Catecholamine-induced hypertensive crises: current insights and management

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Phaeochromocytomas and paragangliomas (PPGLs) release catecholamines leading to catecholamine-induced hypertensive (CIH) crises, with blood pressure greater than or equal to 180/120 mm Hg. CIH crises can be complicated by tachyarrhythmias, hypotension, or life-threatening target organ damage while treatment remains undefined, often requiring co-management between endocrinologists and cardiologists. Furthermore, biochemical diagnosis of a PPGL as a cause of a CIH crisis can be difficult to identify or confounded by comorbid conditions, potentially resulting in misdiagnosis. Here, we combine relevant evidence, 60 years of collective clinical experience, insights derived from assessing over 2600 patients with PPGL, and supplementary outcomes from 100 patients (treated at the National Institutes of Health) with a CIH crisis to inform diagnosis and treatment of CIH crises. Recognising that disparities exist between availability, cost, and familiarity of various agents, flexible approaches are delineated allowing for customisation, given institutional availability and provider preference. A CIH crisis and its complications are readily treatable with available drugs, with effective intervention defining an avenue for mitigating consequent morbidity and mortality in patients with PPGL.

Introduction

Severe hypertension, presenting as a hypertensive crisis defined by a blood pressure greater than or equal to 180/120 mm Hg, is conventionally divided into hypertensive urgency and emergency—the critical distinction being new or worsening target organ damage in the latter.[1] Target organ damage, when immediately life-threatening (eg, myocardial infarction, haemorrhagic stroke, or aortic dissection), requires expeditious intervention.[1] One of the most perilous secondary causes of a hypertensive crisis is catecholamine excess. Catecholamines—noradrenaline and adrenaline—in excess, can lead to catecholamine-induced hypertension (CIH) and more severely a CIH crisis, with a high risk of life-threatening cardiovascular complications.[2–4]

Chromaffin cell tumours—phaeochromocytoma and paraganglioma (PPGL)—are a major cause of CIH and CIH crises. However, diagnosing a PPGL as the cause of a CIH crisis is challenging upon presentation in the acute setting, as comorbid conditions and severe mental and physical stress (eg, panic disorder, hypoglycaemia, ischaemic heart disease, or admission to the emergency department) can interfere with biochemical evaluation, leading to misdiagnosis.[5–7] Appropriately diagnosing a CIH crisis in acute settings is essential and is therefore discussed in this Review.[8,9] Up to 95% of patients with PPGL have hypertension, either sustained (50%) or paroxysmal (45%), whereas up to 0·6% of patients with hypertension have PPGLs.[8–12] Adverse cardiovascular events are the number one cause of death among those with PPGL (71% mortality), with hypertension being a clinically significant determinant.[13–15] Severe hypertension is common (75%) in patients with PPGL and 7–17% present with a CIHC.[2–4,15,16] Poor cardiovascular outcomes are associated with CIH crises. As such, one-in-ten patients have cardiovascular complications (17–50% myocardial infarctions, 14–17% strokes, and approximately 15% arrhythmias), with 80% having a hypertensive crisis.[2–4] Furthermore, 23–30% of patients with a CIH crisis develop hypotension or even shock during treatment.[2–4] Although diagnosis and treatment of a CIH crisis in acute settings might be difficult and associated with clinically significant morbidity and mortality, there is a paucity of guidance regarding evaluation and management.

Catecholamine-induced hypertensive crises: uncertainties

A CIH crisis is a unique secondary cause of hypertension, often requiring an unorthodox approach to management; however, a CIH crisis might be seen as or treated with stereotyped strategies for undifferentiated hypertension.[12,17] Therefore a CIH crisis might be misunderstood and underestimated, leading to unrecognised potential for decompensation or complications if mismanaged.[18] Fortunately, familiarity with the core principles that define a CIH crisis allows for optimal management, thus minimising morbidity and mortality. As such, the role of the endocrinologist is instrumental in guiding the treatment of a CIH crisis.

PPGLs store tremendous quantities of catecholamines, at times exceeding 3 million pg/g of tissue, leading to an approximate 1000-fold rise in plasma catecholamines if released.[19,20] Therefore, if triggered, erratic blood pressure elevations can occur even if blood pressure is first normalised with treatment.[21,22] Furthermore, unexpected complications might occur because excessive catecholamines directly stimulate and ultimately damage the heart (eg, myocarditis) and vasculature (eg, coronary artery vasoconstriction resulting in myocardial infarction), independent of the severity of hypertension.[16,23–25] Additionally, standard first-line interventions for rapid blood pressure control in severe hypertension (eg, labetalol or hydralazine) can be counterproductive or even harmful in CIH crises, paradoxically worsening hypertension and target organ

damage (eg, stroke, aortic dissection, or flash pulmonary oedema).[18,26,27] Moreover, patients might have hypotension which could progress to shock (rarely multiorgan failure) and tachyarrhythmias (in some instances decompensating into cardiac arrest) over the course of a CIH crisis and treatment, due to either excessive catecholamine levels or various pharmacotherapies.[18,28–30] In addition, many agents recommended for the treatment of CIH (referred to hereafter as conventionally recommended agents) might be unavailable, costly, or less often used in routine practice (eg, phentolamine, phenoxybenzamine, or clevidipine) in clinical settings where CIH crises and their complications most often occur.[23,28,31] Finally, CIH crisis treatment can fall into a grey area, whereby neither endocrinologists or cardiologists are best suited to treat patients in isolation (leading to delays in decisive management) and therefore the expertise of both services is often necessary. Thus, the course of a CIH crisis and its treatment can be unpredictable, with common approaches (eg, labetalol or hydralazine) possibly worsening hypertension, recommended or conventional agents (eg, phentolamine) remaining out of reach, and definitive management requiring interdisciplinary collaboration. These challenges might lead to great uncertainty in clinical settings where CIH crises are often treated and where complications arise. Therefore, a clear need exists to define proper therapeutic approaches that use agents readily available across the spectrum of practice environments where patients are treated.

Catecholamine-induced hypertensive crises: defining the path forward

Over the last 20 years, 1822 of 2615 patients with PPGL referred to our institution (National Institutes of Health, Bethesda, MD, USA) had electronic blood pressure measurements, with 153 (8·4%) patients having an in-hospital hypertensive crisis (appendix p 6). Additionally, as a tertiary care centre, we often aid in the management of patients at outside institutions. Thus, we have experience in treating CIH crises with readily available agents (eg, nicardipine, nitroprusside, or verapamil) and with conventionally recommended agents (eg, phentolamine or phenoxybenzamine) in different clinical circumstances and settings. Our experience and insights gathered from caring for these patients with both conventionally recommended and commonplace agents forms the basis of this Review. Hypotension is a frequent and sometimes life-threatening condition that can occur when treating a CIH crisis. Therefore, we present an approach to hypotension rationalised by available evidence and specific data from our institution (appendix pp 6, 15).

Endocrine physiology and pathophysiology

The physiology and pathophysiology of catecholamines and their excess defines the signs, symptoms and management of a CIH crisis. These core physiology and pathophysiology principles are therefore elaborated upon in the appendix (pp 3–5), with major clinically relevant aspects highlighted in this Review. Exemplary management of a CIH crisis is most often provided, in part, by endocrinologists familiar with these principles, as CIH crises are an endocrine anomaly.

Catecholamines are synthesised, stored, and then either undergo metabolism or release and reuptake (appendix pp 12–13).[21,32] Many agents, including steroids, catecholamine reuptake inhibitors, sympathomimetics, and tyramine-containing foods (appendix pp 12–13) can interfere in these processes and increase catecholamine availability and release, subsequently triggering or worsening a CIH crisis.[21,32,33] Alternatively, metirosine can inhibit catecholamine biosynthesis, defining the value of metirosine in treating a CIH crisis.[34] Providers should be familiar with these agents to provide the most appropriate management.

After release into the circulatory system, catecholamines bind to adrenoceptors in the heart and vasculature.[35,36] Adrenoceptors, when stimulated, act via second messengers (eg, cyclic AMP) that influence calcium or actin–myosin crossbridge cycling, or both, leading to a change in blood pressure and heart rate (appendix pp 12–13).[33,37] Stimulation of α_1-adrenoceptors found on small precapillary sphincters increases total peripheral resistance and blood pressure.[9,33,36,38] In contrast, stimulation of presynaptic α_2-adrenoceptors can reduce neuronal noradrenaline release, decreasing blood pressure (a negative feedback mechanism).[39,40] Stimulation of β_1-adrenoceptors on cardiomyocytes and the cardiac conduction system collectively increases heart rate, cardiac output, and blood pressure (figure 1).[33,35,36,41] β_2-adrenoceptors are present on blood vessels, where stimulation can lead to vasodilation, and on cardiomyocytes, where stimulation, if excessive or chronic, can suppress inotropy.[42–44] β_2-Adrenoceptor stimulation on blood vessels and cardiomyocytes can decrease blood pressure and, if excessive, lead to profound hypotension.[36,41–43,45]

See Online for appendix

Biochemical phenotypes

Cardiovascular implications

Noradrenaline and adrenaline are stored and released in different patterns from PPGLs and have differing affinities for adrenoceptors, leading to different clinical manifestations known as phenotypes.[46] Catecholamine metabolites, measured in plasma, include metanephrine (from adrenaline), normetanephrine (from noradrenaline), and 3-methoxytyramine (from dopamine).[20,46–48] Concentrations of these metabolites define the adrenergic phenotype. The adrenergic phenotype is defined by an elevated plasma metanephrine above the upper reference limit (usually 61 pg/mL) and an increase in plasma metanephrine of greater than 5% of the total increments in plasma metanephrine, normetanephrine,

and 3-methoxytyramine above their respective upper reference limits (appendix p 6).[49] Other biochemical patterns represent the noradrenergic and dopaminergic phenotypes.[20,46–50]

Prototypical adrenergic tumours release adrenaline episodically and can be associated with paroxysmal hypertension and increased (β_1-adrenoceptor-mediated) tachycardia, whereas prototypical noradrenergic tumours continuously release noradrenaline and can be associated with continuous hypertension and less prominent (β_1-adrenoceptor-mediated) tachycardia.[19,20,36,41,45–48,51–53] Importantly, adrenaline is primarily a hormone and is largely synthesised and released from the adrenal medulla.[41,45,54] However, noradrenaline is principally a neurotransmitter and thus, despite its location of synthesis, can undergo reuptake and accumulate in excess throughout the sympathetic nervous system.[54] Thus, noradrenaline released from neurons (not only tumours) in response to general sympathetic stimuli can precipitate a CIH crisis.[54,55] Therefore, in patients with a CIH crisis, limit or treat sympathetic stimuli (pain or anxiety, positional changes, etc) and assess tumours, especially adrenal tumours, for dynamic changes.[19,56]

Cardiovascular complications

As a natural extension of receptor affinity and mode of catecholamine release, patients with the noradrenergic phenotype might have more sequelae of excessive α_1-adrenoceptor stimulation (eg, flash pulmonary oedema, coronary artery vasospasm and myocardial infarction, or aortic dissection), whereas those with the adrenergic phenotype might have more sequelae of excessive β-adrenoceptor stimulation (eg, tachyarrhythmia, myocarditis, and demand myocardial ischaemia or infarction) in addition to the sequelae of α_1-adrenoceptor stimulation (figure 1; appendix pp 12–13).[9,16,23,24,30,33,57–61] Moreover, some patients with adrenaline-releasing tumours might have excessive β_2-adrenoceptor-mediated vasodilation or suppression of myocardial contractility (as in Takotsubo-like cardiomyopathy), leading to hypotension or shock (figure 1; appendix p 14).[19,21,29,43,51,53,62] This hypotension is an uncommon but clinically divergent aspect of the adrenergic phenotype and must be recognised, as patients can become gravely ill.[3,29]

Diagnosis

Although rare, recognising the specific clinical features of a CIH crisis can inevitably prompt a diagnosis. There should be evaluation for other secondary causes of hypertension (eg, renal artery stenosis or primary aldosteronism). However, if a PPGL is suspected, interfering agents should be discontinued (appendix pp 12–13) and comorbid conditions (including acid-base disturbances, endocrinopathies, etc) should be addressed, as both approaches might reduce catecholamine turnover or mitigate the effects of catecholamines or both.[21,33]

The prime diagnostic priority when suspecting a CIH crisis in the emergency setting is immediate imaging, not biochemical testing,[5] as strong sympathetic activation during hypertensive crises and in the emergency department or intensive care unit often elevates catecholamines or metanephrines (or both), falsely suggesting a PPGL.[5]

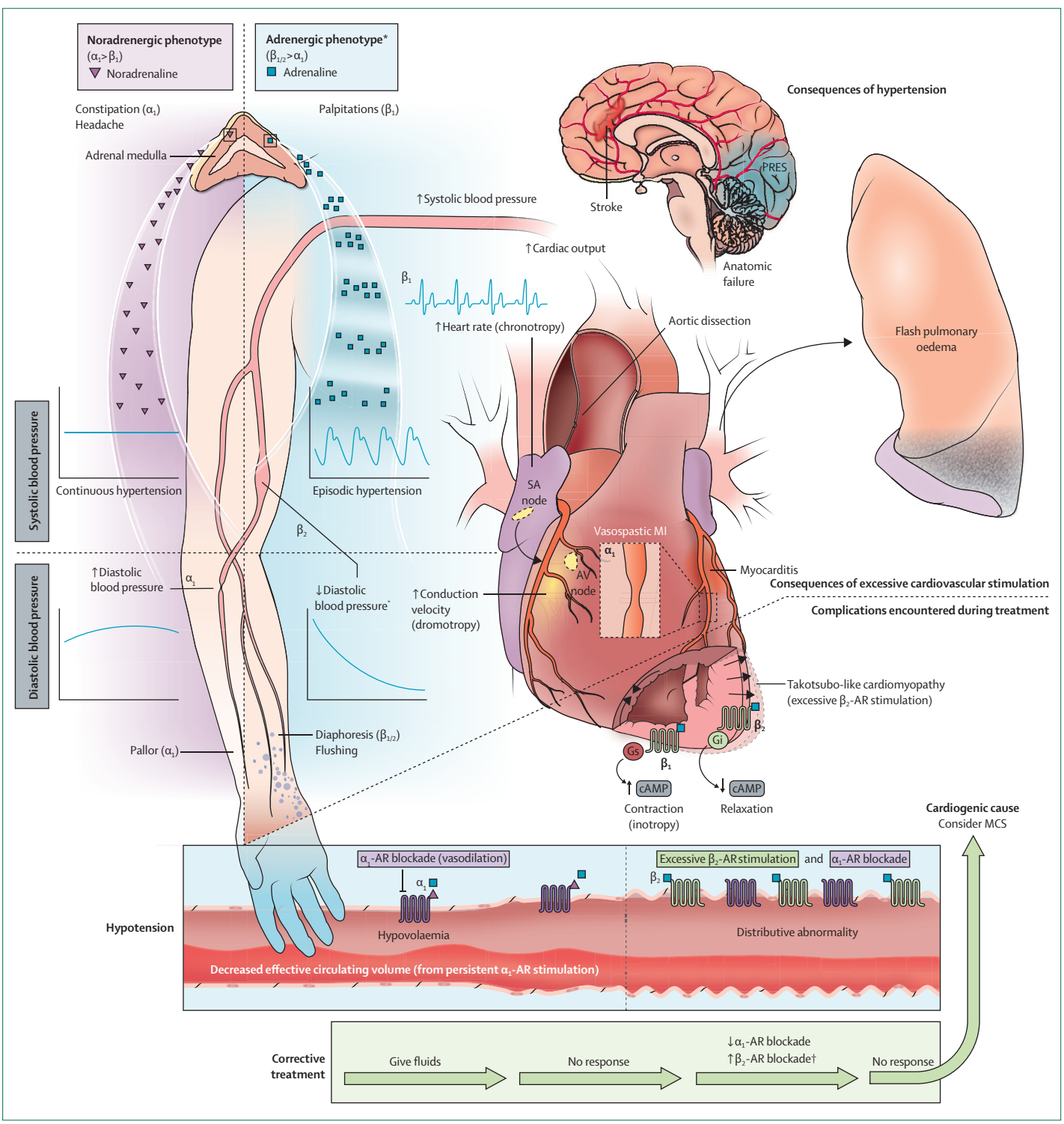
Recognising clinical manifestations

In emergency circumstances, providers can consider gathering the medical history from the patient or relatives to identify a history of, or predisposition to PPGL. Second, if a personal history of PPGL is identified, clarifying the aspects of how it was diagnosed should be considered, as certain conditions might lead to labile blood pressure and biochemical elevations, with a consequent diagnosis of possible PPGL yet to be confirmed by definitive testing (as discussed later in this Review).[63,64] In some instances, a PPGL might not be present upon further evaluation.[64,65] For example, in patients with anxiety or frank panic disorder in medical settings, this circumstance can mimic a CIH crisis from a PPGL.[65,66] This hypertension can be a so-called white coat phenomenon.[63,66] Thus, by soliciting whether a PPGL has been more definitively confirmed (eg, by imaging), providers can consider proceeding with caution to avoid overzealous treatment.

Figure 1: **Biochemical phenotypes, cardiovascular implications of excess catecholamines, and complications encountered while treating a catecholamine-induced hypertensive crisis**

Biochemical phenotypes have stereotypical manifestations related to adrenoceptor affinity (top left of the image). Excessive catecholamines can lead to cardiovascular complications that might arise as a direct consequence of hypertension (top right of the image). Chronic α_1-adrenoceptor stimulation might lead to arterial stiffening and hypertension compromising vessel structure with consequent anatomic failure (eg, haemorrhagic stroke and aortic dissection). Haemodynamic consequences of catecholamine-induced hypertension include PRES and flash pulmonary oedema. Non-haemodynamic consequences of excess catecholamines can arise from intense cardiovascular stimulation with coronary artery vasoconstriction and myocardial infarction and myocarditis. Furthermore, excessive cardiac β_2-adrenoceptor stimulation might lead to adrenoceptor trafficking (or a switch from G_s to G_i protein-coupled receptors) within cardiomyocytes. This action suppresses myocardial contraction and leads to a Takotsubo-like cardiomyopathy and might be encountered when treating a CIHC. Hypotension that occurs when treating a CIHC might be due to hypovolaemia, a distributive abnormality of blood flow, or a cardiogenic cause (bottom of the image). Treatment includes fluid administration, adjusting AR blockade, and obtaining an echocardiogram if hypotension persists or is severe. MCS and extracorporeal membrane oxygenation are preferred initial strategies in severe, especially cardiogenic, shock. AR=adrenoceptor. AV=atrioventricular. BP=blood pressure. cAMP=cyclic AMP. CIHC=catecholamine-induced hypertensive crisis. G_i=inhibitory G protein-coupled receptor. G_s=stimulatory G protein-coupled receptor. MCS=mechanical circulatory support. MI=myocardial infarction. PRES=posterior reversible encephalopathy syndrome. SA=sinoatrial. *In rare circumstances, excessive β_2-adrenoceptor stimulation might occur in the adrenergic phenotype; this physiology is clinically relevant. †Excessive vascular (distributive abnormality of blood flow) and cardiac (Takotsubo-like cardiomyopathy) β_2-adrenoceptor stimulation can lead to low BP, and propranolol (the $\beta_{1/2}$-adrenoceptor blocking agent) could be used, as BP permits.

Unlike isolated, subjective signs and symptoms, three or more signs and symptoms of catecholamine excess (such as hyperhidrosis, palpitations, pallor, tremor, or nausea) combined with a BMI less than 25 kg/m² and a heart rate greater than 85 beats per min suggests (with 7·5-times greater likelihood) an underlying PPGL.[8,46,67] Clinically overt or distinctive presentations (clinical pearls) that should engender suspicion for a PPGL include: (1) apparent treatment resistant hypertension despite three or more antihypertensive agents plus signs



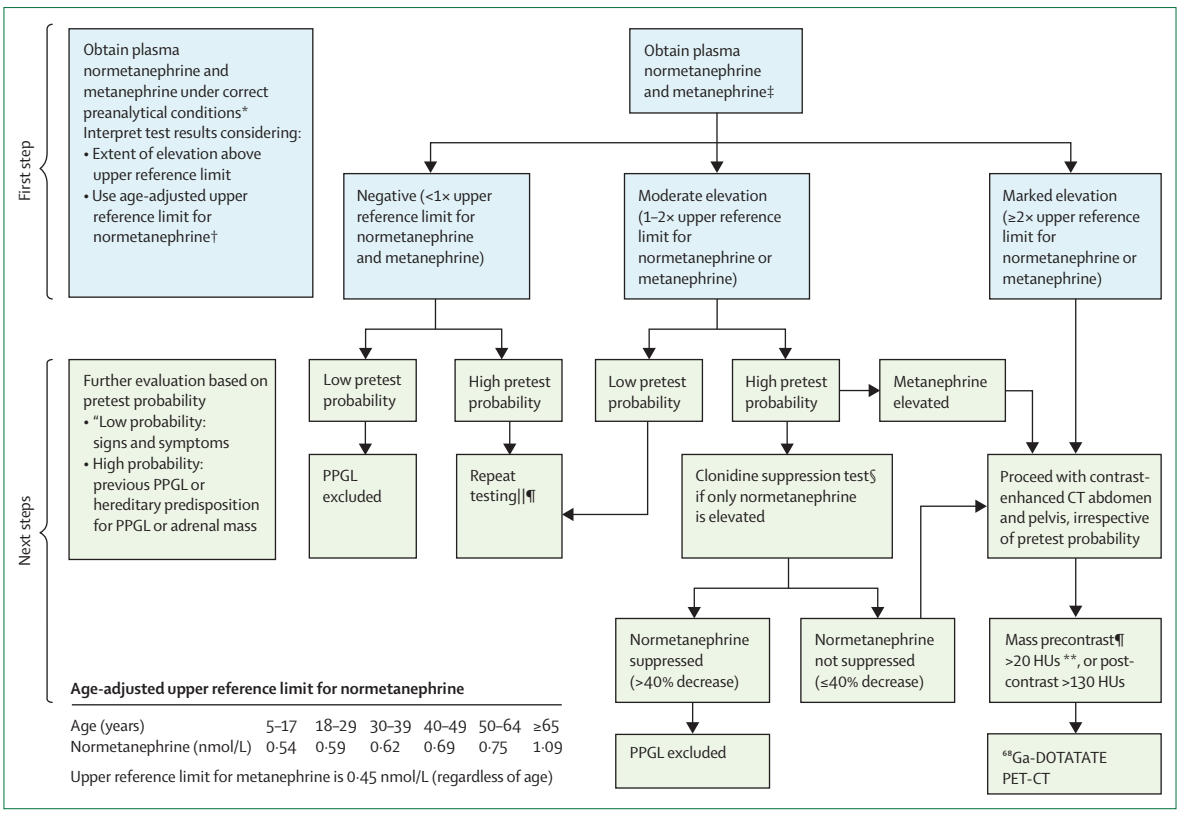


Figure 2: **Interpreting metanephrines in non-critically ill patients with suspected PPGL**
CT AP=computed tomography of the abdomen and pelvis. HU=Hounsfield unit. PPGL=phaeochromocytoma and paraganglioma. ^{68}Ga-DOTATATE PET-CT=^{68}Gallium-DOTATATE positron emission tomography-CT. *Preanalytical conditions for blood sampling of normetanephrine and metanephrine include: stop agents (appendix pp 12–13) that interfere with measuring plasma metanephrines as they might cause false-positive test results; place intravenous line first, then draw plasma metanephrines after at least 30 min of supine rest in a stress-free environment; if pain occurs, treat with fentanyl (other opiates interfere with catecholamine turnover leading to abnormal metanephrine and normetanephrine levels); avoid hypoglycaemia; and ensure patients are not cold. †Age-adjusted upper reference limit for normetanephrine is displayed in the table shown in the figure (bottom row) and can also be approximated with the following equation: $(2{\cdot}07 \times 10^{-6} \times \text{age}^3) + 0{\cdot}545$ (based on liquid chromatography-mass spectrometry or mass spectrometry measurements). ‡Plasma methoxytyramine might not be readily available in many countries, but in countries where it is available, it can be used, and the algorithm can be followed using an upper reference limit of 0·10 nmol/L. §The clonidine suppression test is performed with baseline normetanephrine obtained under the correct preanalytical conditions followed by a dose of clonidine (0·3 mg/70 kg) with repeat normetanephrine obtained 180 min after the dose is given; it is advised to monitor heart rate and blood pressure during the test. ¶Mass either within or outside the adrenal gland. ||If plasma metanephrines have already been repeated and again found to be elevated, proceed with contrast-enhanced CT AP. **On unenhanced CT (precontrast) 10–20 HUs is a grey zone for a PPGL and <10 HUs indicates that a PPGL is highly unlikely.

and symptoms of catecholamine excess; (2) new-onset diabetes in unexpectedly lean patients (epinephrine is diabetogenic); (3) prolific antihypertensive response to α_1-adrenoceptor blockade (as discussed later in this Review); (4) paradoxical and excessive hypertension in response to β-adrenoceptor blockade, anaesthesia, intubation, or during invasive procedures; and (5) postural hypotension in the setting of hypertension.[28,33,68,69] An example is intravenous labetalol: if a patient's blood pressure remains elevated or worsens with repeated doses of intravenous labetalol (such as in the emergency department) a CIH crisis due to a PPGL should be considered. Any clinical suspicion that the patient might have a PPGL precludes the use of labetalol.

Diagnosis: initial imaging

Most PPGLs (80%) are intra-adrenal (phaeochromocytomas), and the minority (20%) are extra-adrenal, arising from paraganglia (paragangliomas).[7] Sympathetic catecholamine-producing paragangliomas cause CIH crises and occupy the abdomen or pelvis (85%) or chest (15%).[7,70] Parasympathetic, largely non-catecholamine-producing paragangliomas involving the skull-base or neck rarely cause CIH crises.[7,70]

Given secretory PPGLs are mostly located in the abdominopelvic space (97%), contrast-enhanced abdominopelvic CT is the modality of choice for emergently excluding their presence.[71] If haemodynamic stability precludes CT evaluation, ultrasound might rapidly identify adrenal tumours; however, ultrasound is an inaccurate imaging method.[5] Nevertheless, 2–7% of patients have adrenal incidentalomas, whereas 1–5% of incidentalomas are phaeochromocytomas.[72–74] Thus, imaging of an intra-abdominal mass supports clinical suspicion in emergency settings, but is not diagnostic.[5] PPGLs must, therefore, be biochemically confirmed

once patients are stabilised and are without obvious stress.[5]

Diagnosis: biochemical evaluation

Plasma metanephrines are the screening test of choice for PPGLs in patients who are not critically ill, detecting tumours greater than or equal to 0·6 cm.[6] However, plasma metanephrines can be misleading in emergency settings, as physical (eg, trauma and comorbid conditions such as heart failure) and emotional (eg, pain or anxiety) stress cause catecholamine release or elevated metanephrines, falsely suggesting a PPGL.[5,6] Finally, biochemical evaluation of metanephrines can be time-consuming, if the laboratory test is sent out, and if some drugs that interfere with evaluation cannot be withheld (appendix pp 12–13), thus limiting the diagnostic use of plasma metanephrines in CIH crises.[5–7] Despite such constraints, biochemical tests are essential for definitive diagnosis. Endocrinologists are therefore invaluable in minimising interference and in interpreting plasma metanephrine results given the multitude of considerations that might confound biochemical testing.

Certain agents (appendix pp 12–13) and various conditions (eg, panic disorder, hypothermia, hypoglycaemia, drug withdrawal, pain, and kidney insufficiency) can falsely elevate metanephrines in patients who are not critically ill.[21,75] Accuracy can be optimised by ensuring appropriate preanalytical conditions during sample collection and adjusting for age and glomerular filtration rate when interpreting upper reference limits (figure 2).[76] A negative (<1×upper reference limit) plasma normetanephrine and metanephrine suggests low risk for PPGL (negative predictive value 99·7%), with repeat testing advised in patients with high pretest probability (eg, a personal or family history of, or known susceptibility gene for, PPGL).[75] Markedly elevated (>2×upper reference limit) plasma normetanephrine or metanephrine suggests a PPGL (positive predictive value ≥95%), and contrast-enhanced abdominopelvic CT is recommended.[75] A mass with attenuation greater than 20 Hounsfield units (HUs) precontrast or greater than 130 HUs postcontrast, or both, suggests a PPGL, and ^{68}Gallium-DOTATATE PET-CT might be performed for confirmation.[77] In patients with moderately elevated (1–2×upper reference limit) plasma metanephrine or normetanephrine, pretest probability and the clonidine suppression test (figure 2) should be considered to determine if further imaging is warranted.[78] In the inpatient environment, plasma metanephrine testing might be largely inconclusive as it can be impractical to optimise all preanalytical conditions, and unmodifiable conditions leading to elevated plasma metanephrines might be present (eg, heart failure, myocardial infarction, drugs or alcohol, or clonidine withdrawal). In these instances, we recommend initial imaging with contrast-enhanced abdominopelvic CT.

The approach to treating a patient with a catecholamine-induced hypertensive crisis

The general approach to treating a patient with a CIH crisis begins with considering the rapidity of onset and severity of hypertension, as well as the presence or worsening of cardiovascular complications (figure 3).

Although a threshold blood pressure greater than or equal to 180/120 mm Hg defines a hypertensive crisis, clinical judgement should not be supplanted if target organ damage is suspected. Rather, given the under-recognised potential for imminent decompensation, this discrete threshold should prompt concern in patients with PPGL before it is too late.[2,29]

Initial steps

Hypertensive crises are numerically defined, but it must be recognised that patients with manifestations of target organ damage despite blood pressure less than 180/120 mm Hg have a hypertensive emergency, whereas asymptomatic patients with blood pressure greater than or equal to 180/120 mm Hg have a hypertensive urgency. Therefore, in asymptomatic patients, close monitoring or outpatient follow-up with return precautions should be considered (figure 3).

Patients with possible CIH crises should promptly be evaluated in the emergency department. Hypertension can herald catecholamine excess much like an initial warning. Then comes the yet-unforseen cardiac (eg, Takotsubo-like cardiomyopathy) and vascular (coronary artery vasoconstriction with myocardial infarction) catecholamine-induced complications. As sudden decompensation might occur, it is critical to identify or monitor patients for target organ damage and to triage patients to an intermediate or intensive care setting (figure 3). We recommend obtaining adequate intravenous access, monitoring with pulse oximetry (eg, flash pulmonary oedema) and telemetry (eg, arrhythmias), and, if desirable, invasive intra-arterial blood pressure or haemodynamic monitoring (eg, haemodynamic fluctuations or acute or worsening heart failure).

Endocrinologists, given their working understanding of CIH crises, are essential in the initial evaluation, triage, and management of patients (recommending beneficial therapeutic strategies, while avoiding harmful ones), whereas cardiologists are proficient in treating severe or dynamic blood pressure fluctuations, and can intervene when cardiovascular complications (eg, tachyarrhythmias or hypotension) arise. Thus, in our opinion, it should be the responsibility of endocrinologists to involve cardiologists when co-management is warranted, such as in the intensive care unit (figure 3). Such teamwork could lead to the development of anticipatory strategies, which when implemented immediately, would prevent a decompensation.

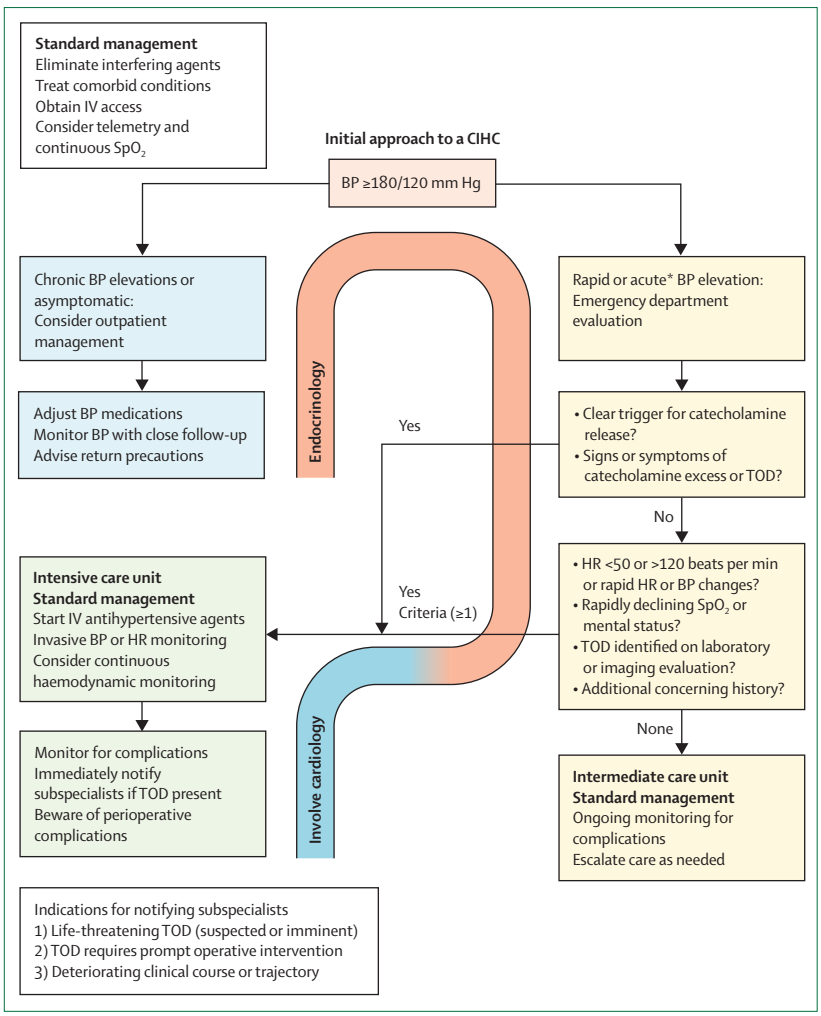


Figure 3: **Initial approach to a patient with a catecholamine-induced hypertensive crisis**
Endocrinologists should aid in initial evaluation and triage of patients with CIHCs. Cardiologists should be involved in the coordinated care of patients within the intensive care unit. For interfering agents refer to the appendix (pp 12–13). Comorbid conditions include hypoxia, hypercapnia, hypomagnesaemia, hypocalcaemia, hypokalaemia, hyperthyroidism, and hypercortisolism. Concerning history includes severe, symptomatic, or frequent tachyarrhythmias, bradyarrhythmias, hypotensive or hypertensive events, obstructive coronary artery or peripheral vascular disease, previous myocardial infarction, stroke, transient ischaemic attack, limb threatening vascular ischaemia, severe valvulopathies or cardiomyopathy, or neuraxial metastatic disease. Triggers for catecholamine release include interfering agents, tumour manipulation or instability (eg, surgery, trauma, necrosis, or haemorrhage), sedation, intubation, and immunotherapy, chemotherapy, or radiotherapy (eg, tumour lysis).BP=blood pressure. CIHC=catecholamine-induced hypertensive crisis. HR=heart rate. IV=intravenous. SpO_2=oxygen saturation. TOD=target organ damage. *Determination of what would be considered a rapid or acute elevation in BP is difficult to define within a clinical context. This determination depends on the clinical judgement of the provider in the setting where a BP derangement compels clinical concern.

Management

Catecholamine-induced hypertension and a CIH crisis begin with adrenoceptor stimulation, followed sequentially by a rise in calcium then actin-myosin crossbridge cycling (appendix pp 12–13). Accordingly, treatment makes use of adrenoceptor or calcium channel blocking agents or nitrates, or a combination of these.[19,79,80] Other antihypertensive agents that do not antagonise the effects of catecholamines might also be useful under certain circumstances.[19,67,80] Collectively, all agents must have favourable drug properties within the dynamic and rapidly changing context in which a CIH crisis is treated (appendix pp 8–11).

Managing catecholamine-induced hypertensive crises: general considerations

Patients with a CIH crisis can have dramatic fluctuations in blood pressure and heart rate.[19,22,80] Immense α_1-adrenoceptor stimulation deprives the gastrointestinal tract of blood flow (splanchnic vasoconstriction) and slows motility, limiting absorption.[80] Thus, titratable or short-acting intravenous agents are preferred to oral medications (excepting α-adrenoceptor blocking agents). This treatment strategy effectively avoids lingering actions (eg, unwanted or prolonged vasodilation from oral amlodipine) if a systemic haemodynamic change rapidly occurs (eg, sudden hypotension). Continuous intravenous infusions are preferred for treating a CIH crisis as most intravenous bolus medications are unsuitable, and chronic α_1-adrenoceptor-mediated vasoconstriction leads to compensatory loss of intravascular volume. As such, it is advisable to refrain from using intravenous diuretics unless patients show signs and symptoms of heart failure.[81,82] Intravenous hydralazine is a cardiostimulatory drug, and intravenous labetalol can worsen hypertension, so both drugs should be avoided.[27] Finally, in the event that a patient has a presumed but unconfirmed diagnosis of PPGL (as discussed earlier in this Review), the use of short-acting titratable intravenous agents and close monitoring can avoid overtreatment in the event the patient does not have a true PPGL.

A further consideration is whether adrenoceptor or non-adrenoceptor blocking agents will be used. Adrenoceptor blocking agents provide the most rational or precise treatment of a CIH crisis.[19,80] Nonetheless, α-adrenoceptor blocking agents might lack availability in some centres (eg, intravenous phentolamine), be less routinely used or familiar (eg, oral phenoxybenzamine), or have prohibitive cost, whereas β-adrenoceptor blockade without adequate α-adrenoceptor blockade might lead to life-threatening hypertension.[18,83] Although other agents (eg, intravenous nicardipine or nitrates) might effectively circumvent the troubles of unbalanced adrenoceptor blockade and be more widely available, routinely used or familiar, and affordable, they can invite harmful pleiotropic effects (eg, nitroprusside and cyanide toxicity).[31,84–86] Such considerations (appendix pp 8–11) are critical to tailoring the best approach to clinical circumstances. Importantly, intravenous phentolamine might be readily available in certain centres, whereas some institutions might not have a supply. Therefore, it is important to check the institutional formulary to avoid delays.

Additionally, the adrenoceptor selectivity, pharmacological properties (eg, onset or duration), and adverse effects or contraindications of various agents must be considered (appendix pp 8–11).[19,79,80]

Given that multiple strategies exist, we provide two approaches to treatment. The conventional approach makes use of recommended agents that might not be as easy to obtain at all institutions. The alternative approach makes use of agents that might be more routinely used or accessible (figure 4). Each approach provides interchangeable and sequential options for various agents. If an intravenous agent is ineffective in a patient already taking the same class of medication orally, a switch to another class of agent should be considered. This approach allows for a customisable strategy where providers can use agents available at their institution, and that they are most familiar with, to deliver optimal and adaptable care in various practice settings.

In some cases, patients might require prompt intervention, without time to involve endocrinologists or cardiologists. In this instance, an abridged guide (appendix p 7) is provided. This guide outlines initial management in acute circumstances.

Agent-specific considerations

α-adrenoceptor blocking agents

The benefit of adrenoceptor blocking agents in providing immediate and effective blood pressure control in CIH crises can be offset by their expense (eg, phentolamine or phenoxybenzamine), a potential lack of availability or familiarity with their use, and the consequent unrecognised risk of unbalanced adrenoceptor blockade (eg, labetalol).[19,31,35,79,80] Unbalanced adrenoceptor blockade worsens hypertension because inhibiting β_2-adrenoceptor-mediated vasodilation allows for unopposed α-adrenoceptor-mediated vasoconstriction.[18,87] Therefore, unbalanced adrenoceptor blockade should be prevented by starting α-adrenoceptor blocking agents before starting β-non-selective adrenoceptor blocking agents.[19,67,79,80,88]

Both selective α_1-adrenoceptor blocking agents (eg, oral doxazosin) and non-selective α-adrenoceptor blocking agents (eg, intravenous phentolamine and intravenous or oral phenoxybenzamine) are available.[19,79] Intravenous phentolamine is a competitive, non-selective, α-adrenoceptor antagonist with an immediate onset (1–2 min) and duration (10–30 min), typically given in 2·5–15·0 mg doses.[19,79,80,88,89] This transient effect in light of unpredictable haemodynamic changes is desirable, avoiding hypotensive overshoot. Unfortunately, elevated catecholamines can outcompete phentolamine as it is a competitive inhibitor, leading to breakthrough hypertension.[19,33,79] In contrast, phenoxybenzamine, a non-competitive and irreversible inhibitor, provides insurmountable antagonism.[19] Thus, superior blood pressure control might be achieved by substituting competitive α-adrenoceptor blocking agents with phenoxybenzamine.[33] Notably, phenoxybenzamine works immediately, but complete α-adrenoceptor blockade requires 5 days. Thus, phenoxybenzamine should be used in combination with other agents, not as monotherapy, in a CIH crisis. Additionally, intravascular volume is often insufficient following rapid α-adrenoceptor blockade with vasodilation, leading to fluid-responsive hypotension and reflex tachycardia.[80–82] Finally, presynaptic α_2-adrenoceptor blockade from phentolamine and phenoxybenzamine disinhibits noradrenaline release upon the sinoatrial node, directly worsening tachycardia.[80] For these reasons, ischaemic cerebrovascular or cardiovascular disease, or a comorbid tachyarrhythmia, are contraindications to using these agents.[19,80]

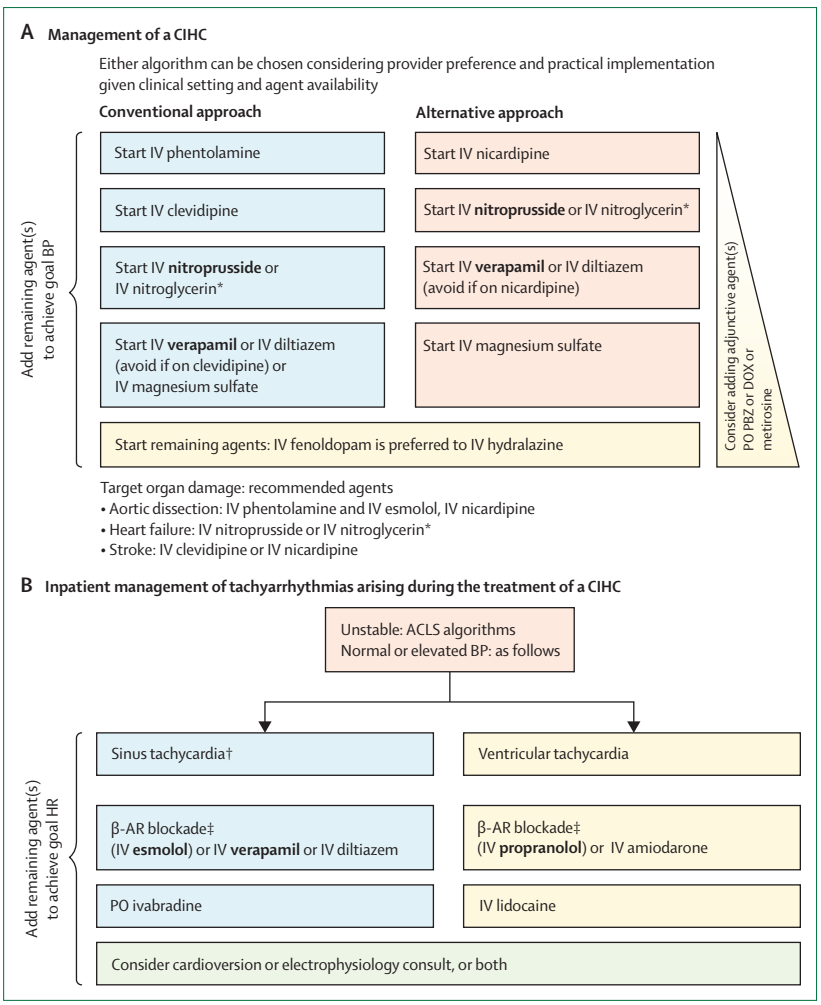


Figure 4: **Management of a catecholamine-induced hypertensive crisis and target organ damage (A) and tachyarrhythmias (B)**

Preferred agents are in bold. ACLS=advanced cardiac life support. AR=adrenoceptor. BP=blood pressure. CIHC=catecholamine-induced hypertensive crisis. DOX=doxazosin. IV=intravenous. PBZ=phenoxybenzamine. *Avoid nitrates in preload dependent states or with concomitant use of phosphodiesterase inhibitors. †In sinus tachycardia, evaluate for and rule out infection, dehydration, haemorrhage, acute coronary syndromes, structural cardiovascular disease, and pulmonary embolism. When optimising treatment of pain and anxiety, consider echocardiography when able. ‡Normotensive and hypertensive patients already taking α-adrenoceptor blocking agents can be given β-adrenoceptor blocking agents; otherwise, if IV phentolamine is unavailable or cannot be given, proceed with the second listed option.

β-adrenoceptor blocking agents

Among the subclasses of β-adrenoceptor blocking agents, β_1-selective adrenoceptor blocking agents are preferred to β-non-selective adrenoceptor blocking agents. Intravenous esmolol is ideal as a short-acting agent (onset 2–10 min, duration 10–30 min), especially when given with intravenous phentolamine, a combination that provides precise and titratable blockade with minimal off-target effects (appendix pp 8–11).[80] Alternatively, intravenous metoprolol is less preferred given its prolonged duration of action (5–8 h). Intravenous labetalol provides an unbalanced α_1-selective to β-non-selective adrenoceptor blockade in a 1:7 ratio and is therefore contraindicated as monotherapy, as it can worsen hypertension.[19]

Calcium channel blocking agents

Titratable intravenous calcium channel blocking agents include the dihydropyridines, nicardipine and clevidipine, which act as effective afterload reducers (sometimes incurring reflex tachycardia), whereas the non-dihydropyridine or cardioselective agents, verapamil and diltiazem additionally act on the heart to repress force of contraction, heart rate, and conduction velocity (often suppressing reflex tachycardia; appendix pp 8–11).[19,33,80] Cardioselective agents are especially useful in the setting of comorbid tachyarrhythmias, with verapamil being a preferred agent in CIH crises given it is also a potent antihypertensive (figure 4).[90] Verapamil and diltiazem should be avoided in heart failure for these same reasons (appendix pp 8–11).[19,33]

Nitrates

Intravenous nitroprusside, a preferential arterial vasodilator, is the preferred nitrate in patients with PPGL.[9,81,82] Intravenous nitroglycerin, a preferential venodilator, reduces preload, causing greater reflex tachycardia in patients with PPGL as these patients have decreased intravascular volume.[9,21,81,82] Nitrates should be avoided in preload-dependent states and in patients taking phosphodiesterase inhibitors (appendix pp 8–11).

Magnesium sulfate

Magnesium sulfate antagonises many calcium-mediated processes within the heart and blood vessels, making it a valuable agent in treating a CIH crisis and concurrent tachyarrhythmia.[91,92] We recommend a loading dose of 40–60 mg/kg (maximum dose 6 g) followed by a continuous infusion of 1–2 g/h (appendix pp 8–11). Furthermore, magnesium sulfate can be used as a first-line agent in pregnant women and is commonly used in paediatric populations.[21,80]

Fenoldopam

Fenoldopam, a selective dopamine-1-receptor agonist, is rarely used but conceptually well-suited for the treatment of CIH crises.[93] This drug results in rapid blood pressure control (onset 5 min, duration ≤10 min) without provoking a substantial adrenergic response, while increasing kidney perfusion (appendix pp 8–11).[93,94] However, fenoldopam is a last resort agent given lack of experience with its use when treating CIH crises.

Other medications

Intravenous hydralazine should be avoided unless necessary as it is cardiostimulatory, demonstrating β-adrenoceptor agonist activity in in vitro studies.[27,95] Additionally, the oral agent metirosine might not be widely available but could be a useful adjunct. It takes 3 days to reach maximum effect, but begins working immediately (figure 4).[96] Metirosine can be dosed at 250 mg once or twice a day, then progressively increased (not exceeding 3–4 g/day).

Transitioning to oral therapy

Once effective intravenous blood pressure treatments are initiated in a CIH crisis, oral agents can be started. We recommend starting α-adrenoceptor blocking agents, such as doxazosin 1–2 mg twice daily, then increasing the dose as intravenous antihypertensive agents are weaned (maximum doxazosin dose 32 mg/day) and effective blood pressure control is achieved. An oral calcium channel blocking agent (eg, amlodipine) might also be added. After 2–3 days of oral doxazosin, β-adrenoceptor blocking agents can be started if catecholamine-induced sinus tachycardia is present. We recommend starting metoprolol succinate 25–50 mg then increasing the dose as necessary. Other adrenoceptor blocking agents or calcium channel blocking agents can also be used, but a full discussion of all approaches is beyond the scope of this Review.

Management of complications

The detailed management of target organ damage is nuanced and complex, and studies investigating the use of specific agents in CIH crises are scarce. The pathophysiology of catecholamine excess combined with current strategies for managing malignant (non-catecholamine-induced) hypertension with target organ damage form the basis for these recommended or preferred agents. Once target organ damage is identified, expert consultation with appropriate subspecialty services should be pursued immediately (figure 4). We recommend intravenous phentolamine then intravenous esmolol in aortic dissection, intravenous nitrates in heart failure, and intravenous dihydropyridine calcium channel blocking agents in stroke (figure 4).

Management of hypotension

Up to 23–30% of patients with PPGL and a CIH crisis experience shock over the course of treatment.[28,29,53,58] Hypotension is therefore common and can be life-threatening, yet is poorly-defined. We provide a concise summary and approach to hypotension that is an

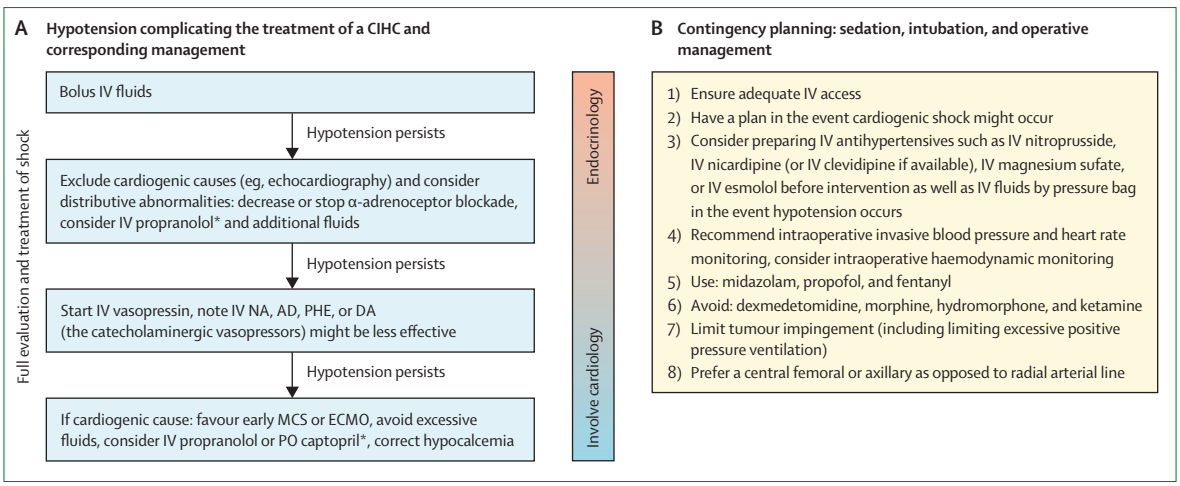


Figure 5: **Management of hypotension in a catecholamine-induced hypertensive crisis (A) and contingency planning (B)**
Initial management should be provided by endocrinologists, with cardiologists involved if hypotension persists or worsens for the evaluation and coordinated management of possible cardiogenic shock. AD=adrenaline. CIHC=catecholamine-induced hypertensive crisis. DA=dopamine. ECMO=extracorporeal membrane oxygenation. IV=intravenous. MCS=mechanical circulatory support. NA=noradrenaline. PHE=phenylephrine. *Propranolol and captopril can be started at a low dose and gradually increased for patients with a low blood pressure; however, this treatment should be avoided if patients have severe hypotension (and avoid propranolol in patients with bradycardia).

amalgamation of our experience, available evidence, and specific data (appendix p 6) from patients treated at the National Institutes of Health (NCT00004847).

Three types of hypotension can be encountered when treating a CIH crisis. The most common is (1) volume-responsive hypotension (figure 1; appendix p 15)—a consequence of both α_1-adrenoceptor-mediated vasoconstriction (with attendant compensatory reduction in intravascular volume by almost 15% or about 500 mL) and α_1-adrenoceptor downregulation, both of which lead to hypotension with rapid vasodilation (eg, with treatment) and changes in position (orthostasis).[28,69,81,97,98] This volume-responsive hypotension (20 [20%] of 100 in our cohort) can often be seen in the noradrenergic phenotype (17 [85%] of 20), and almost always involves α-adrenoceptor blocking agents (20 [100%] of 20), while rapidly correcting with a 1-L bolus of intravenous crystalloid (appendix pp 6, 15). Less commonly, excessive β_2-adrenoceptor-mediated vasodilation or myocardial stunning might occur (eg, in patients with the adrenergic phenotype), leading to hypotension from (2) distributive abnormalities in blood flow or (3) a Takotsubo-like cardiomyopathy.[19,51,53,99]

Treating hypotension first involves bolus intravenous crystalloid and weaning from α-adrenoceptor blocking agents (figure 5). If hypotension persists, β_2-adrenoceptor-mediated distributive abnormalities in blood flow or β_2-adrenoceptor-mediated myocardial stunning (or both) should be considered, and propranolol (as blood pressure permits, recognising its use as a β_2-adrenoceptor blocking agent) should be administered, while also involving cardiology and obtaining an echocardiogram. If hypotension persists or progresses to shock, early cardiac mechanical circulatory support or extracorporeal membrane oxygenation (figure 5) is preferred as an initial intervention.[5,29] Vasopressin is the vasopressor of choice as it is not dependent on adrenoceptors (like caecholaminergic vasopressors) to support blood pressure.[80,100]

Management of tachyarrhythmias

Tachyarrhythmias encountered during CIH crises result from direct β_1-adrenoceptor stimulation and less often from a reflex response to hypotension.[101] Except for sinus tachycardia (seen in up to 99% of patients), atrial fibrillation (60%) is most prevalent, followed by ventricular tachycardia (20%) and bradyarrhythmias (20%).[16,33] Catecholamine-induced tachyarrhythmias can decompensate into cardiac arrest and should therefore be promptly treated with β_1-adrenoceptor blocking agents or by correcting underlying hypotension.[30,33]

Treatment of sinus and ventricular tachycardia is outlined in figure 4. Both occurrences should be treated with initial α-adrenoceptor blockade, followed by β-adrenoceptor blockade.[33] In sinus tachycardia, we recommend intravenous verapamil or diltiazem, followed by oral ivabradine.[33] In ventricular tachycardia, intravenous amiodarone and intravenous lidocaine are effective.[33] In patients with hypotension, intravenous propranolol, as blood pressure permits, should be used, and advanced cardiac life support algorithms should be followed in patients who are haemodynamically unstable.[33,102]

Contingencies: intubation, sedation, and operative management

Prolific catecholamine release can occur with anaesthetic agents, endotracheal intubation, and surgical management (appendix pp 12–13).[19,21,80] In CIH crises, anticipation and advanced planning before intubation are advised to ensure safe execution and use of appropriate agents (figure 5).

Search strategy and selection criteria

References for this Review were identified through searches on PubMed for articles published between Jan 01, 1960, and Dec 31, 2022, with the terms "pheochromocytoma" or "phaeochromocytoma", "paraganglioma", and "catecholamines", in combination with the term "hypertension", with a similar search performed in Ovid MEDLINE, with searches restricted to studies done in humans. Relevant articles published between 1940 and 1960 were identified through searches of the authors' personal files and in the National Library of Medicine archives in print. Articles resulting from these searches and relevant references cited in those articles were reviewed by the authors, with studies selected for their scientific method, rigor, and relevance.

Conclusion

Catecholamine excess is an uncommon but severe cause of hypertension, sometimes demanding unique considerations that guide management, with the occasional use of less common agents for treatment. Fortunately, treatment is informed by the principles of catecholamine physiology, pathophysiology, and pharmacology, which provide a roadmap for specific interventions. As such, endocrinologists possess the fundamental knowledge underpinning the treatment of CIH crises, and cardiologists the expertise to quickly render the treatment for severe haemodynamic disturbances and cardiovascular complications encountered; thus, by working together, optimal management can be achieved. The priority remains safely lowering elevated blood pressure while monitoring for complications and planning for contingencies that require their own treatment. Nonetheless, a variety of strategies and agents, as discussed in this Review, can be used, allowing for the appropriate management of CIH crises across diverse health-care settings.

Contributors

All authors conceptualised, wrote, reviewed, and edited this Review. All authors contributed to the literature review. MAN and KP curated the data. MAN, JWML, RMC, and KP performed formal analysis on the data. MAN, RH, MH, JWML, RMC, and KP investigated the literature and available data. MAN and KP administrated the project. MAN, MH, AM, JWML, RMC, and KP supervised the literature review, composition, and analysis of the available data. MAN and KP directly accessed and verified the underlying data reported in the Review. KP acquired funding for the project. Authors were not precluded from accessing data in the study and accept responsibility for the submission of this Review.

Declaration of interests

We declare no competing interests.

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