U.PORTO
FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2022/2023

Filipa Miranda Domingues

Transient and dynamic left ventricular outflow tract obstruction – a literature review

Obstrução transitória e dinâmica do ventrículo esquerdo – uma revisão da literatura

Junho, 2023

Filipa Miranda Domingues

Transient and dynamic left ventricular outflow tract obstruction – a literature review / Obstrução transitória e dinâmica do ventrículo esquerdo – uma revisão da literatura

Mestrado Integrado em Medicina

Área: Medicina Clínica (Cardiologia)

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Professora Doutora Elisabete Martins

E sob a Coorientação de:

Drª. Tânia Proença

Trabalho organizado de acordo com as normas da revista:

Revista Portuguesa de Cardiologia

Junho, 2023

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, Filipa Miranda Domingues, abaixo assinado, nº mecanográfico 201606713, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 01/07/2023

Assinatura conforme cartão de identificação:
Filipa Miranda Domingues

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

Filipa Miranda Domingues

NÚMERO DE ESTUDANTE | E-MAIL

201606713 | filipa.md98@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências Médicas e da Saúde

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Transient and dynamic left ventricular outflow tract obstruction

ORIENTADOR

Professora Doutora Elisabete Lousada Martins Oliveira Bernardes

COORIENTADOR (se aplicável)

Dra. Tânia Filipa Galvão Prança

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 01/07/2023

Assinatura conforme cartão de identificação: Filipa Miranda Domingues

Agradecimentos

À Professora Doutora Elisabete Martins por toda a ajuda e disponibilidade na escolha do tema da monografia, revisão científica do manuscrito e que permitiu elevar imensuravelmente a qualidade deste. Acima de tudo, pela paciência e sensibilidade que demonstrou para comigo ao longo destes dois anos tão difíceis, e por, mesmo após imensas adversidades, percalços e falhas da minha parte, ter continuado a aceitar ser minha orientadora, deixo o meu sincero e eterno agradecimento.

À Drª. Tânia Proença, agradeço toda a ajuda dispensada na revisão do trabalho e todas as sugestões e comentários que permitiram melhorar o mesmo.

Title: Transient and dynamic left ventricular outflow tract obstruction – a literature review

Título: Obstrução transitória e dinâmica do ventrículo esquerdo – uma revisão da literatura

Filipa Domingues[a]*, Tânia Proença[b], Elisabete Martins [a,b,c]

[a] Faculty of Medicine of Porto University, Porto, Portugal.

[b] Department of Cardiology, São João University Hospital Center, Porto, Portugal.

[c] Research group CardioCare – Ciências Cardiovasculares, CINTESIS, Porto, Portugal.

***Corresponding author**

E-mail : filipa.md98@gmail.com

Phone number: 927798270

Adress: Rua Aldeia do Sol nº16 – Ribeirão, Vila Nova de Famalicão

Abreviations

ACS – Acute coronary syndrome

AMI – Acute myocardial infarction

CAG – Coronary angiography

CS – Cardiogenic shock

BP – Blood pressure

BPM – Beats per minute

ECG – Electrocardiogram

ED – Emergency department

EF – Ejection fraction

HCM – Hypertrophic cardiomyopathy

IABP – Intra-aortic balloon pump

IV – Intravenous

HR – Heart Rate

HTN – Hypertension

LAD – Left anterior descending

LV – Left ventricle

LVH – Left ventricular hypertrophy

LVOT – Left ventricular outflow tract

LVOTO – Left ventricular outflow tract obstruction

MR – Mitral regurgitation

MV – Mitral valve

PG – Pressure gradient

SAM – Systolic anterior motion

STEMI – ST elevation myocardial infarction

TC – Takotsubo cardiomyopathy

TTE – Transthoracic Echocardiogram

Abstract:

Left ventricular outflow tract obstruction (LVOTO) refers to the interference of the ejection of blood flow from the left ventricle to the aorta and is defined by a pressure gradient equal or greater than 30 mmHg. Its exact prevalence in the general population is unknown, however, it is considered a relevant and underdiagnosed cause of hypotension and hemodynamic deterioration in certain clinical scenarios. Traditionally, dynamic LVOTO is associated with hypertrophic cardiomyopathy (HCM), as this is its most common cause, present in approximately 2/3 of patients diagnosed with HCM. However, it has also been described in both anatomically predisposed individuals (with left ventricular hypertrophy, septal hypertrophy, and sigmoid septum), acute myocardial infarction and in structurally normal hearts, associated with various clinical situations, such as takotsubo cardiomyopathy, catecholaminergic overload, by exogenous administration, or in the presence of a pheochromocytoma, and as well as in the setting of change in volume status due to dehydration/ volume depletion. This literature review aims to integrate the most common clinical scenarios associated with LVOTO, other than HCM, to elucidate the pathophysiology behind this phenomenon and to describe the best approach to the diagnosis, management and treatment options for these specific subsets of patients.

Key Words: Left Ventricular Outflow Tract Obstruction, Systolic Anterior Motion of the Mitral Valve, Hypertrophic Cardiomyopathy, Takotsubo Cardiomyopathy, Acute Myocardial Infarction, Catecholamines, Shock, Dehydration, Volume Depletion.

Resumo:

A obstrução do trato de saída do ventrículo esquerdo refere-se à limitação do fluxo sanguíneo do ventrículo esquerdo para a aorta e é geralmente definido como um gradiente de pressão igual ou superior a 30 mmHg. A sua prevalência na população geral é desconhecida, no entanto é considerado uma causa relevante de hipotensão e também de deterioração hemodinâmica em diferentes contextos clínicos. Tradicionalmente, a obstrução do trato de saída do ventrículo esquerdo tem sido estudada associadamente à miocardiopatia hipertrófica, sendo que cerca de 2/3 destes doentes apresentam este fenótipo. No entanto, esta entidade também tem vindo a ser descrita em doentes "anatomicamente predispostos" (com hipertrofia ventricular esquerda, hipertrofia do septo interventricular ou septo sigmóide), ou no enfarte agudo do miocárdio, mas também em doentes com corações estruturalmente normais, quando expostos a certas condições clínicas, nomeadamente miocardiopatia de Takotsubo, sobrecarga catecolaminérgica, por administração exógena ou feocromocitoma, e também na presença de desidratação/depleção de volume. O principal objetivo desta revisão da literatura prende-se com a integração e descrição dos cenários clínicos mais frequentemente associados com obstrução do trato de saída do ventrículo esquerdo, excluindo a miocardiopatia hipertrófica, elucidando a sua patofisiologia, melhores métodos de diagnóstico, gestão e tratamento desta população específica de doentes.

Palavras chave: Obstrução do trato de saída do ventrículo esquerdo, Movimento sistólico anterior da válvula mitral, Cardiomiopatia hipertrófica, Cardiomiopatia Takotsubo, Enfarte agudo do miocárdio, Catecolaminas, Choque, Desidratação, Depleção de volume.

Introduction

Left ventricular outflow tract obstruction (LVOTO) refers to the obstruction of the passage of blood flow from the left ventricle (LV) to the aorta. [1, 2]

Historically, hypertrophic cardiomyopathy (HCM) has been described as the most common cause of dynamic LVOT, [3, 4] defined as a peak instantaneous gradient between the LV and the aorta that is equal to or greater than 30 mmHg. [1, 5-7] A gradient greater than or equal to 50 mmHg is generally considered the threshold for obstruction with hemodynamic impact. [6]

The hypertrophy of the basal septum and systolic anterior motion of the mitral valve leaflet (SAM) cause a dynamic obstruction in the LVOT seen in 30-60% of patients with HCM,[8] evident at rest or after provocation maneuvers. [9, 10] Specifically in patients with HCM, LVOTO is a predictor of heart failure and cardiovascular death. [11-13]

By contrast, the epidemiology, and the prevalence of dynamic LVOTO in other clinical scenarios or in the general population is largely unknown,[14] although it is considered the third most common cause of unexplained hypotension. [8, 15] It is also unknown whether the evidence at any time of a transient LVOTO should impact long-term therapies or prognosis.

LVOTO has been reported in takotsubo cardiomyopathy (TC), acute myocardial infarction (AMI), diverse clinical conditions with volume depletion/dehydration, as well as patients under catecholaminergic overflow, in the case of exogenous administration or in the presence of a pheochromocytoma. [3, 4]

LVOTO is a dynamic phenomenon, and its occurrence requires two conditions: predisposing anatomical factors (such as left ventricular hypertrophy (LVH), sigmoid septum, steep aortic root angle),[16] although it has also been reported to occur in structurally normal hearts [7] Additionally, it is usually necessary for certain physiologic conditions such as fluid status changes, due to volume depletion/hypovolemia, or hypercontractile states (associated with catecholamine administration, pheochromocytoma) to be present to induce this gradient. [5]

In this review we aim to gather information regarding the occurrence of transient LVOTO in different clinical scenarios, excluding the traditional HCM, highlighting the pathophysiology hypotheses, diagnosis, and management. To our knowledge, this is the first literature review in recent years that accomplishes this purpose and therefore we believe in the importance and the clinical relevance of this report, especially for healthcare professionals working in the fields of cardiology, intensive medicine and internal medicine.

Methods

A search was conducted in MEDLINE and Web of Science for either English or Portuguese articles published until May 2023 with the key search terms Left Ventricular Outflow Tract Obstruction OR Dynamic Left Ventricular Outflow Tract Obstruction AND Takotsubo Cardiomyopathy OR Catecholamine OR Pheochromocytoma OR Shock OR Dehydration OR Volume Depletion. Additional papers were identified and analyzed from these articles' reference lists. We mostly considered literature reviews, case reports, case series and cross-sectional studies.

Obstructive Takotsubo

Apical ballooning syndrome, also known as takotsubo cardiomyopathy (TC), is characterized by transient systolic dysfunction and abnormal electrocardiogram (ECG) findings that mimic acute coronary syndrome (ACS). [17-19]

It is usually triggered by physical or emotional stress, predominantly in postmenopausal women. [20-22] However, in approximately 1/3 of cases, no trigger can be definitively identifiable. [21, 23] The real incidence of TC is uncertain regarding the general population. It is estimated to be present in about 1-2% of patients suspected of having ACS. [20]

Its etiology is not completely understood, however, the most widely accepted hypothesis appears to be a catecholamine excess due to the fact that TC is frequently triggered by sudden, unexpected stress and the majority of patients present symptoms of sympathetic activation. [24] Several studies corroborated this hypothesis, showing 3 times higher plasma catecholamines in TC than in patients with ACS. [25]

Typically, individuals present with acute onset chest pain associated with electrocardiographic changes as well as an elevation of cardiac biomarkers, however, when a coronary angiography (CAG) is performed coronary artery disease does not explain the clinical picture, as the regional wall abnormality usually extends beyond a single epicardial vascular distribution.[21, 26] Additionally, cardiac magnetic resonance is gaining importance in the evaluation and management of these patients due to the possibility of detection of myocardial edema, which may be considered a hallmark of TC. [27, 28]

TC appears to have a more favorable outcome than AMI with a self-limiting course and recovery of LV function within a few weeks.[29] However, approximately 18% of patients with TC can have serious acute complications, such as heart failure (HF), cardiogenic shock (CS) and ventricular arrhythmias. [30, 31] CS is frequently caused by dynamic LVOTO, [16] whose diagnosis is a determinant for successful treatment.[29]

There are a few clinical reports of TC associated with LVOTO, however, its exact prevalence is unknown. Previous studies have identified a prevalence of 19-25%. [21, 32, 33] More recently, Kawaji et al (2015) described a slightly higher frequency of 33% (9 in 27 total patients). [17] On the other hand, a cross sectional study by Kobayashi et al (2018) reported that of a population with TTE reporting LVOT PG of ≥ 50 mmHg, TC was reported as being the cause of obstruction in only 2% of these patients. [13]

Some studies report data regarding differences between TC patients with and without LVOTO. A cross sectional study by El Mahmoud R. et al (2008) stated that patients with TC and LVOTO were older (mean age of 81 ± 4 vs 68 ± 13 years, P =0,01) with higher mean NYHA functional class (1.8 ± 0.9 vs 1.1 ± 0.1, P=0,002). [33] On the other hand, Kawaji T. et al (2015) found that there were no significant differences in most baseline characteristics, such as age, comorbidities, clinical presentation, or echocardiographic variables beyond the obstruction, between TC patients with or without LVOTO. [17] However, the prevalence of moderate to severe mitral regurgitation (MR) on presentation (67% vs. 11%, P=0.003) and the prevalence of hospitalization for chronic HF after a three-year follow-up period (78% vs. 28%, P=0.01), were significantly higher in patients with LVOT obstruction than in those without. [17]

It has been postulated that dynamic LVOTO in TC occurs due to hypercontractility of the basal segments together with an increment of septal thickness due to myocardial edema [27] that may lead to an acceleration of blood flow through a narrowed LVOT, producing a suction effect (Venturi effect) on valve apparatus with further SAM of the anterior mitral leaflet of the mitral valve (MV). [27, 34, 35]

Conradi P. et al (2021) described a case of a 73-year-old woman, with a prior medical history of stroke, who was admitted to the emergency department (ED) due to chest pain, syncope, and generalized malaise. Physical examination showed hypotension (82/53 mmHg) with normal heart rate (HR) and a holosystolic mumur on auscultation. ECG showed diffusely subtle elevated ST segments and cardiac enzymes were elevated. TTE showed LV dysfunction with an akinetic apex with hyperdynamic basal segments. It also denoted MR and SAM of the MV causing LVOTO with an estimated PG of 40 mmHg. CAG revealed stenosis at the left anterior descending artery (LAD) with fractional flow reserve 0,75. The most probable diagnosis was considered to be CS due to TC complicated with LVOTO, due to the acknowledgement of a stressful event, which is non-specified in the report, and extensive wall motion abnormalities that could not fully be explained by a lesion of LAD artery. The treatment implemented was fluid therapy to optimize LV filling conditions and beta-blocker (metoprolol) with significant improvement in hemodynamic parameters. Follow up TTE revealed resolution of the SAM as well as related MR with significant decrease of LVOT PG (at 8 mmHg). [20]

Wu H. et al (2013) reported a case of a 51-year-old man, with no relevant prior medical history, who presents to the ED with sudden onset chest pain. He was hemodynamically stable on admission and the cardiovascular examination revealed a 3/6 systolic murmur at the left sternal border. The ECG revealed ST elevation in V2-V3, and initial cardiac biomarkers were slightly elevated. TTE revealed akinesia of the mid to apical portions of the LV, and hyperkinesis of basal segments of the LV with a PG of 40 mmHg. Severe MR duet to SAM of the anterior leaflet of the MV was also described. CAG revealed patent coronary arteries. The patient's condition deteriorated with hypotension (79/45 mmHg), so fluid therapy and IV dopamine infusion were started. The patient's hemodynamic condition immediately stabilized and follow up TTE revealed resolution of the SAM and LVOTO with only mild MR. The patient was discharged with ambulatory beta-blocker therapy. [34]

O' Brien J. et al (2021) also described the case of a woman, 66 years of age, with diagnosis of long-standing hypertension (HTN) under optimized medical therapy, who presented to the ED with acute onset chest discomfort and dyspnea. Aditionally, a recent emotional trigger (death of family member) was reported. Initial ECG showed widespread ST depression, T-wave inversion (V2-V5) and cardiac biomarkers were elevated. The patient was hypotensive and tachycardiac, so IV dobutamine infusion was started. Furthermore, CAG showed patent epicardial coronary vessels and dynamic LVOTO was confirmed upon TTE with SAM of the MV and LVOT PG of 40 mmHg. Aditionally, LVH was also reported along with apical akinesis of the LV with compensatory hyperdynamic basal segments. Unlike the previous two cases, despite adequate beta blocker treatment and phenylephrine infusion, there was continuous clinical deteoration so an IABP (intra-aortic balloon pump) was implemented, which promptly stabilized the patient. This case shows that IABP support showed an immediate clear benefit and may represent the treatment option in patients with where fluids, beta-blockers, and phenylephrine have proven to be ineffective. [36]

These cases illustrate the importance of rapid assessment and detection of LVOTO in unexplained hypotensive patients or with CS for acute treatment decisions. Standard treatment of shock in TC with LVOTO could even be fatal: inotropic agents (such as dobutamine or dopamine) may increase the LV PG due to increasing contractility, therefore worsening SAM and MR, with exacerbation of the obstruction. [20, 29]

Vasopressors, such as norepinephrine or epinephrine, can further activate the catecholamine-related pathways. Pharmacological agents that are indicated in acute heart failure/pulmonary edema, such as vasodilators (e.g., nitroglycerine, diuretics) are counterproductive in TC as well, due to the reduction of preload and afterload that could contribute to the obstruction increase. [29]

LVOTO in TC should be managed similarly to HCM. Beta-blockers and volume therapy are indicated to reduce LV basal segment hypercontractility and to prolong diastole with greater end-diastolic volume. This results in the LVOTO gradient decreasing, arterial pressure elevation and MR downgrading. [20] The ultimate bail-out measure to stabilize the cardiac condition in LVOTO would have been LV mechanical support, such as resorting to Impella or IABP,[37] which but its use has been documented in some case reports. [38, 39]

A recent nationwide cohort study by Rapouseiras-Roubín et al (2023), which tried to determine the impact of the use of beta-blockers in a study population of 970 patients with TC, reported no significant differences in the outcome of mortality or TC recurrence between patients treated and untreated with beta-blockers at 3-year follow-up (hazard ratio of 0,95, 95% CI 0,57-1,13 for the adjusted Cox analysis).[40] However, it must be noted that this study excluded from its analysis the patients diagnosed with TC and LVOTO (9 in total). Therefore, in terms of the management of this specific subset of patients with both TC and LVOTO, we can only rely on small data obtained from a few case reports.[16] In conclusion, we should consider beta-blockers as first-line therapy in patients diagnosed with TC and LVOTO.[35]

LVOTO Catecholaminergic

Related to TC pathophysiology, dynamic LVOTO can occur in patients with excessive catecholamines due to an underlying pheochromocytoma or exogenous administration, in both the presence of LVH, septal hypertrophy or otherwise a structurally normal heart.

In a few case reports, [3, 4, 41, 42] LVOTO developed after treatment with catecholamines. We will briefly describe the clinical cases, including the diagnosis and management of each case.

Auer J. et al (2005) describe a patient, male 31 years of age, who was admitted to the local hospital due to acute pancreatitis complicated with adult respiratory distress syndrome (ARDS). Physical examination at admission was unremarkable. However, the patient hemodyamic state soon deteorated with hypotension, tachycardia and therefore volume reposition and vasopressors (dopamine and norepinephrine) were initiated. Reexamination of the patient revealed a systolic murmur grade 3/6. TTE revealed SAM with severe LVOTO, with a PG of 58 mmHg. The treatment included cessation of catecholamine therapy and parenteral substitution of fluids, which improved the hemodynamic condition of the patient.[41]

Mingo S. et al (2006) reported the case of two patients that in the presence of a structurally normal heart developed LVOTO associated with the administration of catecholamines. The first patient was a woman, 63 years old, diagnosed upon evaluation in the ED with ACS without persistent ST-segment elevation. Cardiac biomarkers were marginally elevated. CAG revealed no major artery stenosis. The patient developed hypotension and tachycardia. Fluid therapy and dopamine were administered. Hemoglobin was 5 g/dL, so a blood transfusion was administered. The patient remained hemodynamically unstable and new systolic murmur in the left sternal border was observed. TTE revealed SAM of the MV with dynamic LVOT obstruction with PG of 64 mm Hg at rest with normal LV function. The treatment of this patient involved blood transfusion and fluid reposition and cessation of amine therapy.[3]

The third case, also reported by Mingo S. et al (2006) refers to a man, age 70, who was admitted to the hospital with suspicion of community-acquired pneumonia. On admission, cardiopulmonary examination was normal. Antibiotic therapy was started but he developed severe hypotension, therefore mechanical ventilation and catecholamine

treatment (dopamine and norepinephrine) were initiated. The patient remained hemodynamically unstable, after which it was decided to perform a TTE that showed SAM and severe LVOT obstruction with mild basal hypertrophy; the peak PG in LVOT at rest was 90 mm Hg with normal LV function. The catecholamine treatment was slowly reduced, and the patient improved and tolerated the increasing dosage of beta-blockers. The TTE was repeated before discharge and showed resolution of the LVOT gradient.[3]

Additionally, Yang J. et al (2008) describe the case of a patient, male 62 years of age, who developed ARDS with shock following planned surgery, and was managed with mechanical ventilation, antibiotics, fluid therapy and dopamine administration. However, over the course of hospitalization, the patient maintained fever and developed hypotensive episodes, which were managed by tailored antibiotic therapy and catecholamines. Because a 3/6 grade systolic murmur was auscultated, it was decided to perform a TTE that revealed SAM with LVOTO with a PG of 73 mmHg. Following volume replacement as well as phasing out the catecholamine treatment the patient's condition improved. Follow up TTE revealed complete resolution of the LVOT obstruction as well as SAM.[4]

The use of inotropic drugs is a common life-saving practice in patients who experience shock and remains a common practice and mandatory mainstay in the field of medicine.[4] However, the administration of catecholamines may result in hemodynamic deterioration, such as in cases here described with dynamic LVOTO secondary to catecholamine therapy.[3] In these cases, the hyperdynamic state after the administration of catecholamines, associated with hypovolemia, resulted in the development of dynamic LVOTO.

We should suspect this clinical scenario if, upon auscultation, we find a new systolic murmur in the left sternal border. However, in order to establish a definitive diagnosis, it is imperative to perform a TTE as soon as possible to quantify the PG of the LVOT. The treatment should contemplate the cessation of catecholamine therapy, the treatment of the basal illness, the maintenance of blood pressure (BP) and correction of hypovolemia and urine output with volume substitution. Additionally, treatment with a beta-blocker might be considered. In the reported clinical cases, the LVOT obstruction, the SAM and the elevated gradient improved with those measures and posterior TTE were normal.

Additionally, there have also been reported cases of dynamic LVOTO in patients who have pheochromocytoma. [43-48]

Pheochromocytoma is a type of tumor that originates in the chromaffin cells, located within the adrenal medulla of the suprarenal gland that produces catecholamines.[49] The clinical presentation of a pheochromocytoma includes sustained paroxysmal HTN, palpitations and sweating as a result of adrenergic stimulation. [50, 51] It represents an uncommon cause of secondary HTN, which occurs approximately in 0,1-1% of all hypertensive patients.[50] However, the clinical presentation is also extremely variable and therefore a high degree of clinical suspicion is necessary in order to establish a correct diagnosis. [52] Surgery is the only definitive treatment of pheochromocytoma. [53]

There have been a few reported cases of pheochromocytoma that have been associated with dynamic LVOTO in both patients with structurally normal hearts as well as with abnormalities such as LVH and asymmetrical septal hypertrophy. In this next section, we describe these clinical cases, as well as try and elucidate the pathophysiology behind them, so that lessons could be taken in regard to the best approach and management of these patients.

Shub C. et al (1981) describe the case of a man, 61 years old, who was referenced to the hospital for evaluation of severe paroxysmal HTN and dizziness. The patient does not have any relevant previous medical history. He was hypertensive and cardiopulmonary auscultation revealed a 2/6 systolic murmur best heard at the left sternal border. ECG performed showed LVH. TTE revealed symmetric LVH with suggestive SAM of the MV with an LVOT PG of 60 mmHg. Both urinary metanephrines and vanillylmandelic acid as well as serum catecholamines were elevated. The

patient was started on propranolol and phenoxybenzamine, which stabilized the BP of the patient. Abdominal CT revealed a left adrenal mass, which was removed surgically, and confirmed as a pheochromocytoma. During the follow-up period, the patient remained normotensive and TTE revealed resolution of both SAM and LVOTO.[43]

Golbasi Z. et al (1999) describes the case of a woman, 37 years old, with a previous medical history of HTN, who resorts to the ED due to prolonged headaches unresponsive to standard ambulatory medical therapy. On physical examination, the patient was hypertensive (180/120 mmHg), as well as tachycardic with (112 beats per minute, bpm). On cardiopulmonary auscultation, it was noted a systolic murmur best heard at the left sternal border. The ECG performed was described as normal. TTE revealed SAM as well as LVOTO with a systolic gradient of 68 mmHg. Urine vanillylmandelic acid was elevated and a right adrenal tumor was revealed using a CT scan, which was confirmed to be a pheochromocytoma. Tumor removal resulted in the improvement of patient's symptoms, as well as normalization of BP levels and resolution of echocardiographic findings.[44]

Gilman G. et al (2006) also reported the case of a woman, 66 years of age, who was referred to her local hospital due to a history of HTN of difficult control. On physical examination, she was hypertensive (180/110 mmHg) and normocardic (72 bpm). Cardiopulmonary auscultation revealed a 2/6 systolic murmur best heard at the left sternal border. Both urinary metanephrines and vanillylmandelic acid as well as serum catecholamines were elevated. TTE showed a hyperdynamic LV with increased LV wall thicknesses and asymmetrical septal hypertrophy. There was also SAM of the mitral valve. A dynamic LVOTO was present, with a PG of 64 mmHg. An adrenal mass was confirmed by abdominal TC and successfully removed by surgery, which normalized the BP. However, no information relative to a follow-up TTE was reported, therefore being difficult to assert whether or not there was resolution of cardiac findings.[45]

More recently, Jóźwik-Plebanek K. et al (2014) describe the case of a woman, 49 years of age, who was referenced to the hospital with a clinical suspicion of pheochromocytoma. Her previous medical history revealed paroxysmal HTN, sweating and headaches. The patient was hypertensive (195/95 mmHg) with a HR of 90 bpm. On cardiopulmonary auscultation, a systolic murmur best heard in the left sternal border was present. TTE revealed an asymmetric hypertrophy of the septum as well as hyperdynamic LV with an EF (ejection fraction) of 80%, SAM of the MV and an LVOT gradient of 88 mmHg. The patient was immediately put on α-blockade with the resolution of clinical symptoms. The diagnosis of pheochromocytoma was based on biochemical and imaging evaluations and then confirmed after surgical removal. Repeat TTE revealed normal LV systolic function with no SAM of MV and resolution of LVOT PG, with no information given regarding the asymmetrical septal hypertrophy reported.[46]

Studies have reported that patients with pheochromocytoma can develop structural abnormalities, such LVH and LVOTO, in response to severe HTN and catecholaminergic overload, that can be reversible following surgical removal of the tumor. [54, 55] The patients reported by these authors had either structural heart abnormalities such as LVH, [43, 45] asymmetrical septal hypertrophy [45, 46] or otherwise a structurally normal heart.[44]

In patients with pheochromocytoma, the net cardiovascular effect of the physiologic variables (increased catecholamines, increased left ventricular afterload and tachycardia) on the dynamic of the LVOT would be complex, variable and unpredictable. [43, 44]

The anatomical predisposition reported in some of these patients, as well as the hyperdynamic state resulting from excessive secretion of catecholamines represents probably the most important mechanisms for the development of

severe, transient, dynamic LVOTO. [44, 46] Additionally, in all of these cases the removal of the tumor provided both symptomatic relief and normalization of BP. Furthermore, in almost all them, there was resolution of the SAM and the PG of the obstruction, as well as resolution of cardiac abnormalities.

Finally, the main takeaway from these reports should be that, although rare, it is important to consider dynamic LVOTO as a clinical presentation/consequence of pheochromocytoma in patients with hemodynamic instability and with findings on physical examination such as systolic murmur. TTE is imperative in the diagnosis of this clinical entity. The treatment should address the cause of the problem, with the implementation of adrenergic α-blockers to stabilize the BP of the patients, followed by surgical removal of the tumor.

Acute Myocardial Infarction with LVOTO

There have been reports of cases of patients diagnosed with AMI with dynamic LVOTO. [56-59]

The mechanical complications of AMI are various. A recent cohort study by Elbadawi A. et al (2019), estimates the incidence of these mechanical complications following AMI as high as 0,9%.[60]

The "classical" mechanical complications of AMI include LV free-wall rupture, ventricular septal rupture, acute MR due to rupture of chordae tendineae or papillary muscle and cardiac tamponade.[56] Some authors consider that LVOTO should also be considered a complication of AMI.[58] The actual incidence of dynamic LVOTO in AMI unclear, but it may be significantly underdiagnosed and can indeed mimic CS in this scenario.[58]

Astute clinical recognition of these complications and emergent evaluation with TTE could be crucial in planning an appropriate therapeutic strategy.[56] In the following section, we will describe the cases reported in the literature and try and elucidate the pathophysiology and mechanisms behind this phenomenon as well as the best management approach for these patients.

Ranjendran K. et al (2022) describe the case of a woman, 75 years of age, with HTN and type 2 diabetes mellitus, who presented to the local ED due to fatigue. On physical examination, BP was 140/80 mmHg and HR was 112 bpm. Cardiopulmonary examination denoted a grade 2/6 systolic murmur, best heard at the left sternal border. The ECG showed ST-segment elevation in V2-V6, which suggested anterior wall AMI. TTE revealed LVH and a small hypercontractile LV with an EF of 70%. It was visible a sigmoid-shaped septum with apical hypokinesia and compensatory hyperkinesia of septal basal segments. The TTE also reported SAM of the mitral valve and a LVOT PG of 43 mmHg. CAG showed a 90% stenosis of the LAD artery. The patient underwent fibrinolysis with streptokinase and 8 hours after was submitted to angioplasty of the LAD artery. After initiating beta-blocker regimen and revascularization of the LAD, the HR stabilized and cardiac auscultation revealed cessation of cardiac murmur. Follow-up TTE revealed reduction of the gradient at the LVOT and resolution of SAM of the MV, which suggests a probable diagnosis of acquired dynamic LVOT obstruction in the setting of acute STEMI (ST elevation myocardial infarction) .[56]

Fujiwara M. et al (2021) also report a case of a woman, 70 years of age, with no previous relevant medical history, who presented herself to the ED due to acute onset constricting chest pain. The patient was normotensive, but was tachycardic (106 bpm) and cardiopulmonary examination revealed a grade 2/6 systolic murmur. ECG revealed no changes within the ST segment. Cardiac biomarkers were elevated. TTE revealed basal hyperkinesis, SAM of the MV, moderate MR, and LVOTO, with a PG of 250 mmHg. The patient was diagnosed with ACS, and CAG revealed severe stenosis (99%) in the LAD artery, as well as stenosis (90%) of each of the two diagonal branches. PCI was successfully

performed, with three stents placed for significant stenosis of the three vases. After the intervention the patient's symptoms improved and HR normalized. Furthermore, follow-up TTE revealed resolution of LVOTO, the disappearance of SAM of the MV.[57]

Chockalingam A. et al (2007) report the case of a woman, 70 years of age, with no relevant previous medical history, who presents herself to the local ED due to acute onset dull chest pain. Physical examination showed stable vital signs and a grade 2/6 systolic murmur. ECG showed ST elevation up to 3 mm in V2 through V6. Cardiac biomarkers were elevated (maximum troponin was 5 ng/mL). TTE revealed LV dysfunction, EF of 35% with SAM and moderate MR. LVOT gradient was not reported. CAG showed a stenosis (90%) of the LAD artery and anteroapical akinesia. During the procedure the patient developed hypotension and tachycardia. Dopamine infusion did not improve BP, and the murmur increased to grade 3/6 intensity. IV betablocker (metoprolol) and phenylephrine were initiated, which stabilized the BP, reduced the HR and the systolic murmur was no longer heard. Follow-up TTE showed no SAM or LVOT obstruction (LVOTO) and only mild MR. [58]

Finally, Haley J. et al (1999) also report the case of a patient, woman, 69 years of age, with prior medical history of mitral valve prolapse who presented herself to the local ED due to acute onset chest pain. Initial physical examination was unremarkable. The ECG showed ST elevation in V1 through V5. Cardiac biomarkers were elevated. Heparin and nitroglycerin were initiated to which the patient responded with hypotension and therefore dopamine infusion was initiated. Reexamination of the patient revealed a 3/6 systolic murmur. Respiratory compromise developed after which mechanical ventilation was implemented. CAG showed a 90% stenosis of the left circumflex artery with otherwise no notable lesions. TTE showed decreased LV function with an estimated EF of 30%, hypokinesis of the mid ventricle, apical akinesis and hyperdynamic basal segments with SAM of mitral valve leaflet with a peak gradient of 49 mmHg. There was also severe MR and concentric LVH. Phenylephrine infusion allowed for stabilization of BP and subsequently dopamine weaning and beta-blocker therapy were started, allowing extubation. Follow-up TTE showed normal LV function, no SAM of the mitral valve or LVOT obstruction. [59]

Chokalingam A. et al (2007) propose that along with acute MR, ventricular septal defect, and free wall rupture, dynamic LVOTO be included in the differential diagnosis of AMI and CS. [58] In accordance with the cases here reported it appears that this phenomenon is more common in female patients after anterior AMIs.[61] The development of a dynamic LVOTO has important therapeutic implications. The occurrence of hypotension and a systolic murmur in the setting of an ACS suggests the development of the classical mechanical complications of acute MR or ventricular septal rupture, however, the presence of a dynamic LVOTO must also be included in the differential diagnosis when confronted with the above physical signs.[59] In the presence of this clinical suspicion, a TTE should be considered the diagnostic modality of choice and should be performed at the earliest possible time. If the images are unclear a transesophageal echocardiogram could be considered. [57, 59] Furthermore, echocardiography allows the exclusion of other causes of hypotension in the setting of an acute MI, including ventricular septal rupture and acute MR. [59] However, catheterization should be the initial study to avoid delays in diagnosis and relief of coronary occlusions.

The proposed mechanism mechanisms of acquired LVOT obstruction in acute AMI are apical dysfunction and compensatory hypercontractility of the basal segments.[57] Akinesia at the apex may result in increased motion of the basal portions of the left ventricle as a compensatory mechanism, thus generating the dynamic LVOTO.[57, 59] This compensatory hyperkinesis decreases the systolic LVOT cross-sectional area, resulting in acceleration of blood flow through the LVOT, which can create a Venturi effect, where the accelerated jet flow decreases pressure above the MV, pushing the anterior MV leaflet toward the septum, during systole, resulting in further LVOT obstruction.[59]

Furthermore, the failure of the MV leaflets to coapt during systole results in MR, which was observed in some of these patients.[14] It is also noteworthy that some of these patients were anatomically predisposed with factors such as sigmoid-shaped septum [56, 57], long standing HTN associated with LVH [56] and small left ventricular cavity [57] that combined with these mechanisms of apical dysfunction and compensatory basal hypercontractility, lead to the obstruction. The consequences of this obstruction include increased myocardial oxygen demand, which consequently expands the area of myocardium susceptible to ischemia[14] and increases systolic wall stress, which has been associated with reports of myocardial rupture.[62, 63]

Therapeutic measures that may be beneficial in this setting include beta-blockers and α-agonists. Beta-Blockers, by reducing basal segment hyperkinesia, increasing LV filling size and reducing HR, may act to decrease the size of the LVOT gradient. [58, 59] However, a beta-blocker alone may not be tolerated, if systolic function is markedly reduced. α-agonists increase systemic arteriolar resistance, leading to an increase in both the end-systolic and the end-diastolic LV volume. Phenylephrine may selectively improve vascular tone and reduce LVOTO. [64] The subsequent increase in the LV volume results in a larger functional outflow tract and subsequent reduction in the LVOT gradient. α-agonists were used in some of the patients presented, and the initiation of this therapy promoted improvement in each case. [51]

Additionally, measures such as IV fluids would be beneficial by increasing intravascular and LV volumes, thereby reducing the SAM. Coronary revascularization would improve the contractility of apical segments and reduce the basal hypercontractility. MR often improves with the reduction of SAM and LVOTO. An IABP could induce or worsen LVOTO by reducing afterload. [58, 61]

These cases illustrate the importance of defining the mechanism of CS in AMI so treatment can be targeted. Most commonly, the cause will be pump failure that requires inotropes and revascularization, or a ventricular septal defect or acute MV rupture, requiring a surgery, but occasionally, the cause may be dynamic LVOTO. [65] In conclusion, treatment of dynamic LVOTO due to acute STEMI includes adequate IV, early beta-blockers to reduce the basal hypercontractility, urgent revascularization [58] and cautious use of inotropes [65, 66] that might perpetuate LVOTO. [56]

LVOTO associated with volume depletion.

As we have previously stated in this literature review, dynamic LVOTO resulting from SAM of the MV is a typical feature of HCM. However, this phenomenon can appear under certain clinical conditions associated with hyperdynamic LV contraction and intravascular volume depletion (due to dehydration, hemorrhage or even emesis). In these patients, the occurrence of dynamic LVOTO is serious, because it can significantly compromise cardiac output. In this section we will discuss four case reports that illustrate this phenomenon to understand the pathophysiology behind them and the best strategy for the diagnosis and management of these patients. [67]

Kim S. et al (2015) report the case of a man, 72 years old, with history of chronic obstructive pulmonary disease, who presented himself to the local ED due to aggravating dyspnea and new onset cough with purulent sputum. Upon physical examination, the patient was tachycardic with peripheral bilateral edema of the legs. Cardiopulmonary examination denoted a grade 4/6 systolic murmur, best heard at the left sternal border. ECG was described as normal. Laboratory findings revealed leukocytosis, elevated C reactive protein and Pro-BNP levels. Chest CT revealed findings compatible with community-acquired pneumonia. TTE revealed a small hyperdynamic LV, EF of 80%, suggesting LV volume depletion. Additionally, SAM of the MV and flow acceleration across the LVOT was observed, with an estimated PG of 98 mmHg. A diagnosis of acute exacerbation of COPD due to pneumonia was considered and oxygen

and antibiotic therapy were started. Management of the coexisting AHF resulting from dynamic LVOTO was given to the patient, with a cardio-selective beta-blocker (bisoprolol) and IV fluid therapy to improve hyperdynamic LV and left-heart filling, respectively. This allowed for symptomatic relief as well as the disappearance of the cardiac murmur. Follow-up TTE showed resolution of SAM and the LVOT obstruction and normalization of Pro BNP levels. [67]

The most likely mechanism for this patient's clinical presentation was the acute exacerbation of COPD which might have caused an increase in pulmonary vascular resistance with impaired LV filling and LV volume reduction. Sequentially, SAM of the MV and concomitant dynamic LVOTO occurred in a volume-depleted but structurally normal LV, which caused transient acute heart failure as was evidenced by the elevated Pro-BNP levels.[67]

Additionally, Kim D. et al (2012) report the case of a woman, 59 years old, who presented herself to the local ED due to dyspnea with several days of evolution. It should be noted that the patient had a previous medical history of stroke and epilepsy. During the previous week, the patient had a minimal intake of food and water due to the anorexia associated with her brain conditions. Upon physical examination the patient was hypotensive, tachycardic with dry mucous membranes. Cardiopulmonary auscultation revealed a systolic murmur, grade 3/6, best heard at the left sternal border. In terms of diagnostic workup, chest radiography revealed pulmonary congestion and ECG was normal. Additionally, laboratory findings revealed hypernatremia, increased uremia and increased creatinine levels, which were all suggestive of systemic dehydration. In order to study the new cardiac murmur, a TTE was performed that revealed a small LV cavity with hyperdynamic LV, EF of 78%, suggesting intracardiac volume depletion. Additionally, SAM of the MV with moderate MR was present with LVOT obstruction with a PG of 119 mm Hg. The management of this patient included nutritional support and fluid therapy with crystalloid to restore the patient's systemic volume. This could be considered counterintuitive due to pulmonary congestion that was observed during chest radiography; however, it is important to note that the most likely cause of this was intracardiac volume maldistribution resulting from SAM of the MV in a volume-depleted heart. Following treatment, the patient's condition stabilized, and laboratory findings normalized. Follow-up TTE revealed complete resolution of SAM of the MV and disappearance of the dynamic LVOT obstruction. [68]

This patient developed acute heart failure with hemodynamic impairment precipitated by extreme dehydration with intraventricular obstruction and significant MR. The patient's medical history of stroke might have affected thirst and satiety centers in the brain providing a plausible explanation for the patient's symptoms. In the present case, pulmonary congestion was considered to be a consequence of increased left atrial pressure which resulted from LVOTO and MR. Therefore, the cause of the patient's hypotension was cardiogenic rather than hypovolemic and echocardiography was an invaluable tool to define the etiology of the shock.[68]

Hioki H. et al (2010) also report the case of a patient, 71-year-old woman, with previous medical history of peptic ulcer, who presented to the ED due to new onset dyspnea. The patient vital signs were stable, with pale conjunctivae and cardiopulmonary examination revealed a grade 3/6 systolic murmur. Chest X ray showed moderate pulmonary congestion and laboratory findings showed microcytic anemia (hemoglobin 7,4 g/dL), which was assumed to be caused by the ulcer and posteriorly confirmed by endoscopy. ECG performed showed sinus rhythm and TTE revealed a hyperkinetic LV, with normal wall thickness and a marked bulging of sigmoid septum. There was also SAM of the MV with moderate MR and LVOT pressure gradient was estimated at 156 mmHg. The patient was treated with a beta blocker, blood transfusion and proton pump inhibitor, which improved her symptoms. Follow up TTE revealed resolution of LVOT obstruction and MR.[69]

Finally, Sobczyk D. (2014) also reports the case of a 76-year-old woman who presented to the ED due to transient loss of consciousness. Her previous medical hystory include HTN, under optimized medical therapy. The patient had also a 2 day history of vomiting, likely due to a dietary condition. On physical examination, the patient was tachycardic and hypotensive with dehydrated mucous membranes. Cardiopulmonary auscultation revealed a systolic murmur. ECG revealed sinus tachycardia with no morphological abnormalities. TTE showed a small LV end diastolic size, LVH and sigmoid shaped interventricular septum bulging into the LVOT, preserved LV function with EF of 60% and LVOTO with PG of 70 mm Hg. Dynamic LVOTO, subsequent to sigmoid septum and hypovolemia due to emesis was considered the most likely diagnosis. After IV fluid delivery, the hemodynamic parameters improved and a follow up TTE revealed diminished gradient of LVOT.[8]

Sigmoid septum is used to describe a localized hypertrophy of the basal interventricular septum. [16] It is considered the result of aging and appears most times to have no clinical significance. [69] However when associated with LVH,[8, 70] and/or hypercontractile state with decrease in intravascular blood volume it could be sufficient to induce a dynamic LVOTO.

These cases illustrate once again the importance of a timely performed echocardiographic evaluation for the accurate diagnosis of the LVOTO, The management of these patients required and careful intravenous fluid therapy by increasing intravascular and LV volume, which results in a larger functional outflow tract and subsequent reduction in the LVOT gradient.[67] Beta blocker therapy was also beneficial in some of these patients.

Conclusion

As we have previously stated, dynamic LVOTO is usually described within the context of patients with HCM. However, as we tried to describe within this review dynamic LVOTO can manifest in a variety of other clinical situations. Still, its prevalence in the general population is widely unknown, understudied, and a lot of authors consider it to be a severely underdiagnosed cause of hypotension.[71] The cardiovascular outcomes in patients diagnosed with HCM with LVOTO, are well studied, however the impact of an event of transient LVOTO, outside of these population of patients, is unknown in terms of prognosis for long term cardiovascular outcomes or death. The clinical presentation of the patients described in this literature review is wide and usually associated with the base pathology that is affecting the patient, however, it appears that chest discomfort, dyspnea and sweating are some of the most prevalent initial symptoms. Tachycardia and hypotension were also frequently observed, however the most important sign upon physical examination, is the presence of a systolic murmur, usually best heard at the left sternal border, which in most cases motivated additional investigation with a TTE. In particular, TTE is the ideal first-step imaging technique for the diagnosis and quantification of LVOTO gradient as well as determining the presence of SAM of MV apparatus. In terms of treatment, these patients respond well to beta-blocker therapy by reducing inotropy, cronotropy and, in particular in patients diagnosed with TC, are important in the shutting of catecholamine hyperactivity, a mechanism important in the pathogenesis of this clinical entity. Aditionally IV fluids appear to also be beneficial by increasing intravascular and LV volume. These measures appear to reduce LV hypercontractility and prolong diastole with greater end-diastolic volume. The subsequent increase in the LV volume results in a larger functional outflow tract and subsequent reduction in the LVOT gradient. Inotropes, widely used in acute settings, should be discontinued as they are known to aggravate the gradient of obstruction and, as was the case of a lot of patients that presented with hypotension, selective α-agonists, such as phenylephrine, allow for BP stabilization without increasing inotropy of the heart. Treatment was also specific to the base pathology of the patient, such as PCI/CABG for AMI or surgical tumor removal such as in pheochromocytoma. Other measures, reported by some authors,[72] such as control of cardiovascular risk factors, for example, HTN, to help maximize LVH regression, and regular exercise, to improve vagal tone, could also be considered as long-term therapies for these patients.

The present report has a lot of limitations, concerned mainly with the fact that is based in case reports and small case series, therefore the evidence that could be extracted is of inferior quality. We believe that longitudinal long term studies that address this population of patients with LVOTO, independent of the cause, should be undertaken so as to determine if these are at greater risk of life time incidence of posterior cardiovascular events or death.

Referências Bibliográficas

1. Vilcant, V. and O. Hai, *Left Ventricular Outflow Tract Obstruction*, in *StatPearls*. 2023, StatPearls Publishing

Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

2. Gharibeh, L., N.G. Smedira, and J.B. Grau, *Comprehensive left ventricular outflow tract management beyond septal reduction to relieve obstruction.* Asian Cardiovasc Thorac Ann, 2022. **30**(1): p. 43-52.
3. Mingo, S., et al., *Dynamic left ventricular outflow tract obstruction secondary to catecholamine excess in a normal ventricle.* Int J Cardiol, 2006. **112**(3): p. 393-6.
4. Yang, J.H., et al., *Dynamic left ventricular outflow tract obstruction without basal septal hypertrophy, caused by catecholamine therapy and volume depletion.* Korean J Intern Med, 2008. **23**(2): p. 106-9.
5. Slama, M., C. Tribouilloy, and J. Maizel, *Left ventricular outflow tract obstruction in ICU patients.* Curr Opin Crit Care, 2016. **22**(3): p. 260-6.
6. Gabrielle Norrish, J.P.K., *Diagnosis and Management of Adult Congenital Heart Disease (Third Edition)*, ed. G.D.W. Michael A. Gatzoulis, Piers E.F. Daubeney. 2018: Elsevier.
7. Farkas, J. *Dynamic left ventricular outflow tract obstruction (LVOTO)*. The Internet Book of Critical Care 2021 [cited 2023 May 2023]; Available from: https://emcrit.org/ibcc/lvoto/.
8. Sobczyk, D., *Dynamic left ventricular outflow tract obstruction: underestimated cause of hypotension and hemodynamic instability.* J Ultrason, 2014. **14**(59): p. 421-7.
9. Veselka, J., *How to Treat Obstructions in Patients with Hypertrophic Cardiomyopathy.* Int J Angiol, 2015. **24**(2): p. 121-6.
10. Batzner, A., et al., *Hypertrophic Obstructive Cardiomyopathy.* Dtsch Arztebl Int, 2019. **116**(4): p. 47-53.
11. Maron, M.S., et al., *Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy.* N Engl J Med, 2003. **348**(4): p. 295-303.
12. Maron, M.S., et al., *Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction.* Circulation, 2006. **114**(21): p. 2232-9.
13. Kobayashi, S., et al., *Causes of an increased pressure gradient through the left ventricular outflow tract: a West Coast experience.* J Echocardiogr, 2018. **16**(1): p. 34-41.
14. Khan, S., et al., *Left ventricular outflow tract obstruction following an uncomplicated primary percutaneous coronary intervention: a recognized but rare cause of cardiogenic shock.* Eur Heart J Acute Cardiovasc Care, 2013. **2**(1): p. 68-71.
15. Helmy, S.M., *Dynamic LVOT obstruction*, E.S.o. Cardiology, Editor. 2019: Qatar.
16. Evans, J.S., et al., *Left ventricular outflow tract obstruction-be prepared!* Anaesth Intensive Care, 2017. **45**(1): p. 12-20.
17. Kawaji, T., et al., *Clinical impact of left ventricular outflow tract obstruction in takotsubo cardiomyopathy.* Circ J, 2015. **79**(4): p. 839-46.
18. Kono, T. and H.N. Sabbah, *Takotsubo cardiomyopathy.* Heart Fail Rev, 2014. **19**(5): p. 585-93.
19. Dawson, D.K., *Acute stress-induced (takotsubo) cardiomyopathy.* Heart, 2018. **104**(2): p. 96-102.
20. Conradi, P.M., R.B. van Loon, and M.L. Handoko, *Dynamic left ventricular outflow tract obstruction in Takotsubo cardiomyopathy resulting in cardiogenic shock.* BMJ Case Rep, 2021. **14**(3).
21. Assad, J., et al., *Takotsubo Syndrome: A Review of Presentation, Diagnosis and Management.* Clin Med Insights Cardiol, 2022. **16**: p. 11795468211065782.

22. Templin, C., et al., *Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy.* N Engl J Med, 2015. **373**(10): p. 929-38.
23. Nóbrega, S. and D. Brito, *[The "broken heart syndrome": state of the art].* Rev Port Cardiol, 2012. **31**(9): p. 589-96.
24. Lyon, A.R., et al., *Pathophysiology of Takotsubo Syndrome: JACC State-of-the-Art Review.* J Am Coll Cardiol, 2021. **77**(7): p. 902-921.
25. Wittstein, I.S., et al., *Neurohumoral features of myocardial stunning due to sudden emotional stress.* N Engl J Med, 2005. **352**(6): p. 539-48.
26. Ghadri, J.-R., et al., *International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology.* European Heart Journal, 2018. **39**(22): p. 2032-2046.
27. Di Vece, D., et al., *Dynamic Left Intraventricular Obstruction Phenotype in Takotsubo Syndrome.* J Clin Med, 2021. **10**(15).
28. Eitel, I., et al., *Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy.* Jama, 2011. **306**(3): p. 277-86.
29. Ishihara, M., *Takotsubo cardiomyopathy and left ventricular outflow tract obstruction.* Circ J, 2015. **79**(4): p. 758-60.
30. Pelliccia, F., et al., *Pathophysiology of Takotsubo Syndrome.* Circulation, 2017. **135**(24): p. 2426-2441.
31. Donohue, D. and M.R. Movahed, *Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome.* Heart Fail Rev, 2005. **10**(4): p. 311-6.
32. De Backer, O., et al., *Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: a two-year, two-center experience.* BMC Cardiovasc Disord, 2014. **14**: p. 147.
33. El Mahmoud, R., et al., *Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome.* Am Heart J, 2008. **156**(3): p. 543-8.
34. Wu, H.M. and B.H. Tzeng, *Dynamic Left Ventricular Outflow Tract Obstruction with Cardiogenic Shock in Apical Ballooning Syndrome.* Acta Cardiol Sin, 2013. **29**(4): p. 370-3.
35. Ozaki, K., et al., *Manifestation of Latent Left Ventricular Outflow Tract Obstruction in the Acute Phase of Takotsubo Cardiomyopathy.* Intern Med, 2016. **55**(23): p. 3413-3420.
36. O'Brien, J., et al., *Dynamic left ventricular outflow tract gradient resulting from Takotsubo cardiomyopathy ameliorated by intra-aortic balloon pump counterpulsation: a case report.* Eur Heart J Case Rep, 2021. **5**(3): p. ytab082.
37. Ghadri, J.R., et al., *International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management.* Eur Heart J, 2018. **39**(22): p. 2047-2062.
38. Beneduce, A., et al., *Mechanical Circulatory Support With Impella Percutaneous Ventricular Assist Device as a Bridge to Recovery in Takotsubo Syndrome Complicated by Cardiogenic Shock and Left Ventricular Outflow Tract Obstruction.* JACC Cardiovasc Interv, 2019. **12**(4): p. e31-e32.
39. Mohammedzein, A., et al., *Impella Use in Cardiogenic Shock Due to Takotsubo Cardiomyopathy With Left Ventricular Outflow Tract Obstruction.* JACC Case Rep, 2019. **1**(2): p. 161-165.
40. Raposeiras-Roubín, S., et al., *Long-term prognostic impact of beta-blockers in patients with Takotsubo syndrome: Results from the RETAKO Registry.* Rev Port Cardiol, 2023. **42**(3): p. 237-246.

41. Auer, J., et al., *Catecholamine therapy inducing dynamic left ventricular outflow tract obstruction.* Int J Cardiol, 2005. **101**(2): p. 325-8.
42. Mampuya, W.M., J. Dumont, and F. Lamontagne, *Norepinephrine-associated left ventricular outflow tract obstruction and systolic anterior movement.* BMJ Case Rep, 2019. **12**(12).
43. Shub, C., et al., *Dynamic left ventricular outflow tract obstruction associated with pheochromocytoma.* Am Heart J, 1981. **102**(2): p. 286-90.
44. Gölbaşi, Z., et al., *Dynamic left ventricular outflow tract obstruction in a patient with pheochromocytoma.* Jpn Heart J, 1999. **40**(6): p. 831-5.
45. Gilman, G., et al., *Increased mitral regurgitation during the valsalva maneuver in a patient with pheochromocytoma, uncontrolled hypertension, cardiac hypertrophy, and dynamic outflow tract obstruction.* Echocardiography, 2006. **23**(1): p. 53-5.
46. Jóźwik-Plebanek, K., et al., *Transient dynamic left ventricular outflow tract obstruction in a patient with pheochromocytoma.* Kardiol Pol, 2014. **72**(5): p. 472.
47. Gallet, B., et al., *[Dynamic left ventricular obstruction associated with a pheochromocytoma reversible after tumor ablation].* Arch Mal Coeur Vaiss, 2001. **94**(11): p. 1195-8.
48. Hashimoto, Y., et al., *[A case of pheochromocytoma developing dynamic left ventricular outflow tract obstruction].* Nihon Naika Gakkai Zasshi, 1982. **71**(12): p. 1727-33.
49. Antunes, E., et al., *Pheochromocytoma: A Case Report.* Cureus, 2022. **14**(11): p. e31409.
50. Soltani, A., M. Pourian, and B.M. Davani, *Does this patient have Pheochromocytoma? a systematic review of clinical signs and symptoms.* J Diabetes Metab Disord, 2015. **15**: p. 6.
51. Gu, Y.W., et al., *Cardiovascular Manifestations of Pheochromocytoma.* Cardiol Rev, 2017. **25**(5): p. 215-222.
52. Reisch, N., et al., *Pheochromocytoma: presentation, diagnosis and treatment.* J Hypertens, 2006. **24**(12): p. 2331-9.
53. Farrugia, F.A. and A. Charalampopoulos, *Pheochromocytoma.* Endocr Regul, 2019. **53**(3): p. 191-212.
54. Huddle, K.R., B. Kalliatakis, and J. Skoularigis, *Pheochromocytoma associated with clinical and echocardiographic features simulating hypertrophic obstructive cardiomyopathy.* Chest, 1996. **109**(5): p. 1394-7.
55. Lopes, H.F., et al., *[A false diagnosis of hypertrophic myocardiopathy in pheochromocytoma].* Arq Bras Cardiol, 1995. **65**(2): p. 167-9.
56. Rajendran, K., S. Kunjukrishnanpillai, and B. Rajan, *Acquired Dynamic Left Ventricular Outflow Tract Obstruction: A Rare Complication of Acute Myocardial Infarction.* CASE (Phila), 2022. **6**(2): p. 77-82.
57. Fujiwara, M., et al., *Dynamic left ventricular outflow tract obstruction in a patient with acute coronary syndrome and without the apical akinesia: Potential alternative mechanisms causing a dynamic left ventricular outflow tract obstruction other than a compensatory basal hyperkinesis.* Echocardiography, 2021. **38**(3): p. 460-468.
58. Chockalingam, A., et al., *Dynamic left ventricular outflow tract obstruction in acute myocardial infarction with shock: cause, effect, and coincidence.* Circulation, 2007. **116**(5): p. e110-3.
59. Haley, J.H., et al., *Dynamic left ventricular outflow tract obstruction in acute coronary syndromes: an important cause of new systolic murmur and cardiogenic shock.* Mayo Clin Proc, 1999. **74**(9): p. 901-6.
60. Elbadawi, A., et al., *Temporal Trends and Outcomes of Mechanical Complications in Patients With Acute Myocardial Infarction.* JACC Cardiovasc Interv, 2019. **12**(18): p. 1825-1836.

61. Liu, S., et al., *Dynamic Left Ventricular Outflow Tract Obstruction in the Setting of Acute Myocardial Infarction.* J Cardiothorac Vasc Anesth, 2019. **33**(12): p. 3423-3426.

62. Bartunek, J., M. Vanderheyden, and B. de Bruyne, *Dynamic left ventricular outflow tract obstruction after anterior myocardial infarction. A potential mechanism of myocardial rupture.* Eur Heart J, 1995. **16**(10): p. 1439-42.

63. Bartunek, J., M. Vanderheyden, and B. De Bruyne, *Dynamic left ventricular outflow tract obstruction as a potential mechanism of myocardial rupture after acute myocardial infarction.* J Am Coll Cardiol, 1999. **34**(7): p. 2150-1.

64. Cohen, R., J. Rivagorda, and S. Elhadad, *Asymmetric septal hypertrophy complicated by dynamic left ventricular obstruction after intra-aortic balloon counterpulsation placement in the setting of anterior myocardial infarction.* J Invasive Cardiol, 2006. **18**(7): p. E207-8.

65. Taylor, J.S., R. Purnell, and Z.R. Yousef, *Acquired left ventricular outflow tract obstruction and cardiogenic shock treated with beta-blockers.* Am J Emerg Med, 2009. **27**(3): p. 373.e1-373.e3.

66. Di Chiara, A., et al., *Dynamic left ventricular outflow tract obstruction: an unusual mechanism mimicking anterior myocardial infarction with cardiogenic shock.* Ital Heart J, 2001. **2**(1): p. 60-7.

67. Kim, S., et al., *Dynamic obstruction induced by systolic anterior motion of the mitral valve in a volume-depleted left ventricle: an unexpected cause of acute heart failure in a patient with chronic obstructive pulmonary disease.* J Thorac Dis, 2015. **7**(9): p. E365-9.

68. Kim, D., et al., *Paradoxical heart failure precipitated by profound dehydration: intraventricular dynamic obstruction and significant mitral regurgitation in a volume-depleted heart.* Yonsei Med J, 2013. **54**(4): p. 1058-61.

69. Hioki, H., et al., *Dynamic left ventricular outflow tract obstruction due to anemia in a 71-year-old patient with sigmoid septum.* J Cardiol Cases, 2010. **1**(3): p. e144-e146.

70. Konishi, C., et al., *Beneficial effect of cibenzoline on left ventricular pressure gradient with sigmoid septum.* Circ J, 2004. **68**(10): p. 968-71.

71. Ricksten, S.E., *Refractory shock in the intensive care unit--don't fail to spot obstruction of the left ventricular outflow tract!* Crit Care Med, 2009. **37**(2): p. 793-4.

72. Chockalingam, A., et al., *Unexplained hypotension: the spectrum of dynamic left ventricular outflow tract obstruction in critical care settings.* Crit Care Med, 2009. **37**(2): p. 729-34.

List of Figures

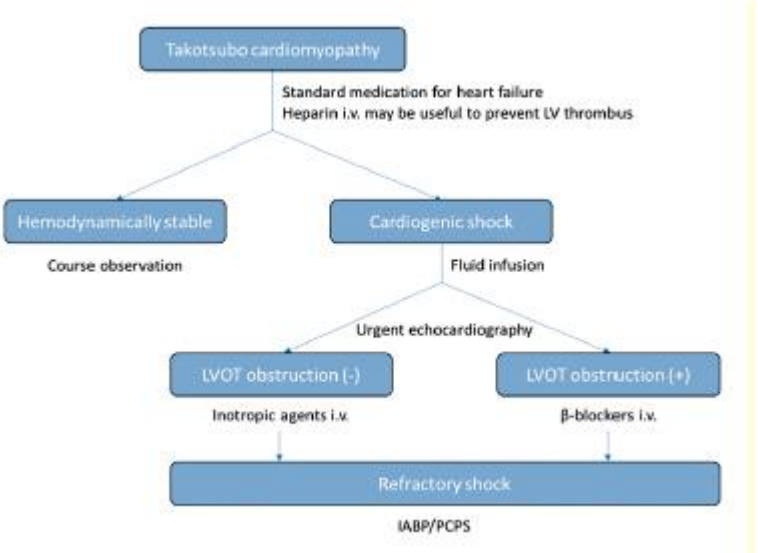

Figure 1 – Management algorithm for TC (Takotsubo cardiomyopathy). LVOTO (left ventricular outflow tract obstruction); IABP (intra-aortic balloon pump); PCPS (percutaneous cardiopulmonary support)

Adapted from Conradi P. et al (2021). Permission asked to the authors.[20]

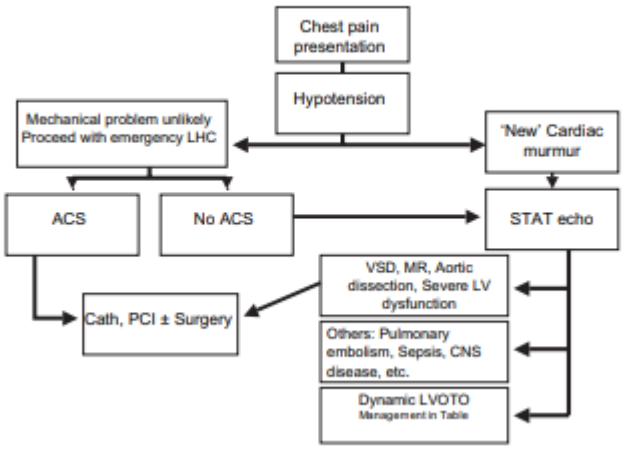

Figure 2 – Management algorithm for LVOTO. ACS (acute coronary syndrome); Cath (catheterization); Echo (echocardiography); PCI (percutaneous coronary intervention); MR (mitral Regurgitation); STAT (start as soon as possible); VSD (ventricular septal defect) and CNS (central nervous system).

Adapted from Chockalingam A. et al (2007). Permission asked to the authors.[58]

Anexos

I – Scale for the Assessment of Narrative Reviews Reporting Guidelines

II – Guidelines Revista Portuguesa de Cardiologia da Sociedade Portuguesa de Cardiologia

Scale for the Assessment of Narrative Review Articles – SANRA

Please rate the quality of the narrative review article in question, using categories 0–2 on the following scale. For each aspect of quality, please choose the option which best fits your evaluation, using categories 0 and 2 freely to imply general low and high quality. These are not intended to imply the worst or best imaginable quality.

1) Justification of the article's importance for the readership

The importance is not justified. — 0
The importance is alluded to, but not explicitly justified. — 1
The importance is explicitly justified. — 2

2

2) Statement of concrete aims or formulation of questions

No aims or questions are formulated. — 0
Aims are formulated generally but not concretely or in terms of clear questions. — 1
One or more concrete aims or questions are formulated. — 2

2

3) Description of the literature search

The search strategy is not presented. — 0
The literature search is described briefly. — 1
The literature search is described in detail, including search terms and inclusion criteria. — 2

2

4) Referencing

Key statements are not supported by references. — 0
The referencing of key statements is inconsistent. — 1
Key statements are supported by references. — 2

2

5) Scientific reasoning

(e.g., incorporation of appropriate evidence, such as RCTs in clinical medicine)

The article's point is not based on appropriate arguments. — 0
Appropriate evidence is introduced selectively. — 1
Appropriate evidence is generally present. — 2

2

6) Appropriate presentation of data

(e.g., absolute vs relative risk; effect sizes without confidence intervals)

Data are presented inadequately. — 0
Data are often not presented in the most appropriate way. — 1
Relevant outcome data are generally presented appropriately. — 2

2

Sumscore 12

Fig. 1 SANRA - Scale

SANRA – explanations and instructions

This scale is intended to help editors assess the quality of a narrative review article based on formal criteria accessible to the reader. It cannot cover other elements of editorial decision making such as degree of originality, topicality, conflicts of interest or the plausibility, correctness or completeness of the content itself. SANRA is an instrument for editors, authors, and reviewers evaluating individual manuscripts. It may also help editors to document average manuscript quality within their journal and researchers to document the manuscript quality, for example in peer review research. Using only three scoring options, 0, 1 and 2, SANRA is intended to provide a swift and pragmatic sum score for quality, for everyday use with real manuscripts, in a field where established quality standards have previously been lacking. It is not designed as an exact measurement of the quality of all theoretically possible manuscripts. For this reason, the extreme values (0 and 2) should be used relatively freely and not reserved only for perfect or hopeless articles.

We recommend that users test-rate a few manuscripts to familiarize themselves with the scale, before using it on the intended group of manuscripts. Ratings should assess the totality of a manuscript, including the abstract. The following comments clarify how each question is designed to be used.

Item 1 – Justification of the article's importance for the readership

Justification of importance for the readership must be seen in the context of each journal's readership.
Consider how well the manuscript outlines the clinical problem and highlights unanswered questions or evidence gaps – thoroughly (2), superficially (1), or not at all (0).

Item 2 – Statement of concrete/specific aims or formulation of questions

A good paper will propose one or more specific aims or questions which will be dealt with or topics which will be reviewed.
Please rate whether this has been done thoroughly and clearly (2), vaguely or unclearly (1), or not at all (0).

Item 3 – Description of the literature search

A convincing narrative review will be transparent about the sources of information on which the text is based. Please rate the degree to which you think this has been achieved. To achieve a rating of 2, it is not necessary to describe the literature search in as much detail as for a systematic review (searching multiple databases, including exact descriptions of search history, flowcharts, etc.), but it is necessary to specify search terms, and the types of literature included. A manuscript which only refers briefly to its literature search would score 1, while one not mentioning its methods would score 0.

Item 4 – Referencing

No manuscript references all statements. However, those that are essential for the arguments of the manuscript – "key statements" – should be backed by references in all or almost all cases. Exceptions could reasonably be made for rating purposes where a key statement has uncontroversial face-validity, such as "Diabetes is among the commonest causes of chronic morbidity worldwide."
Please rate the completeness of referencing: for most or all relevant key statements (2), inconsistently (1), sporadically (0).

Item 5 – Scientific reasoning

The item describes the quality of the scientific point made. A convincing narrative review presents evidence for key arguments. It should mention study design (randomized controlled trial, qualitative study, etc), and where available, levels of evidence.
Please rate whether you feel this has been done thoroughly (2), superficially (1), or hardly at all (0). Unlike item 6, which is concerned with the selection and presentation of concrete outcome data, this item relates to the use of evidence and of types of evidence in the manuscript's arguments.

Item 6 – Appropriate presentation of data:

This item describes the correct presentation of data central to the article's argument. Which data are considered relevant varies from field to field. In some areas relevant data would be absolute rather than relative risks or clinical versus surrogate or intermediate endpoints. These outcomes must be presented correctly. For example, it is appropriate that effect sizes are accompanied by confidence intervals. Please rate how far the paper achieves this – thoroughgoingly (2), partially (1), or hardly at all (0). Unlike item 5, which relates to the use of evidence and of types of evidence in the manuscript's arguments, this item is concerned with the selection and presentation of concrete outcome data.

Fig. 2 SANRA—explanations and instructions document

Reporting Guidelines SANRA

1. Justification of the article's importance for the readership

Page 4 «To our knowledge, this is the first literature review in recent years that accomplishes this purpose and therefore we believe in the importance and the clinical relevance of this report, especially for healthcare professionals working in the fields of cardiology, intensive medicine and internal medicine.»

2. Statement of concrete aims or formulation of questions

Page 4 «In this review we aim to gather information regarding the occurrence of transient LVOTO in different clinical scenarios, excluding the traditional HCM, highlighting the pathophysiology hypotheses, diagnosis, and management.»

3. Description of the literature research

Page 4 «A search was conducted in MEDLINE and Web of Science for either English or Portuguese articles published until May 2023 with the key search terms Left Ventricular Outflow Tract Obstruction OR Dynamic Left Ventricular Outflow Tract Obstruction AND Takotsubo Cardiomyopathy OR Catecholamine OR Pheochromocytoma OR Shock OR Dehydration OR Volume Depletion. Additional papers were identified and analyzed from these articles' reference lists. We mostly considered literature reviews, case reports, case series and small cross-sectional studies.»

4. Referencing

Page 5 «There are a few clinical reports of TC associated with LVOTO, however, its exact prevalence is unknown. Previous studies have identified a prevalence of 19-25%. [21, 32, 33] More recently, Kawaji et al (2015) described a slightly higher frequency of 33% (9 in 27 total patients). [17] On the other hand, a cross sectional study by Kobayashi et al (2018) reported that of a population with TTE reporting LVOT PG of ≥ 50 mmHg, TC was reported as being the cause of obstruction in only 2% of these patients. [13]»

5. Scientific reasoning

Page 7 «A recent nation wide cohort study by Rapouseiras-Roubín et al (2023), which tried to determine the impact of the use of beta-blockers in a study population of 970 patients with TC, reported no significant differences in the outcome of mortality or TC recurrence between patients treated and untreated with beta-blockers at 3-year follow-up (hazard ratio of 0,95, 95% CI 0,57-1,13 for the adjusted Cox analysis).[40]»

6. Appropriate presentation of data

Page 5 «A cross sectional study by El Mahmoud R. et al (2008) stated that patients with TC and LVOTO were older (mean age of 81 ± 4 vs 68 ± 13 years, P =0,01) with higher mean NYHA functional class (1.8 ± 0.9 vs 1.1 ± 0.1, P=0,002). [33] On the other hand, Kawaji T. et al (2015) found that there were no significant differences in most baseline characteristics, such as age, comorbidities, clinical presentation, or echocardiographic variables beyond the obstruction, between TC patients with or without LVOTO. [17] However, the prevalence of moderate to severe mitral regurgitation (MR) on presentation (67% vs. 11%, P=0.003) and the prevalence of

hospitalization for chronic HF after a three-year follow-up period (78% vs. 28%, P=0.01), were significantly higher in patients with LVOT obstruction than in those without. [17]»

Revista Portuguesa de Cardiologia

AUTHORS INFORMATION PACK

GUIDE FOR AUTHORS

INTRODUCTION

The Portuguese Journal of Cardiology, the official journal of the Portuguese Society of Cardiology, was founded in 1982 with the aim of keeping Portuguese cardiologists informed through the publication of scientific articles on areas such as arrhythmology and electrophysiology, cardiovascular surgery, intensive care, coronary artery disease, cardiovascular imaging, hypertension, heart failure and cardiovascular prevention.The Journal is a monthly publication with high standards of quality in terms of scientific content and production. Since 1999 it has been published in English as well as Portuguese, which has widened its readership abroad.

Please, take into account that as of January 2021, *Revista Portuguesa de Cardiologia* will require new article submissions to be written in English language.

The Journal accepts the following categories of articles:

Research (Original Investigation and Meta-Analysis), **Review and Education** (Narrative Reviews, Systematic Reviews -without meta-analysis, Guidelines, Case Reports, Images in Cardiology and Snapshots), **Opinion** (Current Perspective), **Correspondence** (Editorial Comment, Letters to the Editor, Research Letter and Observation)

Types of article

Manuscripts submitted for publication should be prepared in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" of the International Committee of Medical Journal Editors (ICMJE). This document is available at http://www.icmje.org/recommendations/.

Summary table of *Revista Portuguesa de Cardiologia* types of article characteristics.

Original Investigation

Original Investigation articles cover areas of clinical or basic research: Clinical trial, Meta-analysis, Intervention study, Cohort study, Case-control study, Epidemiologic assessment, Survey with high response rate, Cost-effectiveness analysis, Decision analysis, Study of screening and diagnostic tests, Other observational studies) . They should have a maximum of 5000 words, with a total of up to 15 tables and/or figures, and should be structured as follows: Abstract (maximum 250 words; divided into Introduction and Objectives, Methods, Results and Conclusion(s)); 3-10 keywords; Introduction; Objectives; Methods; Results; Discussion; Conclusion(s); Acknowledgements, if any; References (up to 75); and figure legends, if any. Follow EQUATOR Reporting Guidelines.

Review Articles and Systematic Reviews

Review Articles should have a maximum of 5000 words, with a total of up to 15 tables and/or figures, and should be structured as follows: Abstract (maximum 250 words; unstructured); 3-10 keywords; Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgements, if any; References (up to 100); and figure legends, if any.

Systematic Reviews should be structured as Introduction, Methods, Results, Discussion and Conclusion(s). The subject should be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis.

Systematic Reviews should not normally exceed 4000 words, with a total of up to 6 tables and/or figures and up to 100 references.

Authors are strongly recommended to consult the PRISMA statement (http://www.prisma-statement.org/), which is intended to help improve the reporting of systematic reviews and meta-analyses. We encourage authors to develop a systematic review protocol (e.g. following PRISMA-P) and register with PROSPERO.

Guidelines

It is recommended to consult the AGREE II instrument for which items should be reported that highlighted particular quality aspects of guideline development. In general, published statements intended to guide clinical care (e.g., guidelines, practice parameters, recommendations, consensus statements and position papers) should describe the clinical problem to be addressed, the mechanism by which the statement was generated, a review of the evidence for the statement (if available), and the statement on practice itself.

To minimize confusion and to enhance transparency, such statements should begin with the following questions, followed by brief comments addressing each question:

- What other guideline statements are available on this topic?
- Why was this guideline developed?
- How does this statement differ from existing guidelines?
- Why does this statement differ from existing guidelines?

The statement should have an unstructured abstract of up to 350 words, 3 to 10 keywords and can include up to 4000 words, a total of up to 6 tables and/or figures and up to 100 references.

Case Reports

Authors should use the CARE guidelines as a guiding framework. Case reports should not exceed 1500 words of body text, with up to 15 references and four tables or figures. They must include an abstract (unstructured, maximum 250 words) and bulleted statements (maximum 70 words) in answer to the following questions: What's already known about this topic? and What does this study add?
Please see the Ethics section of the Instructions regarding preservation of patients' privacy. Case Reports must have no more than 5 authors.

Images in Cardiology

Images in Cardiology should have a maximum of 250 words, without Abstract, keywords, tables, or division into sections and up to 5 references may be included.

Snapshots

This section is intended for the publication of rare or educational cases or novel techniques in cardiology. The text should not exceed 500 words and up to 3 figures with brief captions and up to 5 references may be included. Snapshots must have no more than 3 authors.

Current Perspective

This type of manuscript is submitted upon invitation by the Editorial Board. It may cover a broad diversity of themes focusing on cardiology and healthcare: current or emerging problems, management and health policies, history of medicine, society issues and epidemiology, among others. An author who wishes to propose a manuscript in this section is requested to send an abstract to the Editor-in-Chief including the title and Author list for evaluation. The text should not exceed 1200 words, and up to 10 references, two tables or two figures are allowed. An abstract is not required.

Editorial Comment

Editorials are submitted at the invitation of the Editor. They should not exceed 1500 words and can contain up to 20 references and 1 table and 1 figure. They do not have an Abstract or keywords.

Letters to the Editor

Letters to the Editor on articles previously published in the Journal will be considered up to 8 weeks after the publication of the article in question. They should not exceed 800 words and can contain up to 2 figures but without Abstract, keywords or tables. They should have no more than 3 authors.

Research Letter

Research Letters are concise, focused reports of original research. These should not exceed 600 words of text and 6 references and may include up to 2 tables or figures. Online supplementary material is not allowed. Research Letters may have no more than 7 authors.

Observation

Observations consisting of short reports of 1 or 2 complicated, unique cases should not exceed 600 words of text (not including acknowledgment, tables, figures, acknowledgments, and references) and 6 references and may include up to 2 tables or figures. Online supplementary material is not allowed. Observations may have no more than 7 authors.

If the patient(s) described in these manuscripts is identifiable, a Patient Permission form must be completed and signed by the patient(s) and submitted with the manuscript. Omitting data or making data less specific to deidentify patients is acceptable but changing any such data is not acceptable.

Contact details for submission

You can send your manuscript at https://www.editorialmanager.com/repc

Language

This journal is published in Portuguese and in English language.

The title (and abstract and key words if applicable) must be submitted in both English and Portuguese.
Articles submitted to the Journal should be clearly written in Portuguese (from Portugal) and/or English of a good standard. Text may be edited to maintain linguistic quality and to conform with standard American English.

ADVANCE NOTICE FOR AUTHORS
Please, take into account that as of January 2021, *Revista Portuguesa de Cardiologia* will require new article submissions to be written in English language.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.
Ensure that the following items are present:
One author has been designated as the corresponding author with contact details:
¿ E-mail address
¿ Full postal address
All necessary files have been uploaded:
Manuscript:
¿ Include keywords
¿ All figures (include relevant captions)
¿ All tables (including titles, description, footnotes)
¿ Ensure all figure and table citations in the text match the files provided
¿ Indicate clearly if color should be used for any figures in print
Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)
Further considerations
¿ Manuscript has been 'spell checked' and 'grammar checked'
¿ All references mentioned in the Reference List are cited in the text, and vice versa
¿ **Permission has been obtained for use of copyrighted material from other sources (including the Internet)**
¿ A competing interests statement is provided, even if the authors have no competing interests to declare
¿ Journal policies detailed in this guide have been reviewed
¿ Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human

populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

The privacy rights of human subjects must always be observed. A statement must be included to the effect that the study was conducted in accordance with the amended Declaration of Helsinki, that the local institutional review board or independent ethics committee approved the protocol, and that written informed consent was obtained from all patients. The name of the committee, the name of the chairperson of the committee (or the person who approved the protocol), the date of approval and the approval number should follow this statement in the Methods section. For multicenter studies, a list of the relevant approvals may be provided in a separate document to be published as supplementary material.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Conflicts of Interest and Financial Disclosures

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. A conflict of interest may exist when an author (or the author's institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author's decisions, work, or manuscript. All authors are required to report potential conflicts of interest including specific financial interests relevant to the subject of their manuscript.

Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' section of our ethics policy for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service Crossref Similarity Check.

Authorship

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. According to the guidelines of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on the following 4 criteria:

1. substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; and
2. drafting of the work or revising it critically for important intellectual content; and
3. final approval of the version to be published; and
4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Changes to authorship. Role of the corresponding author

A single corresponding author (or coauthor designee in the event that the corresponding author is unavailable) will serve on behalf of all coauthors as the primary correspondent with the editorial office during the submission and review process. If the manuscript is accepted, the corresponding author will review an edited manuscript and proof, make decisions regarding release of information in the manuscript to the news media or federal agencies, handle all postpublication communications and inquiries, and will be identified as the corresponding author in the published article. The corresponding author also is responsible for ensuring that the Acknowledgment section of the manuscript is complete and that the conflict of interest disclosures reported of the manuscript are accurate, up-to-date, and consistent with the information provided in each author's potential conflicts of interest section in the Authorship Form.

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.

Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Clinical trial results

In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of

the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

Reporting clinical trials

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the cause-and-effect relationship between an intervention and a health outcome. Interventions include but are not limited to drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, process-of-care changes, and the like.

All manuscripts reporting clinical trials, including those limited to secondary exploratory or post hoc analysis of trial outcomes, must include the following:·
· CONSORT flow diagram
· Completed trial checklist
· Registry at an appropriate online public clinical trial registry
· A Data Sharing Statement to indicate if data will be shared or not. Specific questions regarding the sharing of data are included in the manuscript submission system.

Trial Registration

In concert with the ICMJE, our journal requires, as a condition of consideration for publication, registration of all trials in a public trials registry that is acceptable to the ICMJE (ie, the registry must be owned by a not-for-profit entity, be publicly accessible, and require the minimum registration data set as described by ICMJE).
Acceptable trial registries include the following and others listed at http://www.icmje.org:

anzctr.org.au
clinicaltrials.gov
isrctn.org
trialregister.nl
umin.ac.jp/ctr

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Author rights
As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing

Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in

study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Open Access

Please visit our Open Access page from the Journal Homepage for more information.

Elsevier Researcher Academy

Researcher Academy is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Language (usage and editing services)

Please write your text in good American English. Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop.

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include patient descriptions, photographs, video, and pedigrees of patients and any other individuals (parents or legal guardians for minors) who can be identified (including by the patients themselves) in such patient descriptions, photographs, video, and pedigrees. Written consents must be retained by the author but copies should not be provided to the journal. Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Patient Identification

Omitting data or making data less specific to deidentify patients is acceptable, but changing any such data is not acceptable. Only those details essential for understanding and interpreting a specific case report or case series should be provided. Although the degree of specificity needed will depend on the context of what is being reported, specific ages, race/ethnicity, and other sociodemographic details should be presented only if clinically or scientifically relevant and important. Cropping of photographs to remove identifiable personal features that are not essential to the clinical message may be permitted as long as the photographs are not otherwise altered. Please do not submit masked photographs of patients. Patients' initials or

other personal identifiers must not appear in an image.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article

Please submit your article via https://www.editorialmanager.com/repc

Referees

Please submit the names and institutional e-mail addresses of several potential referees. For more details, visit our Support site. Note that the editor retains the sole right to decide whether or not the suggested reviewers are used.

PREPARATION

Peer review

This journal operates a rigorous single blind peer review process, in which manuscripts are sent to external reviewers selected from an extensive database. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Peer reviewers will respond to the Editor within 30 days recommending acceptance, revision or rejection. The Editor will decide within 10 days whether to accept the manuscript without modification, to send the reviewers' comments to the authors for modification, or to reject it. When modifications are proposed, the authors have 30 days (which can be extended on request) to submit a revised version of the manuscript, incorporating the comments of the reviewers and the Editor. Any amendments should be highlighted in a different colour. The Editor will decide within 10 days whether to accept the new version, reject it, or send it for further review by one or more reviewers.

Letters to the Editor and Editorials will be reviewed by the Editorial Board, but external peer review may also be requested.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your

figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'. Use generic names of drugs (first letter: lowercase) whenever possible. Registered trade names (first letter: uppercase) should be marked with the superscript registration symbol ® or ™ when they are first mentioned.

The Journal recommends the guidelines for publication of the EQUATOR network (http://www.equator-network.org), including the CONSORT statement and its extensions for randomized trials (http://www.consort-statement.org/), STROBE for observational (cohort, case-control and cross-sectional) studies (http://www.strobe-statement.org/), STARD for diagnostic accuracy studies (http://www.stard-statement.org/), PRISMA for systematic reviews and meta-analyses (http://www.prisma-statement.org/), SQUIRE for quality improvement studies (http://www.squire-statement.org/) and CARE for case reports (http://www.care-statement.org/). Reporting of the statistical aspects of studies should be in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines (http://www.equator-network.org/reporting-guidelines/sampl/).

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Cover letter and Essential title page information

Submission of an article must include a cover letter with the following information:

1. a brief description of the article's significance and/or interest;
2. a declaration of originality, specifying that none of the paper's contents have been published or are under consideration elsewhere;
3. a declaration that all authors have read and approved the manuscript;
4. a full disclosure of any potential conflict of interest for any of the authors;
5. and which manuscript type is being submitted for publication.

Title page must contain the following information:

• ***Title*.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. Preferably not exceed 12 words. It may also include a subtitle of up to 4 words. All nouns, adjectives and verbs in the title and subtitle must begin with a capital letter.
• ***Author names and affiliations*.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author*.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address*.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.
• ***Word count*** of the manuscript text.

Structured abstract

A structured abstract, by means of appropriate headings, should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations.

Abstracts for all article types should not contain any references. Abbreviations should be avoided or kept to a minimum.

The headings will consist of: Introduction and Objectives, Methods, Results and Conclusion(s))

Keywords

Immediately after the abstract, provide the keywords, using British spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. Keywords

should ideally be selected from the list of MeSH terms available at www.nlm.nih.gov/mesh/. These keywords will be used for indexing purposes.

Abbreviations, Product Names and Gene Names

Do not use abbreviations in the title or abstract and limit their use in the text. Expand all abbreviations at first mention in the text.

Ensure consistency of abbreviations throughout the article.

Do not use abbreviations in the title or abstract and limit their use in the text. Expand all abbreviations at first mention in the text.

Ensure consistency of abbreviations throughout the article.

Names of Drugs, Devices, and Other Products

Use nonproprietary names of drugs, devices, and other products and services, unless the specific trade name of a drug is essential to the discussion. In such cases, use the trade name once and the generic or descriptive name thereafter. Do not include trademark symbols.

Gene Names, Symbols, and Accession Numbers

Authors describing genes or related structures in a manuscript should include the names and official symbols provided by the US National Center for Biotechnology Information (NCBI) or the HUGO Gene Nomenclature Committee. Before submission of a research manuscript reporting on large genomic data sets (eg, protein or DNA sequences), the data sets should be deposited in a publicly available database, such as NCBI's GenBank, and a complete accession number (and version number if appropriate) must be provided in the Methods section or Acknowledgment of the manuscript.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.)

Units of Measure

Laboratory values are expressed using conventional units of measure, with relevant Système International (SI) conversion factors expressed secondarily (in parentheses) only at first mention. Articles that contain numerous conversion factors may list them together in a paragraph at the end of the Methods section. In tables and figures, a conversion factor to SI should be presented in the footnote or legend. The metric system is preferred for the expression of length, area, mass, and volume. For more details, see the Units of Measure conversion table on the website for the AMA Manual of Style.

Artwork

Tables and Figures. Image manipulation

Restrict tables and figures to those needed to explain and support the argument of the article

and to report all outcomes identified in the Methods section. Number each table and figure and provide a descriptive title for each. Every table and figure should have an in-text citation. Verify that data are consistently reported across text, tables, figures, and supplementary material.

Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

Electronic artwork

General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Embed the used fonts if the application provides that option.
• Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Provide captions to illustrations separately.
• Size the illustrations close to the desired dimensions of the published version.
• Submit each illustration as a separate file.
• Ensure that color images are accessible to all, including those with impaired color vision.

A detailed guide on electronic artwork is available.
You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.
Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
• Supply files that are too low in resolution;
• Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF) or

MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then, at no additional charge, these figures will appear in color online (e.g., ScienceDirect and other sites) in addition to color reproduction in print. Further information on the preparation of electronic artwork.

Figures

Number all figures (graphs, charts, photographs, and illustrations) in the order of their citation in the text. The number of figures should be limited. Avoid complex composite or multipart figures unless justified.
See Categories of Articles for limits on the number of figures and/or tables according to article type.

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used written out in full and in alphabetical order. Different panels in a figure should be identified by capital letters (Figure 1A, Figure 2C, Figure 3A and B, etc. in the text and (A), (B), (C-E), etc. in the captions).

Text graphics

Text graphics may be embedded in the text at the appropriate position. See further under Electronic artwork.

Tables

Include a brief title for each table (a descriptive phrase, preferably no longer than 10 to 15 words) and number all tables in the order of their citation in the text. Refer to Categories of Articles for limits on the number of tables.

Do not embed tables as images in the manuscript file or upload tables in image formats, and do not upload tables as separate files. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end.

Place any table notes below the table body. Please avoid using vertical rules and shading in table cells.

All abbreviations used in the table must be written out in full, in alphabetical order, in the table legend immediately below the table. Footnotes may be used if necessary, indicated by superscript lower-case letters ([a], [b], [c] etc.) in the table and in the legend. Asterisks (*, **, *** etc.) may be used to indicate p values only. If a table contains a reference cited in the text, it should be cited with the name of the first author and "et al." followed by the reference number without space (e.g. Millard et al.[9]).

References

Citation in text. Reproduced material.

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with

either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Personal Communications and Unpublished Data

A signed statement of permission should be included from each individual identified as a source of information in a personal communication or as a source for unpublished data, and the date of communication and whether the communication was written or oral should be specified. Personal communications should not be included in the list of references but added to the text parenthetically.

Reproduced material

Please verify that all information and materials in the manuscript are original. The journal generally does not republish text, tables, figures, or other material from other publishers, except in rare circumstances. If you believe that you must include content that is owned by a third party, please let us know and provide information about all material that has been previously published and, when applicable, include author(s), title of article, title of journal or book or other publication, and complete citation, doi, and/or URL.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: Ribeiro J. Left ventricular noncompaction and Fabry disease: An unlikely association. Rev Port Cardiol. 2019. https://doi.org/10.1016/j.repc.2019.12.001. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. This identifier will not appear in your published article.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference style

Text: Indicate references by superscript numbers in the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references in the list in the order in which they appear in the text.
Examples:
Reference to a journal publication:
17. Reis L, Paiva L, Costa M, Silva J, Teixeira R, Botelho A, et al. Registry of left atrial appendage closure and initial experience with intracardiac echocardiography. Rev Port Cardiol. 2018;**37**:763-72. https://doi.org/10.1016/j.repc.2018.03.009.

Reference to a journal publication with an article number:
2. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;**19**:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.

Reference to a book:
30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993.

Reference to a chapter in an edited book:
23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. In: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American;1995.p.79-96.
Reference to a website:
12. Portuguese Registry on Acute Coronary Syndromes (ProACS). Available at: http://www.clinicaltrials.gov/identifier NCT01642329 [accessed 26 October 2013].
Reference to a dataset:
[dataset] 5. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. https://doi.org/10.17632/xwj98nb39r.1.

Note shortened form for last page number. e.g., 51–9, and that for more than 3 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;**277**:927–34)(see also Samples of Formatted References).

Journal abbreviations source

Journal names should be abbreviated according to the PubMed list.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation

files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

RESEARCH DATA

This journal encourages you to share data that supports your research publication in an appropriate data repository, and enables you to interlink the data with your published articles. If you are sharing data, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation.

Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Mendeley Data

This journal supports *Mendeley Data*, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. Before submitting your article, you can deposit the relevant datasets to Mendeley Data. Please include the DOI of the deposited dataset(s) in your main manuscript file. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

AFTER ACCEPTANCE

Proofs

One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or a link will be provided in the e-mail so that authors can download the files themselves. To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Elsevier now provides authors with PDF proofs which can be annotated; for this you will

need to download the free Adobe Reader, version 9 (or higher). Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site.
If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and scan the pages and return via e-mail. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will be notified and receive a link to the published version of the open access article on ScienceDirect. This link is in the form of an article DOI link which can be shared via email and social networks. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Author Services.

AFTER PUBLICATION

Corrections

Requests to publish corrections should be sent to the editorial office. Corrections are reviewed by editors and authors, published promptly, and linked online to the original article.

Postpublication Correspondence

For accepted manuscripts, the corresponding author will be asked to respond to letters to the editor.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also check the status of your submitted article or find out when your accepted article will be published.