Tako-Tsubo (Stress) Cardiomyopathy: Pathophysiology and Natural History.

By

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Abstract

Introduction. Tako-Tsubo cardiomyopathy (TTC), also known as apical ballooning syndrome, is a recently described form of acute cardiac dysfunction of uncertain pathogenesis, which occurs with greatest frequency among post-menopausal women. Presentation generally mimics that of an acute myocardial infarction (AMI) but is independent of the presence of fixed coronary artery disease and is classically preceded by severe stress. While patients with TTC with ST elevation are typically diagnosed at emergent cardiac catheterization, the majority does not exhibit initial ST elevation. It is not known whether TTC can be reliably distinguished for AMI non-invasively on the basis of clinical and laboratory tests. Although there is considerable uncertainty about the pathogenesis of TTC, pronounced catecholamine release and an acute inflammatory process are implicated. Systolic dysfunction most commonly affects the apex of the left ventricle and has generally been considered self-limiting and fully reversible. Although obvious hypokinesis resolves and left ventricular ejection fraction tends to return to normal, data that challenge this view include abnormal elevation of natriuretic peptide concentrations, 3 months from the index event, together with the late persistence of some inflammatory cells on LV biopsy.

Methods. In three experimental chapters, this thesis examines aspects of (a) diagnosis (b) pathogenesis and (c) recovery, in a cohort of 125 TTC patients (mean age 67 years; 95% female). As regards diagnosis, it was hypothesized that an arbitrarily derived 'TTC score', incorporating NT-proBNP levels, might facilitate early differentiation from a cohort of females with AMI (n = 56; mean age 70 years). The primary comparison was based on data available at 24 hours post-admission. In a subset of 49 TTC patients, acute multisequential

cardiac magnetic resonance imaging was performed and repeated at 3 months. Pathogenetic investigations:- Extent of oedema was quantified both regionally and globally from T_2 weighted images, with comparison to data from 10 age-matched female controls. Correlations were sought between oedema and the extent of hypokinesis, catecholamine release, N-terminal proBNP release and markers of systemic inflammatory activation. Functional recovery was assessed via 2D speckle-tracking echocardiography (n = 36) and 15 patients, ≥1 year from their index TTC admission, underwent T_1 mapping via CMR in order to address the question of whether residual fibrosis is present after TTC.

Results.

A. Diagnosis: TTC scores were significantly different (TTC group median was 4, vs. 2 in the ACS group; $P < 0.0001$). Receiver operator curve analysis demonstrated an area under the curve (AUC) of 0.74 ($P < 0.0001$), with 62% sensitivity and 75% specificity for a score ≥4; when stressor exposure was scored in both groups, AUC was 0.89 ($P<0.0001$), with 78% sensitivity and 82% specificity (TTC score ≥4). The TTC score separated groups when haemodynamic compromise was absent (AUC 0.80, $P<0.0001$), but not when hypotension or heart failure were evident (P = NS).

B. Pathogenesis: In the acute phase of TTC, T_2-weighted signal intensity was greater at the apex than at the base ($P < 0.0001$) but was nevertheless significantly elevated at the base ($P < 0.0001$), relative to control values; over three months, T_2-weighted signal decreased substantially but remained abnormally elevated ($P = 0.02$). Regional extent of edema correlated inversely with radial myocardial strain. There were also direct correlations between global T_2-weighted signal and plasma normetanephrine ($r=0.33$, $p=0.028$), peak NT-proBNP ($r=0.40$, $p=0.0045$), C-reactive protein ($r=0.34$, $p=0.023$) and troponin T release ($r=0.29$, $p=0.045$).

C. Recovery: Patients exhibited lower global longitudinal strain than controls [mean 17.9 ± 3.1 (SD)%, versus 20.3 ± 1.6; $P = 0.0057$], but did not differ significantly from controls in values of apical twist. Three month global longitudinal strain correlated with the extent of residual NT-pro-BNP elevation ($r=0.38$, $P=0.027$), but did not correlate with markers of the acute severity of the TTC attack. Finally, patients with a remote history of TTC,

demonstrated significant intramyocardial fibrosis (V_e = 0.24), versus controls (V_e = 0.21, P = 0.013), but extent of which was not correlated with global longitudinal strain.

Conclusions. (1) The TTC score, while not of itself diagnostic, may facilitate the differentiation of TTC in patients with presumed ACS, but with diminished efficacy in the presence of haemodynamic compromise. (2) TTC is associated with slowly resolving global myocardial edema, the acute extent of which is correlated with regional contractile disturbance and acute release of both catecholamines and NT-proBNP. (3) Imaging data after TTC indicate that, at 3 months, recovery is substantial, but not complete; at ≥1 year there is evidence of diffuse interstitial myocardial fibrosis. Further efforts to expedite diagnosis, delineate pathogenesis and evaluate residual disability may assist in the development of appropriate treatment regimens.

Declaration

This thesis is the result of my own investigation, except where otherwise stated. It contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signed:

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Christopher J. A. Neil, 17th December 2012

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My colleagues, Dr Thanh Ha Nguyen, Dr Yuliy Chirkov, Ms Jeanette Stansborough and Ms Angela Kucia have all been of great assistance in the TTC project, with both intellectual contributions as well as involvement in the day-to-day work of the study.

This thesis relied heavily on cardiac imaging personnel: in this regard, notable thanks goes to Ms Sue Collings, Mr David Lockyer, Ms Kerry Williams, Ms Tharshy Pasupathy, Mr Matthew Chapman, Mr Brett Stocker, Dr Betty Raman, Dr Devan Mahadevan, Professor John Beltrame and Dr Ewan Choo.

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Finally, I would like to thank my wife, Sally, and children, Ella, Jonah, Daisy and Shiloah, for their support, patience and understanding.

Statement of contribution to research

The studies were conceived and designed jointly by Professor Horowitz and myself.

Execution

I performed all the recruitment and organization of patients into the studies, with the assistance of Ms Jeanette Stansborough (research nurse). I collected all clinical data, also with assistance from Ms Stansborough. I performed echocardiographic studies and cardiac magnetic resonance scans at The Queen Elizabeth Hospital. Dr Yuliy Chirkov performed the platelet aggregometry studies. Metanephrine assays were performed by Dr Malcolm Whiting at SA Pathology, Adelaide. Collagen biomarker assays was performed by Dr Michael Metz at ClinPath, Adelaide.

Analysis

All data were collated and analyzed by myself. Inter-observer analyses were performed with Dr Thanh Ha Nguyen, Mr Matthew Chapman and Ms Tharshy Pasupathy.

List of published studies

This thesis is based in part on the following original studies, which exist in published form:

1. Nguyen TH, Neil CJ, Sverdlov AL, et al. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. The American Journal of Cardiology 2011, 108, 1316-1321.

2. Neil CJ, Nguyen TH, Sverdlov AL, et al. Can we make sense of takotsubo cardiomyopathy? An update on pathogenesis, diagnosis and natural history. Expert Rev Cardiovasc Ther 2012, 10, 215-221.

3. Neil CJ, Nguyen TH, Kucia A, et al. Slowly resolving global myocardial inflammation/oedema in Tako-Tsubo cardiomyopathy: evidence from T_2-weighted cardiac MRI. Heart 2012, 98, 1278-1284.

4. Neil CJ, Chong CR, Nguyen TH, Horowitz JD: Occurrence of Tako-Tsubo cardiomyopathy in association with ingestion of serotonin/noradrenaline reuptake inhibitors. Heart, Lung & Circulation 2012, 21, 203-205.

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List of abbreviations used

MI	Myocardial Infarction
STEMI	ST-Elevation Myocardial Infarction
NSTEMI	Non-ST-Elevation Myocardial Infarction
TTC	Tako-Tsubo Cardiomyopathy
ACS	Acute Coronary Syndrome
LV	Left Ventricle
CAD	Coronary Artery Disease
TIA	Transient Ischaemic Attacks
ANP	Atrial Natriuretic Peptide
BNP; NT-proBNP	B-Type Natriuretic Peptide; Amino-Terminal Prohormone Of BNP
ET-1	Endothelin 1
NPR-C	Natriuretic Peptide Receptor C
cGMP	Cyclic Guanosine Monophosphate
AR; βAR	Adrenoceptor; Beta-Adrenoceptor
SR	Sarcoplasmic Reticulum
SERCA	Sarco(Endo)Plasmic Reticulum Calcium ATPase
NET	Norepinephrine Transporter
COMT	Catecholamine O-Methyl Transferase
MAO	Monoamine Oxidase
VMA	Vanillylmandelic Acid
HPLC	High Performance Liquid Chromatography
LVEF	Left Ventricular Ejection Fraction
WMSI	Wall Motion Score Index
PCWP	Pulmonary Capillary Wedge Pressure
LGE	Late Gadolinium Enhancement
CMR; CE-CMR	Cardiovascular Magnetic Resonance; Contrast-Enhanced CMR
SPECT	Single Photon Emission Computed Tomography
SNT	Sympathetic Nerve Terminal
LVOT	Left Ventricular Outflow Tract
LAD	Left Anterior Descending
PDA	Posterior Descending Artery
NOS	Nitric Oxide Synthase
Pl3K	Phosphoinositide 3-Kinase
PKB	Protein Kinase B
PARP	Poly-ADP Ribose Polymerase
GRK5	G Protein-Coupled Receptor Kinase 5
LPS	Lipopolysaccharide
TNF-α	Tumour Necrosis Factor Alpha
IL	Interleukin
SPAIR	SPectral Attenuated Inversion Recovery
SENSE	SENSitivity Encoding
T_2-W SI	T_2-Weighed Signal Intensity
2DS	2D-speckle tracking
V_e	Extracellular volume