Left ventricular outflow tract obstruction in ICU patients

Michel Slama\textsuperscript{a,c}, Christophe Tribouilloy\textsuperscript{b,c}, and Julien Maizel\textsuperscript{a,c}

Purpose of review
Left ventricular (LV) outflow tract (LVOT) obstruction (LVOTO) is not unusual in ICU patients particularly with septic shock.

Recent findings
LVOT was first described in patients with hypertrophic cardiomyopathy and was defined as LV wall thickness at least 15 mm. LVOT is usually because of systolic anterior motion of the mitral valve. By convention, LVOTO is defined as an instantaneous peak Doppler LVOT pressure gradient at least 30 mmHg at rest or during physiological provocation such as Valsalva maneuver. Recently, it has been demonstrated that LVOT can be present in patients with severe hypovolemia or hyperkinesia with or without LV hypertrophy and can lead to hemodynamic compromise. LVOT is because of a combination of precipitating factors, which may or may not be associated with anatomical abnormalities. Decreased preload because of hypovolemia or decreased afterload because of septic shock, increased heart rate, and LV hyperkinesis produced by dobutamine infusion can induce a change of LV shape and induce LVOTO.

Summary
LVOTO is not uncommon in ICU patients and can be observed at the early phase of septic shock. Treatment should include discontinuation of dobutamine infusion and fluid infusion. \( \beta \) blockers can be useful in this clinical situation.

Keywords
echocardiography, hypertrophic cardiomyopathy, left ventricular outflow tract obstruction, septic shock, systolic anterior motion

INTRODUCTION
Left ventricular (LV) outflow tract (LVOT) obstruction (LVOTO) was first described in patients with hypertrophic cardiomyopathy (HCM). LVOTO usually is because of systolic anterior movement (SAM) of the anterior leaflet of the mitral valve and is characterized by a saber-shaped Doppler flow curve with late acceleration [1]. However, many clinical case reports indicate that critical care patients without HCM may also develop LVOTO [2\textsuperscript{**}]. In these cases, an anatomical predisposition is associated with precipitating factors such as hypovolemia or catecholamine exposure.

HYPERTROPHIC CARDIOMYOPATHY
HCM is an inherited heart disease defined by increased LV wall thickness of at least 15 mm in one or more LV myocardial segments that cannot be explained by abnormal loading conditions [1]. It is an autosomal dominant condition, caused in up to 60\% of adolescents and adults by mutations in cardiac sarcomere protein genes and is present in one in 500 individuals of the general adult population, which makes it the commonest genetic cardiovascular disease. This genetic disorder is associated with myocardial disarray, hypertrophy, and energetic dysfunction of LV myocytes, along with interstitial fibrosis.

The clinical spectrum of HCM is complex and includes a variety of phenotypes [3,4]. Hypertrophy can be confined to the apical, anterolateral, posterior (inferior), or septal regions of the LV.
chamber. Asymmetric hypertrophy located in the basal septum is the most common cause of HCM. The incidence of apical HCM varies considerably in the literature, ranging from 1 to 25% [5]. Predominant hypertrophy of the middle third of the left ventricle can lead to severe midventricular narrowing and obstruction, which can also be associated with the formation of apical aneurysms, because of increased systolic pressures in the cardiac apex caused by the midventricular obstruction or apical infarction [6]. HCM is only a septal disease. Mitral valve disease is also a key component that must be addressed [7]. Symmetric hypertrophy is present in about 4% of HCM cases and should raise the suspicion of other causes of LV thickening.

Various clinical features have been described. Although most patients are asymptomatic, around 25% develop symptoms, such as dyspnea, chest pain, palpitations, syncope, and are at risk of arrhythmia and sudden cardiac death.

The standard 12-lead ECG can be normal at presentation (6% of patients in referral cohort studies), but generally shows a variable combination of LVH, ST and T-wave abnormalities, and pathological Q-waves [8].

Echocardiography and Doppler examination are central to the diagnosis of HCM and LVOTO. The mainstay of the diagnosis is increased LV wall thickness of at least 15 mm [1]. A number of echocardiographic indices provide a semiquantitative score of LVH, but the single most relevant parameter for diagnostic purposes is the maximum LV wall thickness at any level. In patients with known or suspected HCM, it is essential to examine all LV segments from base to apex, ensuring that wall thickness is recorded at mitral, mid-LV, and apical levels.

Approximately one-third of patients have resting SAM of the mitral valve leaflets that results in LV outflow tract obstruction, whereas another third have latent obstruction only during maneuvers that change loading conditions and LV contractility. SAM is observed on two-dimensional echocardiography on a parasternal view or apical view, but can also be recorded by M-mode.

Mechanical obstruction seems to be because of SAM with prolonged basal ventricular septal contact (Figs 1 and 2). Initially this was believed to be because of a ‘Venturi’ effect, it has now been demonstrated that SAM begins at normal low velocity and then hydrodynamic ‘drag’ or the ‘pushing’ force of flow might be the dominant operant mechanism, based on temporal observations of flow and dynamic cross-sectional analysis of mitral apparatus geometry [9]. Other morphological features that contribute to LVOTO include papillary muscle abnormalities (hypertrophy, anterior and internal displacement, and direct insertion into the anterior mitral valve leaflet) and mitral leaflet abnormalities such as elongation or accessory tissue [1]. Obstruction also can be unrelated to SAM, and to subaortic membranes, mitral valve leaflet abnormalities, and midcavity obstruction [1].

A high-velocity, late-peak ‘dagger-shaped’ continuous-wave Doppler signal on examination of the LV outflow tract is the hallmark of dynamic outflow obstruction (Fig. 3). The modified Bernoulli equation is used to estimate the peak gradient across the outflow tract. By convention, LVOTO is defined as an instantaneous peak Doppler LV outflow tract pressure gradient at least 30 mmHg at rest or...
during physiological provocation, such as Valsalva maneuver, standing, and exercise. A gradient at least 50 mmHg is usually considered to be the threshold at which LVOTO becomes hemodynamically important. This concept is based on studies demonstrating progressive impedance to flow above this value [10]. In total, 75% of HCM patients develop LVOTO at rest or on provocation. Valsalva maneuver, glyceryl trinitrate, amyl nitrite, or exercise may also induce obstruction.

Doppler color flow imaging can be used to determine the presence of mitral regurgitation and provide a semiquantitative estimate of its severity. SAM of the mitral valve nearly always results in failure of normal leaflet coaptation and mitral regurgitation, which is typically mid-to-late systolic and inferolaterally oriented; measurement of the velocity and timing of the mitral jet helps to differentiate it from LV outflow tract turbulence.

SAM-related mitral regurgitation is inherently dynamic and its severity varies with the degree of LVOTO.

LVOTO and mitral regurgitation further impair left atrium mechanics [11]. In HCM, the left atrium is often enlarged and its size provides important prognostic information [12]. Left atrium volume is largely determined by the presence of diastolic dysfunction, mitral regurgitation, atrial myopathy severity, and chronicity of left atrium pressure elevation. The American Society of Echocardiography recommends indexing left atrium volume derived from biplane area length or method of disks to body surface area for quantification of left atrium size. Normal-indexed left atrium volume is less than $22 \pm 6 \text{ml/m}^2$ [13]. Left atrium volume is an independent indicator of long-term functional capacity and a left atrium volume index more than $34 \text{ml/m}^2$ has been shown to be predictive of more severe diastolic dysfunction, and adverse cardiovascular outcomes [14].

Patients with HCM often have diastolic dysfunction and assessment of LV filling pressures is useful for evaluation of symptoms and disease staging. A reduction of chamber compliance (increased LV mass) and increased stiffness (myocardial fibrosis) coupled with a reduction of ventricular volume and suction play a role in the pathophysiology of diastolic dysfunction in patients with HCM. Similarly, regional asynchrony, postsystolic shortening, and heterogeneity of relaxation appear to be important underlying contributory mechanisms.

Radial contractile function (ejection fraction or fractional shortening) is typically normal or increased in patients with HCM. Myocardial longitudinal velocities and deformation parameters (strain and strain rate), derived from Doppler myocardial imaging or speckle tracking techniques, are often reduced despite a normal ejection fraction and can be abnormal before the development of increased wall thickness in genetically affected relatives. Myocardial longitudinal deformation is typically reduced at the site of hypertrophy [15]. Terminally in the disease process, myocardial fibrosis results in progressive impairment of systolic function (end-stage HCM).

Many severe complications are described in patients with HCM included syncope, heart failure, arrhythmia, and sudden death. Most contemporary series of adult patients with HCM report an annual incidence for cardiovascular death of 1–2%. The most commonly recorded fatal arrhythmic event is spontaneous ventricular fibrillation, but asystole, AV block, and pulseless electrical activity also are described [1].
Treatment is based on symptoms and on the estimation of the risk of sudden cardiac death.

In patients with cardiac failure and an ejection fraction at least 50% and no evidence for resting or provokable LVOTO, β blockers, verapamil, or diltiazem can be considered, to improve heart failure symptoms. In patients with heart failure and ejection fraction less than 50%, ACE inhibitor should be considered, in addition to a β blocker, for patients without LVOTO. Patients with HCM who survive ventricular fibrillation or sustained ventricular tachycardia are at very high risk of subsequent lethal cardiac arrhythmias and should receive an implantable cardioverter defibrillator [1].

**LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN ICU PATIENTS**

LVOTO is not unusual in ICU patients and various clinical situations are particularly prone to this obstruction [2]. LVOTO is currently considered to be a dynamic phenomenon, and onset of LVOTO requires the coexistence of two elements: predisposing anatomical factors; and a physiological condition that induces this type of phenomenon. SAM and LVOTO can, therefore, be transient in so-called high-risk patients (anatomically predisposed) because of a change of fluid status, because of volume depletion, surgical procedures, and hypotension associated with general anaesthesia.

**Anatomical substrate**

Many anatomical substrates have been described as being responsible for LVOTO. LV hypertrophy in patients with HCM, hypertension or aortic stenosis, myocardial infarction, mitral valve replacement or repair, ballooning syndrome (Takotsubo), sigmoid septum, steep aortic root angle, abnormalities of the mitral subvalvular apparatus, acute cor pulmonale, or atrial fibrillation can be responsible for LVOT in ICU patients.

However, in a significant number of patients no anatomical predisposition is identified.

**Precipitating factors**

Factors that may decrease afterload, preload or increased heart rate or, contractility can induce LVOTO. These functional abnormalities can result in a small and hypercontractile LV, which predispose to LVOTO. Clinical situations, such as hypovolemia, bleeding, and surgery with blood loss can cause a decreased preload with a small LV, which can induce LVOTO. Pain, arrhythmias, inotropic agents, and fever can lead to tachycardia and be precipitating factors of LVOTO. Vasoplegia because of septic shock or anaesthetic drugs has also been reported to be associated with LVOTO. LVOTO may be because of catecholamines such as dobutamine, which increases LV contractility, reduces LVOT during systole and induces LVOTO. It has been demonstrated that 17–43% of patients can also develop LVOT gradient during dobutamine stress echocardiography [16,17] during routine cardiology testing.

**Clinical situations associated with left ventricular outflow tract obstruction**

LVOTO associated with mitral regurgitation can be responsible for severe shock in ICU patients or in patients during or after surgery [18].

**Intraoperative left ventricular outflow tract obstruction**

A hyperdynamic contractile state of the LV triggered by intraoperative stimuli, anaesthetic drug-induced vasoplegia, and hypovolemia secondary to bleeding can occur during surgery. In this setting, dynamic LVOTO can occur intraoperatively, even in patients who were asymptomatic preoperatively and had no predisposing anatomical abnormalities of the left ventricle.

**Postoperative left ventricular outflow tract obstruction**

LVOTO can occur postoperatively after noncardiac or cardiac surgery, even in patients with no known heart disease. LVOTO can be transient and as in intraoperative cases can be because of hypovolemia and use of sedative drugs that cause vasodilatation. It is one of the more common causes of unexplained hypotension in the postoperative setting [19].

**Mitral valve repair or mitral valve replacement**

Published reports indicate that mitral valve repair surgery can be complicated by SAM and LVOTO in approximately 5% of cases [20,21]. SAM/LVOTO probably is directly related to technical factors in the mitral valve repair, including use of a rigid ring, general anaesthesia, and administration of inotropic agents such as dobutamine.

**Aortic valve replacement**

Dynamic LVOTO can occur following aortic valve replacement for aortic stenosis [14]. LV hypertrophy combined with immediate postcardiac surgical conditions, such as hypovolemia, blood loss, or dobutamine infusion are contributing factors for the LVOTO.
Acute or chronic cor pulmonale
LVOTO can be observed in patients with acute or chronic cor pulmonale [22]. In this condition, the right ventricle is enlarged and LV size is decreased with modification of the shape of the LV. The mitral valve is close to the septum and as with the previous conditions precipitating factors, such as anaesthesia, catecholamine infusion, or tachycardia can induce LVOTO.

Myocardial infarction
Myocardial infarction can induce LVOTO [23,24]. The mechanism of dynamic LVOTO in this setting is compensatory hyperkinesis of preserved myocardial segments. It is more commonly observed when only a single coronary artery (usually the left anterior descending artery) is affected. The remaining uninjured myocardial segments can become hyperdynamic while compensating for the hypokinetic segment and distortion of the normal ventricular geometry may result in downward angulation of the ventricular system, and lead to dynamic LV outflow tract obstruction. In addition, mitral annulus calcifications and redundant mitral leaflet tissue can contribute to anterior displacement of the mitral valve. A portion of the mitral valve leaflet passes beyond the coaptation point and protrudes into the outflow tract, thus causing dynamic LVOTO. However, dynamic LVOTO also can occur in other settings, including successful percutaneous coronary interventions followed by hypovolemia resulting in a hyperdynamic LV.

Takotsubo cardiomyopathy
LVOTO can occur in patients with Takotsubo cardiomyopathy [25] which is characterized by transient, pronounced LV apical wall motion abnormalities with preserved function of the base of the heart in the absence of significant coronary artery disease. Dynamic LVOT gradient was observed in almost 15% of patients with Takotsubo cardiomyopathy in a series by Sharkey et al. [26]. Proposed mechanisms for Takotsubo cardiomyopathy include catecholamine toxicity which impairs coronary microcirculation, and multivessel coronary spasm, among others. Higher levels of circulating plasma catecholamines may then increase LV contractility, induce a reduction of the LVOT, and result in LVOTO.

Hypertension
It must be emphasized that SAM commonly occurs in patients with severe untreated arterial hypertension [27]. However, LVOTO can be latent and dynamic LVOTO has been reported in hypertensive patients during dobutamine stress echocardiography, but most of these cases did not show any significant clinical or hemodynamic changes [28,29]. A history of hypertension with LV hypertrophy as an anatomical substrate is frequently observed in ICU patients with LVOTO.

Mechanical ventilation
Mechanical ventilation in the context of hypovolemia also can induce LVOTO [30]. During the inspiratory phase of mechanical ventilation, intrathoracic pressure increases and venous return then decreases, resulting in increased right ventricular afterload and decreased right ventricular stroke volume. Consequently, several seconds later, LV preload decreases and the left ventricle is then underfilled which causes modification of the shape of the left ventricle [31]. In the presence of hypovolemia, this phenomenon is magnified and LVOT can occur [30].

Normal heart
LVOT can be observed in ICU patients with no significant LV hypertrophy or HCM [2**,32,33]. In a recent study by Brown et al. [34], nine critically ill patients were found to have LVOTO on echocardiography over a period of 1 year. None of these patients had a history of HCM or echocardiographic evidence of asymmetrical septal hypertrophy. Patients with LVOTO without LV hypertrophy usually respond to an increase of intravascular volume, reduction, or discontinuation of infused inotropic agents or β-blocker infusion [22].

Left ventricular outflow tract obstruction in septic shock patients
LVOTO appears to be not unusual in septic shock patients [2**]. Over a period of 28 months, in a consecutive series of 218 patients with septic shock, we observed 47 (22%) patients with LVOTO. Mortality was high in this group of patients, up to 53% compared with patients with septic shock without LVOTO (24%). The LV was hypercontractile. Only two patients had preexisting LV hypertrophy, 43% had an end-diastolic posterior wall thickness at least 12 mm, 4% had a septal end-diastolic thickness at least 13 mm, and 19% had a maximum thickness septal bulge at least 15 mm. In the majority of these patients, the calculated LV mass was within the normal range, despite apparent thickening. This indicates that the wall thickening seen on two-dimensional echocardiography actually corresponded to pseudohypertrophy [2**]. All LVOTO patients responded to fluid infusion (despite the absence of pulse pressure variations) with decreased LVOTO, increased cardiac output, and clinical improvement.
TREATMENT OF LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN ICU PATIENTS

The treatment of LVOTO is designed to increase afterload, increase preload, decrease heart rate, and decrease LV contractility, which have been identified as precipitating factors. Treatment of precipitating factors generally allows resolution of LVOTO.

Firstly, if possible all inotropic agents, β agonists, diuretics, and nitrate infusion should be stopped or at least reduced; this may be sufficient to allow resolution of LVOTO.

Secondly, a fluid infusion can be used to increase preload and LV size in the absence of right ventricular dilatation. I.v. fluid infusion has been shown to be especially useful in ICU patients with LVOTO and septic shock. It decreases the LV obstruction, increases cardiac output, and improves clinical [2**].

Thirdly, when LVOTO persists despite stopping inotropic drugs and i.v. fluid infusion, drug treatment may be considered. First-line drug treatment consists of nonvasodilating β blockers titrated to the maximum tolerated dose. By decreasing heart rate, improving diastolic volume, and exerting a negative inotropic effect or blunting catecholamine overactivity as in apical ballooning syndrome and subsequently decreasing LV hypercontractility, β blockers can improve clinical and hemodynamic signs. Morelli et al. [35] recently demonstrated that, in septic shock patients without systolic dysfunction and tachycardia, which may include a proportion of patients with LVOTO, β blockers can reduce mortality rate without any deleterious hemodynamic effects. In patients with severe asthma, verapamil, or diltiazem may be used instead of β blockers. Disopyramide has also been used successfully in patients with severe LVOTO [36] which works by decreasing cardiac contractility.

CONCLUSION

LVOTO is an underestimated dynamic phenomenon in ICU patients. It is thought that SAM and LVOTO require the coexistence of predisposing anatomic factors and a physiological precipitating condition such as hypovolemia or catecholamine infusion. Hypotension and low cardiac output syndrome, which are consequences of SAM/LVOTO, do not respond to typical treatment or may even worsen following administration of positive inotropic and vasodilating agents. When the presence of SAM/LVOTO is confirmed, inotropic drug infusion should be stopped or at least reduced and followed by echo-Doppler studies. Fluid infusion can decrease LVOTO, particularly when it occurs in septic shock patients. β blockers should be considered if the clinical situation has not been improved by the previous actions. Echocardiography with evaluation of LVOT in terms of obstruction is essential to diagnose SAM/LVOTO in ICU patients with shock.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest


The first study which demonstrated that LVOTO can be observed in up to 22% of patients with septic shock.


Excellent review on HCM.


Cases of obstruction in ICU patients.


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