10	-	18
Missov & Mair[28]	33	I - IV	0.10	15	-
La Vecchia et al.[29]	26	-	0.30	-	23
Setsuta et al[30]	58	II - IV	0.02	52	-
		(II; III; IV)		(18; 68; 92)	
Sato et al.[31]	60	I - III	0.02	45	-
Hudson[32]	136	II	0.02	24	-
			0.10	4	-
Miller et al.[33]	13	III - IV	0.10	61	-
			0.10	-	69
Perna et al.[34]	84	I - IV	0.10	55	-
		(I - II; III - IV)		(38; 80)	

Evidence linking the presence of increased norepinephrine levels in patients with heart failure and evidence of the cardiotoxicity of catecholamines has led to the question, as to whether it is associated with release of cardiac marker proteins into the circulation. Table 1 summarizes the results of recent studies on patients with heart failure using the troponins as biochemical markers.[27-34] As can be seen, the frequency of increased cardiac troponin concentrations is highly variable, ranging from 4% in one study to 69 % in another. These differences are mainly attributed to the different cut-off levels used and the severity of cardiac dysfunction as estimated by the New York Heart Association (NYHA) functional class. A higher percentage of patients with high heart failure functional class had elevated cardiac troponin levels (Table 1).[30,34] In several trials, the mean cardiac troponin concentration was slightly (1-3 times) above the upper reference limit, whereas the CK-MB levels were reported to be in normal or near-normal range in the majority of heart failure patients.[28,33-35] Patients presenting with acute congestive heart failure showed a higher mean concentration of the troponins than those with stable heart failure.[36,37] Importantly, long-term follow-up studies have provided evidence that elevated baseline troponin levels are associated with an increased risk of death or rehospitalization for worsening heart failure.[30,32,34] Furthermore, persistently increased cardiac troponin concentrations during follow-up were found to be closely related to deterioration of heart function.[31,36] Thus, measurements of cardiac troponin concentrations at baseline may indicate the severity of cardiac dysfunction and provide prognostic information, and serial determinations may allow identification of heart failure patients in need of more aggressive treatment.[38]

Myocarditis/Pericarditis

Early diagnosis of acute myocarditis is essential because the disease may have a fatal outcome or may progress to dilated cardiomyopathy, a major cause of congestive heart failure.[39-41] Clinical diagnosis of myocarditis, however, is often difficult since the disease is usually asymptomatic and has an insidious clinical course.[41,42] Furthermore, electrocardiographic findings of acute myocarditis are highly variable : a picture of ventricular arrhythmia, heart block or changes mimicking acute myocardial ischemia and infarction may be present.[39,43] At present, an endomyocardial biopsy is regarded as the standard method for a definitive diagnosis of myocarditis.[44] However, apart from the invasive nature of the procedure with its' inherent risk, especially when performed in children,[45] biopsies have produced highly variable results, partly because of the insensitivity of a test performed on a single sample and large intraobserver variability in the histological diagnosis of myocarditis.[46,47]

Recent experimental and clinical studies performed on animals and humans have shown that measurements of cardiac troponin concentration provide a useful method for detecting cardiac damage in myocarditis. In a murine model of autoimmune myocarditis, Bachmaier et al.[48] reported that cTnT is a more sensitive marker for the diagnosis of myocardial damage than the CK-MB isoenzyme (Table 2). A trend for cTnI elevation to parallel the histological severity of myocarditis has been observed in a similar model of autoimmune myocarditis reported by Smith et al.[49] In this study, as well as in 2 other trials,[50,51] cTnI and cTnT were also found to be superior to CK-MB in detecting cardiac myocyte injury in patients with endomyocardial biopsy-proven myocarditis (Table 2). Recently, a significant increase in cTnI[52] and cTnT[53] levels has been observed in a certain number of children with acute myocarditis. These results imply that, determination of cardiac troponins may be a useful tool for the diagnostic evaluation of patients with suspected myocarditis.

The frontier between acute myocarditis and pericarditis is sometimes not clear cut, and the pathogenic mechanism in both conditions, caused either by infective agents or toxic substances, is mediated by an inflammatory process that leads to myocardial cell damage. Thus it is not unexpected to find increased cardiac marker protein levels in patients with pericarditis. In two recent studies on patients with clinical signs and symptoms suggesting acute pericarditis (inspiratory or positional chest pain, ST-T changes on the ECG and pericardial friction rub), detectable cTnI levels were observed in a high percentage (49 and 71 %) of patients.[54,55] In one study,[55] detectable levels of cTnI were found more frequently

Table 2. Diagnostic performance of cardiac marker proteins in experimental and clinical studies of myocarditis.

			CK-MB		cTnT		cTnI	
	Subject	**n**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Bachmaier et al.[48]	mice	22	0.00*	1.00	0.43*	1.00	-	-
	mice	10	0.33**	1.00	0.50**	1.00	-	-
Smith et al.[49]	human	53	0.06	1.00	-	-	0.34	0.89
Lauer et al.[51]	human	80	0.02	1.00	0.53	0.94	-	-

Sensitivity at different time points after autoimmunization-induced myocarditis : *day 12; **day 19.

than positive CK-MB levels. Bonnefoy et al.[54] also reported a strong relationship between ST-segment elevation and an increase in cTnI. These results indicate that, similar to myocarditis, cTnI increase is common in acute pericarditis. The prognostic significance of a positive troponin, however, is at present not known and remains to be determined by future investigations.

Acute pulmonary diseases

Pulmonary embolic disease can present with several clinical features similar to those of acute coronary syndromes. Previous experimental and clinical studies have shown that the disease is often associated with myocardial ischemia as a result of increased wall tension and oxygen demand as well as reduced coronary perfusion and oxygen supply.[56,57] Right ventricular infarction with a significant increase in CK-MB isoenzyme has been observed in patients with severe pulmonary embolism.[58,59] Myocardial cell necrosis is not uncommon in moderate and severe pulmonary embolism as evidenced by reports from 5 recent clinical trials that showed an increase in cardiac troponin between 21-56 % of patients with pulmonary embolism.[60-64] The median peak concentration of cTnT of 0.48 ng/ml found in one study is indicative of minor myocardial injury.[62] Recently, Meyer et al.[61] reported that positive cTnI tests, and not CK-MB levels or D-dimer concentrations, were significantly associated with echocardiographic signs of right ventricular dysfunction and dilatation. Of particular importance was the finding in the study of Giannitsis et al.[63] and Konstantinides et al.[64] that cTnT and cTnI were independent predictors of in-hospital death. The results imply that cardiac troponins may be used for risk stratification in patients with pulmonary embolic disease and may identify a subset of patients in need of more aggressive therapy.

Cardiac troponin T has recently been reported to be elevated during the course of lobar pneumonia in patients without clinical evidence of cardiac involvement,[65] and it has been used as a criterion to exclude cardiac damage in patients with acute bronchial asthma.[66,67] In these patients, raised levels of CK and CK-MB were observed frequently. There was, however, no increase in cTnT level in all 15 patients with acute severe asthma in the study of Lovis et al.[66] In another study,[67] only 3 (10%) out of 29 pediatric patients receiving intravenous terbutaline for the treatment of severe asthma showed detectable cTnT concentrations. These 3 patients required prolonged mechanical ventilation and had the longest duration of terbutaline infusion which could explain the observed increase in cTnT levels.

Sepsis and septic shock

Myocardial dysfunction has long been recognized as a complication of sepsis and septic shock. In a canine model of sepsis, gram-negative bacteremia produced both severe systolic and diastolic cardiac dysfunction.[68] Left ventricular systolic

depression with a reduced ejection fraction and left ventricular dilatation have been frequently observed in patients with septic shock.[69] There is accumulating evidence that the condition is associated with myocardial cell damage. Autopsy results in one recent study have demonstrated contraction band necrosis in many patients dying of severe septic shock due to multiple organ failure.[70] Myocardial injury may be a consequence of the hypotension that develops in septic shock and has been linked with the effect of circulating myocardial depressant substances such as tumor necrosis factor α (TNF-α) and interleukins.[14,71]

In patients with sepsis and septic shock, a high prevalence of elevated cardiac marker protein levels was found, with values ranging from 36 to 85 percent (Table 3).[70,72-75] The median peak concentrations of cTnT and cTnI of 0.66 and 1.4 ng/ml, respectively, reported in the study of Ver Elst et al.[70] as well as that of cTnI of 2.4 ng/ml found in the study of Turner et al.[73] are indicative of minor but significant myocardial injury. In septic shock patients, elevated cardiac troponin levels have been reported to correlate significantly with left ventricular dysfunction as assessed by two-dimensional transesophageal echocardiography.[70] A significant negative correla-

Table 3. Prevalence of increased cardiac marker protein levels in sepsis and septic shock.

	n	Percent increased cardiac markers		
		cTnT	cTnI	CK-MB
Ver Elst et al.[70]	46	36	50	41
Spies et al.[72]	26	69	-	-
Turner et al.[73]	15	-	80	-
Thiru et al.[74]	37	-	62	37
Ammann et al.[75]	20	-	85	45

tion between peak cTnI levels and minimum left ventricular stroke work index and minimum left ventricular ejection fraction, both markers of ventricular dysfunction, has also been observed in these patients.[73,74] Importantly, elevations of both cTnT and cTnI concentrations were found to be associated with an increased mortality rate,[72,74] suggesting that the troponins may be useful as prognostic markers in patients with sepsis and septic shock.

Thermal injury

Patients with burn injury are prone to the development of multiple organ dysfunction and failure. Cardiac failure developing after thermal burns, in particular, has been shown to be significantly correlated with a high mortality rate.[76] In the past decade, the pathophysiologic mechanism of cardiac dysfunction in thermal injury has been to a certain extent elucidated. It has been shown in an animal model of burn injury that circulating myocardial depressant factors such as tumor necrosis factor (TNF), interleukins or oxygen-derived free radicals produced by neutrophils contribute to cardiac myocyte injury. Furthermore, inhibition of TNF was capable of preventing myocardial dysfunction during burn shock.[77,78]

In an experimental study with guinea pigs, Horten et al.[79] found that the enzyme CK was significantly elevated in the coronary perfusate of hearts from scald burned animals. The same research group also reported a significant correlation between increased cTnI levels and left ventricular systolic dysfunction in rabbits with postburn injury.[80] In another recent study,[81] elevation of biochemical markers of myocardial damage (cTnT, CK-MB, cardiac myosin light chain 1) was observed in parallel with an increase in TNF level in rats after severe burns.

To our knowledge, there have been thus far 2 trials utilizing the cardiac-specific troponins as an indicator of myocardial damage after thermal injury in human patients. Chen et al.[82] reported that the mean cTnI concentration in patients with a total body surface area (TBSA) of burn > 30 % (0.34 ng/ml) was significantly higher than in those with less severe burns (0.09 ng/ml). In another study,[83] it was found that all patients with greater than 15 % TBSA injury had detectable cTnI levels compared with none in those with lesser thermal injury. Nevertheless, the effect of postburn myocardial injury on clinical outcome is at present largely unknown and will require further investigation.

Acute neurologic diseases

Cardiac dysfunction is a well-known and frequent complication of several acute neurologic disorders including acute subarachnoid hemorrhage, ischemic stroke and cranial trauma.[13] In an experimental study on dogs with subarachnoid hemorrhage, significant increases in heart rate and cardiac output with ischemic electrocardiographic and echocardiographic changes were observed.[84] Electron microscopic examination has revealed characteristic myocardial cell lesions, with disruption of the cell architecture and disappearance of cross striations as well as subendocardial microinfarcts in most of animals studied. There is experimental evidence that links catecholamines to cardiac injury.[85] Contraction band lesions developed after isoproterenol infusion were found to be associated with electrocardiographic and biochemical changes.[86] A significant elevation in catecholamine levels in parallel with CK, CK-MB and cTnT increases were also observed in dogs with experimentally induced subarachnoid hemorrhage.[84,87]

Results from recent trials also pointed to the existence of myocardial ischemia in patients with acute intracerebral disease. An abnormal electrocardiogram occurs frequently in these clinical settings, with ST- and T-wave changes being the most prevalent. Patients with subarachnoid hemorrhage may show echocardiographic wall motion abnormalities and often have small but significant increases in the concentration of cardiac enzymes.[88,89] Abnormal myocardial perfusion as determined by thallium-201 scintigraphy has been demonstrated in around one-third of the patients with subarachnoid hemorrhage and an abnormal electrocardiogram.[90] Recently, cardiac involvement in acute neurologic diseases has been affirmed by two studies using cardiac troponins as biochemical markers. In these clinical settings, Dixit et al.[91] and James et al.[92] found raised cTnI and cTnT concentrations in 19% and 17%, respectively, of patients. Dixit et al. also reported that, in most cases, an elevated cTnI level was associated with electrocardiographic and echocardiographic evidences of cardiac injury. Of particular importance was the observation in both studies that patients with cardiac troponin elevation had significantly higher mortality at short- and long-term follow-up. These results, again, point to the value of cardiac troponins as powerful predictors of adverse outcome in patients with acute neurologic diseases.

CONCLUSION

Cardiac troponin testings have been proved to be useful as biochemical methods for the detection of myocardial injury arising from a variety of clinical conditions other than acute coronary syndromes. In particular, measurement of the troponins seems to be of value in evaluating the severity and extent of cardiac damage as well as in providing prognostic information in patients with heart failure, pulmonary embolism, sepsis and acute neurologic disease. The prognostic significance of cardiac troponins in patients with myocarditis and thermal injury is at present not known and remains to be determined in future investigations.

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REFERENCES

1. Coudrey L. The troponins. Arch Intern Med 1998; **158:** 1173-80.
2. Chapelle JP. Cardiac troponin I and troponin T : recent players in the field of myocardial markers. Clin Chem Lab Med 1999; **37:** 11-20.
3. Sribhen K. Cardiac troponins : novel myocardial markers with high diagnostic performance and prognostic value. Siriraj Hosp Gaz 2001; **53:** 609-15.
4. Collinson PO. Cardiac markers into the new millenium. Ann Clin Biochem 2000; **37:** 109-13.
5. Wu AHB, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R. National Academy of Clinical Biochemistry standards of laboratory practice : recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999; **45:** 1104-21.
6. Olatidoye AG, Wu AHB, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. Am J Cardiol 1998; **81:** 1405-10.
7. Ottani F, Galvani M, Nicolini FA, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Heart J 2000; **140:** 917-27.
8. Antman EM, Fox KM, for the International Cardiology Forum. Guidelines for the diagnosis and management of unstable angina and non-Q-wave myocardial infarction : proposed revisions. Am Heart J 2000; **139:** 461-75.
9. Hamm CW, Bertrand M, Braunwald E. Acute coronary syndrome without ST elevation : implementation of new guidelines. Lancet 2001; **358:** 1533-38.
10. Sarko J, Pollack CV. Cardiac troponins. J Emerg Med 2002; **23:** 57-65.
11. A report of the American College of Cardiology / American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction : executive summary and recommendations. Circulation 2000; **102:** 1193-209.
12. Recommendations of the task force of the European Society of Cardiology. Management of acute coronary syndromes : acute coronary syndromes without persistent ST segment elevation. Eur Heart J 2000; **21:** 1406-32.
13. Bailen MR. Reversible myocardial dysfunction in critically ill, noncardiac patients : a review. Crit Care Med 2002; **30:** 1280-90.
14. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill patients : a frequently unrecognized complication. JAMA 1995; **273:** 1945-49.
15. Panteghini M. The measurement of cardiac markers. Where should we focus ? Am J Clin Pathol 2002; **118:** 354-61.
16. Ferrara R, Mastrorilli F, Pasanisi G, et al. Neurohormonal modulation in chronic heart failure. Eur Heart J 2002; **4 (Suppl D):** D3-D11.
17. Francis GS. Pathophysiology of chronic heart failure. Am J Med 2001; **110(7A):** 37S-46S.
18. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. Circulation 2000; **102:** IV-14 - IV-23.
19. Matsumori A. Insights into the pathophysiology of heart failure based on a new concept. Asian Med J 2001; **44:** 36-41.
20. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure : A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990; **82:** 1724-29.
21. Redfield MM, Aarhus LL, Wright RS, Burnett Jr JC. Cardiorenal and neurohumoral function in a canine model of early left ventricular dysfunction. Circulation 1993; **87:** 2016-22.
22. Van Vleet JF, Ferrans VJ. Myocardial diseases of animals. Am J Pathol 1986; **124:** 98-178.
23. Mann DL, Kent RL, Parsons B, et al. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992; **85:** 790-804.
24. Mann DL. Basic mechanism of disease progression in the failing heart: The role of excessive adrenergic drive. Prog Cardiovasc Dis 1998; **41(Suppl 1):** 1-8.
25. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. Circulation 2000; **102:** 1216-20.
26. Bertinchant JP, Robert E, Polge A, et al. Comparison of the diagnostic value of cardiac troponin I and T determinations for detecting early myocardial damage and the relationship with histological findings after isoprenaline-induced cardiac injury in rats. Clin Chim Acta 2000; **298:** 13-28.
27. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. Circulation 1997; **96:** 2953-58.
28. Missov E, Mair J. A novel biochemical approach to congestive heart failure : Cardiac troponin T. Am Heart J 1999; **138:** 95-99.
29. La Vecchia L, Mezzena G, Ometto R, et al. Detectable serum troponin I in patients with heart failure of

nonmyocardial ischemic origin. Am J Cardiol 1997; **80:** 88-90.
30. Setsuta K, Seino Y, Takahashi N, et al. Clinical significance of elevated levels of cardiac troponin T in patients with chronic heart failure. Am J Cardiol 1999; **84:** 608-11.
31. Sato Y, Yamada T, Taniguchi R, et al. Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 2001; **103:** 369-74.
32. Hudson MP. Ongoing myocardial necrosis among outpatients with heart failure : Implications of elevated troponin T and C-reactive protein concentrations (abstract). Am Heart J 2001; **141:** 169-70.
33. Miller WL, Wright RS, McGregor CG, et al. Troponin levels in patients with amyloid cardiomyopathy undergoing cardiac transplantation. Am J Cardiol 2001; **88:** 813-15.
34. Perna ER, Macin SM, Parras JI, et al. Cardiac troponin T levels are associated with poor short- and long-term prognosis in patients with acute cardiogenic pulmonary edema. Am Heart J 2002; **143:** 814-20.
35. Sribhen K, Tribuddharatana T, Kiartivich S, Sribhen C. Biochemical evidence of myocardial cell damage in heart failure : A canine model of cardiac injury. Siriraj Hosp Gaz 2001; **53:** 138-44.
36. Chen YN, Wei JR, Zeng LJ, Wu MY. Monitoring of cardiac troponin I in patients with acute heart failure. Ann Clin Biochem 1999; **36:** 433-37.
37. Logeart D, Beyne P, Cusson C, et al. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. Am Heart J 2001; **141:** 247-53.
38. Del Carlo CH, O'Connor CM. Cardiac troponins in congestive heart failure. Am Heart J 1999; **138:** 646-53.
39. Kearney MT, Cotton JM, Richardson PJ, Shah AM. Viral myocarditis and dilated cardiomyopathy : Mechanisms, manifestations, and management. Postgrad Med J 2001; **77:** 4-10.
40. Lenghaus C, Studdert MJ. Acute and chronic viral myocarditis. Acute diffuse nonsuppurative myocarditis and residual myocardial scarring following infection with canine parvovirus. Am J Pathol 1984; **115:** 316-19.
41. D' Ambrosio A, Patti G, Manzoli A, et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy : A review. Heart 2001; **85:** 499-504.
42. Feldman AM, McNamara D. Myocarditis. N Engl J Med 2000; **343:** 1388-98.
43. Narula J, Khaw BA, Dec Jr GW, et al. Brief report : recognition of acute myocarditis masquerading as acute myocardial infarction. N Engl J Med 1993; **328:** 100-4.
44. Seferovic PM, Maksimovic R, Vasiljevic JD, et al. Endomyocardial biopsy : a meta-analysis of diagnostic value. Postgrad Med J 1994; **70(Suppl 1):** S21-S28.
45. Webber SA, Boyle GJ, Jaffe R, Pickering RM, Beerman LB, Fricker FJ. Role of right ventricular endomyocardial biopsy in infants and children with suspected or possible myocarditis. Br Heart J 1994; **72:** 360-63.
46. Davies MJ, Ward DE. How can myocarditis be diagnosed and should it be treated? Br Heart J 1992; **68:** 346-47.
47. Shanes JG, Ghali J, Billingham ME, et al. Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 1987; **75:** 401-5.
48. Bachmaier K, Mair J, Offner F, Pummerer C, Neu N. Serum cardiac troponin T and creatine kinase-MB elevations in murine autoimmune myocarditis. Circulation 1995; **92:** 1927-32.
49. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997; **95:** 163-68.
50. Franz WM, Remppis A, Kandolf R, Kuebler W, Katus HA. Serum troponin T : diagnostic marker for acute myocarditis (letter). Clin Chem 1996; **42:** 340-41.
51. Lauer B, Niederau C, Kuel U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol 1997; **30:** 1354-59.
52. Williams RV, Olson TM, Young PC, Shaddy RE. Cardiac troponin I levels in pediatric patients with acquired heart disease (abstract). Pediatrics 1999; **104 (Suppl):** 666.
53. Soongswang J, Sangtawesin C, Sittiwangkul R, et al. Myocardial diseases in Thai children. J Med Assoc Thai 2002; **85 (Suppl 2):** S648-S657.
54. Bonnefoy E, Godon P, Kirkorian G, Fatemi M, Chevalier P, Touboul P. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. Eur Heart J 2000; **21:** 832-36.
55. Brandt RR, Filzmaier K, Hanrath P. Circulating cardiac troponin I in acute pericarditis. Am J Cardiol 2001; **87:** 1326-28.
56. Vlahakes GJ, Turley K, Hoffman JIE. The pathophysiology of failure in acute right ventricular hypertension : Hemodynamic and biochemical correlations. Circulation 1981; **63:** 87-95.
57. Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism : Pathophysiologic

factors, detection, and therapeutic implications. Am Heart J 1995; **130:** 1276-82.
58. Adams III JE, Siegel BA, Goldstein JA, Jaffe AS. Elevation of CK-MB following pulmonary embolism : a manifestation of occult right ventricular infarction. Chest 1992; **101:** 1203-6.
59. De la Cal FJA, Borruey JMA, Bermcjo JMN, Garrido AP. Pulmonary embolism and occult right ventricular infarction (letter). Chest 1994; **105:** 1617.
60. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med 2002; **162:** 79-81.
61. Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB. Cardiac troponin I elevation in acute pulmonary embolism is associated with right-ventricular dysfunction. J Am Coll Cardiol 2000; **36:** 1632-36.
62. Mueller–Bardorff M, Weidtmann B, Giannitsis E, Kurowski V, Katus HA. Release kinetics of cardiac troponin T in survivors of confirmed severe pulmonary embolism. Clin Chem 2002; **48:** 673-75.
63. Giannitsis E, Mueller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000; **102:** 211-17.
64. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002; **106:** 1263-68.
65. Weinberg I, Cukierman T, Chajek-Shaul T. Troponin T elevation in lobar lung disease. Postgrad Med J 2002; **78:** 244-45.
66. Lovis C, Mach F, Unger PF, Bouillie M, Chevrolet JC. Elevation of creatine kinase in acute severe asthma is not of cardiac origin. Intensive Care Med 2001; **27:** 528-33.
67. Chiang VW, Burns JP, Rifai N, Lipshultz SE, Adams MJ, Weiner DL. Cardiac toxicity of intravenous terbutaline for the treatment of severe asthma in children : A prospective assessment. J Pediatr 2000; **137:** 73-77.
68. Natanson C, Fink MP, Ballantyne HK, MacVittie TJ, Conklin JJ, Parrillo JE. Gram-negative bacteremia produces both severe systolic and diastolic cardiac dysfunction in a canine model that simulates human septic shock. J Clin Invest 1986; **78:** 259-70.
69. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984; **100:** 483-90.
70. Ver Elst KM, Spapen HD, Nguyen DN, Garber C, Huyghens LP, Gorus FK. Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. Clin Chem 2000; **46:** 650-57.
71. Wu AHB. Increased troponin in patients with sepsis and septic shock : myocardial necrosis or reversible myocardial depression? Intensive Care Med 2001; **27:** 959-61.
72. Spies C, Haude V, Fitzner R, et al. Serum cardiac troponin T as a prognostic marker in early sepsis. Chest 1998; **113:** 1055-63.
73. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Crit Care Med 1999; **27:** 1775-80.
74. Thiru Y, Pathan N, Bignall S, Habibi P, Levin M. A myocardial cytotoxic process is involved in the cardiac dysfunction of meningococcal septic shock. Crit Care Med 2000; **28:** 2979-83.
75. Ammann P, Fehr T, Minder EI, Guenther C, Bertel O. Elevation of troponin I in sepsis and septic shock. Intensive Care Med 2001; **27:** 965-69.
76. Saffle JR, Sullivan JJ, Tuohig GM, Larson CM. Multiple organ failure in patients with thermal injury. Crit Care Med 1993; **21:** 1673-83.
77. Horton JW. Cellular basis for burn-mediated cardiac dysfunction in adult rabbits. Am J Physiol 1996; **271(Heart Circ Physiol 40):** H 2615-H2621.
78. Giroir BP, Horton JW, White DJ, McIntyre KL, Lin CQ. Inhibition of tumor necrosis factor prevents myocardial dysfunction during burn shock. Am J Physiol 1994; **267(Heart Circ Physiol 36) :**H118-H124.
79. Horton JW, White J, Maass D. Protein kinase C inhibition improves ventricular function after thermal trauma. J Trauma 1998; **44:** 254-65.
80. Horton JW, Garcia NM, White DJ, Keffer J. Postburn cardiac contractile function and biochemical markers of postburn cardiac injury. J Am Coll Surg 1995; **181:** 289-98.
81. Huang YS, Yang ZC, Yan BG, et al. Pathogenesis of early cardiac myocyte damage after severe burns. J Trauma 1999; **46:** 428-32.
82. Chen YN, Luo ZR, Zeng LJ, Wu MY, Wu YZ, Lin ZY. Cardiac troponin I : A marker for post-burn cardiac injury. Ann Clin Biochem 2000; **37:** 447-51.
83. Murphy JT, Horton JW, Purdue GF, Hunt JL. Evaluation of troponin-I as an indicator of cardiac dysfunction after thermal injury. J Trauma 1998; **45:** 700-4.
84. Elrifai AM, Bailes JE, Shih SR, Dianzumba S, Brillman J. Characterization of the cardiac effect of acute subarachnoid hemorrhage in dogs. Stroke 1996; **27:** 737-42.
85. MacMillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid haemorrhage : time for active management ? Intensive Care Med 2002; **28:** 1012-23.

86. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS. Experimental catecholamine-induced myocardial necrosis. II. Temporal development of isoproterenol-induced contraction band lesions correlated with ECG, hemodynamic and biochemical changes. J Mol Cell Cardiol 1985; **17:** 647-56.
87. Masuda T, Sato K, Yamamoto SI, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke 2002; **33:** 1671-76.
88. Mayer SA, LiMandri G, Sherman D, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 1995; **83:** 889-96.
89. Mayer SA, Fink ME, Homma S, et al. Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 1994; **44:** 815-20.
90. Szabo MD, Crosby G, Hurford WE, Strauss HW. Myocardial perfusion following acute subarachnoid hemorrhage in patients with an abnormal electrocardiogram. Anesth Analg 1993; **76:** 253-58.
91. Dixit S, Castle M, Velu RP, Swisher L, Hodge C, Jaffe AS. Cardiac involvement in patients with acute neurologic disease. Confirmation with cardiac troponin I. Arch Intern Med 2000; **160:** 3153-58.
92. James P, Ellis CJ, Whitlock RML, McNeil AR, Henley J, Anderson NE. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. BMJ 2000; **320:** 1502-1504.