Review

Catecholamine-induced cardiomyopathy: an endocrinologist's perspective

Aman Kumar[1], Joseph M Pappachan[2,3,4,*], Cornelius James Fernandez[5]

[1] Department of Medicine, University of Birmingham Medical School, B15 2TH Birmingham, UK

[2] Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, PR2 9HT Preston, UK

[3] Faculty of Science, Manchester Metropolitan University, M15 6BH Manchester, UK

[4] Faculty of Biology, Medicine and Health, The University of Manchester, M13 9PL Manchester, UK

[5] Department of Endocrinology and Metabolism, Pilgrim Hospital, PE21 9QS Boston, UK

*Correspondence: drpappachan@yahoo.co.in (Joseph M Pappachan)

DOI:10.31083/j.rcm2204130

Submitted: 29 July 2021 Revised: 27 August 2021 Accepted: 22 September 2021 Published: 22 December 2021

Although many endocrine diseases can be associated with acquired cardiomyopathy and heart failure, conditions except hypothyroidism, hyperthyroidism, phaeochromocytoma-paraganglioma (PPGL), and primary hyperaldosteronism are rare. PPGL is a rare catecholamine-secreting neuroendocrine tumour arising from the adrenal gland in 80–85% or extra-adrenal chromaffin cells of the autonomic neural ganglia in the remainder. The annual incidence of PPGL is 3–8 cases per million per year in the general population. Catecholamine-induced cardiomyopathy (CICMP) has got a prevalence of 8–11% among patients with PPGL. Hypertension, either sustained or episodic, is present in the vast majority (95%) of PPGL patients. However, among patients with CICMP, hypertension is present only in 65% of cases and the classical triad of paroxysmal headache, sweating, and palpitation is present only in 4%. Based on the cardiac remodelling in response to endogenous catecholamine excess, PPGL patients might present with one of the three CICMPs, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or Takotsubo cardiomyopathy (TCM). Regardless of the subtypes, all CICMPs have many features in common — a dramatic clinical presentation, reversible cardiomyopathy, similar repolarisation electrocardiography changes, mild-moderate cardiac biomarker elevation, and normal coronary arteries on coronary angiography. CICMP should be suspected in patients with non-ischaemic, non-valvular forms of cardiomyopathy, even in those without definite features of catecholamine excess. PPGL associated TCM should be suspected in all acute coronary syndrome (ACS) patients exhibiting pronounced blood pressure variability with no culprit lesions on coronary angiography. This article will provide a review of the various CICMPs, their pathophysiology, clinical features, and the management options.

Keywords

Catecholamine-induced cardiomyopathy; Phaeochromocytoma; Heart failure

1. Introduction

Cardiomyopathies are myocardial disorders characterized by structural/functional abnormalities of the cardiac muscles sufficient to cause observed myocardial abnormality in the absence of coronary artery disease (CAD), hypertension, valvular heart disease and congenital heart disease [1]. The cardiac muscle disorders caused by CAD, hypertension, valvular heart disease and congenital heart disease were considered as exclusion criteria because their diagnosis and management were quite distinct from most other cardiomyopathies. Nevertheless, ischaemic cardiomyopathy, hypertensive cardiomyopathy, and congenital heart disease with co-existent cardiomyopathy are well-known entities [2–5]. Ischaemic cardiomyopathy is characterized by left ventricular systolic dysfunction in patients with previous myocardial infarction, myocardial revascularisation, or more than 75% stenosis in the left coronary artery main stem or left anterior descending artery [2]. Hypertensive cardiomyopathy is characterised by left ventricular hypertrophy associated with left ventricular diastolic and/or systolic dysfunction in hypertensive patients, in the absence of other conditions known to cause left ventricular hypertrophy or left ventricular dysfunction [3]. Congenital heart disease can co-exist with cardiomyopathy as the mutations that are known to cause congenital heart disease can also result in cardiomyopathy [4].

The European Society of Cardiology (ESC) working group in 2008 grouped cardiomyopathies into specific morphological and functional phenotypes including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified cardiomyopathies, the latter including left ventricular non-compaction (LVNC) and Takotsubo cardiomyopathy (TCM) [1]. Each of these phenotypes can be subclassified into a genetic form (associated with single gene mutations) and a non-genetic form. The genetic form is mostly familial but can rarely be caused

by *de novo* mutations. The non-genetic form can either be idiopathic (with no identifiable cause) or acquired (complication of other diseases) [1, 5]. A classification proposed by the World Heart Federation in 2013, known as MOGE(S) incorporates the morpho-functional phenotype (M), organ involvement (O), genetics (G), etiology (E) and the functional status (S) of the disease [6]. According to this classification, the term "idiopathic cardiomyopathy" is no-longer appropriate, as the cause and the mechanisms are increasingly identified in a significant proportion of cardiomyopathies [7].

Many endocrine diseases are associated with acquired cardiomyopathies and heart failure [8]. The phaeochromocytoma and paraganglioma (PPGL) are associated with DCM (38.7%), TCM (23.3%), inverted TCM (19.6%), HCM (6.1%), myocarditis (4.9%), and unspecified cardiomyopathy (8.6%) [9]. Severe hypothyroidism [10], thyrotoxicosis [11], primary hyperaldosteronism [12, 13], Cushing's syndrome [14], acromegaly [15], hypocalcaemia [16] and vitamin D deficiency [17] are associated with DCM. Carcinoid syndrome [18] is associated with RCM, whereas lipodystrophy syndrome (both generalised and partial lipodystrophy) [19] is associated with predominantly HCM and rarely DCM.

PPGLs are rare catecholamine-secreting neuroendocrine tumours arising from either the adrenal gland or the extra-adrenal chromaffin cells of autonomic neural ganglia [20]. Catecholamine-induced cardiomyopathies (CICMPs) are rare, dreadful, and difficult-to-treat complications of PPGL with an unexpectedly high surgical risk [21]. CICMP has got a prevalence of 8–11% among patients with PPGL [22, 23]. This is a potentially reversible cause of cardiomyopathy. With an early diagnosis, adrenergic blockade, and timely surgical treatment the prognosis is quite favorable in most cases.

2. Discussion

2.1 Catecholamines and the heart

Catecholamines are tyrosine-derived neurotransmitters including dopamine, norepinephrine, and epinephrine [24, 25]. They also act as hormones regulating key physiological processes across nearly all body tissues, and thus are involved in the pathogenesis of many systemic diseases [24–26]. They are predominantly synthesised by the chromaffin cells of the adrenal medulla and sympathetic postganglionic neurons. The adrenal medulla releases epinephrine (80%) and norepinephrine (20%) in response to its sympathetic supply, commonly as part of an acute stress response. This release is in conjunction with norepinephrine secretion from sympathetic nerve terminals. The catecholamines have a short half-life of 1–3 minutes and are deaminated by monoamine oxidases or methylated by catechol-O-methyl transferases. These enzymes are also found in other tissues such as the liver [25].

The concentration and type of catecholamine determine the cardiovascular response to it. Acutely, catecholamines increase heart rate, systemic vascular resistance and myocardial contractility while reducing venous compliance [23]. They are considered the most potent positive inotropic agents in relation to the heart and are the main regulators of cardiac output. Epinephrine also acts as a bronchodilator and increases the rates of glycogenolysis, lipolysis and oxygen consumption [25]. In the heart, the norepinephrine that is released upon activation of sympathetic nervous system acts through α_1, β_1 and β_2 adrenoceptors to exert positive inotropic and chronotropic effects. In the blood vessels, the norepinephrine-mediated α_1 adrenoreceptor and β_1 adrenoreceptor stimulation, though the latter is less in number in blood vessels, promotes vasoconstriction, whereas the norepinephrine mediated β_2 adrenoreceptor stimulation promotes vasodilation. As the α_1 adrenoreceptors predominate over β_2 adrenoreceptors in the blood vessels, vasoconstriction remains the primary vascular response of norepinephrine. As the β_1 adrenoreceptors (predominantly in the heart) and β_2 adrenoreceptors (predominantly in the vascular tree) have greater affinity for epinephrine compared to norepinephrine, the β_2 adrenoreceptor mediated vasodilatation remains the primary vascular response of epinephrine at lower doses [27]. However, at high doses, epinephrine may attach to the α_1 adrenoreceptors in the blood vessels resulting in vasoconstriction [21].

The β_1 adrenoceptors are instrumental for autonomic regulation of the heart and are found in the sinoatrial (SAN) and atrioventricular (AVN) nodes as well as in both the atrial and the ventricular cardiomyocytes [21, 27]. They function through increasing the intracellular calcium concentration, calcium release from the sarcoplasmic reticulum, and by increasing the AVN conduction velocity. Concomitant β_1 adrenoceptor-mediated renin release by the kidneys supports the blood pressure, plasma sodium levels and the blood volume [27].

2.2 Pathophysiology of catecholamine-induced cardiomyopathy

Catecholamine excess states have been implicated in the pathogenesis of various types of cardiomyopathies including tachycardia-related cardiomyopathy, HCM, DCM, and TCM. The catecholamine excess may also aggravate preexisting cardiac conditions in patients with phaeochromocytoma [28–31]. Fig. 1 summarizes the major pathophysiological mechanisms of catecholamine-induced cardiomyopathy. Cardiomyocyte remodelling following sustained catecholamine excess leads to the development of different types of CICMPs. Acute excessive adrenergic stimulation may result in overstimulation of β_1 adrenoceptors leading to an increase in oxygen demand in the heart leading to hypoxia in some areas [21]. Acute excessive adrenergic stimulation may also result in severe vasoconstriction including epicardial coronary artery vasospasm, myocardial ischaemia, and irreversible damage and necrosis [21, 32].

Prolonged exposure to raised catecholamine levels leads to blunting of the β adrenoceptor response to catecholamines, and consequently a desensitisation of the heart to further inotropic stimulation [21, 28]. Fig. 2 (Ref. [33]) displays the

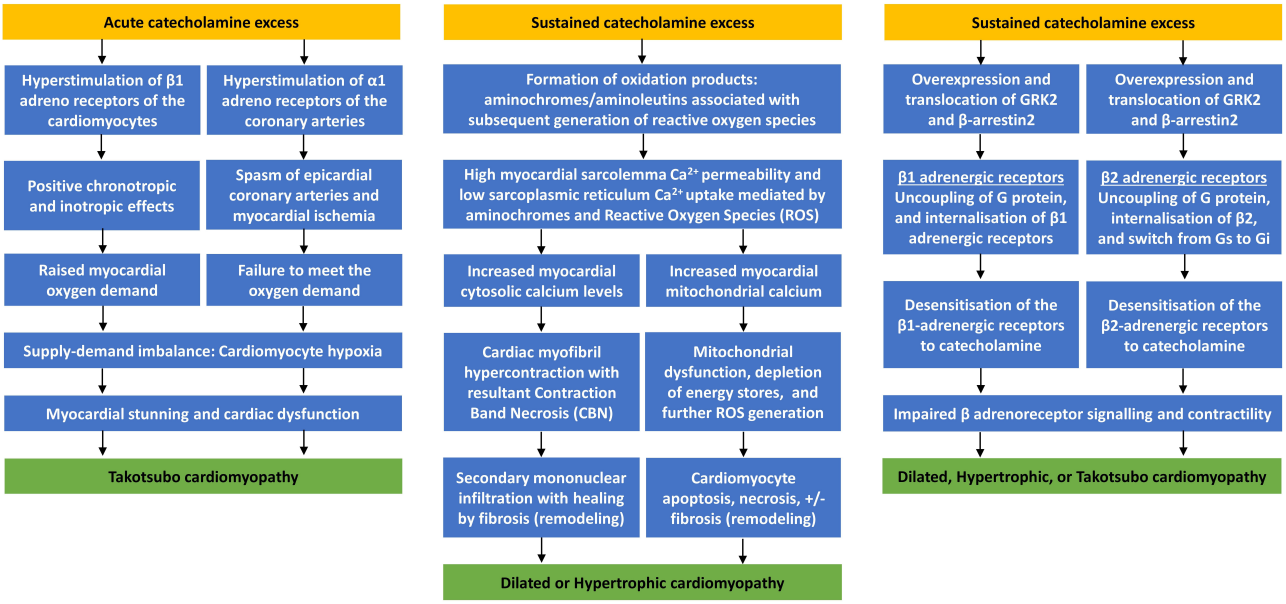

Fig. 1. Major pathophysiological mechanisms of catecholamine-induced cardiomyopathy. Catecholamine excess states are associated with supply-demand imbalance, myocardial stunning ad cardiac dysfunction. Catecholamine excess states are associated with formation of oxidation products and reactive oxygen species resulting in cardiomyocyte apoptosis, necrosis, and cardiac remodelling by fibrosis. Finally, catecholamine excess states are also associated with impaired β adrenoreceptor signalling and impaired myocardial contractility.

proposed mechanisms for β_1 and β_2 adrenergic receptor desensitisation. Desensitisation is mediated by adrenergic receptor phosphorylation via G protein coupled receptor kinases (GRKs), followed by binding to the protein β-arrestin2. GRK2/β-arrestin2 facilitate uncoupling of G protein from β_1 adrenoreceptor and internalisation of β_1 adrenoreceptor. Similarly, GRK2/β-arrestin2 facilitate uncoupling of G protein from β_2 adrenoreceptor, internalisation of β_2 adrenoreceptor, and a switch from Gs to Gi in β_2 adrenoreceptor. The β_2 adrenoreceptor-Gi coupling results in decreased cardiac contractility [33].

The Gs to Gi switch is described only with β_2 adrenoreceptors, not with β_1. Moreover, the switch happens only with epinephrine excess, not with norepinephrine excess [34]. Epinephrine activates both Gs and Gi pathways (Gs at lower and Gi at higher concentrations), whereas norepinephrine activates only the Gs pathway through β_2 adrenoceptors [35]. Moreover, affinity of norepinephrine towards β_2 adrenoceptor is 20-fold lower than towards β_1 adrenoreceptor [35]. Catecholamine storms caused by epinephrine-secreting phaeochromocytomas are more commonly associated with TCM in comparison to norepinephrine-secreting and dopamine-secreting PPGLs [36]. Although the Gs to Gi switch via β_2 adrenoreceptor is mechanically detrimental by impairing the cardiac contractility, it protects the heart against β_1 adrenoreceptor mediated proapoptotic and proarrhythmogenic effect of catecholamine excess [37]. GRK2 and β-arrestin regulate the secretion of catecholamines in the adrenal medulla, suggesting a GRK2/β-arrestin-mediated crosstalk between adrenal and heart [38, 39]. Polymorphisms in β_1 adrenergic receptors are implicated in causing heart failure, likely secondary to their effect on the sympathetic nervous system [40].

Catecholamines produce a direct toxic effect on the myocardium by increasing the sarcolemmal permeability and cellular calcium influx [28, 31]. These deleterious effects of catecholamine excess are mediated by the oxidation products of catecholamines rather than catecholamines per se [41]. Under physiological conditions catecholamines are metabolized mainly by catechol-O-methyl transferase and monoamine oxidase pathways. However, under conditions of catecholamine excess, these pathways are overwhelmed and the catecholamines (epinephrine released from adrenal medulla and norepinephrine released from sympathetic nerve endings) undergo oxidation to form aminochromes (active metabolite) and aminoleutins (inactive metabolite). The oxidation of catecholamines into aminochromes and aminoleutins are associated with the generation of reactive oxygen species (ROS) [41]. The oxidative stress resulting from the ROS molecules together with the aminochromes leads to calcium handling abnormalities inside the cardiomyocytes including high calcium permeability through the sarcolemma and low calcium uptake by the sarcoplasmic reticulum (SR) [42]. The resultant increase in myocardial cytosolic and mitochondrial calcium levels causes mitochondrial dysfunction, depletion of energy stores, and augments the ROS generation culminating in myocardial apoptosis, necrosis, with/without fibrosis. Similarly, the raised intracellular calcium levels mediated by the aminochromes inside the vascular smooth muscle cells results in coronary spasm, myocar-

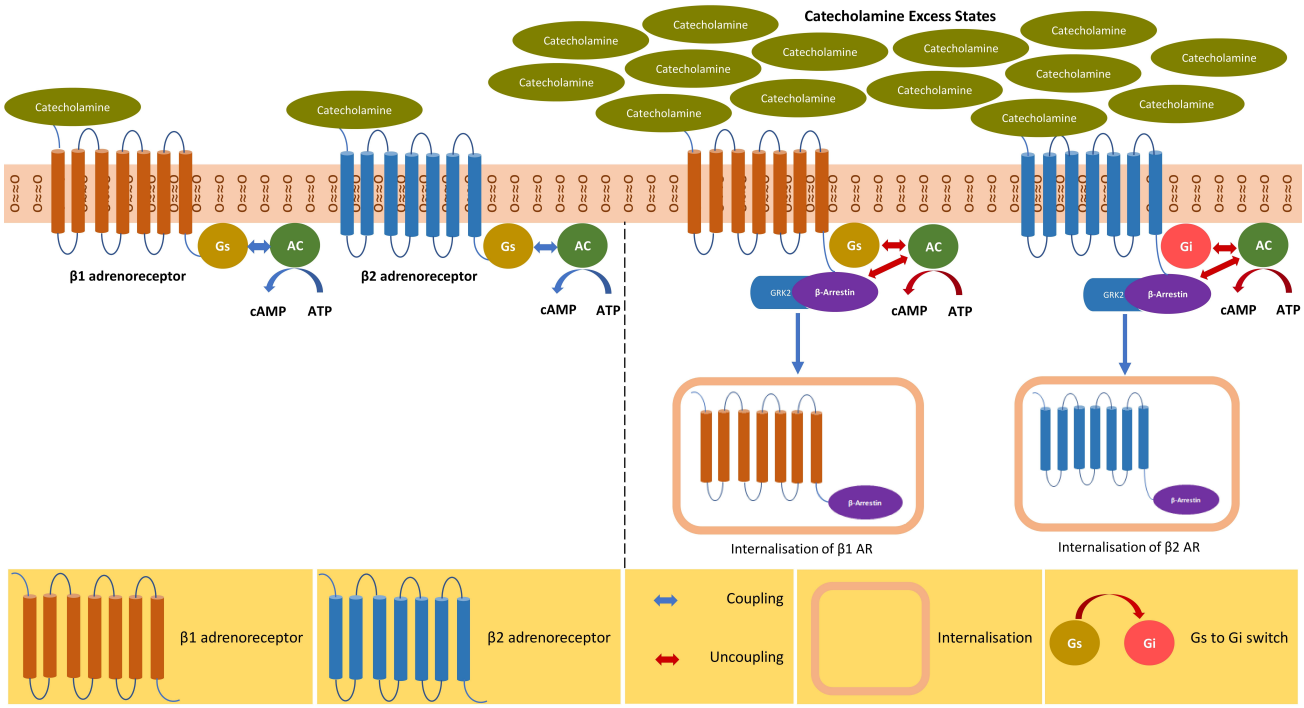

Fig. 2. Proposed mechanism for β_1 and β_2 adrenergic receptor desensitisation (Left half physiological and right half pathological state) [33]. Binding of catecholamines to β_1 and β_2 adrenoreceptors results in GRK2 mediated phosphorylation and β-arrestin2 binding. GRK2/β-arrestin2 facilitate uncoupling of G protein from β_1 adrenoreceptor and internalisation of β_1 adrenoreceptor. GRK2/β-arrestin2 also facilitate uncoupling of G protein from β_2 adrenoreceptor, internalisation of β_2 adrenoreceptor, and a switch from Gs to Gi in β_2 adrenoreceptor.

dial ischaemia, ventricular arrhythmias, and contractile dysfunction [43].

Catecholamine-mediated myocardial stunning has been implicated in the pathogenesis of TCM. The name TCM came from the shape of cardiac apex that resembles 'takotsubo', a conical Japanese pot used for catching octopus. Inverted TCM with apical sparing has also been described [44, 45]. In the mammalian left ventricle (LV), there is an apical-basal gradient for β adrenoreceptors and sympathetic nerve density [46]. The LV apex has the highest β adrenoreceptor density, and the lowest sympathetic nerve density. On the other hand, the LV base has the lowest β adrenoreceptor density, which explains the hyperkinetic base that occurs in the classic TCM. The apical hypokinesia and ballooning is explained by the fact that the Gs to Gi switch of β_2 adrenoceptors predominantly happen at LV apex leading to decreased contractility and myocardial stunning [46].

In contrast to the above theory of epinephrine mediated Gs to Gi switch, a systematic review and meta-analysis of 156 published case reports of TCM patients where the TCM was induced by exogenous epinephrine, exogenous norepinephrine, or endogenous catecholamine (PPGL) did not find any direct causal relation between epinephrine and TCM [47]. However, epinephrine excess was found to have an indirect effect via hyperactivation of the sympathetic nervous system (SNS) which in turn leads to disruption in cardiac sympathetic nerve terminals with norepinephrine spillover [48, 49]. This would explain the multifocal histological changes (contraction band necrosis) and patchy cardiac MRI changes seen in PPGL-related CICMPs [50]. Moreover, the SNS hyperactivation can explain the LV basal hypokinesia seen in inverted TCM.

Excess catecholamines that are released directly into the myocardium via sympathetic nerve terminals are more toxic in comparison to the excess catecholamines reaching the myocardium via blood stream [50]. Increased cardiac SNS activity, increased norepinephrine synthesis/release, decreased norepinephrine reuptake by the terminal nerve axons, increased sensitivity to catecholamines, myocardial ischaemia due to epicardial coronary artery spasm, and transient LV outflow tract obstruction have all been suggested as possible pathophysiologic mechanisms for TCM [51–54]. Additionally, oestrogen-induced downregulation of the adrenergic receptors of the heart may also have a role, as TCM is more common in postmenopausal women [53, 55].

2.3 Clinical features of phaeochromocytoma and paraganglioma (PPGL)

PPGLs are rare catecholamine-secreting neuroendocrine tumours arising from either the adrenal gland or the extra-adrenal chromaffin cells of autonomic neural ganglia. The annual incidence of phaeochromocytoma has been estimated as 3–8 cases per million per year in general population, and it occurs in less than 0.5% of patients with hyperten-

sion [56, 57]. The frequency can be higher in those with adrenal incidentalomas, where up to 4.2% can have PPGL [58]. Phaeochromocytomas can be sporadic or familial. Sporadic forms usually present between the ages of 40–50 years, whereas the hereditary forms including multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), von Hippel-Lindau syndrome (VHL), and succinate dehydrogenase (SDH) subunit B, C and D mutations (SDHB, SDHC, and SDHD, respectively), usually present in childhood or early adulthood [59]. The hereditary PPGLs related to VHL mutations secrete norepinephrine, SDH mutations secrete dopamine and norepinephrine, whereas RET mutations (MEN2A) secrete norepinephrine and epinephrine [60].

These tumours secrete catecholamines including epinephrine, norepinephrine, and dopamine. Phaeochromocytomas arising from the adrenal medulla accounts for nearly 80–85%, whereas the paragangliomas arising from autonomic neural ganglia account for 15–20% of PPGL [60]. While normal adrenals predominantly secrete epinephrine, majority of PPGLs predominantly secrete norepinephrine with only about 15% secreting predominantly epinephrine [61]. The PPGLs predominantly secreting dopamine are rare and these are malignant PPGLs in which the dopamine decarboxylase enzyme is missing [62]. Usual presenting features of PPGL include the classical triad (headache, hyperhidrosis, and palpitation), tachycardia, tremor, anxiety, pallor, chest pain, dyspnea, and sometimes local tumoral symptoms like abdominal pain, although many patients can be asymptomatic. Hypertension is present in nearly 95% of patients with PPGL, with sustained hypertension noted in 55% and episodic hypertension in 45% [63].

The PPGLs predominantly secreting norepinephrine presents with sustained hypertension, those predominantly secreting epinephrine presents with episodic hypertension, and those predominantly secreting dopamine presents with no hypertension [61]. Fluctuating hypertension with cyclic bouts of hypertension and hypotension is well described in phaeochromocytoma patients possibly due to spontaneous infarction of the tumour during the phaeochromocytoma crisis [64–67]. The proposed mechanisms for spontaneous necrosis include catecholamine-induced vasoconstriction, embolic infarction, haemorrhage into the tumour, high intracapsular pressure, or antihypertensive therapy induced hypotension [67]. Hypertension can be absent in PPGL patients, and the various proposed mechanisms include secretion of dopamine as the predominant catecholamine, conversion of catecholamines into inactive metabolites within the tumour itself, secretion of other molecules together with catecholamines - including vascular endothelial growth factor that suppresses catecholamine action, reduction in sensitivity of receptors to catecholamine, or significant reduction in cardiac function due to CICMP [68].

2.4 Clinical features of catecholamine-induced cardiomyopathy including TCM

Cardiovascular complications of phaeochromocytomas include left ventricular hypertrophy, ACS including myocardial infarction, acute pulmonary oedema, myocarditis, cardiac arrythmias, cardiomyopathies, thromboembolism, and shock [21, 57, 69]. Based on the cardiac remodelling in response to the endogenous catecholamine excess, PPGL patients might present with either one of the three types of CICMPs, including DCM, HCM, or TCM [70]. DCM characterised by congestive cardiac failure, pulmonary oedema or cardiogenic shock associated with diffuse left ventricular or even biventricular dysfunction can be one of the presenting manifestations of PPGL [71]. DCM can occur spontaneously or can occur after initiation of β blockade [71, 72]. The DCM can be transient in most cases with early detection/appropriate resection [73] or can be chronic/progressive with late detection [74]. Obstructive HCM can be another presenting manifestation in cases of undiagnosed PPGL due to long standing hypertension [30, 75]. Furthermore, a picture of apical HCM of the Japanese type (in electrocardiography and echocardiography) is also described in PPGL patients [76]. HCM improves after surgical resection of the PPGL [75, 76].

TCM patients often present with acute chest pain, acute severe heart failure, dynamic ST-T changes, elevated cardiac biomarkers, and left ventricular regional wall motion abnormalities (RWMA) in a circumferential apical, midventricular, or basal distribution, without evidence of significant CAD on coronary angiographic studies [77]. Thus, TCM closely mimics ACS and hence these patients are often misdiagnosed and treated as ACS. Nearly 1–3% of all patients presenting with suspected ST-segment elevation myocardial infarction has in fact TCM [77]. The diagnostic hallmark of TCM is the reversibility of cardio depression occurring within weeks of initial presentation [57].

The clinical picture of TCM associated with PPGL and that not associated with PPGL are quite divergent. Nearly two-thirds of TCM patients associated with PPGL develop cardiac complications in comparison to only one-fifth of TCM patients without PPGL. The TCM-PPGL patients are associated with higher recurrence rate (17.7% vs 3.26%). These patients are younger (fourth or fifth decade). The TCM localisation pattern was different in TCM-PPGL patients, with the basal pattern contributed to almost 1/3 of cases and global pattern contributed to 1/5 of the cases [78]. The contributions of TCM-PPGL to apical, mid-ventricular, basal, and global TCM patterns were 43.9%, 5.6%, 26.2%, and 20.6%, whereas the corresponding contributions of TCM cases in general were 81.7%, 14.6%, 2.2%, and 0% respectively [47]. When compared to the classical TCM pattern, the inverted TCM that was commonly seen in TCM-PPGL was associated with higher complication rates, including, cardiogenic shock, heart failure, acute renal failure, and arrhythmias. This higher complication rates could be related to the

higher levels of circulating catecholamines in TCM-PPGL patients. Moreover, the precipitating factors are often not clear in TCM-PPGL patients [79].

A catecholamine crisis or phaeochromocytoma multisystem crisis is a rare, acute, severe complication of catecholamine-induced haemodynamic compromise and collapse [80]. The term 'type A crisis' is used to describe a more limited crisis without sustained hypotension, whereas 'type B crisis' is used to describe a severe presentation with sustained hypotension, shock and multi-organ dysfunction [45]. Fever can be present in a minority of cases without a focus of sepsis, possibly related to secretion of interleukin-6 by the tumour [81–83]. Phaeochromocytoma crisis can mimic other conditions leading to misdiagnosis and phaeochromocytomas are often found as an incidental finding on imaging performed for an alternative diagnosis [44, 84]. Nearly 11% of phaeochromocytoma patients required in-hospital treatment on intensive care units due to complications caused by unsuspected phaeochromocytomas [85]. Phaeochromocytoma-crisis is associated with an overall mortality of 15%, with a higher (28%) mortality in those developing 'type B crisis' compared to those developing 'type A crisis' (6%) [45].

2.5 Diagnosis of catecholamine excess state (PPGL)

The diagnosis of CICMP is often delayed due to atypical presentations. In a study on 163 PPGL patients with CICMP, hypertension was the presenting symptom only in 65% of patients [86]. Among the various CICMP subgroups, hypertension was common with DCM (83%), and HCM (80%), compared to TCM. The classical PPGL triad of headache, sweating, and palpitation was present in only 4% of patients. Among the subgroups, the classical triad was common in HCM patients, whereas the DCM patients commonly presented with congestive heart failure [86]. Hence, CICMP should be suspected in all cardiomyopathy patients that is non-ischaemic, and non-valvular, even in those without definite features of catecholamine excess. Similarly, PPGL associated TCM should be suspected in all ACS patients exhibiting pronounced blood pressure variability with no culprit lesions on coronary angiography. The diagnosis is important as surgical removal of PPGL would improve CICMP in 96% of cases. Moreover, if not undergoing surgical resection, the disease would lead to mortality or cardiac transplantation in 44% of cases [86].

Consider possibility of catecholamine-induced cardiomyopathy when a known PPGL patient presents with symptoms of heart failure, hypotension, and multisystem crisis [21]. However, the diagnosis of CICMP can often be missed initially in patients who are not already known to have a phaeochromocytoma [87]. Fig. 3 (Ref. [60]) shows an algorithm for the diagnostic workup of PPGL. In asymptomatic patients, the phaeochromocytoma often comes to light whilst investigating for an adrenal incidentaloma with non-contrast computed tomography (CT) with an attenuation value of more than 10 Hounsfield units (>10 HU). Elevated levels of plasma free metanephrines, and urinary fractionated metanephrines are required for biochemical confirmation, as outlined in the 2014 Endocrine Society Clinical Practice Guidelines [87]. Urinary fractionated metanephrines has a comparable sensitivity to that of plasma free metanephrines (97% vs 99%), but the specificity of urinary fractionated metanephrines is lower than that of plasma free metanephrines [88].

The 2016 European Endocrine Society guidelines recommend the addition of 3-methoxytyramine (the dopamine metabolite) in the initial screening panel for the diagnosis and follow-up of patients with PPGLs [89]. The addition of 3-methoxytyramine along with free metanephrines would improve the sensitivity (97.2% vs 98.6%) but reduce the specificity (95.9% vs 95.1%) [90]. The dopamine producing malignant PPGLs are not missed with this addition. The 2016 European Endocrine Society guidelines also recommend using plasma chromogranin as a screening tool in cases with a clinical probability for PPGL once plasma free metanephrines and 3-methoxytyramine are negative [89]. Plasma and urinary catecholamines and urine vanillylmandelic acid (VMA) are less often used currently because of suboptimal sensitivities and specificities [60].

Cardiac failure due to any cause would be associated with catecholamine release, with a likely consequent rise in plasma metanephrine levels. As metanephrine levels are not yet validated in patients with cardiac failure, routine use of serum fractionated metanephrines or urinary free metanephrines in all cardiomyopathy patients would result in significantly high false-positive results [91]. These tests should be used only when the pre-test probability of CICMP is high. The factors that increase the pre-test probability of CICMP include younger age at diagnosis of cardiomyopathy; genetic diseases associated with PPGL (MEN2, NF1, VHL, SDH); patients with symptoms suggestive of PPGL including classical PPGL triad; blood pressure (sustained, episodic, or fluctuating blood pressure); inverted TCM (with higher risk for cardiogenic shock, heart failure, acute renal failure, and arrhythmias); and adrenal incidentalomas with radiological features of phaeochromocytoma [91].

These patients with clinical features suggestive of PPGL or CICMP should undergo anatomical localisation studies using computed tomography (CT) or magnetic resonance imaging (MRI) after the initial step of biochemical confirmation. CT should be the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis. However, MRI is recommended in patients with residual/recurrent/metastatic PPGL, for detection of skull base and neck paragangliomas, in patients with surgical clips that could cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, those with known germline mutations, and those with recent excessive radiation exposure) [87].

The anatomical imaging should be followed by functional imaging. The Iodine-123-tagged MIBG (metaiodobenzyl-

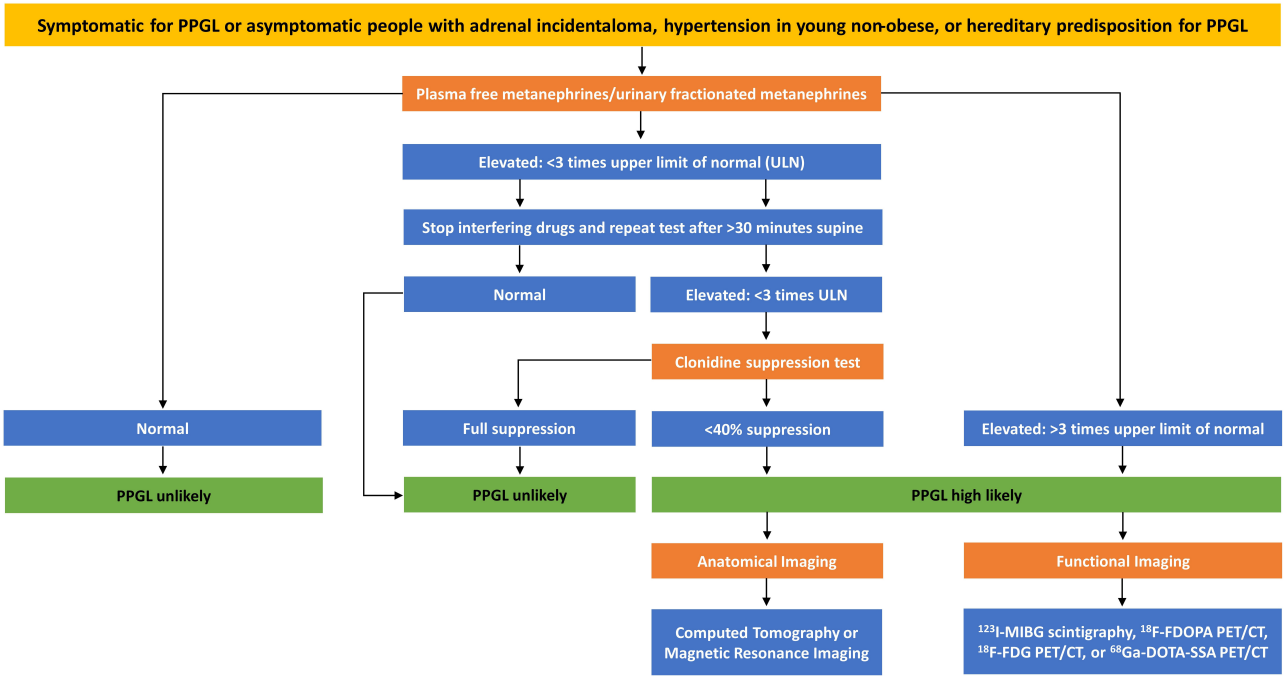

Fig. 3. An algorithm for the diagnostic workup of phaeochromocytoma and paraganglioma [60]. This algorithm should be used in the evaluation of people who are either symptomatic for PPGL or who are asymptomatic, but with presence of adrenal incidentaloma, hypertension in young non-obese people, or hereditary predisposition for PPGL. Abbreviations: PPGL, Phaeochromocytoma and Paraganglioma; ULN, Upper Limit of Normal; CT, Computed Tomography; ^{123}I-MIBG, ^{123}I metaiodobenzylguanidine; ^{18}F-FDOPA, ^{18}F-fluorodihydroxyphenylalanine; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{68}Ga-DOTA-SSA, ^{68}Gallium-labeled somatostatin analog.

guanidine) scintigraphy can detect tumours that were undetected by CT or MRI and is useful to establish the diagnosis of PPGL in cases where tumours were already detected on anatomical imaging [92]. The ^{123}I-MIBG scintigraphy is not useful in subjects with SDH mutations. On the other hand, 18F-fluorodeoxyglucose positron emission tomography CT scanning (^{18}F-FDG PET/CT) is very useful due to Warburg effect: impairment of mitochondrial function due to loss of SDH function causes the tumour cells to shift from oxidative phosphorylation to aerobic glycolysis [93]. Similarly, the ^{18}F-FDG PET/CT is the preferred functional imaging over ^{123}I-MIBG scintigraphy in patients with metastatic PPGL. Genetic testing is recommended in all patients with phaeochromocytoma [87].

2.6 Diagnosis of catecholamine-induced cardiomyopathy

Electrocardiogram (ECG) and 2-dimensional echocardiogram should be performed in all cases of suspected or confirmed PPGL/CICMP. Electrocardiographic changes range from unremarkable, sinus tachycardia, wandering pacemaker, and repolarisation ECG changes. The latter include ST-segment elevation, ST-segment depression, peaked T-waves, or giant inverted T-waves. The ST-segment elevation with giant inverted T-waves is seen in apical TCM, whereas ST-segment depression with peaked T-waves is seen in basal TCM [69]. The echocardiographic features of different CICMPs are given in Table 1 [21, 94]. In TCM, echocardiography helps to identify the pattern and extent of disease. In other CICMPs, echocardiography helps to assess mechanical complications including dynamic LV outflow tract obstruction, with or without systolic anterior motion of the anterior mitral leaflets, and/or functional mitral valve regurgitation.

Coronary angiogram and cardiac MRI should be performed in selected cases with cardiovascular involvement [87]. Left ventriculography performed during coronary angiogram should not be considered as the sole investigation to assess the myocardial function, as right ventricle (RV) could be involved in one-fourth of the TCM cases [95]. Cardiac Magnetic Resonance (CMR) can differentiate TCM from myocarditis and ischaemic cardiomyopathy. CMR in patients with TCM exhibits high-intensity signal on T2-weighted images in a transmural distribution, without significant late gadolinium enhancement, in regions with wall motion abnormalities. Occasionally, the CMR in TCM patients might show areas of myocarditis, focal fibrosis as small foci of late gadolinium enhancement [96].

PPGL was one of the exclusion criteria for the diagnosis of TCM as per the Mayo Clinic criteria that has been used historically [97]. However, in 2018 the Heart Failure Association-European Society of Cardiology (HFA-ESC) TCM task force developed an international takotsubo diagnostic criteria, which is also known as InterTAK Diagnostic Criteria, wherein PPGL was included as the secondary cause of TCM [77]. An InterTAK diagnostic score can be calculated as given in Table 2. Patients with symptoms sugges-

Table 1. Echocardiographic features various catecholamine-induced cardiomyopathies [21, 94].

Type	Echocardiographic features various catecholamine-induced cardiomyopathies
DCM	Dilated LV and possibly RV; no or minimal eccentric left ventricular hypertrophy with or without LVSD; global hypokinesia is common, but RWMA can occur
HCM	Concentric hypertrophy; normal or reduced internal chamber dimensions with or without systolic anterior motion of anterior mitral valve leaflet (SAM)
TCM	Classic TCM: apical ballooning (apical akinetic segment, hyperkinetic base) Inverted TCM: akinetic base/mid-ventricular segment, hyperkinetic apex Mid-ventricular TCM: normal apex and base, mid-ventricular dyskinesia Localized TCM: segmental dyskinesia in coronary artery distribution

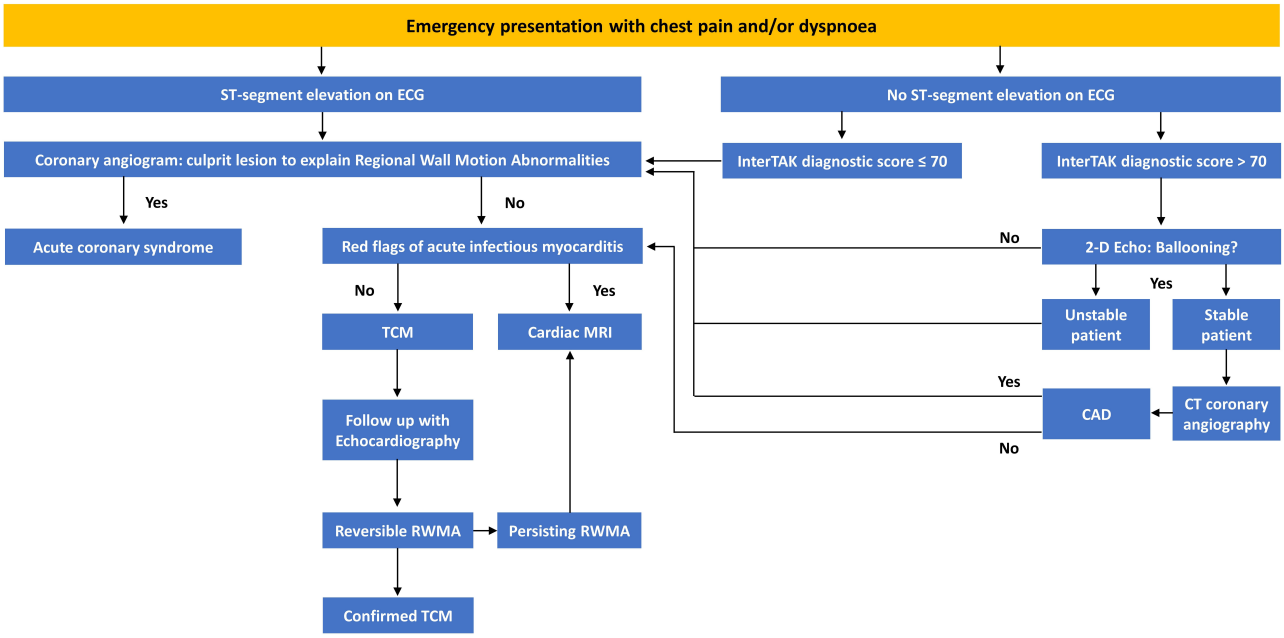

Fig. 4. Algorithm for the diagnosis of Takotsubo cardiomyopathy as per HFA-ESC TCM task force [98].

Table 2. International Takotsubo diagnostic criteria score (InterTAK diagnostic score) [77].

International Takotsubo diagnostic criteria	InterTAK diagnostic score
Female sex	25 points
Emotional stress	24 points
Physical stress	13 points
No ST-segment depression	12 points
Psychiatric disorders	11 points
Neurological disorders	9 points
QTc-Interval prolongation	6 points

tive for an ACS, however, with no ST-elevations in the ECG, but with high probability of TCM should undergo screening using the InterTAK Diagnostic Score. If the score is positive with $>$70 points, echocardiography should be done. If echocardiographic features are suggestive of TCM, a CT coronary angiography should be done. On the other hand, patients achieving $\leq$70 points should undergo coronary angiography with left ventriculography [98]. These recommendations from HFA-ESC TCM task force is displayed in Fig. 4.

2.7 Management of catecholamine excess state (PPGL)

High index of suspicion and prompt diagnosis is important for a favourable outcome from this potentially fatal condition. The diagnosis should be considered in all patients presenting with acute cardiomyopathy and cardiogenic shock without a clear ischaemic or valvular aetiology [99]. The diagnosis should be confirmed immediately as several medications including dopamine D2 receptor antagonists, β adrenergic receptor blockers, sympathomimetics, opioid analgesics, tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, corticosteroids, peptides and neuromuscular blocking agents are implicated in adverse reactions in patients with phaeochromocytoma and can precipitate or worsen a crisis [87, 100, 101].

The initial management of phaeochromocytoma crisis should be in a setting where expertise and access to mechanical circulatory support is available. Stabilisation of blood pressure with α adrenoceptor blockers followed by β adrenoceptor blockers and surgical resection of the phaeochromocytoma is the cornerstone of treatment. Retrospective studies have shown that selective α_1 adrenergic receptor block-

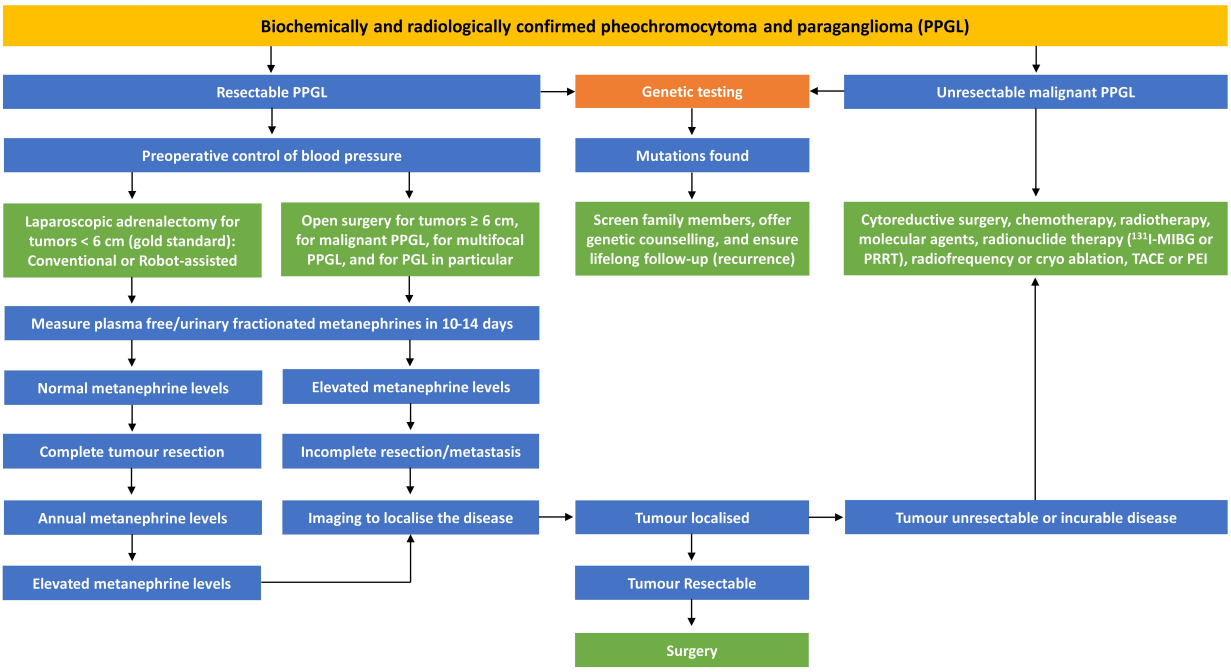

Fig. 5. An algorithm for the management of phaeochromocytoma and paraganglioma [60]. Laparoscopic adrenalectomy, either conventional or robot-assisted, is the gold standard technique for adrenalectomy in tumors <6 cm. However, open adrenalectomy is the preferred technique I those with tumors ≥6 cm, for multifocal PPGL, those with high risk of malignancy including PGL. Abbreviations: ^{131}I-MIBG, ^{131}I metaiodobenzylguanidine; PRRT, Peptide Receptor Radionuclide Therapy; TACE, Transarterial Chemoembolisation; PEI, Percutaneous Ethanol Injection.

ers were associated with lower preoperative diastolic pressure, a lower intraoperative heart rate, better postoperative haemodynamic recovery, and fewer adverse effects such as reactive tachycardia and sustained postoperative hypotension than nonselective adrenergic blockers. In patients presenting with phaeochromocytoma crisis, use of α adrenoceptor blockade is associated with significantly lesser mortality of 40% compared to 99% in those without use of α adrenoceptor blockade [44].

The β adrenoceptor blockers should be added after appropriate α adrenoceptor blockade to control the tachycardia [87, 102]. Failure to optimise α adrenoceptor blockade prior to β adrenoceptor blocker initiation can result in hypertensive crisis (due to unopposed α receptor stimulation) and worsening of the haemodynamic instability. Patients should have medical treatment for 7–14 days to allow adequate time to normalize blood pressure and heart rate prior to surgery [94]. An algorithm for the management of PPGL is given in Fig. 5.

2.8 Management of catecholamine-induced cardiomyopathy

In patients with acute decompensated cardiomyopathy, phentolamine given as intravenous bolus or infusion is preferred because of its short half-life and rapid reversal of adverse effects. Phenoxybenzamine, which has a half-life of 24 hours, can be started once haemodynamic stability has been achieved [94]. Doxazosin is a competitive α_1 selective blocker and is therefore theoretically less appropriate than phenoxybenzamine. However, a sequential study of 35 patients with phaeochromocytoma reported that doxazosin (2–16 mg/day) provided safe, efficacious preoperative/perioperative control of arterial pressure, causing fewer side-effects, and allowing more rapid postoperative recovery of adrenoceptor function versus phenoxybenzamine. Co-administration of β adrenoceptor antagonists to control the heart rate was not required except in patients with known epinephrine-secreting tumours [103]. Calcium channel blockers can be added to optimise blood pressure control if α adrenoceptor blockers alone are not adequate. However, monotherapy with calcium channel blockers is not recommended unless patients have very mild preoperative hypertension or have severe orthostatic hypotension with α adrenergic receptor blockers [87].

Management of patients presenting with acute heart failure requires adequate diuretics, but this is often complicated by hypotension due to intravascular volume depletion or systolic heart failure [21]. Indiscriminate use of inotropes and vasopressors should be avoided as they precipitate a phaeochromocytoma-crisis and may cause cardiogenic shock by causing LV outflow tract obstruction. Hence these drugs should be initiated judiciously, utilizing the lowest possible dose in patients with CICMP and hypotension. Fluid status needs to be monitored carefully and intra-arterial balloon counter-pulsation, the Impella system, the TandemHeart de-

vice or veno-arterial extra-corporeal membrane oxygenation (VA ECMO) can be considered in refractory cases of catecholamine crisis associated with hypotension [44, 104–108]. Severe hypotension may occur once the tumour is resected, which might result from the abrupt cessation of catecholamine secretion and depleted blood volume.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers may have a role in managing heart failure in patients with phaeochromocytoma. Clinical signs of congestive heart failure may resolve within two weeks following treatment with captopril. Myocardial performance can also become normal within two weeks of medical therapy, with one week with captopril monotherapy and with another week with captopril-phenoxybenzamine combination therapy [109]. Proposed mechanisms include the inhibition of the cardiac renin-angiotensin axis and inhibition of free radicals from long chain fatty acids described in phaeochromocytoma [110, 111]. Orthostatic hypotension in combination with sustained hypertension has been reported to be a feature in 10–50% of the individuals with phaeochromocytoma [112]. Treatment should primarily focus on restoring circulating volume. Mineralocorticoids should not be administered in patients with phaeochromocytoma [100, 101].

In summary, there is no specific treatment approach for the management of patients with CICMP. The preoperative management of CICMP should include control of blood pressure variability by lowering sympathetic activation with the help of α and β adrenergic blockade, maintenance of adequate blood volume, diuretics administration in case of volume overload, and the use of left ventricular assist devices in refractory cases of catecholamine crisis related with hypotension [113]. These preoperative management together with optimal anaesthetic techniques can minimise the perioperative haemodynamic instability (modifiable). However, factors like size of the tumour, location of the tumour, association with genetic syndromes, and secretory activity of the tumour are the nonmodifiable factors that can result in perioperative haemodynamic instability [114].

3. Areas of uncertainty

Studies have shown that sustained catecholamine excess is associated with cardiac remodelling characterized by cardiomyocyte hypertrophy, apoptosis, and fibrosis mediated by coronary ischaemia, increased mechanical stress, cytokines and neurohormones [115]. Catecholamine excess is associated with inflammation and aging (senescence) of cardiomyocytes, upregulation of tumour suppressors including p53, and generation of adhesion molecules, all of which together mediating the cardiac dysfunction [116]. Animal studies have also shown that catecholamine-induced lipotoxicity is one of the mechanisms for causing myocardial dysfunction and TCM [117].

4. Summary and conclusions

In response to endogenous catecholamine excess, PPGL patients might present with one of the three CICMPs, including DCM, HCM, or TCM. Regardless of the subtypes, all CICMPs have many features in common — a dramatic clinical feature, reversible cardiomyopathy (if diagnosed early, optimally treated: medically or surgically), similar repolarisation electrocardiographic changes, mild to moderate cardiac biomarker elevation, normal coronary angiography, and focal or multifocal contraction band necrosis with secondary mononuclear cell infiltrations on histology. CICMP should be suspected in all non-ischaemic, and non-valvular cardiomyopathy patients, even in those without definite features of catecholamine excess. Similarly, PPGL-associated TCM should be suspected in all ACS patients exhibiting pronounced blood pressure variability with no culprit lesions on coronary angiography. There is no specific treatment approach for the management of CICMP. The preoperative management of CICMP should include control of blood pressure variability by lowering sympathetic activation with the help of α and β adrenergic blockade, maintenance of adequate blood volume, diuretics administration in case of volume overload, and the use of left ventricular assist devices in refractory cases of catecholamine crisis associated with hypotension. These preoperative management strategies together with optimal anaesthetic techniques can minimise the perioperative haemodynamic instability and improve the post-operative outcomes.

5. Learning points

- Suspect CICMP in patients with non-ischaemic and non-valvular acute cardiomyopathy, or in patients with inverted TCM, especially in those with young age at diagnosis, genetic diseases, marked blood pressure variability, with or without PPGL related symptoms.
- Cardiac failure due to any cause would result in catecholamine release, with a consequent falsely elevated plasma fractionated metanephrine levels. Hence these tests should be used only when the pre-test probability of CICMP is high.
- With an early diagnosis, adrenergic blockade, and timely surgical treatment using the optimal anaesthetic techniques, the prognosis is quite favorable most of the time.

Author contributions

AK drafted the paper initially with advice & Guidance from JMP and CJF who further developed, edited and approved it in the current form with mutual agreement between all the authors.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, *et al.* Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. European Heart Journal. 2008; 29: 270–276.

[2] Briceno N, Schuster A, Lumley M, Perera D. Ischaemic cardiomyopathy: pathophysiology, assessment and the role of revascularisation. Heart. 2016; 102: 397–406.

[3] Hinton RB, Ware SM. Heart Failure in Pediatric Patients with Congenital Heart Disease. Circulation Research. 2017; 120: 978–994.

[4] Kuroda K. Hypertensive cardiomyopathy: a clinical approach and literature review. World Journal of Hypertension. 2015; 5: 41.

[5] Rapezzi C, Arbustini E, Caforio ALP, Charron P, Gimeno-Blanes J, Helio T, *et al.* Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. a position statement from the ESC Working Group on Myocardial and Pericardial Diseases. European Heart Journal. 2013; 34: 1448–1458.

[6] Arbustini E, Narula N, Tavazzi L, Serio A, Grasso M, Favalli V, *et al.* The MOGE(S) classification of cardiomyopathy for clinicians. Journal of the American College of Cardiology. 2014; 64: 304–318.

[7] Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, *et al.* The MOGE(S) Classification for a Phenotype-Genotype Nomenclature of Cardiomyopathy: Endorsed by the World Heart Federation. Global Heart. 2013; 8: 355–382.

[8] Khatiwada S, Boro H, Farooqui FA, Alam S. Endocrine causes of heart failure: a clinical primer for cardiologists. Indian Heart Journal. 2021; 73: 14–21.

[9] Agrawal S, Shirani J, Garg L, Singh A, Longo S, Longo A, *et al.* Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis. World Journal of Cardiology. 2017; 9: 255–260.

[10] Rastogi P, Dua A, Attri S, Sharma H. Hypothyroidism-induced reversible dilated cardiomyopathy. Journal of Postgraduate Medicine. 2018; 64: 177–179.

[11] Oliveros-Ruiz L, Vallejo M, Diez Canseco LF, Cárdenas M, Hermosillo JAG. Determinants of thyrotoxic cardiomyopathy recovery. BioMed Research International. 2013; 2013: 452709.

[12] Zhang J, Yang J, Li Y. Dilated cardiomyopathy and aldosteronoma: a causal link? ESC Heart Failure. 2020; 7: 331–333.

[13] Frustaci A, Letizia C, Verardo R, Grande C, Francone M, Sansone L, *et al.* Primary aldosteronism-associated cardiomyopathy: Clinical-pathologic impact of aldosterone normalization. International Journal of Cardiology. 2019; 292: 141–147.

[14] Pingle S, Shah T, Mosleh W, Kim AS. Cushing syndrome cardiomyopathy: an unusual manifestation of small-cell lung cancer. ESC Heart Failure. 2020; 7: 3189–3192.

[15] Yokota F, Arima H, Hirano M, Uchikawa T, Inden Y, Nagatani T, *et al.* Normalisation of plasma growth hormone levels improved cardiac dysfunction due to acromegalic cardiomyopathy with severe fibrosis. BMJ Case Reports. 2010; 2010: bcr1220092559.

[16] Bansal B, Bansal M, Bajpai P, Garewal HK. Hypocalcemic cardiomyopathy-different mechanisms in adult and pediatric cases. The Journal of Clinical Endocrinology and Metabolism. 2014; 99: 2627–2632.

[17] Hunter L, Ferguson R, McDevitt H. Vitamin D deficiency cardiomyopathy in Scotland: a retrospective review of the last decade. Archives of Disease in Childhood. 2020; 105: 853–856.

[18] Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart. 2004; 90: 1224–1228.

[19] Lupsa BC, Sachdev V, Lungu AO, Rosing DR, Gorden P. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. Medicine. 2010; 89: 245–250.

[20] Lenders JWM, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005; 366: 665–675.

[21] Santos JRU, Brofferio A, Viana B, Pacak K. Catecholamine-Induced Cardiomyopathy in Pheochromocytoma: how to Manage a Rare Complication in a Rare Disease? Hormone and Metabolic Research. 2019; 51: 458–469.

[22] Park J, Kim KS, Sul J, Shin SK, Kim JH, Lee J, *et al.* Prevalence and patterns of left ventricular dysfunction in patients with pheochromocytoma. Journal of Cardiovascular Ultrasound. 2011; 19: 76–82.

[23] Giavarini A, Chedid A, Bobrie G, Plouin P, Hagège A, Amar L. Acute catecholamine cardiomyopathy in patients with phaeochromocytoma or functional paraganglioma. Heart. 2013; 99: 1438–1444.

[24] Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine Metabolism: a Contemporary View with Implications for Physiology and Medicine. Pharmacological Reviews. 2004; 56: 331–349.

[25] Pocock G, Richards CD. Human physiology: the basis of medicine. 3rd edn. Oxford University Press: Oxford. 2006.

[26] Gubbi S, Nazari MA, Taieb D, Klubo-Gwiezdzinska J, Pacak K. Catecholamine physiology and its implications in patients with COVID-19. The Lancet Diabetes & Endocrinology. 2020; 8: 978–986.

[27] Gordan R, Gwathmey JK, Xie L. Autonomic and endocrine control of cardiovascular function. World Journal of Cardiology. 2015; 7: 204–214.

[28] Kassim TA, Clarke DD, Mai VQ, Clyde PW, Mohamed Shakir KM. Catecholamine-induced cardiomyopathy. Endocrine Practice. 2008; 14: 1137–1149.

[29] Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. Mayo Clinic Proceedings. 2000; 75: 790–795.

[30] Jacob JL, da Silveira LC, de Freitas CG, Cêntola CA, Nicolau JC, Lorga AM. Pheochromocytoma with echocardiographic features of obstructive hypertrophic cardiomyopathy: a case report. Angiology. 1994; 45: 985–989.

[31] Fleckenstein A, Janke J, Doring HJ, Pachinger O. Ca overload as the determinant factor in the production of catecholamine induced myocardial lesion. Recent Advances in Studies on Cardiac Structure and Metabolism. 1973; 2: 455–266.

[32] Rona G, Kahn DS, Chappel CI. Studies on infarct-like myocardial necrosis produced by isoproterenol: a review. Revue Canadienne De Biologie. 1996; 22: 241–255.

[33] Nakano T, Onoue K, Nakada Y, Nakagawa H, Kumazawa T, Ueda T, *et al.* Alteration of β-adrenoceptor signalling in left ventricle of acute phase Takotsubo syndrome: a human study. Scientific Reports. 2018; 8: 12731.

[34] Paur H, Wright PT, Sikkel MB, Tranter MH, Mansfield C, O'Gara P, *et al.* High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. Circulation. 2012; 126: 697–706.

[35] Heubach JF, Ravens U, Kaumann AJ. Epinephrine activates both Gs and Gi pathways, but norepinephrine activates only the Gs pathway through human beta2-adrenoceptors overexpressed in mouse heart. Molecular Pharmacology. 2004; 65: 1313–1322.

[36] Zieleń P, Klisiewicz A, Januszewicz A, Prejbisz A, Kabat M, Peczkowska M, *et al.* Pheochromocytoma-related 'classic' takotsubo cardiomyopathy. Journal of Human Hypertension. 2010; 24: 363–366.

[37] Chesley A, Lundberg MS, Asai T, Xiao RP, Ohtani S, Lakatta EG, *et al.* The beta(2)-adrenergic receptor delivers an antiapoptotic signal to cardiac myocytes through G(i)-dependent coupling to phos-

phatidylinositol 3'-kinase. Circulation Research. 2000; 87: 1172–1179.
[38] Santulli G, Campanile A, Spinelli L, Assante di Panzillo E, Ciccarelli M, Trimarco B, *et al.* G protein-coupled receptor kinase 2 in patients with acute myocardial infarction. The American Journal of Cardiology. 2011; 107: 1125–1130.
[39] Batisse-Lignier M, Pereira B, Motreff P, Pierrard R, Burnot C, Vorilhon C, *et al.* Acute and Chronic Pheochromocytoma-Induced Cardiomyopathies: Different Prognoses?: a Systematic Analytical Review. Medicine. 2015; 94: e2198.
[40] Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and risk of congestive heart failure. The New England Journal of Medicine. 2002; 347: 1135–1142.
[41] Dhalla NS. Formation of Aminochrome Leads to Cardiac Dysfunction and Sudden Cardiac Death. Circulation Research. 2018; 123: 409–411.
[42] Adameova A, Abdellatif Y, Dhalla NS. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. Canadian Journal of Physiology and Pharmacology. 2009; 87: 493–514.
[43] Dhalla NS, Adameova A, Kaur M. Role of catecholamine oxidation in sudden cardiac death. Fundamental & Clinical Pharmacology. 2010; 24: 539–546.
[44] Whitelaw BC, Prague JK, Mustafa OG, Schulte KM, Hopkins PA, Gilbert JA, *et al.* Phaeochromocytoma crisis. Clinical Endocrinology. 2014; 80: 13–22.
[45] Kimura S, Mitsuma W, Ito M, Suzuki H, Hosaka Y, Hirayama S, *et al.* Inverted Takotsubo contractile pattern caused by pheochromocytoma with tall upright T-waves, but not typical deep T-wave inversion. International Journal of Cardiology. 2010; 139: e15–e17.
[46] Lyon AR, Rees PSC, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy–a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nature Clinical Practice. Cardiovascular Medicine. 2008; 5: 22–29.
[47] Y-Hassan S, Falhammar H. Clinical features, complications, and outcomes of exogenous and endogenous catecholamine-triggered Takotsubo syndrome: a systematic review and meta-analysis of 156 published cases. Clinical Cardiology. 2020; 43: 459–467.
[48] Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. Circulation Research. 2013; 113: 739–753.
[49] Ramchandra R, Hood SG, Xing D, Lambert GW, May CN. Mechanisms underlying the increased cardiac norepinephrine spillover in heart failure. American Journal of Physiology-Heart and Circulatory Physiology. 2018; 315: H340–H347.
[50] Kume T, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, *et al.* Assessment of Coronary Microcirculation in Patients with Takotsubo-Like Left Ventricular Dysfunction. Circulation Journal. 2005; 69: 934–939.
[51] Goldstein DS, Eisenhofer G, Kopin IJ. Sources and Significance of Plasma Levels of Catechols and their Metabolites in Humans. Journal of Pharmacology and Experimental Therapeutics. 2003; 305: 800–811.
[52] Wittstein IS, Thiemann DR, Lima JAC, Baughman KL, Schulman SP, Gerstenblith G, *et al.* Neurohumoral features of myocardial stunning due to sudden emotional stress. The New England Journal of Medicine. 2005; 352: 539–548.
[53] Merli E, Sutcliffe S, Gori M, Sutherland GGR. Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology. European Journal of Echocardiography. 2006; 7: 53–61.
[54] Coupez E, Eschalier R, Pereira B, Pierrard R, Souteyrand G, Clerfond G, *et al.* A single pathophysiological pathway in Takotsubo cardiomyopathy: Catecholaminergic stress. Archives of Cardiovascular Diseases. 2014; 107: 245–252.
[55] Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, *et al.* Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation. 2005; 111: 472–479.
[56] Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clinic Proceedings. 1983; 58: 802–804.
[57] Satendra M, de Jesus C, Bordalo e Sá AL, Rosário L, Rocha J, Bicha Castelo H, *et al.* Reversible catecholamine-induced cardiomyopathy due to pheochromocytoma: Case report. Revista Portuguesa De Cardiologia. 2014; 33: 177.e1–177.e6.
[58] Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Alì A, *et al.* A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. The Journal of Clinical Endocrinology and Metabolism. 2000; 85: 637–644.
[59] Ho AD, Feurle G, Gless KH, Brandeis WE. Normotensive familial phaeochromocytoma with predominant noradrenaline secretion. British Medical Journal. 1978; 1: 81–82.
[60] Pappachan JM, Tun NN, Arunagirinathan G, Sodi R, Hanna FWF. Pheochromocytomas and Hypertension. Current Hypertension Reports. 2018; 20: 3.
[61] Soltani A, Pourian M, Davani BM. Does this patient have Pheochromocytoma? A systematic review of clinical signs and symptoms. Journal of Diabetes & Metabolic Disorders. 2016; 15: 6.
[62] Hamidi O, Young WF, Iñiguez-Ariza NM, Kittah NE, Gruber L, Bancos C, *et al.* Malignant Pheochromocytoma and Paraganglioma: 272 Patients over 55 Years. The Journal of Clinical Endocrinology and Metabolism. 2017; 102: 3296–3305.
[63] Malindretos PM, Sarafidis PA, Geropoulou EZ, Kapoulas S, Paramythiotis DD, Lasaridis AN. Sustained Hypotension Complicating an Extra-adrenal Pheochromocytoma. American Journal of Hypertension. 2008; 21: 840–842.
[64] Kometani M, Yoneda T, Maeda Y, Oe M, Takeda Y, Higashitani T, *et al.* Pheochromocytoma crisis with cyclic fluctuation in blood pressure mimics acute coronary syndrome. Endocrinology, Diabetes & Metabolism Case Reports. 2020; 2020: 20-0115.
[65] Ionescu CN, Sakharova OV, Harwood MD, Caracciolo EA, Schoenfeld MH, Donohue TJ. Cyclic rapid fluctuation of hypertension and hypotension in pheochromocytoma. Journal of Clinical Hypertension. 2008; 10: 936–940.
[66] Kobal SL, Paran E, Jamali A, Mizrahi S, Siegel RJ, Leor J. Pheochromocytoma: cyclic attacks of hypertension alternating with hypotension. Nature Clinical Practice Cardiovascular Medicine. 2008; 5: 53–57.
[67] Ohara N, Uemura Y, Mezaki N, Kimura K, Kaneko M, Kuwano H, *et al.* Histopathological analysis of spontaneous large necrosis of adrenal pheochromocytoma manifested as acute attacks of alternating hypertension and hypotension: a case report. Journal of Medical Case Reports. 2016; 10: 279.
[68] Kaneto H, Kamei S, Tatsumi F, Shimoda M, Kimura T, Nakanishi S, *et al.* Case report: malignant pheochromocytoma without hypertension accompanied by increment of serum VEGF level and catecholamine cardiomyopathy. Frontiers in Endocrinology. 2021; 12: 688536.
[69] Y-Hassan S, Falhammar H. Cardiovascular manifestations, and complications of pheochromocytomas and paragangliomas. Journal of Clinical Medicine. 2020; 9: 2435.
[70] Sedaia E, Esanu A, Ivanov V, Dumanschi C, Moiseeva A, Abraș M, *et al.* Catecholamine-induced cardiomyopathy in a patient with pheochromocytoma and polycystic kidney and liver disease: a case report. European Heart Journal-Case Reports. 2019; 3: ytz062.
[71] Quigg RJ, Om A. Reversal of severe cardiac systolic dysfunction caused by pheochromocytoma in a heart transplant candidate. The Journal of Heart and Lung Transplantation. 1994; 13: 525–532.
[72] McEntee RK, Coyle D, Meyer M. Severe dilated cardiomyopathy after propranolol treatment in an undiagnosed adrenal pheochromocytoma. Circulation: Heart Failure. 2011; 4: e10–e12.
[73] Gatzoulis KA, Tolis G, Theopistou A, Gialafos JH, Toutouzas PK. Cardiomyopathy due to a pheochromocytoma. A reversible entity. Acta Cardiologica. 1998; 53: 227–229.

[74] Wilkenfeld C, Cohen M, Lansman SL, Courtney M, Dische MR, Pertsemlidis D, *et al.* Heart transplantation for end-stage cardiomyopathy caused by an occult pheochromocytoma. The Journal of Heart and Lung Transplantation. 1992; 11: 363–366.
[75] Wani A, Adil A, Gardezi SAA, Jain R, Galazka P, Waples MJ, *et al.* Pheochromocytoma Presenting as Hypertrophic Obstructive Cardiomyopathy. JAMA Cardiology. 2021; 6: 974.
[76] Schuiki ER, Jenni R, Amann FW, Ziegler WH. A reversible form of apical left ventricular hypertrophy associated with pheochromocytoma. Journal of the American Society of Echocardiography. 1993; 6: 327–331.
[77] Ghadri J, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, *et al.* International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. European Heart Journal. 2018; 39: 2032–2046.
[78] Y-Hassan S. Clinical Features and Outcome of Pheochromocytoma-Induced Takotsubo Syndrome: Analysis of 80 Published Cases. The American Journal of Cardiology. 2016; 117: 1836–1844.
[79] Agarwal V, Kant G, Hans N, Messerli FH. Takotsubo-like cardiomyopathy in pheochromocytoma. International Journal of Cardiology. 2011; 153: 241–248.
[80] Newell KA, Prinz RA, Pickleman J, Braithwaite S, Brooks M, Karson TH, *et al.* Pheochromocytoma multisystem crisis. A surgical emergency. Archives of Surgery. 1988; 123: 956–959.
[81] Davlouros PA, Velissaris D, Tsiola A, Filos KS, Alexopoulos D. Fever with multiple organ failure: not always sepsis. Anaesthesia and Intensive Care. 2010; 38: 1090–1093.
[82] Kang JM, Lee WJ, Kim WB, Kim TY, Koh JM, Hong SJ, *et al.* Systemic inflammatory syndrome and hepatic inflammatory cell infiltration caused by an interleukin-6 producing pheochromocytoma. Endocrine Journal. 2005; 52: 193–198.
[83] Minetto M, Dovio A, Ventura M, Cappia S, Daffara F, Terzolo M, *et al.* Interleukin-6 producing pheochromocytoma presenting with acute inflammatory syndrome. Journal of Endocrinological Investigation. 2003; 26: 453–457.
[84] Lee T, Lin K, Chang C, Lew W, Lee T. Pheochromocytoma mimicking both acute coronary syndrome and sepsis: a case report. Medical Principles and Practice. 2013; 22: 405–407.
[85] Riester A, Weismann D, Quinkler M, Lichtenauer UD, Sommerey S, Halbritter R, *et al.* Life-threatening events in patients with pheochromocytoma. European Journal of Endocrinology. 2015; 173: 757–764.
[86] Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: Analysis and review of the literature. International Journal of Cardiology. 2017; 249: 319–323.
[87] Lenders JWM, Duh Q, Eisenhofer G, Gimenez-Roqueplo A, Grebe SKG, Murad MH, *et al.* Pheochromocytoma and Paraganglioma: an Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2014; 99: 1915–1942.
[88] van Berkel A, Lenders JWM, Timmers HJLM. Diagnosis of endocrine disease: Biochemical diagnosis of phaeochromocytoma and paraganglioma. European Journal of Endocrinology. 2014; 170: R109–R119.
[89] Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JWM, *et al.* European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. European Journal of Endocrinology. 2016; 174: G1–G10.
[90] Rao D, Peitzsch M, Prejbisz A, Hanus K, Fassnacht M, Beuschlein F, *et al.* Plasma methoxytyramine: clinical utility with metanephrines for diagnosis of pheochromocytoma and paraganglioma. European Journal of Endocrinology. 2017; 177: 103–113.
[91] Mamoojee Y, Arham M, Elsaify W, Nag S. Lesson of the month 2: Catecholamine-induced cardiomyopathy - pitfalls in diagnosis and medical management. Clinical Medicine. 2016; 16: 201–203.
[92] Bravo EL. Pheochromocytoma: new concepts and future trends. Kidney International. 1991; 40: 544–556.
[93] Timmers HJLM, Gimenez-Roqueplo A, Mannelli M, Pacak K. Clinical aspects of SDHx-related pheochromocytoma and paraganglioma. Endocrine-Related Cancer. 2009; 16: 391–400.
[94] Alsidawi S. Regional wall motion abnormalities in patients with pheochromocytoma. Hypertension Research. 2012; 35: 1135.
[95] Agarwal V. Takotsubo Cardiomyopathy with Pheochromocytoma. JACC: Case Reports. 2019; 1: 91–93.
[96] Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB, *et al.* Pheochromocytoma is Characterized by Catecholamine-Mediated Myocarditis, Focal and Diffuse Myocardial Fibrosis, and Myocardial Dysfunction. Journal of the American College of Cardiology. 2016; 67: 2364–2374.
[97] Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. Herz. 2010; 35: 240–243.
[98] Ghadri J, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, *et al.* International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. European Heart Journal. 2018; 39: 2047–2062.
[99] Casey RT, Challis BG, Pitfield D, Mahroof RM, Jamieson N, Bhagra CJ, *et al.* Management of an acute catecholamine-induced cardiomyopathy and circulatory collapse: a multidisciplinary approach. Endocrinology, Diabetes & Metabolism Case Reports. 2017; 2017: 17-0122.
[100] Eisenhofer G, Rivers G, Rosas AL, Quezado Z, Manger WM, Pacak K. Adverse drug reactions in patients with phaeochromocytoma: incidence, prevention and management. Drug Safety. 2007; 30: 1031–1062.
[101] Takagi S, Miyazaki S, Fujii T, Daikoku S, Sutani Y, Morii I, *et al.* Dexamethasone-induced cardiogenic shock rescued by percutaneous cardiopulmonary support (PCPS) in a patient with pheochromocytoma. Japanese Circulation Journal. 2000; 64: 785–788.
[102] Hoffman BB. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In Hardman JG, Limbird LE (eds.) Goodman & Gillman's: the pharmacological basis of therapeutics (pp. 215–268). McGraw-Hill: Philadelphia. 2001.
[103] Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World Journal of Surgery. 2002; 26: 1037–1042.
[104] Min D. Catastrophic catecholamine-induced cardiomyopathy rescued by extracorporeal membrane oxygenation in recurrent malignant pheochromocytoma. Yeungnam University Journal of Medicine. 2019; 36: 254–259.
[105] Bouabdallaoui N, Bouchard D, Jolicoeur EM, Chronopoulos A, Garneau PY, Lamarche Y. Extracorporeal membrane oxygenation in pheochromocytoma-induced cardiogenic shock. Asian Cardiovascular & Thoracic Annals. 2018; 26: 314–316.
[106] Matteucci M, Kowalewski M, Fina D, Jiritano F, Meani P, Raffa GM, *et al.* Extracorporeal life support for phaeochromocytoma-induced cardiogenic shock: a systematic review. Perfusion. 2020; 35: 20–28.
[107] Patel SM, Lipinski J, Al-Kindi SG, Patel T, Saric P, Li J, *et al.* Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with Impella is Associated with Improved Outcomes in Refractory Cardiogenic Shock. ASAIO Journal. 2019; 65: 21–28.
[108] Shawa H, Bajaj M, Cunningham GR. Pheochromocytoma-Induced Atrial Tachycardia Leading to Cardiogenic Shock and Cardiac Arrest: Resolution with Atrioventricular Node Ablation and Pacemaker Placement. Texas Heart Institute Journal. 2014; 41: 660–663.
[109] Salathe M, Weiss P, Ritz R. Rapid reversal of heart failure in a patient with phaeochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril. British Heart Journal. 1992; 68: 527–528.
[110] Singal PK, Kapur N, Dhillon KS, Beamish RE, Dhalla NS. Role of free radicals in catecholamine induced cardiomyopathy. Canadian Journal of Physiology and Pharmacology. 1982; 60: 1390–1397.

[111] Przyklenk K, Kloner RA. Relationship between structure and effects of ACE inhibitors: comparative effects in myocardial ischaemic/reperfusion injury. British Journal of Clinical Pharmacology. 1989; 28: 167–175.
[112] Prejbisz A, Lenders JWM, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of phaeochromocytoma. Journal of Hypertension. 2011; 29: 2049–2060.
[113] Jia X, Guo X, Zheng Q. Perioperative management of paraganglioma and catecholamine-induced cardiomyopathy in child- a case report and review of the literature. BMC Anesthesiology. 2017; 17: 142.
[114] Ramachandran R, Rewari V. Factors affecting the haemodynamic behaviour of patients undergoing pheochromocytoma and paraganglioma removal: a review. Cardiovascular Endocrinology. 2017; 6: 73–80.
[115] Bonnefont-Rousselot D, Mahmoudi A, Mougenot N, Varoquaux O, Le Nahour G, Fouret P, *et al.* Catecholamine effects on cardiac remodelling, oxidative stress and fibrosis in experimental heart failure. Redox Report. 2002; 7: 145–151.
[116] Katsuumi G, Shimizu I, Yoshida Y, Hayashi Y, Ikegami R, Suda M, *et al.* Catecholamine-Induced Senescence of Endothelial Cells and Bone Marrow Cells Promotes Cardiac Dysfunction in Mice. International Heart Journal. 2018; 59: 837–844.
[117] Shao Y, Redfors B, Stahlman M, Tang MS, Miljanovic A, Mollmann H, *et al.* A mouse model reveals an important role for catecholamine-induced lipotoxicity in the pathogenesis of stress-induced cardiomyopathy. European Journal of Heart Failure. 2013; 15: 9–22.