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SECONDARY TAKOTSUBO SYNDROME: AN UPDATED LITERATURE REVIEW AND CASE REPORT

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1.0 – Introduction

Takotsubo syndrome (TTS), also commonly referred to as "stress cardiomyopathy", "transient left ventricular apical ballooning syndrome", "neurogenic stunned myocardium", "broken heart syndrome" or "ampulla-shaped cardiomyopathy", has steadily increased in prevalence since its primary identification circa 32 years ago (Sato, *et al.,* 2020). This rare condition is characterised by an apical myocardial contractile dysfunction, without the presence of coronary artery obstruction (Prokudina et al., 2020). Despite increasing awareness among researchers and medical professionals, the precise mechanisms governing the pathophysiology of this disease are somewhat unclear (Lyon et al., 2008). Nevertheless, the association between TTS and a preceding immense, stressful trigger has been long-established (Wittstein et al., 2005). Similarly, recent evidence has shown that the connection

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between the heart and the nervous system plays a role in the development of this disease (Klein et al., 2017; Silva et al., 2019; Templin et al., 2019; X. Wang et al., 2020).

This article presents an updated literature review on TTS with an emphasis on secondary TSS, followed by a case report on the presentation, investigation and management of an 87 year old Caucasian male with secondary TTS, occurring in the setting of a post-mechanical fall, and a right basi-cervical hip fracture. His secondary TTS is also believed to have been precipitated by the patient receiving the news of the passing away of his wife.

Keywords: *Takotsubo, Broken Heart Syndrome, Stress Cardiomyopathy, Apical Ballooning, Neurogenic.*

2.0 – Literature Review

2.1 – The aetiology of primary and secondary Takotsubo syndrome

TTS is often preceded by a trigger factor. Approximately 70% of patients report having experienced a strong emotional event or physical ailment prior to developing TTS. Emotional triggers were generally considered as episodes of acute, immense grief, hence the term 'broken-heart-syndrome'(Cramer et al., 2007). However, recent evidence has also documented the development of TTS following episodes of strong positive-emotions, resulting in the term 'happy-heart-syndrome' (J. R. Ghadri, Sarcon, et al., 2016). The polarity of emotional triggers preceding TTS warrants further investigation to not only clarify the aetiology of this syndrome, but also determine a connection between the extremes of human emotion. Physical stressors which may lead to TTS are innumerable, ranging from life-threating disease such as intracerebral haemorrhage to normal physiological processes, such as sexual intercourse (Sharkey et al., 2010).

The Heart Failure Association of the European Society of Cardiology has issued a statement on TTS, delineating its major clinical subtypes. Patients with primary TTS tend to seek medical care in response to acute cardiac symptoms, which may or may not have clearly recognisable stressful triggers. Potential pre-existing co-morbidities may predispose to developing TTS, but as such, do not cause the rise in catecholamine or nervous system activation, which is elucidated to cause TTS. On the other-hand, secondary TTS tends to develop in those patients who were already hospitalised for another unrelated, medical or surgical condition. It is noted that the sudden activation of the sympathetic nervous system or elevations in catecholamines in these types of patients, often occur as a complication to the primary condition which has resulted in hospitalisation (Lyon et al., 2016). Nevertheless, a complete understanding regarding the exact cause of TTS is still incomplete (Klein et al., 2017).

2.2 – Epidemiology and demographic characteristics of Takotsubo syndrome

Prior to its identification in 1990, patients with TTS were classified under different diagnoses. Since then, the syndrome is being increasingly recognised around the globe, attributable to increased awareness and better terminology. Veritably Minhas *et al*. (2015)

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have demonstrated a 20-fold increase in TTS diagnoses over a six-year period (from years 2006 to 2012), More recent literature discussing the rates of diagnoses of TTS are unavailable. To the authors' knowledge, since the Heart Failure Association of the European Society of Cardiology published their position paper, only one study has investigated the prevalence of primary and secondary TTS respectively. Murugiah *et al.* (2016) have demonstrated that between the years 2007 and 2012, the number of hospitalisations related to primary TTS have increased from 2.3 to 7.1 per 100,000 persons. Similarly, the incident hospitalisations of secondary TTS have increased from 3.4 to 10.3 per 100,000 persons over a five-year period (Murugiah et al., 2016).

Recently, the prevalence of TTS has been reported to be approximately 2% of patients presenting with an acute coronary syndrome (ACS), however this prevalence increases to 10%, if only women are taken into consideration (Akashi et al., 2015). Most patients with TTS (90%) are post-menopausal women with a mean age of 67 to 70 years, and 80% of patients with TTS are older than 50 years (Templin et al., 2015). Moreover, women over the age of 55 years have a 5-fold increased risk of developing TTS compared to their younger counterparts, and a 10-fold increased risk compared to men (Deshmukh et al., 2012). Nevertheless, TTS has been reported in all age groups, including children (Lyon et al., 2016; Templin et al., 2015). The prevalence of secondary TTS is higher in men, while primary patients with TTS are mainly women (Y-Hassan & Tornvall, 2018), suggesting that gender differences play a role in the aetiology of this syndrome. However, this statistic requires further investigation given the recent introduction of this terminology.

A recent study by Imori *et al.* (2022) showed that ethnic disparities have a crucial role in TTS. Such authors have demonstrated that Japanese patients with TTS were more likely to be older, of the male gender, and experienced physical triggers, compared to their European counterparts. Moreover, Japanese individuals were more likely to experience in-hospital mortality and cardiogenic shock. In addition, previous studies conducted in the United States of America have reported that TTS occurs more frequently in Caucasians compared to African-American and Hispanic individuals (Deshmukh et al., 2012; Nascimento et al., 2013; Regnante et al., 2009), however African-American patients with TTS experienced higher rates of in-patient complications (Franco et al., 2016). These studies suggest that ethnicity is an important factor which may determine the clinical outcome of patients with TTS, however it is important to note that TTS is likely to be underreported since its symptoms greatly mimic that of ACS, coupled with the fact that subclinical TTS is likely to remain undetected (J.-R. Ghadri et al., 2018).

2.3 - The pathophysiology of Takotsubo syndrome

Even though the pathophysiology of TTS is not well understood, there are several publications which have reviewed the potential pathophysiological mechanisms, which characterize the clinical manifestations that may govern TTS (Akashi et al., 2015; Boyd & Solh, 2020; Fan et al., 2022; J.-R. Ghadri et al., 2018; Komamura et al., 2014; Lyon et al., 2016; Y-Hassan & Tornvall, 2018).

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Wittstein, *et al.* (2005) were amongst the first to undoubtedly demonstrate supraphysiologic levels of catecholamines and neuropeptides in patients with TTS. These have remained elevated for a duration ranging from a few days to a week, following the onset of symptoms. Moreover, elevations in these stress hormones were several times higher than those in patients with myocardial infarction (MI). Overactivation of the adrenomedullary hormonal system and increased sympathoneural signalling have been postulated to result in these observed elevations of catecholamines. Nevertheless, the mode of action of the excess catecholamines which results in left ventricular apical ballooning is yet to be confirmed. Albeit, it has been suggested that excess catecholamines may act through direct catecholamine myocardial stunning (Szakacs & Cannon, 1958; Van Vliet et al., 1966), via inducing microcirculatory disturbance (Sadamatsu et al., 2000); as well as ischaemia from epicardial coronary artery spasm (Nef et al., 2007).

Cardiac biopsies from patients with conditions which results in states of catecholamine excess, such as TTS, subarachnoid haemorrhage and pheochromocytoma, have demonstrated contraction-band necrosis in cardiomyocytes (Neil-Dwyer et al., 1978; Wilkenfeld et al., 1992). Furthermore, this histological alteration has been noted in biopsies taken post-mortem from individuals who have died under circumstances which may generate exuberant levels of catecholamines such as violent assault or fatal asthma (Cebelin & Hirsch, 1980; Drislane et al., 1987). These findings suggest a direct link between emotional stress and cardiac injury. Moreover, direct catecholamine toxicity may induce cardiomyocyte damage via three primary mechanisms. Primarily, increased catecholamine levels may result in a cAMP-mediated calcium overload, reducing myocytes' viability (Mann et al., 1992). In addition, the oxidation of catecholamines may lead to the formation of reactive oxygen species (ROS), which in animal models, have induced cardiomyocyte injury (Fineschi et al., 2001; Singal et al., 1982). Lastly, ROS may disturb calcium transporters, which might result in a trans-sarcolemmal calcium influx, further exacerbating the calcium overload (Bolli & Marbán, 1999).

Catecholamine mediated microvascular disturbance is further evidenced by reports of reduced coronary flow velocity in the absence of CAD, in patients with TTS (Bybee et al., 2004; Kurisu et al., 2003). Moreover, a diminished coronary flow reserve in patients with TTS has also been demonstrated (Sadamatsu et al., 2000), suggesting that microcirculatory dysfunction may be mediated by the activation of sympathetic efferents (Wittstein et al., 2005). In addition, Mori, *et al.* (1993) revealed that the apical myocardium has an increased responsiveness to sympathetic stimulation. This is further consolidated by Nef, *et al.* (2007), who have published histological findings of local accumulation of inflammatory infiltrates and increased fibrosis, which are also signs of sympathetic cardiac modulation (Huang et al., 2007; Levick et al., 2010; Y. Wang et al., 2021). Nef, *et al.* (2007) have also found cellular evidence, in the form of large glycogen filled cellular areas, indicating energy deprivation which may be caused by ischaemia. However, no signs indicating cell death were present. The presence of ubiquitin vacuoles demonstrates a disturbance in protein metabolism, postulated to prevent cell death. In addition, Nef, *et al.* (2009) have demonstrated that

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cardiomyocytes activate cell survival signalling cascades in patients with TTS, which might further protect cardiomyocytes from cell death. Nonetheless, further research is needed to consolidate the effect of ischaemia from epicardial coronary artery spasm in TTS.

Of note is the predominance of post-menopausal female patients with TTS, which might postulate a biological susceptibility to developing TTS (Wittstein, *et al.* 2005). Conflicting evidence has polarised oestrogen's role in TTS. Kuo, *et al.* (2010) have suggested that levels of reduced oestrogen during menopause, might put such women at risk for developing TTS, while a more recent study by Waqar, *et al.* (2022) alludes to the oestrogen's cardioprotective role. Similarly, genetic and epigenetic factors are thought to have prominence in TTS, however, attempts to characterise such factors have met several limitations, thus requiring further research to characterise how such factors contribute to the pathogenesis of TTS (Ferradini et al., 2021; Limongelli et al., 2016).

2.3.1 - The heart-brain axis in Takotsubo syndrome

Both the sympathetic overactivation and the excess catecholamines which are often triggered by stressful events or physical injury indicate that the nervous system plays a major role in the development of TTS. Cardiac alterations are frequently observed following acute neurological conditions, such as acute MI and arrythmias (Tahsili-Fahadan & Geocadin, 2017). Similarly, TTS has been observed to occur in approximately 6.7% of patients with acute neurological disorders. Moreover, these patients were demonstrated to have a 3.2-fold increased risk for an in-hospital mortality compared to patients with TTS who did not have any neurological disorders (Cammann et al., 2021).

Recent studies have documented neural changes which occur in patients with TTS (Wang et al., 2020). In the acute phase of this condition, patients were observed to have decreased cerebral blood flow (CBF) to the prefrontal cortex. Contrastingly, the CBF was increased in the hippocampus, brainstem, and basal ganglia (Suzuki et al., 2014). The hippocampus and basal ganglia are known major components of the limbic system, which is involved with sympathetic activation and emotional regulation. Moreover, the brainstem houses the sympathetic central nucleus, together with the origins of the sympathetic nerves which descend to the spinal cord (X. Wang et al., 2020). Similarly, Hiestand, *et al.* (2018) and Templin, *et al.* (2019) both have demonstrated functional and structural alterations in the limbic system of patients with TTS, in comparison to healthy age matched controls. Specifically, these patients have decreased connectivity in the autonomic nervous system (Hiestand et al., 2018; Templin et al., 2019). Similarly, Silva, *et al.* (2019) have revealed that patients with TTS also have cortical and subcortical network reorganization, especially in the regions of the brain that are associated with autonomic regulation and emotional responses. Hence, Silva, *et al.* (2019) conclude that the dysregulation of the autonomic nervous system at a central level, might contribute to the pathogenesis of TTS. Contrastingly, Suzuki, *et al.* (2014) hypothesised that the sympathetic overactivation following a stressful trigger may result in TTS. Notwithstanding, through machine learning, Klein, *et al.* (2017) have found consistent brain alterations in the MRI data of patients with TTS, with an accuracy of more than 82%, which could also potentially aid in diagnosing TTS.

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2.4 – The clinical presentation, diagnosis, management and prognosis of Takotsubo syndrome

TTS often arises following an emotional or physical stressor; however, their absence does not exclude such condition (Sharkey et al., 2010). The most significant comorbidities are neurological and psychiatric disorders (Templin et al., 2015). Other significant comorbidities include thyroid diseases, malignancy, renal diseases and pulmonary diseases (Pelliccia et al., 2015). Older patients usually present with symptoms of chest pain and dyspnoea. Signs often include moderate elevations in myocardial necrosis markers and prolonged QT-interval, in approximately half of TTS patients. Furthermore, signs sometimes may include elevations in the ST-segment, elevations in brain natriuretic peptide (nt ProBNP) levels, epicardial coronary artery spasm, ventricular arrythmias as well as myocardial oedema (Prokudina et al., 2020).

Atypical TTS often presents in younger individuals with more frequent ST-segment depression, less pronounced decreased left ventricular ejection fraction (LVEF) and decreased nt ProBNP levels. Moreover, atypical patients with TTS were more likely to present with neurological disorders in comparison to typical patients with TTS. Despite this, the outcomes of atypical TTS are comparable to those of typical TTS, requiring careful follow-up (J. R. Ghadri, Cammann, et al., 2016). It is worth noting that most patients who present with TTS have abnormal ECG findings which resemble ACS. However, it is crucial to distinguish TTS from ACS, as misdiagnosis of both conditions may result in improper care and possible death of the patient.

The diagnosis of Takotsubo cardiomyopathy may be difficult upon presentation. Nonetheless, there are four recognised diagnostic criteria of TTS, all of which are required to make a diagnosis (Scantlebury, *et al.*, (2014). These criteria include:
1) A transient left ventricular systolic dysfunction, including hypokinesis, akinesis or dyskinesis. The wall motion abnormalities are typically regional and extend beyond a single epicardial coronary distribution. Rare exceptions may also include the focal and the global types;
2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. If coronary artery disease is found, the diagnosis of TTS can still be made if the wall motion abnormalities are not in the same distribution of the coronary artery disease;
3) New electrocardiographic abnormalities, either ST segment elevation, QT-interval prolongation, and/or T wave inversion;
4) A negative or a modest elevation in cardiac troponin levels.

TTS has generally been considered a self-limiting disease, spontaneously resolving over the course of days to weeks, so the management is generally supportive. Treatment is dependent on whether patients experience heart failure, acute hypotension and shock. In many individuals, left ventricular function normalizes within two months (Scantlebury, *et al.*, (2014).

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In mild TTS, supportive therapy coupled with aspirin and β-blockers may be considered (Dias et al., 2016; Lyon et al., 2016). In cases where the condition is complicated by heart failure, conventional treatment with angiotensin-converting enzyme or angiotensinogen receptor blockers, β-blockers and diuretics is often used (Brunetti et al., 2017; Templin et al., 2015). Patients with TTS should be monitored using telemetry and any-emerging arrhythmias should be managed appropriately (Lyon et al., 2016).

Additionally, thromboembolism is a serious complication of TTS. Hence, anticoagulation therapy is recommended in patients with extensive mid-apical ballooning, embolic complications or left ventricular thrombi, until the ballooning or the left ventricular thrombi resolve, as confirmed by echocardiography (El-Battrawy et al., 2016; Lyon et al., 2016). Further treatment may include the adoption of healthy lifestyle changes and effective stress management (Scantlebury, *et al.,* (2014).

Most of the patients tend to survive the initial acute event, with a very low rate of in-hospital mortality or complications. The long-term prognosis is excellent for most patients. Although infrequent, recurrence of TTS has also been reported (Scantlebury, *et al.,* (2014).

2.5 – Case report

2.5.1 – Case history and patient examination

An 87 year old, non-smoker, Caucasian male, with a known history of Type 2 Diabetes Mellitus, Hypertension, Non-ST Elevation Myocardial Infarction (N-STEMI), Severe Ischaemic Heart Disease (IHD), Chronic Kidney Disease, Cataracts, and Ischaemic Cerebro-Vascular Accident (CVA) presented to the accident and emergency department in view of right hip pain and being unable to weight-bear, following a mechanical fall in his own home. On admission, he was on the following medications: Bumetanide, Metformin, Trimetazidine, Isosorbide mononitrate, Aspirin, Gliclazide, Clopidogrel, Omeprazole, Doxazocin, Perindopril, Atorvastatin and Glycerin Tri-Nitrate.

On initial examination, a shortened and externally rotated right lower limb was elicited. A pelvic x-ray has confirmed the presence of a basi-cervical fracture of the right femur. A right hip hemi-arthroplasty was successfully performed. An immediate post op wound infection arose, whereby a highly mixed culture consisting of *Pseudomonas aeruginosa*, three types of *Coagulase Negative Staphylococci* and *Staphylococcus aureus* was cultivated, which was successfully treated with aggressive intravenous antibiotic therapy.

2.5.2 – Pathological tests and other investigations

Approximately five days post-op, the patient has received the news that his wife has passed away. Later that evening, the patient had a routine post-op ECG organized and T-wave inversions in V1 to V3 were noted (Refer to Figure 1 & Figure 2), in the absence of any associating symptoms, such as chest pain or shortness of breath. His parameters were all within normal limits, and he was not showing any signs of heart failure, acute hypotension or shock.

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A high-sensitivity cardiac troponin rise was also noted from 700 ng/L to 774 ng/L within a time span of four hours. A bed-side echocardiogram has revealed apical akinesia as well as mild aortic stenosis. There was a good global left ventricular ejection fraction of 60%, normal mitral valve and normal right ventricle size and contractility. Given these findings, the most likely diagnosis in this case is of secondary TTS, occurring in the setting of a post mechanical fall and a right basi-cervical hip fracture. This condition might have also been precipitated by the patient's wife passing away, whilst he was still admitted in the acute hospital.

2.5.1 – Treatment plan

Given the patient's relatively stable condition at the time of the secondary TTS diagnosis, the patient has received supportive care. Moreover, his Atorvastatin dosing regimen was increased to 80mg daily. Given that the patient was already on dual-antiplatelet therapy on admission, there was no indication to add any further anti-platelet or anti-coagulating agents to his treatment regime, at this stage. No emerging arrhythmias or thrombo-embolic events have occurred in the acute setting.

2.5.1 – Actual patient outcome

Within fifteen days of the secondary TTS episode, the patient was discharged in a reasonably well condition to a rehabilitation hospital, and a cardiology follow up was organized. Approximately three months after being discharged, the patient was re-admitted to the acute hospital, in view of runs of supra-ventricular tachycardia (SVT) at a rate of 150 beats per minute. Moreover, his initial investigations have revealed the presence of an N-STEMI, which was managed conservatively in view of being asymptomatic, his multiple existing co-morbidities and advanced age.

Within six months from the TTS episode, a repeat echocardiogram has revealed persistent akinesia of the apical cap, the apical anterior left ventricular wall and the apical septal left ventricular wall, as well as severe hypokinesia of the inferior wall and the infero-lateral left ventricular walls. Moreover, normal left ventricular dimensions were present, with a moderately impaired left ventricular ejection fraction. The ejection fraction was estimated to be approximately 37%. A severely dilated left atrium with an end systolic volume of 92 mls, along with a calcified tricuspid valve were also present. The inter-atrial septum was intact. At this stage, Carvedilol and Amlodipine were also added to his treatment regimen.

A year later, the patient has developed congestive heart failure (CHF) and he was re-admitted to hospital with an acute CHF exacerbation. On repeat echocardiogram, his aortic stenosis has also progressed from mild to moderately severe, along with the presence of pulmonary hypertension, a mild posterior mitral valve annular calcification, a mild mitral and tricuspid regurgitation, as well as trace pulmonary regurgitation. Two years from the initial TTS episode, the patient has passed away of an unrelated cause, that is, intra-abdominal sepsis.

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2.6 – Conclusion

This case report describes the challenging case of an 87-year-old male with multiple comorbidities who suffered a right hip basi-cervical fracture after a mechanical fall. Despite successful hip surgery, he developed a postoperative wound infection that required aggressive antibiotic treatment. The patient experienced secondary TTS after learning of his wife's passing, likely due to the emotional and physical stress. He received supportive care and an increased dose of Atorvastatin during his hospital stay, but later faced complications such as supra-ventricular tachycardia (SVT) and an N-STEMI, which were managed conservatively. Over time, his cardiac function deteriorated, leading to CHF and other cardiac issues. Unfortunately, the patient passed away due to an unrelated cause.

This case emphasizes the significance of understanding potential cardiac complications in elderly patients with multiple comorbidities and emotional stress. It underscores the importance of a multidisciplinary approach and close monitoring to promptly address cardiac issues. Managing such patients requires personalized treatment plans to optimize outcomes in complex medical situations.

List of Figures

Figure 1 – ECG changes in Secondary TTS

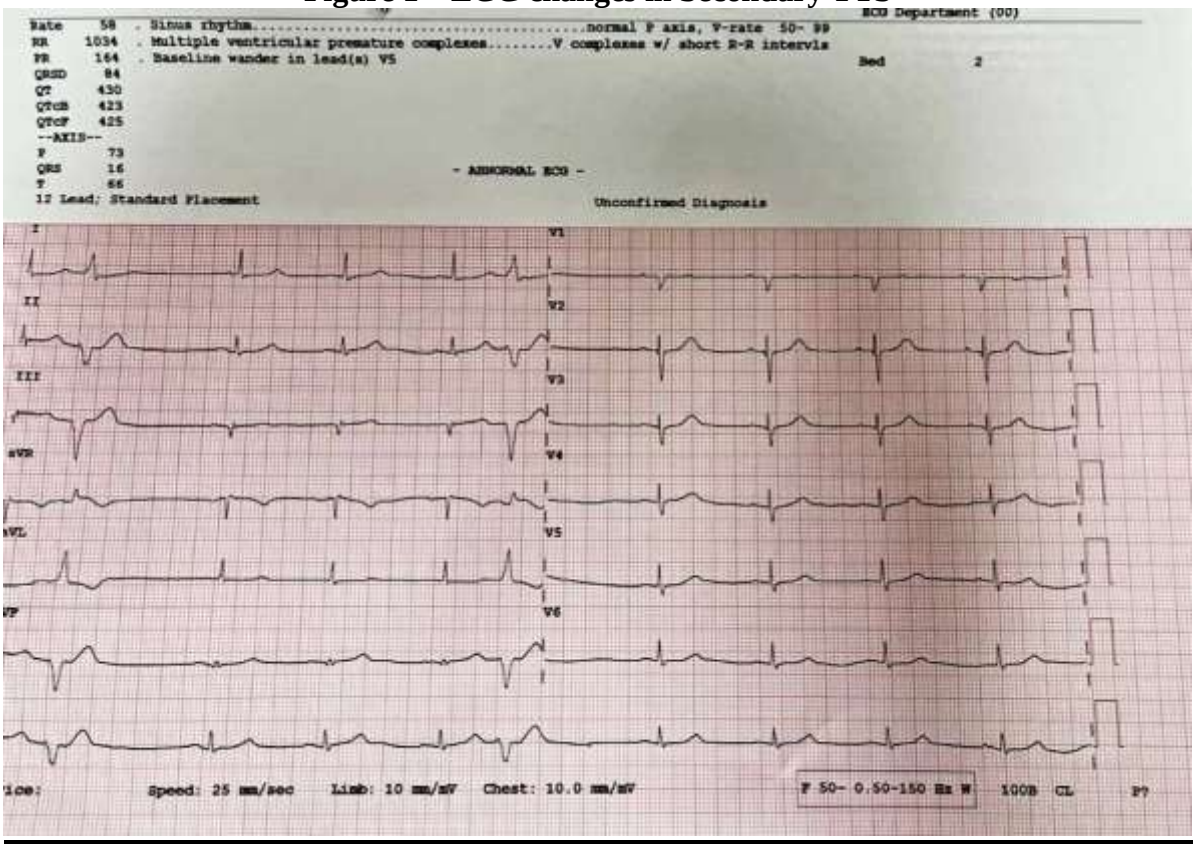

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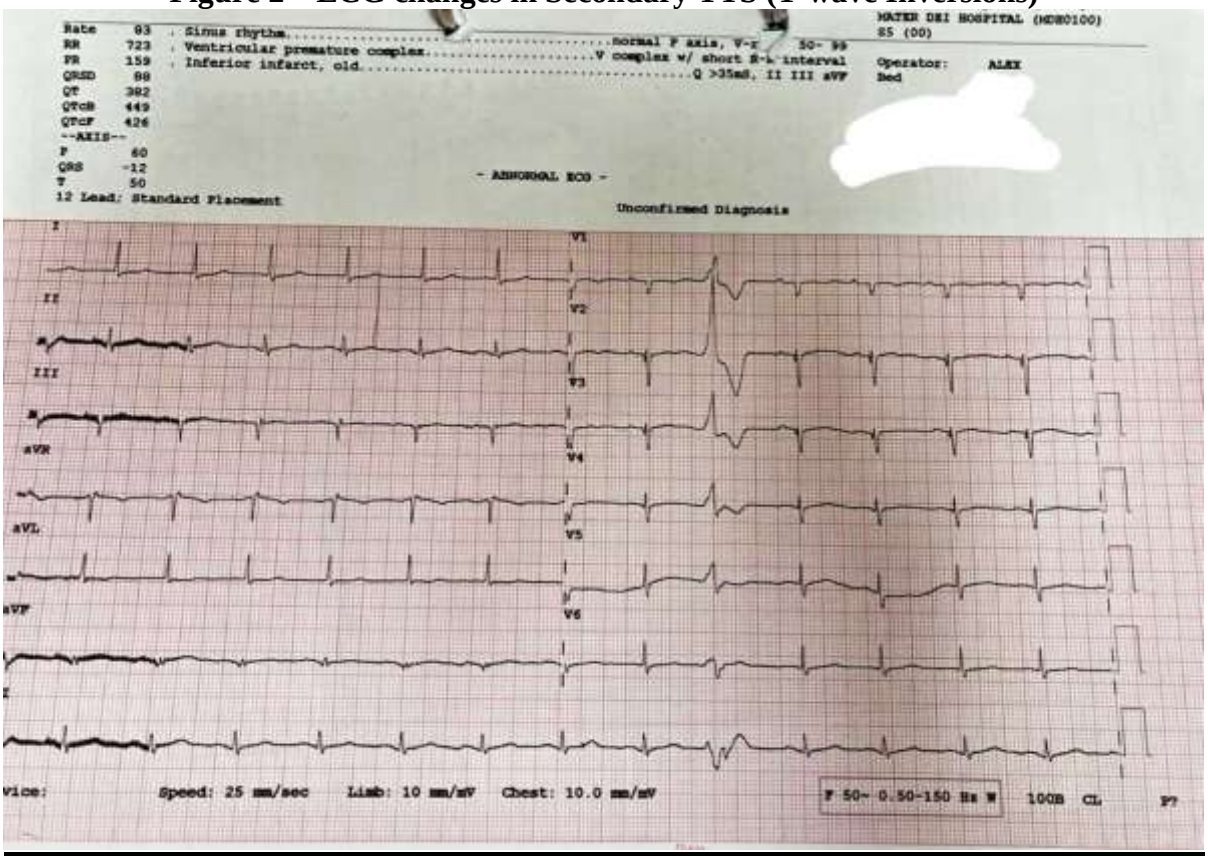
Figure 2 – ECG changes in Secondary TTS (T-wave Inversions)



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A Brief Author Biography

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