

**TITLE PAGE:**

**(a) Title:** Relation of Delayed Recovery of Myocardial Function after Takotsubo Cardiomyopathy to Subsequent Quality of Life.

**(b) Authors:**

Christopher J. Neil\* MBBS, PhD, FRACP <sup>1,2</sup>

Thanh H. Nguyen\* MD, M.Med.Sci, PhD <sup>1,2</sup>

Kuljit Singh MBBS, FRACP <sup>1,2</sup>

Betty Raman MBBS, FRACP <sup>1,2</sup>

Jeanette Stansborough RN <sup>1</sup>

Dana Dawson DM, FRCP, D.Phil, FESC <sup>3</sup>

Michael P. Frenneaux MBBS, MD, FRCP <sup>3</sup>

John D. Horowitz MBBS, B.Med.Sci(Hons), PhD, FRACP <sup>1,2</sup>

1. Department of Cardiology, the Queen Elizabeth Hospital,
2. Basil Hetzel Institute, The University of Adelaide,
3. The University of Aberdeen, Aberdeen AB24 3FX, United Kingdom

\* These authors contributed equally to the study.

**(c) Address for correspondence:**

Professor John D Horowitz

Postal address: Cardiology Unit, The Queen Elizabeth Hospital, 28 Woodville Road,

Woodville South, SA 5011, Australia

E-mail: [john.horowitz@adelaide.edu.au](mailto:john.horowitz@adelaide.edu.au)

Telephone: 61(08) 8222 6725

Fax: 61(08) 8222 6422

**ABSTRACT**

Takotsubo cardiomyopathy (TTC) has generally been regarded as a relatively transient disorder, characterised by reversible regional left ventricular systolic dysfunction. However, the majority of TTC patients experience prolonged lassitude/dyspnoea following acute attacks. While this might reflect continued emotional stress, myocardial inflammation and accentuated BNP release persist for at least 3 months. We therefore tested the hypotheses that (i) this continued inflammation is associated with persistent contractile dysfunction and (ii) consequent impairment of quality of life. Echocardiographic parameters [global longitudinal strain (GLS), longitudinal strain rate (LSR) and peak apical twist (AT)] were compared acutely and after 3 months in 36 female TTC patients and 19 age-matched female controls. Furthermore, correlations were sought between putative functional anomalies, inflammatory markers (T2 score on CMR, plasma NT-proBNP and hs-CRP levels), and the physical composite component of SF36 score (SF36-PCS). Among TTC cases, LVEF returned to normal within 3 months. GLS, LSR and AT improved significantly over 3 months' recovery, but GLS remained reduced compared to controls even at follow-up ( $-17.9 \pm 3.1\%$  vs.  $-20.0 \pm 1.8\%$ ,  $p = 0.003$ ). Impaired GLS at 3 months was associated both with persistent NT-proBNP elevation ( $p = 0.03$ ) and reduced SF36-PCS at  $\geq 3$  months ( $p = 0.04$ ). In conclusion, despite normalization of LVEF, GLS remains impaired for at least 3 months, possibly as a result of residual myocardial inflammation. Furthermore, perception of impaired physical exercise capacity  $\geq 3$  months post TTC may be explained by persistent myocardial dysfunction.

Word counts: 240

**Key words:** Takotsubo cardiomyopathy, global longitudinal strain, inflammation, N-terminal pro-B-type natriuretic peptide, quality of life

**MAIN TEXT**

Takotsubo cardiomyopathy (TTC), also known as acute stress-induced cardiomyopathy, apical ballooning syndrome and “broken heart syndrome”, is a form of regional left ventricular systolic dysfunction most commonly seen in aging women after physical or emotional stress<sup>1-4</sup>, which can be attributed to a dysfunctional myocardial reaction to high concentrations of catecholamines<sup>5-7</sup>. The classical course of TTC is “spontaneously reversible” left ventricular (LV) systolic dysfunction: initially hypokinetic/akinetic (usually apical) regions recover to apparently normal wall motion within days in most cases<sup>8,9</sup>. However, recent clinical studies report persistence of symptoms well beyond this<sup>10</sup>, while myocardial inflammation persists on LV biopsy<sup>11</sup> and myocardial edema on MRI<sup>12</sup> 3 months after acute attacks. Similarly, the associated (inflammatory) release of BNP/NT-proBNP persists for at least that duration<sup>13</sup>. We have now performed an echocardiographic comparison of TTC and matched control subjects, in order to test two hypotheses: (1) that LV systolic function remains abnormal 3 months post TTC, despite normal LVEF, reflecting underlying myocardial inflammation, and (2) that the extent of putative LV dysfunction after 3 months correlates with symptomatic limitation of physical performance.

## **Methods**

TTC patients were eligible for inclusion on the basis of an acute diagnosis, according to the Mayo Clinic criteria<sup>14</sup> including: (1) a presentation with abnormalities of ST segments/T waves, with or without chest pain or dyspnoea, (2) a sustained elevation of cardiac troponin levels, (3) demonstration of a characteristic wall motion abnormality, not confined to a single epicardial coronary territory and the exclusion of obstructive coronary disease, via selective coronary angiography, in the territory subserving the regional wall motion abnormality. Exclusion criteria were pre-existing LV or valvular disease, pheochromocytoma and myocarditis, each of which was prospectively considered. Age- and gender matched controls were recruited by advertisement and were eligible in the absence of known cardiac disease. The study complies with the Declaration of Helsinki and

was approved by the institutional ethics of human research committee. All participants in each group provided written informed consent.

Echocardiography was performed, utilizing a Vivid 7 echocardiography machine) with a M5 ultrasound transducer (GEHVingmed, Horton, Norway). In patients with TTC, echocardiography was performed at the time of initial diagnosis, 10 days and 3 months thereafter. Standardised echocardiographic data included pulse wave Doppler, tissue Doppler and two dimensional grey scale imaging in all conventional views, as recommended by the American Society of Echocardiography<sup>15</sup>. Loops of three consecutive cardiac cycles, with a minimum frame rate of 50s were stored offline, for subsequent analysis with a dedicated software package (EchoPAC version BT11, GE-Vingmed, Horton, Norway). LVEF, left ventricular end-systolic volume index (LVESVi) and end-diastolic volume index (LVEDVi) (corrected to body surface area of individual subjects) were calculated utilizing Simpson's biplane method. The wall motion score index (WMSI) was determined as previously described<sup>12</sup>.

For speckle tracking analyses, the endocardium was manually traced at end systole to generate a segmented region of interest, the width of which was adjusted to include the thickness of the LV myocardium. Segmental motion was then automatically tracked throughout a cardiac cycle. Strain was defined as the change in the length of the segment studied, as a percentage of its final (end-diastolic) length, with respect to the three orthogonal directions of tissue deformation (longitudinal, radial and circumferential, in relation to the cardiac axis); strain rate (SR) was defined as the rate at which this deformation occurs. Peak values were derived from strain-time and SR-time curves, respectively. Mean global longitudinal strain/SR were derived from the three individual apical views and thus represent triplanar averages. Radial and circumferential function was studied as strain and SR (averaged from all segments) at the base, mid-ventricle and apex. Twist mechanics were studied at the LV base and apex and the average peak rotation and rotation rate were determined from automatically generated curves. Counter-clockwise rotation, as observed at the apex, was expressed as a positive value, whilst basal clockwise rotation was

expressed as negative <sup>16</sup>. LV twist was defined as the net difference between peak apical and peak basal rotation, whereas LV torsion was defined as LV twist, normalized for LV diastolic length, as elsewhere described <sup>16</sup>.

Cardiovascular magnetic resonance imaging (CMR) imaging was performed both acutely and after 3 months in order to quantitate myocardial oedema via integrated estimates of T2-weighted signal intensity (T2 SI) within the entire left ventricle, as previously described<sup>12</sup>.

A number of biochemical investigations were performed in order to quantitate the initial catecholamine stimulus towards development of TTC, together with the extent of inflammatory response and cellular damage. Furthermore, most of these investigations were repeated at 3 months' follow-up.

- (a) Catecholamine release was measured via plasma metanephrine and normetanephrine concentrations<sup>13</sup>.
- (b) Inflammatory activation was quantitated via hs-CRP and NT-proBNP concentrations.
- (c) Extent of myocardial necrosis was quantitated via release of troponin T and creatine kinase to (CK).

We sought to evaluate patients' quality of life as assessed by the Short Form health survey (SF36), completed at  $\geq 3$  months by 24 patients. The SF36 questionnaire includes a physical composite score (SF36-PCS), which was utilized for assessment of hypothesis 2.

The data were analysed using the SPSS version 20 software (SPSS, Chicago, Illinois, USA), and presented as mean  $\pm$  1SD unless otherwise specified. To evaluate functional indices of recovery, three indices were chosen as potential markers of recovery of LV systolic function. These were (i) global longitudinal strain (GLS), (ii) longitudinal strain rate (LSR), and (iii) peak apical twist (AT). It was prospectively elected that correlations between recovery and ongoing inflammation would utilize whichever of these parameters displayed the most consistent impairment during recovery from TTC. As regards testing of hypothesis 2, we elected to seek correlations between GLS at 3 months and SF36-PCS utilizing Pearson's correlation and correlations with the total SF36 were also evaluated as a secondary

consideration. Comparisons between controls and TTC patients were performed utilizing the 3-month TTC data. Methodology included non-paired t-tests or Wilcoxon signed rank tests for quantitative data and  $\chi^2$  tests for categorical data. Correlations within the TTC group were performed via Pearson's or Spearman's rank correlation as appropriate.

## Results

TTC patients (n = 36) and controls (n = 19) were well matched for age and distribution of coronary risk factors (Table 1). Among the TTC cohort, 33% presented with S-T elevation and all had abnormally elevated plasma troponin T ( $0.46 \pm 0.39$  mg/dl) and NT-proBNP levels ( $7557 \pm 8626$  pg/ml). 75% of the TTC patients were treated with ACE inhibitors for at least the first 3 months post presentation.

Over the first 3 months of follow-up, all parameters of LV systolic function improved progressively (Table 2). For example, LVEF increased from  $52 \pm 14\%$  at presentation to  $60 \pm 7\%$  ( $p = 0.003$ ), with significant reductions in LV end-systolic and end-diastolic volumes. Furthermore, there was significant improvement in all rotational and longitudinal parameters measured (Table 2). Transmitral E/A ratio fell from  $1.1 \pm 0.5$  to  $0.9 \pm 0.4$  ( $p < 0.05$ ).

Of three indices evaluated, in normal controls the greatest heterogeneity of data was seen with LV apical twist (SD 43% of mean) and the least with GLS (SD 8% of mean, see Table 2). GLS was therefore chosen as a primary basis for comparison between groups. On this basis, a study of the size of the current investigation had approximately 80% power to detect  $> 2\%$  difference in GLS values between recovering TTC patients and controls at  $p < 0.05$ .

The primary comparison related to echocardiographic deformational indices persisting in TTC patients at 3 months, as summarised in Table 2.

All of the parameters evaluated were numerically lower in TTC patients than in control subjects, with inter-group differences ranging from 5 to 18%. However, only the differences in GLS at 3 months were statistically significant ( $p=0.003$ ) (Figure 1).

GLS at 3 months was not significantly correlated with any indices of the acute TTC episode (plasma normetanephrine levels, troponin T, peak NT-proBNP levels, echo-derived

WMSI or extent of myocardial oedema on CMR)<sup>12</sup>. Correlations were also sought between markers of residual inflammation at 3 months and simultaneous GLS. For hs-CRP, there was no significant correlation; however residual NT-proBNP levels were directly correlated with GLS ( $r = 0.4$ ,  $p = 0.03$ ; Figure 2). No clinical or biochemical correlates were found to predict extent of improvement in GLS over 3 months.

There was also a significant correlation between SF36-PCS and GLS at 3 months ( $r = -0.41$ ,  $p = 0.04$ ; Figure 3).

## **Discussion**

The findings of the current investigation reveal that subtle but clinically relevant, impairment of LV systolic function, as measured by GLS, persists 3 months after an acute episode of TTC, despite normalisation of LVEF and of most other echocardiographic indices. The extent of impairment of GLS in individual patients was directly correlated with that of quality of life, as measured from SF36-PCS domain. Furthermore, there was a significant correlation in individual patients between extent of residual NT-proBNP elevation and that of GLS impairment. These data therefore add to previous evidence that cardiac recovery from TTC is substantially slower than was appreciated by original investigations, and provide the first evidence that residual symptoms in TTC reflect continued disease activity.

Although initially regarded as a relatively rare disorder of little prognostic importance, TTC is emerging as a relatively common cause of cardiac disability in aging women<sup>3,4</sup>. In spite of occasional mortality, especially due to early development of cardiogenic shock, the majority of patients appear to be at little risk of cardiac events (other than recurrence of TTC) thereafter. However, a consistent observation in large series has been of ongoing symptomatic status<sup>17</sup>; the issue is whether this reflects associated depressive status of many patients or whether it results from continued impairment of cardiac function.

There are several pieces of evidence that the slow resolution of symptoms after acute TTC episodes is not purely of psychosomatic origin. For example, we have previously demonstrated that 3 months post-acute episodes, plasma levels of BNP and NT-proBNP

remain elevated above population norms<sup>13</sup>. Furthermore, quantitation of myocardial oedema via T2-weighted CMR imaging reveals the presence of slowly resolving global changes, with persistent oedema at 3 months<sup>12</sup>. We have recently demonstrated myocardial energetic impairment both during the acute phase of TTC and persistent for at least 4 months thereafter<sup>18</sup>: this may indicate that energetic impairment parallels with myocardial inflammation. As BNP/NT-proBNP release appear to be inflammatory activation (rather than distensive) in origin<sup>13</sup>, the correlation between NT-proBNP and GLS at 3 months suggests that residual inflammation may contribute to this subtle impairment.

The finding that impairment of GLS at 3 months in individual patients correlates with that of SF36-PCS is of great importance. It can be argued on this basis that (1) continued impairment of quality of life long after acute TTC episodes represents (at least predominantly) the impact of ongoing myocardial dysfunction rather than purely emotional “strain” and (2) that the extent of impairment of GLS at 3 months is not purely an academic finding, but one of considerable clinical importance. Indeed, these data provide a basis for attempting to identify prospectively which TTC patients are likely to suffer ongoing impairment of LV function, as currently measured, and whether such impairment is potentially permanent.

The main conceptual limitation of the current study is that evaluation of the residual echocardiographic changes has been performed only at rest, under which conditions the abnormalities appear minor. On the other hand, most residual symptoms in this cohort of patients were of lassitude and exertional dyspnoea. Given the recent data show that TTC is associated with prolonged impairment of myocardial energetics<sup>18</sup>, it is certainly possible that contractile dysfunction may be accentuated during exercise. Furthermore, hypertension was marginally more common among TTC patients than controls, which could contribute to GLS differences.

To date, therapeutic interventions in TTC have been nonspecific and generally transient: for example the use of early anticoagulation to prevent LV mural thrombosis. The



current findings argue for the development of strategies to accelerate recovery of LV function post TTC, and therefore ultimately for better understanding of the pathogenesis of this extraordinary condition.

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***Legends for figures:***

Figure 1: Time course of recovery of LV function, expressed in terms of mean absolute values (left hand site) and as percentage of control group-derived normal values (right hand side), for global longitudinal strain (A and B), longitudinal strain rate (C and D), and apical twist (E and F).

Figure 2: Relationship between global longitudinal strain at 3 months and simultaneous NT-proBNP concentrations ( $r = 0.4$ ,  $p = 0.03$ ).

Figure 3: Relationship between residual global longitudinal strain and SF36-PCS at  $\geq 3$  months ( $r = -0.41$ ,  $p = 0.04$ ).