Takotsubo Cardiomyopathy Associated with the Administration of Intranasal Phenylephrine/Lignocaine for Epistaxis

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We present a case of a 67 year old female with an unusual precipitant for Takotsubo cardiomyopathy, following the administration of a phenylephrine/lignocaine nasal spray for epistaxis.

Takotsubo cardiomyopathy (TTC) was first described in 1990 in a Japanese text as a reversible form of left ventricular dysfunction, followed up by a case series in five patients. Although previously considered rare, over the past two decades there has been a marked rise in the number of publications relating to TTC, with the current estimation being that the condition accounts for over 1% of all cases of acute coronary syndrome presentations. The condition is defined by transient, reversible left ventricular systolic dysfunction with no macrovascular coronary artery disease, as confirmed by coronary angiography. Epidemiologically, post-menopausal women seem to be at highest risk, however the condition has been seen in multiple different patient populations. Although classically described in the setting of acute emotional or physical stress and associated with catecholamine overstimulation, exogenous administration of sympathomimetic agents has been reported to cause stress induced left ventricular dysfunction, particularly when administered intravenously.

A 67 year old lady with a background of hypertension, Raynaud’s phenomenon and gastroparesis requiring PEJ (percutaneous endoscopic jejunostomy) feeding, presented with persistent recurrent epistaxis to the emergency department on a Friday evening. She had previously had episodes of nitrate responsive angina over the past decade, and previous coronary angiography in 2008 had demonstrated no significant lesions, with a diagnosis of presumptive microvascular disease noted in the history. She also had a history of ventricular tachycardia, for which she had been treated with flecainide, with a structurally normal heart on previous echocardiography, and no other significant cardiovascular risk factors.

On this presentation, clinical examination revealed obvious epistaxis from the right nostril, and no cardiac or respiratory abnormality identified. A combination 5% lignocaine/0.5% phenylephrine hydrochloride solution was sprayed three times into the bleeding nostril, and the patient developed central crushing chest pain approximately one minute after administration. Immediate electrocardiogram (ECG) demonstrated sinus rhythm with no significant ischaemic changes. A Rapid Rhino® intranasal splint was deployed and the patient was admitted to the coronary care unit. Sublingual glyceryl trinitrate was administered with good effect. Blood pressure was 142/78, and the oxygen saturations were 100% on room air. The high sensitivity troponin T peaked at 1214 ng/L, and the CK at 642 IU/L (reference range <14 ng/L and <180 IU/L respectively). The patient was planned for coronary angiography on Monday morning, however late Friday evening she developed a recurrence of her chest pain associated with slight elevation of the ST segments in leads I and aVL (Figure 1), and as such, a decision was made for urgent transfer to the cardiac catheterisation laboratory.

Coronary angiography, performed with mild pain present, demonstrated mild irregularities within the right coronary artery with no significant disease within the left system. Left ventriculography revealed a large area of mid to apical hypokinesis with severe systolic dysfunction (Figure 2), with a left ventricular end diastolic pressure of 17mmHg. Medical therapy for left ventricular systolic function was instituted and uptitrated, and flecainide was ceased. Serial ECGs demonstrated progressive widespread T wave inversion across all praecordial leads as well as I and aVL, with no further episodes of pain. A transthoracic echocardiogram was performed 48 hours later, demonstrating a marked improvement in systolic function, with an estimated ejection fraction of 45-50%, and mild to moderate apical hypokinesia without evidence of left ventricular outflow tract obstruction. Follow up transthoracic echocardiography performed six weeks later demonstrated return to normal biventricular systolic function.

Patients with TTC can present in a multitude of ways - angina, atypical chest pain, dyspnoea, arrhythmia, and even syncope. The disease severity ranges from mild through to cardiogenic...
shock, with an in hospital mortality rate of over 4%, although much of this can be attributed to the underlying disease state. Despite the syndrome being more common in females, there is a higher rate of mortality amongst men. As was done in this case, patients should be treated for an acute coronary syndrome until proven otherwise, and coronary angiography is the required element in the diagnosis of the syndrome of TTC.

The pathophysiology of TTC is incompletely understood; a combination of a dramatic sudden rise in endogenous catecholamines and coronary microvascular dysfunction are the primary suspects. In drug related TTC, direct toxicity of exogenous catecholamines has been demonstrated, with the induction of apoptosis in subsets of cells. Furthermore, adrenaline has been associated with coronary vasospasm and stunning of cardiac myocytes. On direct coronary visualisation during the onset of pain, slow flow without obvious vasospasm has been directly visualised previously.

Phenylephrine is a sympathomimetic amine without significant beta adrenergic effects, resulting in hypertension without a resulting increase in cardiac output. As a stimulator of alpha-1 adrenoreceptors, it has a marked effect on the peripheral vasculature, but has no significant effect on coronary vasospasm on direct infusion. It is most commonly used as a decongestant and as a vasoconstrictor, however is also used in epistaxis in combination with lignocaine (known as ‘co-phenylcaine’).

Ocular use of phenylephrine has been associated with cardiac complications, including vasospasm, myocardial infarction, and severe hypertension. Intranasal phenylephrine has been associated with non-Q-wave myocardial infarction in combination with cocaine in a 23 year old female, as well as in a 63 year old female however such cases are rare, and the definition of myocardial infarction is variable – TTC is clinically virtually indistinguishable from myocardial infarction, without invasive angiography.

This case highlights several important characteristics. Firstly, the development of TTC during hospitalisation is uncommon but not entirely unique; it has been reported after anaesthesia, coronary angiography, and relevant to our patient, it has been described after nasal packing. Secondly, our case does share similarities with the generic TTC phenotype, being a post menopausal female with persistent atypical chest pain and ST elevation on the electrocardiogram. Importantly, our patient had a background history of Raynaud’s phenomenon, which has been described to occur in increased frequency in those with TTC, potentially due to predilection toward vasospasm. Furthermore, an association between TTC and treatment with flecainide has also been postulated. Thirdly, the case highlights the importance of the use of topical vasopressors and their association with TTC. Although it is difficult to prove causation, the temporal association between the administration of a vasoactive agent such as phenylephrine and the development of the clinical syndrome suggest an association, and further study is required in this area.

Importantly, agents such as phenylephrine do act as vasoconstrictors, although as previously noted, coronary effects have not been identified. Macrovascular coronary vasospasm is an important differential diagnosis, however the marked ECG and biochemical changes contrast with the rapid improvement and normalisation of ventricular function with no persistent regional wall motion abnormalities.

Takotsubo cardiomyopathy remains a pathophysiological mystery, and the role of endogenous and exogenous catecholamines is still unclear. The treating physician must maintain a high degree of suspicion for the syndrome in patients with a presentation of an acute coronary syndrome after a stressful event or a pharmacological challenge, and proceed to early invasive angiography if there is diagnostic uncertainty.

Declarations of Interest

The author declares no conflicts of interest.
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