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Interpretation of Cardiac Enzymes in Hypertensive Disorders of Pregnancy: Seeking Diagnostic Clarity

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Abstract

A markedly raised cardiac troponin I (cTnI) in a patient is always alarming and usually suggests significant myocardial damage, as seen in acute myocardial infarction. There are, however, other circumstances where raised cTnI may be encountered without overt myocardial necrosis. Prior studies have evaluated serum cTnI levels in preeclampsia, eclampsia and normotensive healthy pregnant women in order to define their diagnostic value. Other factors, such as altered renal function, as in preeclampsia, may also affect the serum troponin levels, leading to misdiagnosis and incorrect management. We highlight the diagnostic and management difficulties faced in the management of our patient who presented with raised cTnI following multiple eclamptic fits, without other signs of an acute cardiac event.

Keywords: Troponin I; Preeclampsia; Eclampsia; Gestational hypertension; Pregnancy; Cardiac enzymes; Diagnosis; Myocardial infarction

Introduction

Significantly elevated plasma cardiac troponins (cTns) in a patient are always alarming and a cause for great concern, as they underpin significant myocardial injury. Acute coronary syndrome (ACS) in a woman of reproductive age is rare. However, the incidence of acute coronary events during the peripartum period is rising, probably on account of increased maternal age, unhealthy lifestyles like smoking and obesity, with an increase in comorbidities like diabetes, hypertension and renal disease. Prior studies have investigated how cTn may be increased in uncomplicated pregnancies and in hypertensive disorders of pregnancy without any overt myocardial necrosis or dysfunction, but clarity in how these results may be interpreted for diagnosis and treatment in acutely unwell pregnant patients is lacking. We describe here a case of a parturient with a significantly raised cardiac troponin I (cTnI) in the peripartum period following eclamptic seizures and discuss how abnormal cardiac enzymes may be interpreted to establish a diagnosis and guide management in the acutely unwell peripartum patient.

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Case Report

Our patient, a 28-year-old primigravida woman of 32 weeks' gestation, presented with a history of three grand-mal seizures witnessed by her husband at home. She was admitted to a nearby hospital with Glasgow coma scale scores of 3 - 6. A diagnosis of eclampsia was made, and magnesium sulphate was administered, 4 g intravenously as a loading dose, followed by 1 g/h by infusion. Blood pressure was high, ranging from 101 - 198 to 68 - 133 mm Hg and this was treated with intermittent bolus doses of intravenous labetalol. She was kept sedated and ventilated for transfer to our hospital for airway protection.

Her past medical history was not significant. At 31 weeks' gestation, she had presented with vaginal bleeding and blurring of vision. Her blood pressure was also raised at 160/90 mm Hg, suggestive of preeclampsia. She was admitted for observation. Her investigations had revealed raised serum uric acid, ranging from 378 to 430 µmol/L, but the full blood count and liver and renal function tests were within normal limits. The urine protein to creatinine ratio was calculated to be 1.2. An abdominal ultrasound scan established that the placenta was not low lying and that fetal growth was normal. No obvious cause for her vaginal bleeding was identified. She was prescribed methyldopa, 250 mg TDS, to manage the blood pressure. Two doses of dexamethasone were also administered to stimulate fetal lung maturity, should delivery be required. Six days later, she was discharged from the hospital as her symptoms had resolved and her blood pressure was controlled. However, 2 days after her discharge, she presented with seizures.

On arrival at our hospital, she was now more conscious, with a blood pressure of 150/90 mm Hg. She was directly transferred to the operating theater for an emergency cesarean section under general anesthesia. The operation was uneventful, and a live baby girl was delivered. The patient was kept sedated and ventilated following surgery and transferred to the ICU. A non-contrast brain computed tomography scan

was performed to exclude intracranial pathology and it showed mild hypodensities in the left and right parieto-occipital regions consistent with eclampsia, but was otherwise normal. As her lungs were clear, sedation was stopped and she was allowed to wake up and was extubated uneventfully. Magnesium was continued postoperatively for 48 h since blurring of vision had persisted.

Whilst she was clinically well in ICU, a routine electrocardiogram (ECG) showed changes suggestive of anteroseptal ischemia, prompting serial measurements of cardiac enzymes, which were found to be elevated. The cTnI peaked on admission at 2,518 ng/L (high sensitivity assay; reference value ≤ 16 ng/L), declining to 205 ng/L after 48 h. Creatine kinase (CK) was 307 U/L (reference values 30 - 160 U/L), peaking at 579 U/L after 24 h and declining to 540 U/L by 48 h. CK-MB was was 15.9 ng/mL (reference value ≤ 3.4 ng/mL), declining to 4.8 ng/mL after 48 h. Her uric acid declined to 351 µmol/L at discharge from a peak of 503 µmol/L. Her other blood investigations remained unremarkable. A bedside transthoracic echocardiogram (ECHO) appeared normal.

After discharge from hospital, she was referred to a cardiologist as an outpatient. A repeat ECHO performed 2 months later was also normal, with an estimated left ventricular ejection fraction (EF) of 62% and no further follow-up was planned.

Discussion

CTns are regulatory proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consists of three subunits: troponin T (cTnT), troponin I, and troponin C. The skeletal and cardiac isoforms of troponins are immunologically distinct, allowing their detection by monoclonal antibody-based immunoassays. Although false positive results are possible in such assays, both cTnT and cTnI are highly sensitive and specific markers of myocardial damage and have become established as the gold standard for biochemical identification of myocardial necrosis. Typically, depending on the degree of cellular damage, cTns appear in the plasma 4 - 6 h after the insult and may persist for 10 - 14 days [1]. A rise and/or fall in their concentration, with at least one value being above the 99th percentile, in association with other clinical or investigational features suggestive of myocardial ischemia, is now required for the diagnosis of an acute myocardial infarction (AMI) [2, 3].

The incidence of AMI in women of child bearing age is low. This risk however increases three- to four-fold in pregnancy, and is estimated to be around 6.2 per 100,000 pregnancies [4] with the likelihood of a further increase due to pregnancies occurring later in life with increasing comorbidities. Anterior wall AMI appears to be the most common, occurring in all stages of pregnancy and more likely to be in multigravidas [5].

Measurement of cardiac enzymes in pregnancy and their interpretation is difficult. CK-MB is synthesized in the uterus and placenta and this may be detected in significant amounts in healthy pregnant women, and is therefore a poor marker for diagnosing myocardial damage [6]. CTnI therefore remains the most sensitive and specific marker for myocardial damage in the presence of ischemic or non-ischemic myocardial injury, including during pregnancy [7, 8].

Myocardial injury usually follows an acute coronary event, such as a coronary plaque rupture or vasospasm, and increased cTnI will help establish the diagnosis. However, AMI will need to be differentiated from conditions in which a rise in cTnI exceeding the 99th percentile may also be present but where myocardial necrosis is not evident, as seen in our patient. These include conditions like pulmonary embolism (PE), heart and renal failure, liver cirrhosis, septic shock and arterial hypertension [9]. These may be attributable to subclinical myocardial necrosis - although this has not been confirmed pathologically - and acute or chronic myocardial strain may then cause the increase in cTnI [10].

To non-invasively identify ACS, typical symptoms of chest pain, shortness of breath and diaphoresis, with ECG or ECHO evidence and raised cTnI are required. The clinical signs may however be mimicked by other conditions, such as severe preeclampsia, and some patients develop AMI in the absence of chest pain, especially in diabetes. Our patient had no clinical signs suggestive of ACS despite her increase in cTnI.

Also, in pregnancy, the ECG may be difficult to interpret, due to QRS and T-wave changes that may be normally seen [11]. Our patient's ECG was suggestive of anteroseptal ischemia, for which the cardiac enzyme tests had been performed.

Lastly, elevation of cTnI in hypertensive disorders of pregnancy is well reported, although the cause remains unclear [7, 12-15]. Fleming et al demonstrated five-fold higher values of cTnI in preeclamptic women than in normotensive pregnant women, indicating possible subclinical cardiac myofibrillatory damage. However, these findings are not consistent and could not be corroborated by Pergialiotis et al in their systematic review [16]. These varying results from different studies may be explained if different cTnI cut-off values for significance were used in the analyses by different authors. Also, the relevance of raised cTnI in the peripartum period is uncertain, as is the value of a single, random cTnI measurement for the diagnosis of myocardial damage in hypertensive disorders of pregnancy. Serial measurements are required to identify any acute or chronic insult to the myocardium, to explain the leakage of cTnI. A rapid decline in the cardiac enzymes may suggest minimal myocardial injury and help exclude ACS, as in our case. We are uncertain as to what may cause the cardiac enzyme increase in preeclampsia and eclampsia. However, based on autopsy data, there appears to be a 10-fold prevalence of myocardial contraction band necrosis in preeclampsia cases when compared with deaths in pregnancy from other causes [17]. Cong et al have reported that cardiac remodeling occurs in patients with preeclampsia, and is associated with eccentric myocardial hypertrophy, with reduced EF [18]. Indeed, cTnI values measured during gestational hypertension and preeclampsia show higher values in the latter [7]. But it is also evident that not all patients with preeclampsia demonstrate a significant rise in cTnI or whether cTnI levels increase during the course of the disease and are affected by the increasing severity of the disease [16, 19]. Perhaps other pathologies related to severe preeclampsia may help to explain these findings. Aboutaleb

Beigi et al observed that differences in the occurrence of an abnormal cTnI test were significant only in patients with severe preeclampsia [20].

Our patient's serial ECGs showed borderline left-axis deviation, prolonged QTc and T-wave inversion in the anteroseptal leads, accompanied by a significantly increased cTnI, both being highly suggestive of a cardiac event. In our practice, troponins are not routinely performed in patients with preeclampsia. However, patients admitted to the ICU with respiratory signs such as shortness of breath or pulmonary crepitations usually undergo serial cTnI tests to exclude acute cardiac events, as was done in this case. Patients with severe hypertensive disorders of pregnancy are at risk of strokes, AMI, heart and renal dysfunction. The interpretation of cTnI for diagnosis and treatment becomes more difficult under the circumstances. As stated earlier, not all patients with raised troponins show myocardial necrosis as seen in AMI, especially in conditions like PE, septic-shock, liver cirrhosis, arterial hypertension and heart or renal failure. There is however a commonality in these conditions, with evidence of acute or chronic changes in myocardial contractility occurring consequent to the disease, acute myocardial strain possibly leading to increased cTnI. A surge in endogenous vasopressor substances like renin, epinephrine or nor-epinephrine occurs at the time of an eclamptic fit, strokes, PE or sustained arteriolar hypertension, and can lead to acute heart failure. Although the pathogenesis of this is poorly understood, there may short-lived subendocardial ischemia and tissue hypoxia due to coronary and systemic hypoperfusion and ventilation-perfusion mismatch, releasing free cytosolic cTnI from transient membrane leakage [21]. Myocardial necrosis does not necessarily follow these events and the myocardium makes complete recovery.

Respiratory signs like shortness of breath at rest and pulmonary crepitations, with a raised cTnI, make the exclusion of AMI even more difficult. Our patient remained tachypnoeic, with persistent pulmonary crepitations after delivery. Many peripartum conditions can mimic an AMI occurring with or without heart failure. In severe preeclampsia or eclampsia, acute heart failure with pulmonary edema can develop rapidly. Cardiomyopathy of pregnancy often presents as pulmonary edema, as do thromboembolic complications of pregnancy. Renal dysfunction seen in severe preeclampsia or eclampsia may lead to fluid overload and pulmonary edema and cause sustained elevations of plasma cTnI levels by delaying excretion. Additionally, cTns are raised in end-stage renal disease and results should be interpreted accordingly [22]. On the other hand, patients with a chest infection in preeclampsia may be treated for pulmonary edema and deteriorate into severe sepsis if timely antibiotics are not administered. In our patient, the respiratory signs were fortunately absent.

A delayed or incorrect diagnosis leads to unnecessary investigations, specialist referrals and incorrect treatment, possibly with poorer outcomes in the sicker patients. Despite the difficulty with interpretation in pregnancy and related disorders, cTnI remains the most sensitive investigation for the diagnosis of acute myocardial injury. The diagnostic and prognostic validity of cTns has been demonstrated in many studies and a higher risk of death with elevated troponins is well substantiated [23]. Serial testing, with demonstration of a low peak and a rapidly declining trend may help to exclude ACS, since its management would require early specialist intervention, including the consideration of thrombolysis or percutaneous coronary intervention, both of which may not always be feasible in a pregnant patient awaiting delivery. We also recommend that a 2D echocardiogram should also be performed in cases of elevated cTnI as soon as possible, to confirm or dispute significant myocardial damage, and this should guide further treatment. A normal ECHO, despite elevated cTnI, is reassuring and suggests a less significant non-myocardial cause, with better prognosis. B-type natriuretic peptide assays, where available, may also help differentiate between cardiac and pulmonary dyspnea [24]. These patients would also need advice about follow-up and long-term health consequences, as cardiac function may not normalize in all cases, even in the absence of overt myocardial necrosis.

Disclosures

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