Implications of catecholamine-related pathophysiology in cardiomyopathy

Thanh Ha Nguyen

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Department of Cardiology

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Abstract

Although secretion of catecholamines is critical to cardiovascular homeostasis, there is ample evidence that prolonged or marked catecholamine release may engender cardiovascular dysfunction, both in the short and long term. The processes involved include induction of oxidative stress and of inflammation, and the consequences include cell death (apoptosis), resultant fibrosis and both temporary and permanent contractile dysfunction of the heart. Congestive heart failure, both acute and chronic, represents a condition in which catecholamine effects are ultimately deleterious, and indeed many treatments of heart failure target this anomaly.

The subject of this thesis is an examination of two particular aspects of catecholamine-related cardiovascular pathophysiology. The first issue examined is the phenomenon of (autonomic) cardiac denervation, a process which occurs extensively in CHF and leads, via impaired catecholamine re-uptake, to increased tissue exposure to catecholamines. The second is Tako-tsubo cardiomyopathy (TTC), a form of "stress-induced" cardiomyopathy occurring predominantly in post-menopausal women, and apparently precipitated at least in part by bursts of catecholamine hypersecretion.

The study of CHF utilised the technique of ^{123}I-MIBG imaging to quantitate cardiac denervation. The implications of the extent of denervation on (a) evolution of LV dysfunction and (b) late arrhythmogenesis were examined in a cohort of 45 patients. The data showed no significant association between extent of denervation and either of these endpoints. The results therefore cast into question the potential utility of such technique as a means of prognostication and therapeutic decision-making in patients with CHF.

The studies concerning TTC have two major components:

(a) an examination of the release of natriuretic peptides in association with TTC, and the potential for this release to be of diagnostic utility in the disease.

and (b) an evaluation of nitric oxide (NO) signalling in the acute and recovery phase of TTC.

Studies with brain natriuretic peptide (BNP) and its inactive co-product, N-terminal proBNP (NT-proBNP), revealed that plasma levels were markedly elevated in TTC, that extent of elevation correlated both with catecholamine markers and with severity of the individual attack, and the levels remained elevated for at least 3 months. Furthermore, comparison with a cohort of age-matched females who presented with acute myocardial infarction (AMI) suggested that NT-proBNP levels might form part of a diagnostic algorithm to separate TTC from AMI.

Studies with NO signalling were initiated in the expectancy that this would be impaired in TTC. However, it was found that there was "paradoxical" accentuation of NO effects and of biochemical determinants of NO formation in TTC. Despite the apparently paradoxical nature of these findings, it is proposed that the adverse impact of catecholamines on the heart in TTC might be potentiated by products of the NO signalling cascade.

In summary, these studies provide new insights into mechanisms of catecholamine toxicity on the heart, and hint at relationships between catecholamines, natriuretic peptides, and NO as complex modulation of both injury and recovery. On the other hand, the CHF studies suggest that extensive treatment with agents such as angiotensin converting enzyme inhibitors (ACEI) and β-adrenoceptor antagonists may blunt cardiac toxicity of catecholamines.

Signed Statement

I, Thanh Ha Nguyen, certify that this work 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.

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Published works in whole or in part contained within this thesis

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Dedication

This work is dedicated to my husband Trung and to my children, Giang and Hieu. Now I will have more time for you.

List of Abbreviations

- ADMA – Asymmetric DiMethylArginine
- ANP – Atrial Natriuretic Peptide
- AC – Adenylyl Cyclase
- ACEI – Angiotensin Converting Enzyme Inhibitors
- AICD – Automated Implantable Cardio-Defibrillator
- APO – Acute Pulmonary Oedema
- ARBs – Angiotensin Receptor Blockers
- ARDS – Adult Respiratory Distress Syndrome
- AT1 – Angiotensin Receptor Type 1
- AT2 – Angiotensin Receptor Type 2
- ATP – Adenosin Triphospate
- BH4 – tetraHydroBiopterin
- BMI – Body Mass Index
- BNP – Brain-type Natriuretic Peptide
- BP – Blood Pressure
- BRS – Baroreceptor Sensitivity

- CAD – Coronary Artery Disease
- cAMP – Cyclic Adenosine Monophosphate
- ^{11}C-HED – ^{11}C-hydroxyephedrine
- CHF – Chronic Heart Failure
- cGMP – Cyclic Guanosine Monophosphate
- CK – Creatine Kinase
- CMR – Cardiovascular Magnetic Resonance
- CNP – C-type Natriuretic Peptide
- COMT – Catechol-Ortho-Methyl Transferease
- CRP – C-Reactive Protein
- CRT – Cardiac Resynchronisation Therapy
- DDAH – Dimethylarginine DimethylAminoHydrolase
- DCM – Dilated Cardiomyopathy
- DE-MRI – Delayed-enhancement Magnetic Resonance Imaging
- DHPG – DiHydroxyPhenylGlycine
- DM – Diabetes Mellitus
- MR – Mineralocorticoid Receptor
- MRB – Mineralocorticoid Receptor Blockers
- ECG – Electrocardiography
- ECTB – Emory Cardiac Toolbox
- ED – Emergency Departments

- eGFR – estimated Glomerular Filtration Rate
- eNEP – Ectoenzyme Neutral EndoPeptidase
- eNOS – endothelial Nitric Oxide Synthase
- EP – Electrophysiological
- ET1 – Endothelin-1
- GC – Guanylyl Cyclase
- Gi – inhibitory G-protein
- Gs – stimulatory G-protein
- GTP – Guanosine Triphosphate
- HMR – Heart to Mediastinum Ratio
- HR – Heart Rate
- HRT – Heart Rate Turbulence
- HRV – Heart Rate Variability
- hs-CRP – high sensitivity C-Reactive Protein
- HT – Hypertension
- iNOS – inducible Nitric Oxide Synthase
- LAD – Left Anterior Descending Coronary Artery
- LBBB – Left Bundle Branch Block
- LV – Left Ventricular
- LVDd – Left Ventricular Diastolic Dimension
- LVDd – Left Ventricular Systolic Dimension

- LVEF – Left Ventricular Ejection Fraction
- MAO – MonoAmine Oxidase
- MI – Myocardial Infarction
- ^{123}I-MIBG – ^{123}I-metaiodobenzylguanidine
- MPI – Myocardial Perfusion Imaging
- MSNA – Muscle Sympathetic Nervous Activity
- MRI – Magnetic Resonance Imaging
- NET – Noradrenaline Transporter
- NGF – Nerve Growth Factor
- nNOS – neuronal Nitric Oxide Synthase
- NO – Nitric Oxide
- NOS – Nitric Oxide Synthase
- NSTEMI – Non-ST Elevation Myocardial Infarction
- NSVT – Non-sustained Ventricular Tachyarrhythmia
- NT-proBNP – N-terminal proBNP
- NYHA – New York Heart Association
- PARP – Poly(ADP-ribose) Polymerase
- PCWP – Pulmonary Capillary Wedge Pressure
- PET – Positron Emission Tomography
- PKA – Protein Kinase A
- PKG – Protein Kinase G

- RAAS − Renin Angiotensin Aldosterone System
- RCA − Right Coronary Artery
- ROS − Reactive Oxygen Species
- SAECG − Signal-averaged ECG
- SCD − Sudden Cardiac Death
- sGC − soluble Guanylate Cyclase
- SPECT − Single Photon Emission Computed Tomography
- STEMI − ST Elevation Myocardial Infarction
- 4D-MSPECT − 4 Dimensional Single photon Emission Computed Tomography
- Tc − Technetium
- Tl − Thallium
- TTC − Tako-Tsubo Cardiomyopathy
- VASP − Vasodilator-Stimulated Phosphoprotein
- VF − Ventricular Fibrillation
- VT − Ventricular Tachyarrhythmia
- WMSI − Wall Motion Score Index
- WR − Wash-out Rate