Stress-Induced (Tako-Tsubo) Cardiomyopathy

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TTC: How much do we know?

• Epidemiology:
  Most common in ageing (postmenopausal) women. Often after physical/emotional stress

• Clinical features:
  (1) Presentation with chest pain/dyspnoea
  (2) Often severely hypotensive (but clear lungs)
  (3) “Multi-regional” S-T elevation or T inversion
  (4) Regional wall motion anomalies, especially periapical
Takotsubo: Background

• First described by Japanese in 1990
  – not widely investigated at the time
  – Plaque rupture/thrombosis theory relatively new
    • more interested in developing thrombolysis and PTCA

• Shape of Japanese octopus trap
SO: Can we make the diagnosis clinically?

- 63-year old woman comes home to find her husband dead
- Develops severe chest pain
- Hospital admission: anterior S-T elevation
- Thrombolysis: S-T resolution
- Subsequent cardiac catheterisation: normal coronaries: periapical hypokinesis
Shock/Arrhythmias early in TTC

- Approximately 20% severely hypotensive at admission: best treatment uncertain
- Outflow tract obstruction and mitral regurgitation MAY contribute, but probably multifactorial
- Pre-hospital arrhythmia rate uncertain, but about 5% develop torsades post admission
TTC: the catheteriser’s view
Diagnosing TTC: “Multiregional” changes
Are there useful biomarkers?

• Troponin/CK elevation usually minor

• Moderate elevation of CRP

• Dramatic elevation of BNP/NT-proBNP at 24 hours

• Marked elevation of catecholamines
Catecholamines and systemic inflammation in TTC

Nguyen et al, Am J Cardiol, 2011
Takotsubo Cardiomyopathy presenting as S-T elevation myocardial infarction
Apical ballooning in TTC
TTC as Pan-carditis
Regional T2 quantitation (Neil et al, 2012)
Catecholamine surges:- Pivotal to onset of TTC?

- Documented in phaeochromocytoma, dobutamine stress imaging, treatment of anaphylaxis
- Catecholamine levels usually but not always markedly elevated
- Probable association with tricyclic and SNRA antidepressant therapy
Beta-2 adrenoceptors and TTC

- In rats, adrenaline induced TTC-like changes via beta-2 stimulation
- This is both negatively inotropic and cardioprotective in long term
- Levosimendan appears to “rescue” hearts
- Beta-2 stimulation also increases ROS production, via NAD(P)H oxidase
Beta-2 adrenoceptors and ROS

(A) NTG vs. TG images showing increased ROS fluorescence in TG samples.

(B) Comparison of NADPH oxidase activity and superoxide production (ESR) between NTG and TG groups.

(C) Fold change in NADPH oxidase activity with a significant increase in TG samples.

(D) NOX2 and NOX4 expression levels showing increased expression in TG samples compared to NTG at 5-month and 15-month time points.
Recovery from TTC

• LVEF is usually normal within 2 weeks
• However, most patients remain symptomatic for at least 3 months
• This reflects slow resolution of myocardial inflammation (and perhaps some permanent fibrosis)
• Recurrence rate approximately 3% per annum
Evidence for slow resolution of TTC myocarditis

• On CMR, T2 score remains abnormal

• Global longitudinal strain remains depressed (about 10%)

• Persistent elevation of BNP and CRP
BNP/NT-proBNP
pro BNP elevation in TTC

Nguyen et al, Am J Cardiol, 2011
New directions: mechanisms

• Female rats develop TTC-like changes 24 hours after isoprenaline injection

• Addressing:-
  (a)Post-receptor signal transduction, given that beta-2 receptors are coupled to NOS
  (b)Inflammasome activation: role of TxNIP
  (c) Energetics deficiency: P-MRS studies
Current Therapeutics

• Try to avoid catecholamine administration, even if patient shocked: ?levosimendan
  ?IABP

• Beta-blockers seem to be ineffective

• Theoretical case for at least 3 months’ ACE inhibitor therapy
Longer term issues

- Avoid tricyclic antidepressants and venlafaxine
- Explain to patient that condition is relatively benign, but patient should be aware of recurrence risk
- Expect lassitude/dyspnoea for 3 months
- If recurrent, ? phaeochromocytoma
Potential future therapy

• Avoidance of nitrosative stress and its consequences:
  (a) peroxynitrite decomposition
  (b) PARP inhibitors

• TxNIP suppression: ACE inhibitors, metformin
Who did the work?

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