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PRE-WORKOUT SUPPLEMENT INDUCED CARDIAC ISCHAEMIA IN A YOUNG FEMALE

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ABSTRACT

The popularity of pre-workout supplements is rising amongst professional athletes and fitness enthusiasts. Despite increased usage, the safety profile of pre-workout supplements is likely to be not well understood. Additionally, many different brands use various undisclosed proprietary blends of active ingredients creating safety regulation difficulties. This lack of oversight could prove unsafe for certain patients. This patient MK is a 33-year-old healthy housewife who presented with central chest tightness, pre-syncope and mild dyspnoea to the emergency department via ambulance. The presentation was in the context of recent strenuous exercise and ingestion of a pre-workout supplement (**Alpha Lean-7**). Most striking in her presentation was a troponin rise of 50 ng/L, while not very high it is unusual given her lack of cardiac risk factors. She had a 3-day uneventful admission with a downtrending troponin prior to discharge. This case highlights the possible dangers of pharmacologically active ingredients in pre-workout supplements.

ARTICLE HISTORY
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KEYWORDS
Pre-workout supplements; cardiac ischaemia; sports nutrition; toxicology

Introduction

Nutrition supplementation is gaining popularity, of particular note is the rising popularity of pre-workout supplements among professional athletes and fitness enthusiasts (Rao et al., 2017). Based on a recent German study, the all-time prevalence of pre-workout supplements is 25.8% in a population of 492 participants across 13 fitness centres (Dreher, Ehlert, Simon, & Neuberger, 2018). A significant prevalence in the usage of pre-workout supplements exists amongst a relatively young population group (Dreher et al., 2018). Despite increased usage, there has been limited literature discussing the safety profile of pre-workout supplements (Harty et al., 2018). Existing literature reporting adverse clinical side effects of pre-workout supplements have been limited to case reports (Cohen, Zeijlon, Nardin, Keizers, & Venhuis, 2015). Examples of serious side effects include haemorrhagic stroke and cardiac arrest when using pre-workout supplements while simultaneously undergoing a physiological stress such as a series of intense physical exercise (Cohen et al., 2015; Karnatovskaia, Leoni, & Freeman, 2015).

These dangerous side effects could be a consequence of the various potentially dangerous pharmacological ingredients found in pre-workout supplements. Examples of stimulants found in pre-workout supplement are DMAA, N,α-DEPEA, DMAE and DMBA (Harty et al., 2018). Complicating the situation is the occurrence of undisclosed proprietary blends of such potentially dangerous pharmacological ingredients (Harty et al., 2018). Therefore, there is a huge discrepancy in levels of pharmacologically active ingredients present between different brands, creating safety regulation difficulties. Another concern is the possibility of the active ingredient interacting with each other, the data in such cases are even more scant and less well understood. This creates safety regulation difficulties and could prove unsafe for certain pharmacologically sensitive patients. However, it is also worth noting that some studies have stated that pre-workout supplements have generally been relatively benign (Joy et al., 2015). But the data is often not extensive enough to cover the various permutations of pre-workout supplements.

Therefore, the situation is most likely that of certain pre-workout supplements with specific blends of pharmacologically active ingredients could produce relatively harmful side effects in pharmacologically sensitive individuals. This case reflects such a situation whereby a pharmacologically sensitive individual experienced significant side effects after consumption of a pre-workout supplement and undergoing intense exercise.

Case report

MK is a 33-year-old healthy housewife who presented with central chest tightness, pre-syncope and mild dysponea to the emergency department via ambulance. Prior to a 5 km coastal run, she ingested a capsule (675 mg) of pre-workout supplements (**Alpha Lean-7**) 1 h prior to her run as per workout supplement instructions and developed symptoms 30 min into the run. This was the first episode of her consuming this particular workout supplement.

This presentation was in the context of recent consumption of regular whey protein pre-workout supplements and intensive gym training over the past month. MK has no medical and family history of cardiovascular and respiratory conditions such as pulmonary embolism, sudden cardiac death and arrhythmias. MK also does not take medications and has no allergies. She has no relevant occupational exposure and substance use history. She did mention that she is exceptionally sensitive to

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caffeine which causes her palpitations and trembling. On examination, MK was slightly tremulous and tachycardic, her vitals, mental status, cardiovascular and respiratory system examinations were otherwise normal.

Suspecting that pre-workout supplements may be associated with the patient's presentation, the list of ingredients and the brand of the supplement was obtained (Table 1). As pre-workout supplements are not as strictly regulated as medications, the exact amount of each ingredient was not declared apart from caffeine. Caffeine comprised 200 mg of each capsule comprising about 30% of the mass in each serving, which is a relatively high amount of caffeine per capsule. The remainder of the ingredients, the company simply states is a proprietary blend and the individual amounts are not declared. Most notable amongst the ingredients possibly responsible for the presentation were caffeine, theophylline, alpha yohimbine, isopropylnorsynephrine, N,N-Dimethylphenethylamine and dimethylethanolamine. They possess sympathomimetic effects and could be detrimental to stimulant sensitive patients. Hypothetically, the stimulants could act synergistically in the patient (Haller, Jacob III, & Benowitz, 2004). This situation could be further aggravated by her simultaneous strenuous exercise, causing a catecholamine surge and subsequent cardiac ischaemia (Paratz, Cunningham, & MacIsaac, 2016). Specific urine toxicology screen was negative for stimulants such as amphetamines, cocaine, phencyclidine, marijuana and opioids.

Table 1. List of ingredients found in the **Alpha Lean-7** supplement.

Alpha Lean-7 Supplement:
Serving size: 1 capsule (675 mg)
Servings per container: 90 capsules
Ingredients: (The amount of each ingredient per capsule was not declared by the manufacturers)
Caffeine Anhydrous (200mg)
Taraxacum Officinate(Dandelion Powder)
Dimethylethanolamine bitartrate
Theophyline Anhydrous (Natural)
N,N-phenyl-dimethylamine (Eria Jarensis extract)
Isopropylnorsynephrine
Betaine anhydrous (Trimethylglycine)
Catechins (50% Green tea extract)
Ketosteroids (5% Cissus Quadrangularis)
L-carnitine
Alpha Yohimbine (90% Rauwolfia vomitoria Root Extract)

Investigations were ordered to rule out occult life-threatening conditions. Serial ECGs were performed, the initial ECG showed sinus rhythm but also had evidence of ischaemia, borderline ST changes in the anterolateral leads (black arrow), borderline right axis deviation (green arrows) and a wandering ECG trace (blue arrows) which may be due to the patient's tremor (Figure 1). A repeat ECG was performed about 2 h later which revealed sinus rhythm and did not display any other worrying findings (Figure 2). Interestingly, troponins and

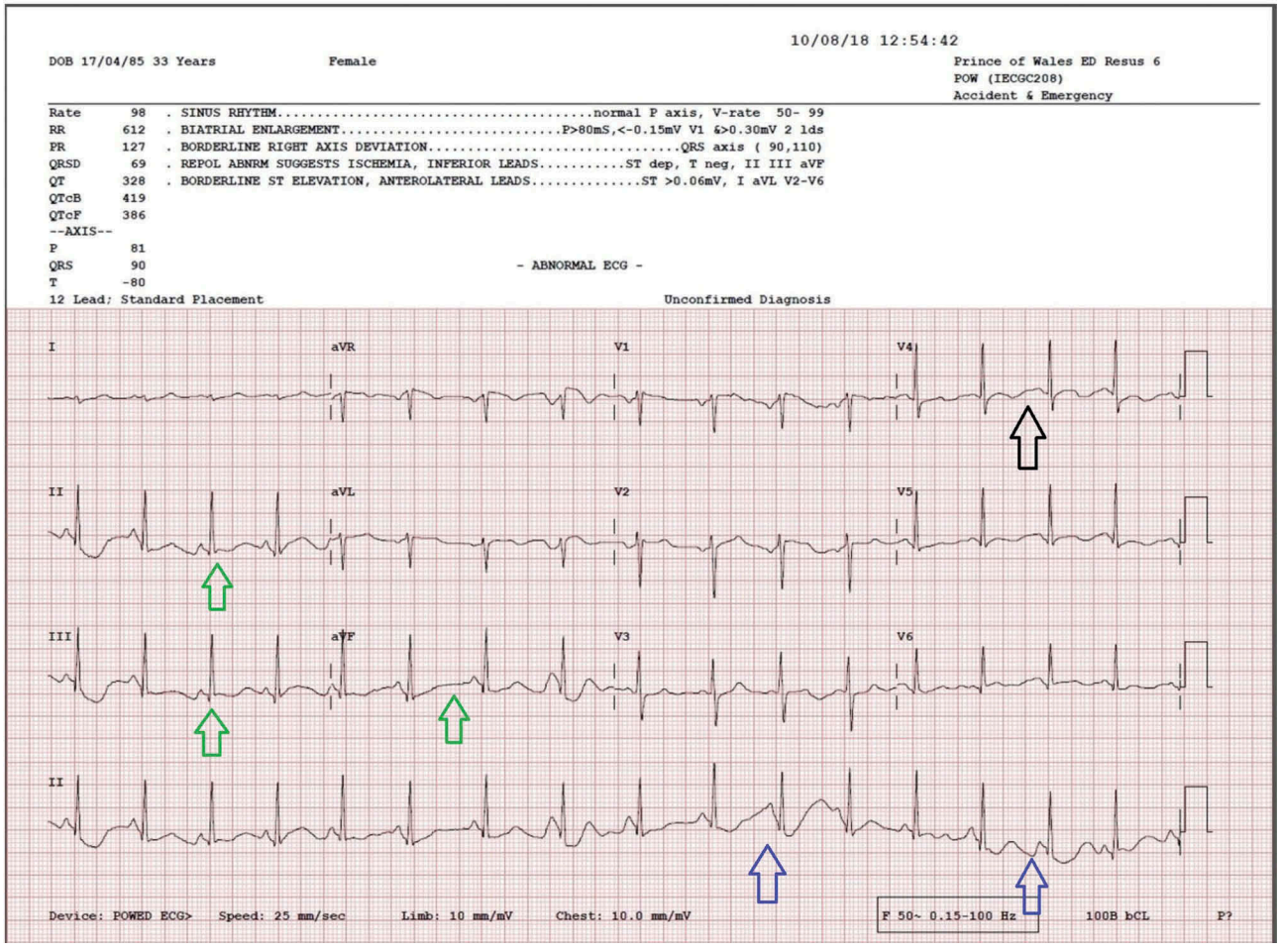

Figure 1. Initial ECG taken when patient was first admitted into hospital. There were borderline ST elevations in the anterolateral leads (black arrow) suggestive of ischaemic changes. Additionally, there was borderline right axis deviation (green arrows) and a wandering ECG trace likely a result of the patient's tremor (blue arrows).

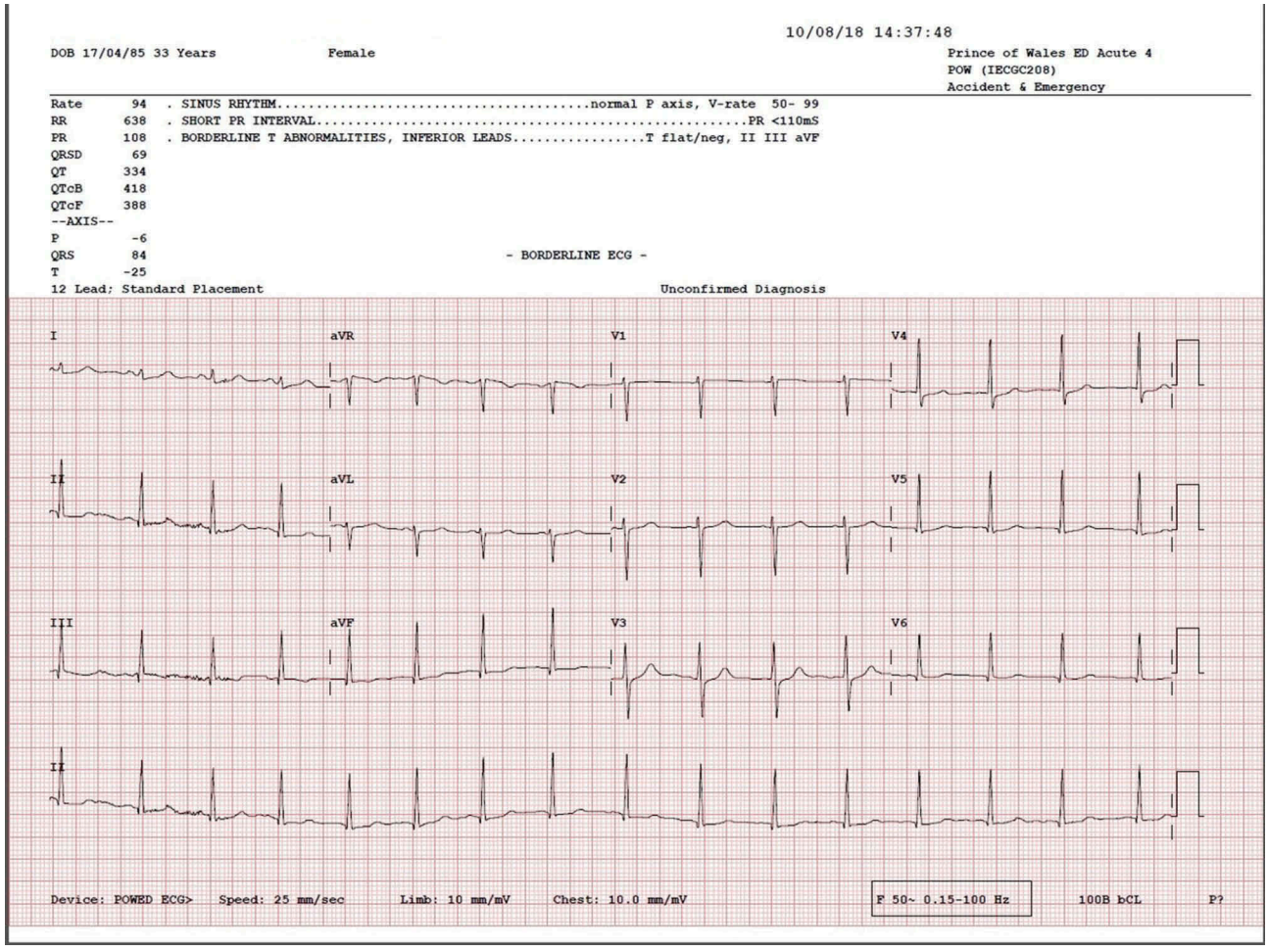

Figure 2. Subsequent ECG taken 2 h after admission into hospital. The borderline ST elevations subsequently resolved.

d-dimer revealed a mild elevation of 50 ng/L (3–14 ng/L) and 0.6 mg/L (<0.5 mg/L) respectively. The remaining electrolytes, full blood count tests and coagulation profile were normal. Subsequent imaging revealed a normal chest radiograph, transthoracic echocardiogram and CT pulmonary angiogram.

MK was admitted for further observation due to elevated troponins. She was started on aspirin and unfractionated heparin while awaiting a coronary angiogram. Her 3-day admission was uneventful with a downtrending troponin from 50 ng/L to 13 ng/L and a negative coronary angiogram. She was discharged with a diagnosis of pre-workout supplement induced cardiac ischaemia, likely due to a catecholamine surge. Instructions were provided for general practitioner follow up, and if necessary, future cardiology referral.

Discussion

Safe discharge for the patient was based on the patient's haemodynamic stability, symptom resolution, downtrending of troponin markers and disappearance of ischaemic changes on ECG. Serious underlying cardiovascular pathology was also excluded through clinical factors such as age, lack of cardiovascular risk factors and a clearly identified precipitating factor for her ischaemic changes in addition to cardiovascular investigations being negative for pathology as shown by a normal coronary angiogram and transthoracic echocardiogram.

In this case, it is postulated that the precipitating factor was the multiple drug interactions between the stimulants found in the supplements i.e caffeine, theophylline, alpha yohimbine and isopropylnorsynephrine. These multiple drug interactions in the context of strenuous physical activity likely triggered a catecholamine surge responsible for the patient's symptoms of chest tightness, pre-syncope, mild dysponea, tachycardia and tremors (Venhuis, Keizers, van Riel, & de Kaste, 2014). The troponin leak is highly likely a consequence of the catecholamine surge, such phenomena can also be seen in cerebrovascular accidents where the acute brain injury causes a massive release of norepinephrine from the myocardial sympathetic nerve terminals to the myocardial interstitium causing a troponin leak (Tanindi & Cemri, 2011).

Theophylline, specifically at high doses can inhibit phosphodiesterase causing increased cyclic adenosine monophosphate activity which triggers increased adrenergic activation and catecholamine release. Toxic levels of theophylline can cause epinephrine and norepinephrine levels to be 4- to 8-times and 4- to 10-times higher than normal, respectively. Such high levels of catecholamine concentrations have a variety of adverse effects such as cardiac arrhythmias (Journey & Bentley, 2018). Another ingredient that likely contributed to

the catecholamine surge is alpha Yohimbine. Yohimbine is a well-known cardiac and central nervous system stimulant of the alpha-2 blocking type (Venhuis et al., 2014). Isopropylnorsynephrine is known for sympathomimetic properties however by itself it is not very potent but its cardiac risks can be potentiated by co-administration of other sympathomimetic drugs and caffeine as seen in this case (Venhuis et al., 2014). Caffeine also contributes to the catecholamine surge by antagonising adenosine receptors, this adenosine receptor antagonism promotes neurotransmitter release of catecholamines and its subsequent sympathetic effects (Robertson et al., 1978).

Troponin leak due to high-intensity exercises is a known phenomenon, and in the context of this patient's presentation, it was a significant differential diagnosis (Baker, Leckie, Harrington, & Richardson, 2019). However, given the initial ECG changes and the patient's recent ingestion of pre-workout supplements, presenting complaint and clinical examination, the author believes that the catecholamine surge is a more likely explanation for the elevated troponin levels. Though the author does not discount the possibility that troponin leak occurring from both high-intensity exercise and the catecholamine surge.

Current literature suggests that troponin leak is more likely when exercise duration is shorter, more intense and the body mass of the individual is lower (Baker et al., 2019). Which is possible in the case of our young female patient who recently started her intense costal run. Presently, the most well-received explanation for the troponin leak is increased membrane permeability of cardiomyocytes allowing unbound cytosolic troponin to diffuse from intra- to extra-cellular compartments (Baker et al., 2019). The cause for the increased membrane permeability is postulated to be due to the mechanical stress during periods of intense exercise causing a temporal sarcolemma disruption (Baker et al., 2019). Such evidence was seen in rat skeletal muscles and in-vivo cardiac muscles, where the disruption of the sarcolemma resolves within 24 h and in keeping with the downtrending of the troponin leak (George et al., 2012). It was also noted that the troponin leak in cardiac muscles has been also associated with growth factor release which reflects the adaptive cellular pathways associated with exercise-induced cardiac remodelling and hypertrophy (George et al., 2012).

Another significant albeit less common differential diagnosis is that of exercise-induced anaphylaxis (Barg, Medrala, & Wolanczyk-Medrala, 2011). The anaphylaxis causing subsequent vasodilation and bronchoconstriction might help account for symptoms of dysponea, presyncope and central chest pain shortly after exercise was initiated. However, other symptoms were incongruent with an anaphylactic reaction, the patient did not have pruritus, hives, flushing and gastrointestinal symptoms of nausea, abdominal cramping and diarrhoea (Robson-Ansley & Du Toit, 2010). Though the patient did have dysponea she did not specifically have wheezing (Young et al., 2012). Additionally, on examination, the patient did not have angioedema, laryngeal oedema, haemodynamic instability and cardiovascular collapse (Robson-Ansley & Du Toit, 2010). Hence, this differential diagnosis is highly unlikely in this patient's case.

Based on literature estimates, significant levels of potentially dangerous ingredients exist in pre-workout supplements (Young et al., 2012), hence there should be increased regulations regarding the clear disclosure of active ingredients (Gabriels, Lambert, & Smith, 2012). Additionally, user warning and education about the common side effects are paramount to promote informed user choice (El Khoury & Antoine-Jonville, 2012). Most of the information that users of pre-workout supplements receive are mainly sourced from coaches, fitness forums and fellow fitness enthusiasts (El Khoury & Antoine-Jonville, 2012). With physicians, dietitians and nutritionists having less input into the information received by pre-workout supplement users (El Khoury & Antoine-Jonville, 2012).

Apart from studying and regulating the pharmacology of the supplements, it is also important to characterise and classify the population of pre-workout supplement users and their usage patterns. This will help us both to understand pre-workout supplement usage patterns and the possible toxic effects. Moreover, by classifying the population, further pharmacokinetics, pharmacodynamics and even pharmacogenetics studies can be conducted to establish safety and optimise efficacy of pre-workout supplement usage in certain gender, age, ethnic, occupation and possibly even sports/user groups.

Healthcare professionals should be vigilant when caring for young fitness enthusiasts with no medical comorbidities and yet develop atypical chest pain, an exercise supplement history may be helpful in such circumstances. But bearing in mind the presentation for pre-workout supplement toxicity can manifest in many ways and may not be limited to chest pain.

In summary, at a public health level, the following case highlights the importance of educating pre-workout supplement users, regulating pre-workout supplements and further studying the pharmacological effects of pre-workout supplements. Specifically, for the clinician, it is important to take note of the possibility of pre-workout supplement-induced symptoms in unusual clinical presentations amongst young and healthy fitness enthusiasts.

Disclosure statement

No potential conflict of interest was reported by the author.

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