HEART FAILURE AND CARDIOMYOPATHY

Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy

C L Hu, Y B Li, Y G Zou, J M Zhang, J B Chen, J Liu, Y H Tang, Q Z Tang, C X Huang

Heart 2007;93:488–490. doi: 10.1136/hrt.2006.087387

See end of article for authors' affiliations

Correspondence to:
Dr C L Hu, Department of
Cardiology, Renmin
Hospital, Wuhan University
School of Medicine, 238
Jiefang Road, Wuchang
District, Wuhan 430060,
People's Republic of China;
chenglinhu@yahoo.com

Accepted 15 August 2006
Published Online First
25 October 2006

Objective: To determine whether measurement of cardiac troponin T (cTnT) concentration in newly diagnosed peripartum cardiomyopathy (PPCM) can be used to predict persistent left ventricular dysfunction after a 6-month follow-up.

Patients and methods: This was a prospective, multiple-centre clinical trial that studied 106 patients with newly diagnosed PPCM surviving over 6 months. cTnT concentration was measured within 2 weeks of the onset of PPCM.

Results: Serum cTnT concentration was negatively correlated with left ventricular ejection fraction (LVEF) at follow-up (LVEF, $r = -0.518$, $p = 0.0001$). Analysis by receiver operator characteristic curve yielded an area under the curve of 0.764 (95% CI 0.669 to 0.860, $p = 0.0001$, vs null hypothesis value 0.5) for cTnT, and a cTnT concentration cut off of >0.04 ng/ml, predicting persistent left ventricular dysfunction with a sensitivity of 54.9% and a specificity of 90.9%. Among 106 recruited patients, there were 33 patients with cTnT concentrations >0.04 ng/ml and 73 patients with cTnT concentrations ≤ 0.04 ng/ml. After a 6-month follow-up, there was significantly smaller LVEF (35.42% (13.04% vs 50.16% (10.48%, $p = 0.0001$) and more persistent left ventricular dysfunction (84.8% vs 31.5%, OR = 12.17 (95% CI 4.17 to 35.57), $p = 0.001$) in patients with cTnT >0.04 ng/ml than in patients with cTnT ≤ 0.04 ng/ml.

Conclusion: Serum cTnT concentration measured within 2 weeks of the onset of PPCM was correlated negatively with LVEF at follow-up. This marker offers a simple, quick, inexpensive, non-invasive method for predicting a persistent LVEF of $\leq 50\%$. A cTnT concentration of >0.04 ng/ml predicted persistent left ventricular dysfunction with a sensitivity of 54.9% and a specificity of 90.9%.

Peripartum cardiomyopathy (PPCM) is a cardiomyopathy of unknown cause that occurs in pregnant females, most commonly in the early postpartum period.¹ In some patients, the clinical and echocardiographic status improves rapidly and has returned to normal by the time of a 6-month follow-up. The long-term prognosis of PPCM seems to be related to the rapid recovery of ventricular function.^{2–3} Many of the patients whose ventricular function returned to normal have resumed active lives, whereas patients who maintain persistent ventricular dysfunction for ≥ 6 months have an extremely poor prognosis. Prompt recognition of the condition at diagnosis is required for initiation of appropriate medical management and counselling regarding future pregnancies.^{4–6}

The initial severity of the left ventricular systolic dysfunction or dilatation is not necessarily predictive of the long-term functional outcome.⁷ Biochemical markers may have predictive values in PPCM. Cytokine and sFas levels are elevated in patients with PPCM.⁸ Baseline levels of C reactive protein correlated positively with baseline left ventricular end-diastolic and end-systolic diameters and inversely with left ventricular ejection fraction (LVEF). Fas/Apo-1 predicted mortality.⁹ The serum cTnT, a specific and highly sensitive marker of myocardial injury, has not been reported in this population. This study was designed to study the prognostic role of cTnT in patients with newly diagnosed PPCM within 2 weeks of the onset of symptoms.

METHODS

Study population

The study was a prospective multiple-centre clinical trial that studied 106 patients with newly diagnosed PPCM surviving over 6 months. This trial was carried out at three teaching hospitals in central China—Renmin Hospital of Wuhan

University School of Medicine, Wuhan, Wuhan Xiehe Hospital, Wuhan and Xiaogan General Hospital, Xiaogan. The local research and ethics committee approved this protocol and each subject gave written informed consent before the start of the study. The criteria for the diagnosis of PPCM included the development of congestive heart failure during the last month of pregnancy or during the first 5 months postpartum, the absence of another identifiable cause of heart failure, and evidence of depressed left ventricular function, defined as an LVEF of $<40\%$, as measured by echocardiography.^{6–10} According to 6-month outcome, patients were divided into two groups: persistent ventricular dysfunction (group 1, LVEF $\leq 50\%$) and recovered ventricular function (group 2, LVEF $>50\%$). This ejection fraction value was considered to have prognostic significance based on previous clinical trials.^{9–11} Pharmacological treatment included angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and β -adrenergic blockers, diuretics, digoxin and anticoagulants. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided during pregnancy, because of severe adverse neonatal effects.

Cardiac marker analyses

Blood samples for measurement of cTnT were taken within 2 weeks of the onset of PPCM. cTnT was analysed with the third-generation TnT test (Troponin T STAT). The third-generation TnT test uses the same monoclonal antibodies (M11.7 and M7) as the second-generation test, but is standardised with human recombinant cTnT instead of bovine

Abbreviations: cTnT, cardiac troponin T; LVEF, left ventricular ejection fraction; PPCM, peripartum cardiomyopathy; ROC, receiver-operating characteristic

cTnT (Roche Diagnostics, Shanghai, PR China). The analytical range, 10% coefficient of variation (CV) value and normal reference range (99th centile of the control population) of the cTnT assay were, respectively, 0.01–25, 0.04 and <0.01 ng/ml.

Echocardiography

Echocardiography was carried out both within 2 weeks of the onset of PPCM and at 6-month follow-up. LVEF was measured echocardiographically by two experts unaware of this study protocol, whose measurements were averaged.

Statistical analysis

The sample size was calculated using MedCalc (release 8.1, written by Frank Schoonjans). To show that an area under the curve of 0.760 is significant for the null hypothesis value 0.5, at least 49 patients should be included in each group to achieve a power of 90% at 95% confidence level (two-sided).

The relation between cTnT concentration and LVEF was studied using Spearman's correlation coefficient. The ability of cTnT to predict the outcome was assessed by receiver-operating characteristic (ROC) curve analysis. The ROC curve was constructed by calculating the sensitivity and specificity of cTnT (the numeric variable) at progressively increasing cut-off concentrations of cTnT. Sensitivity was plotted against 1–specificity to give the ROC plot. The nearer the curve to the top left corner of the graph, the better the test. The point of inflection of the ROC curve allows selection of the best trade-off between sensitivity and specificity.

The data were analysed using SPSS V.11.0. All statistical tests were two-sided. A value of $p < 0.05$ was considered significant.

RESULTS

All patients were seen initially for pulmonary oedema. In all, 18 women were first examined ante partum and 88 post partum. The mean age at diagnosis was 28.0 (6.5) years. Elevated serum cTnT concentrations (≥ 0.01 ng/ml) were found in 86% of the patients. LVEF at the time of diagnosis was 26.58% (5.91%), which improved to 45.26% (13.41%) at follow-up ($p = 0.0001$). Left ventricular dysfunction was maintained in 51 of 106 (48%) patients and LVEF returned to normal in 55 of 106 (52%) patients. Blood samples for cTnT measurement were taken 7.4 (2.4) days (group 1) and 8.2 (3.1) days (group 2) after the onset of PPCM ($p = 0.723$). There was a difference in median (lower, upper quartile) cTnT concentration (0.050

Figure 1 Cardiac troponin T concentration was correlated negatively with LVEF at follow-up.

Figure 2 Receiver operating characteristic (ROC) plots of cTnT to predict persistent left ventricular dysfunction.

(0.020, 0.060) ng/ml vs (0.010, 0.010, 0.020) ng/ml, $p = 0.0001$) between groups 1 and 2.

cTnT concentration was correlated negatively with LVEF at follow-up ($r = -0.518$, $p = 0.0001$, fig 1).

Analysis by ROC to predict persistent left ventricular dysfunction, yielded an area under the curve of 0.764 (95% CI 0.669 to 0.860, $p = 0.0001$, vs null hypothesis value 0.5, fig 2) for cTnT. The best cut-off value was 0.025 ng/ml. But the CV of the assay is $>10\%$ at this concentration. According to the European Society of Cardiology/American Heart Association/Journal of American college of cardiology recommendations, a troponin cut-off with a $<10\%$ CV should be used in routine clinical practice. Hence, we selected 0.04 ng/ml as cut-off value according to the published data on the assay used.¹² A cTnT concentration of >0.04 ng/ml, predicted persistent left ventricular dysfunction with a sensitivity of 54.9 (95% CI 40.3 to 68.9), specificity of 90.9 (95% CI 80.0 to 96.9), positive likelihood ratio of 6.04 and negative likelihood ratio of 0.50.

Among 106 recruited patients, there were 33 patients with cTnT concentrations >0.04 ng/ml and 73 patients with cTnT concentrations ≤ 0.04 ng/ml. After a 6-month follow-up, there was significantly smaller LVEF (35.42% (13.04% vs 50.16% (10.48%), $p = 0.0001$) and more persistent left ventricular dysfunction (84.8% vs 31.5%, OR = 12.17 (95% CI 4.17 to 35.57), $p = 0.0001$) in patients with cTnT >0.04 ng/ml than in patients with cTnT ≤ 0.04 ng/ml.

DISCUSSION

In this study, we found that serum cTnT concentration measured within 2 weeks of the onset of PPCM was correlated negatively with follow-up LVEF, and that it has a moderate predictive capacity for persistent left ventricular dysfunction at 6-month follow-up.

The clinical presentation of patients with PPCM is similar to that of patients with systolic congestive heart failure, but the outcome of patients with PPCM is highly variable. In our study, left ventricular function almost completely normalised in 51% of surviving patients. This finding was similar to the findings in Demakis et al's⁴ and Elkayam et al's¹¹ study. But normalisation of LVEF was observed only in 23% of an African cohort.⁹

The measurement of serum concentration of cTnT is a simple and useful method to detect myocyte injury.¹³ Myocardial

biopsies in PPCM revealed that the most prominent findings were hypertrophy of myocardial fibres and varying degrees of fibrosis. There seemed to be no significant histological differences between the patients with normal heart size and those with persistent cardiomegaly after the onset of heart failure.⁴ In our study, cTnT concentration was higher in patients who maintained cardiomegaly than in patients in whom heart function returned to normal within 6 months. Moreover, at follow-up, more persistent left ventricular dysfunctions occurred in patients with cTnT concentrations >0.04 ng/ml. Serum cTnT in PPCM seems to indicate ongoing myocyte degeneration. This can partly explain the difference in the two groups with respect to haemodynamic change, LV remodelling and different prognosis. The mechanisms of myocyte injury in PPCM are not fully understood. It may be caused by virus infection, autoimmune mechanisms, hormonal changes, genetic disorders and toxemia.^{4 14 15} A possible correlation between these factors and cTnT concentrations warrants further study. Renal failure is also a recognised cause of raised cTnT concentration,¹⁶ but the results were not altered by exclusion of patients with a serum creatine concentration >0.2 mmol/l.

The prognostic values of cTnT have been studied in acute myocarditis¹⁷ and other kinds of cardiomyopathy.^{13 18 19} Among patients with dilated cardiomyopathy (DCM) and secondary cardiomyopathy, there was a subgroup of patients with raised concentrations of serum cTnT for whom short-term prognosis was poor.¹⁸ Persistently increased cTnT concentrations (≥ 0.02 ng/ml) in DCM suggest ongoing subclinical myocyte degeneration associated with deterioration of the patients' clinical status.¹³ An increase in TnT serum concentrations in hypertrophic cardiomyopathy pointed to subclinical myocyte injury. During an average of 21.5 months follow-up, patients with increased serum cTnT level were found to have decreased in ventricular fractional shortening and ventricular septal thickness on echocardiogram.¹⁹ In acute myocarditis, cTnT level was significantly higher than that in DCM. However, it had no significant effect on the outcomes of the patients.¹⁷ In our study, serum cTnT concentration measured within 2 weeks of the onset of PPCM was correlated negatively with LVEF at follow-up. Analysis by ROC to predict persistent left ventricular dysfunction yielded an area under the curve of 0.764 for cTnT, indicating that cTnT concentrations have a moderate predictive capacity.²⁰ A cTnT concentration of >0.04 ng/ml predicted persistent left ventricular dysfunction with a sensitivity of 54.9% and a specificity of 90.9%. Long-term outcomes in PPCM are related to left ventricular function status after 6 months of the onset of PPCM.^{4 21} cTnT might also serve as a useful new prognostic indicator for long-term outcomes in PPCM and thus seems to be important in PPCM. Doctors must be aware of this problem in order to provide prompt diagnosis and effective treatment to ensure a favourable return of heart size and normal left ventricular function to normal.

A limitation of this study is short-term course. A large study on the relationship between serum concentrations of cTnT and long-term outcomes is warranted. In the meantime, our conclusions are valid only for the subpopulation of patients with newly diagnosed PPCM. Moreover, this study was not designed to examine the effects of drug treatment on the evolution of serum cTnT concentrations. Larger clinical drug trials including the monitoring of cTnT concentrations should be planned.

In conclusion, serum cTnT concentration measured within 2 weeks of the onset of PPCM was correlated negatively LVEF at follow-up. This marker offers a simple, inexpensive, quick, non-invasive method of predicting persistent left ventricular dysfunction. An initial cTnT concentration of >0.04 ng/ml predicted persistent left ventricular dysfunction with a sensitivity of 54.9% and a specificity of 90.9% at 6-month follow-up.

Authors' affiliations

C L Hu, J B Chen, J Liu, Y H Tang, Q Z Tang, C X Huang, Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China

Y B Li, Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China

Y G Zou, Department of Cardiology, Xiaogan General Hospital, Xiaogan, People's Republic of China

J M Zhang, Department of Cardiology, Wuhan Xiehe Hospital, Wuhan, People's Republic of China

Competing interests: None.

REFERENCES

- Murali S, Baldisseri MR. Peripartum cardiomyopathy. *Crit Care Med* 2005;**33**:S340–6.
- Skaluba SJ, Berkson DM. Peripartum cardiomyopathy: case report and literature review. *Congest Heart Fail* 2001;**7**:88–92.
- Siu SC, Colman JM. Heart disease and pregnancy. *Heart* 2001;**85**:710–15.
- Demakis JG, Rahimtoola SH, Sutton GC, et al. Natural course of peripartum cardiomyopathy. *Circulation* 1971;**44**:1053–61.
- Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA* 2000;**283**:1183–8.
- Lampert MB, Lang RM. Peripartum cardiomyopathy. *Am Heart J* 1995;**130**:860–70.
- Cole P, Cook F, Plappert T, et al. Longitudinal changes in left ventricular architecture and function in peripartum cardiomyopathy. *Am J Cardiol* 1987;**60**:871–6.
- Sliwa K, Skudicky D, Bergemann A, et al. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. *J Am Coll Cardiol* 2000;**35**:701–5.
- Sliwa K, Forster O, Libhaber E, et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* 2006;**27**:441–6.
- Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* 2001;**344**:1567–71.
- Elkayam U, Akhter MW, Singh H, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation* 2005;**111**:2050–5.
- Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;**50**:327–32.
- 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.
- Sanderson JE, Olsen EG, Gatei D. Peripartum heart disease: an endomyocardial biopsy study. *Br Heart J* 1986;**56**:285–91.
- Thorne SA. Pregnancy in heart disease. *Heart* 2004;**90**:450–6.
- McNeil AR, Marshall M, Ellis CJ, et al. Why is troponin T increased in the serum of patients with end-stage renal disease? *Clin Chem* 1998;**44**:2377–8.
- Soongswang J, Durongpisitkul K, Nana A, et al. Cardiac troponin T: a marker in the diagnosis of acute myocarditis in children. *Pediatr Cardiol* 2005;**26**:45–9.
- Sato Y, Kataoka K, Matsumori A, et al. Measuring serum aminoterminal type III procollagen peptide, 7S domain of type IV collagen, and cardiac troponin T in patients with idiopathic dilated cardiomyopathy and secondary cardiomyopathy. *Heart* 1997;**78**:505–8.
- Sato Y, Taniguchi R, Nagai K, et al. Measurements of cardiac troponin T in patients with hypertrophic cardiomyopathy. *Heart* 2003;**89**:659–60.
- Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;**240**:1285–93.
- Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. *Obstet Gynecol* 1999;**94**:311–16.