Online Case Report

Nonejecting Hearts on Femoral Veno-Arterial Extracorporeal Membrane Oxygenation: Aortic Root Blood Stasis and Thrombus Formation—A Case Series and Review of the Literature

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Objectives: Cardiogenic shock constitutes the final common pathway of cardiac dysfunction associated with tissue hypoperfusion and organ failure. Besides treatment of the underlying cause, temporary mechanical circulatory support serves as a supportive measure. Extracorporeal membrane oxygenation can effectively prevent hypoxemia and end-organ dysfunction, but knowledge about patient selection, risks, and complications remains sparse.

Data Sources: Clinical observation.

Study Selection: Case report and review of the literature.

Data Extraction: Relevant clinical information. Online databases, including PubMed, Web of Science, Scopus, and OVID, were searched for previous publications.

Data Synthesis: We report six cases of patients in refractory cardiogenic shock receiving emergency femoral veno-arterial extracorporeal membrane oxygenation support complicated by echocardiographic evidence of absent blood flow, sedimentation, and thrombus formation in the aortic root.

Conclusions: Patients in cardiogenic shock who require femoral veno-arterial extracorporeal membrane oxygenation support are at risk of developing a state of nonejecting heart with thrombus formation in the aortic root. Echocardiography is the cornerstone of diagnosis and documentation of treatment effects. Depending on the likelihood of the presence of clinically relevant thrombotic material in the aortic root, we propose a treatment algorithm for this group of high-risk patients. (*Crit Care Med* 2018; 46:e459–e464)

Key Words: aortic thrombus; blood stasis; cardiogenic shock; extracorporeal membrane oxygenation; nonbeating heart

Cardiogenic shock constitutes the final common pathway of cardiac dysfunction associated with tissue hypoperfusion and subsequent organ failure (1). Besides treatment of the underlying cause, for example, coronary revascularization (2), temporary mechanical circulatory support is a measure of supportive care in patients with refractory shock or cardiac arrest (3–5). Although extracorporeal membrane oxygenation (ECMO) can effectively prevent hypoxemia and end-organ dysfunction (6, 7), no randomized trial has demonstrated reduced mortality or morbidity in cardiogenic shock. ECMO use in cardiac arrest is referred to as "extracorporeal-cardiopulmonary resuscitation (E-CPR)" (3, 4).

Intracardiac thrombus is a common finding in patients following large myocardial infarction or with severely depressed left ventricular function. It is conceivable that reduced flow across the aortic valve during ECMO support favors clot formation not only in the left ventricle (LV) but also in the aortic root. The reported prevalence of intracardiac thrombus was 3.9% (3/77) in a recent single-center observational study (8), and a case series presented nine cases with intracardiac thrombus formation and five patients with thrombus in the aortic root during ECMO (9). The transition from spontaneous echo contrast to thrombus in formation to a firm thrombotic clot is time dependent and may even occur in the presence of therapeutic anticoagulation. During femoral veno-arterial ECMO, reversed blood flow in the thoracic aorta and aortic arch together with absent blood flow across the aortic valve favors blood sedimentation and thrombus formation in the aortic

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root. The loss of peripheral arterial pulsatility due to a closed aortic valve is therefore an alarm signal during ECMO support.

Here, we report a case series of six patients on femoral veno-arterial ECMO due to cardiogenic shock with consequent thrombus formation in the aortic root despite adequate anticoagulation, review the previously published cases and present our treatment algorithm for this condition.

CASE 1

A 26-year-old female patient was transferred to our center by air medical services under veno-arterial ECMO (E-CPR) from another hospital. Femoral veno-arterial ECMO (Maquet Cardiohelp ECMO system; Getinge Group AB, Göteborg, Sweden) had been initiated during cardiopulmonary resuscitation (CPR) following admittance to the ICU for respiratory failure. At our hospital, workup raised the suspicion of drug-induced hypersensitivity reaction (Drug Reaction with Eosinophilia and Systemic Symptoms) with myocardial involvement most likely following "Minocycline" treatment for acne vulgaris. Endomyocardial biopsy confirmed the diagnosis revealing necrotizing myocarditis with eosinophilia. A transoesophageal echocardiography (TEE) showed severe dysfunction of both ventricles, thickened myocardium (most likely due to edema [10]), and a nonopening aortic valve with echocardiographic features of blood stasis and beginning thrombus formation in the aortic root. Subsequent TEE examinations documented progressive thrombus formation in the aortic root and subsequently also in the LV (**Fig. 1**; and **Supplementary Video 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D169). Repeated cerebral MRI scans showed a star field pattern in the susceptibility weighted imaging sequence and signs of severe ischemic cerebral injury with persistently poor neurologic status not explained by the right-sided parieto-occipital stroke (**Supplementary Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/D170--**legend**, Supplemental Digital Content 9, http://links.lww.com/CCM/D177).

CASE 2

A 19-year-old female patient was admitted to the emergency department (ED) by emergency medical services (EMS) after she had collapsed in the public followed by a short generalized seizure. She remained unconscious with a Glasgow Coma Scale score of 3. Prehospital electrocardiogram (ECG) showed a slow ventricular rhythm at around 30/min without visible p-waves and intermittent episodes of nonsustained ventricular tachycardia (VT). At admission, the patient was in profound shock with absent peripheral pulses and agonal breathing. After 15 minutes of CPR and orotracheal intubation, mechanical circulatory support with femoral veno-arterial ECMO was initiated in the cardiac catheterization laboratory. Local standard operating procedures include administration of a bolus of unfractionated heparin (UFH) followed by an infusion of UFH with a target activated partial thromboplastin time of 50–80 seconds. A transthoracic echocardiogram revealed absence of intrinsic LV function and a persistently closed aortic valve with blood stasis in the ascending aorta. Sedimentation of blood was particularly pronounced in the noncoronary cusp. Repeated TEE examinations were highly suggestive for thrombus formation in the aortic root (**Supplementary Fig. 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/D171--legend, Supplemental Digital Content 9, http://links.lww.com/CCM/D177; and **Supplementary Video 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/D172). The arterial ECMO cannula was surgically switched to the ascending aorta, and an additional venting cannula was placed in the right upper pulmonary vein. During surgery, resumption of aortic valve opening with no macroscopic thrombus on the valve was observed. After 50 hours, the patients' cardiac function had fully recovered, and ECMO therapy was successfully ended. No obvious embolic end-organ

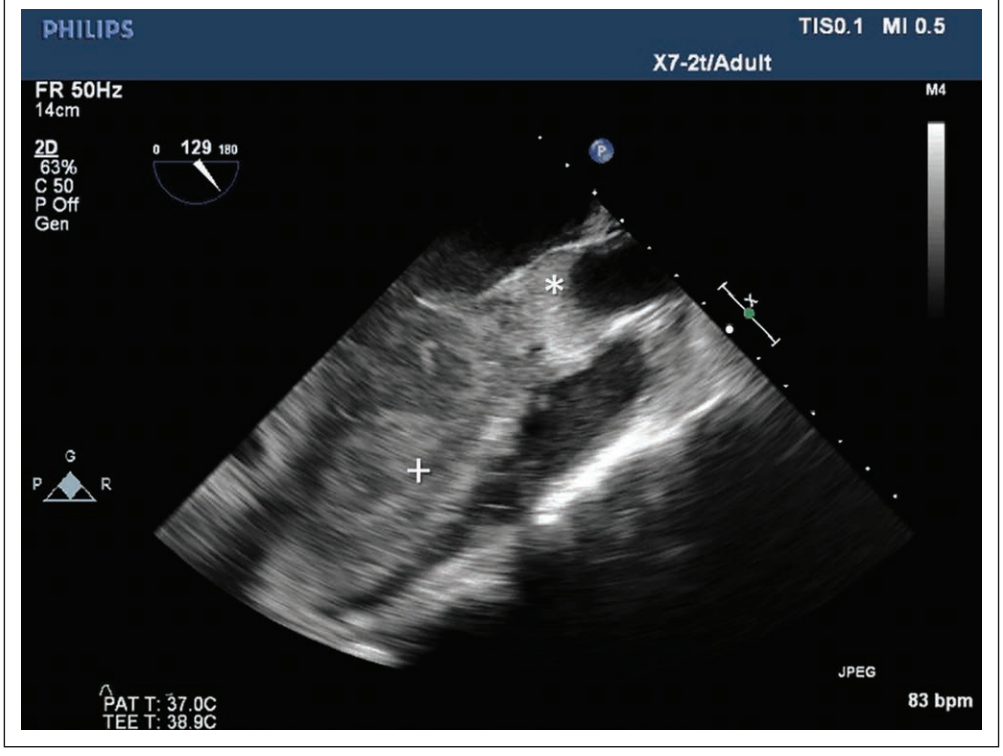

Figure 1. Transoesophageal echocardiogram, mid-oesophageal long axis view. The aortic valve remains closed throughout the electrical cardiac cycle. Thrombus is seen in the aortic root (*) and in the left ventricle (+). bpm = beats/min, G = general, P = penetration (imaging characteristics), PAT = patient, R = resolution, TEE = transoesophageal echocardiography.

damage was observed, and the patient was discharged without neurologic impairment. The cause of the cardiac arrest was self-intoxication with *Taxus baccata*.

CASE 3

A 55-year-old male was brought to the ED by EMS after sudden onset of severe thoracic back pain while loading his truck followed by syncope. At admission, the patient was awake and without neurologic deficits but with persistent thoracic pain. During the primary survey, the patient suffered from cardiac arrest, and ECG telemetry displayed asystole without p-waves. After a brief episode of CPR and orotracheal intubation, return of spontaneous circulation (ROSC) was established. Urgent coronary angiography revealed severe three-vessel coronary artery disease. While advancing the coronary wire through the right coronary artery (culprit lesion), a polymorphic VT with transition to ventricular fibrillation (VF) occurred. Despite termination by external defibrillation with stable sinus rhythm thereafter, the patient developed profound cardiogenic shock. Femoral veno-arterial ECMO was placed followed by successful percutaneous revascularization. TEE examination during the procedure in the cardiac catheterization laboratory depicted persistent closure of the aortic valve and minimal ventricular contraction. Within minutes, blood in the aortic root became hyperechogenic (**Fig. 2*A***; and **Supplementary Video 3**, Supplemental Digital Content 5, http://links.lww.com/CCM/D173). Administration of inotropic agents and reduction of veno-arterial ECMO flow resulted in systolic aortic valve opening and reversal of blood stasis (**Fig. 2*B***; and **Supplementary Video 4**, Supplemental Digital Content 6, http://links.lww.com/CCM/D174). The clinical course of the patient was favorable with successful weaning from circulatory support and full neurologic and hemodynamic recovery.

CASE 4

A 70-year-old male was admitted in cardiogenic shock with a history of intermittent typical angina over the past 8 days. Sudden onset VF was successfully defibrillated, and following a short period of CPR, ROSC was obtained. TEE revealed severely impaired systolic LV function with akinesia of the anterior wall. The coronary angiogram displayed a ruptured plaque in the proximal part of the left anterior descending artery with acute vessel occlusion. A percutaneous treatment attempt had to be aborted due to severe hemodynamic instability, and a femoral veno-arterial ECMO was placed. Subsequently, the patient underwent surgical revascularization and was transferred to the ICU with absent arterial pulsatility. Postoperative TEE confirmed a nonejecting heart and was suggestive for thrombus formation both in the non- and left-coronary aortic cusp. Furthermore, a large pericardial effusion was diagnosed and subsequently evacuated. After surgical revision, temporary opening of the aortic valve was documented. Despite full mechanical circulatory support, multiple organ failure persisted with no signs of LV recovery. Therapeutic efforts were halted, and the patient died subsequently.

CASE 5

A 51-year-old male was brought to the ED after prolonged prehospital CPR with VF as first documented rhythm. On arrival, he was unconscious, had cold extremities, and had weak pulses. The

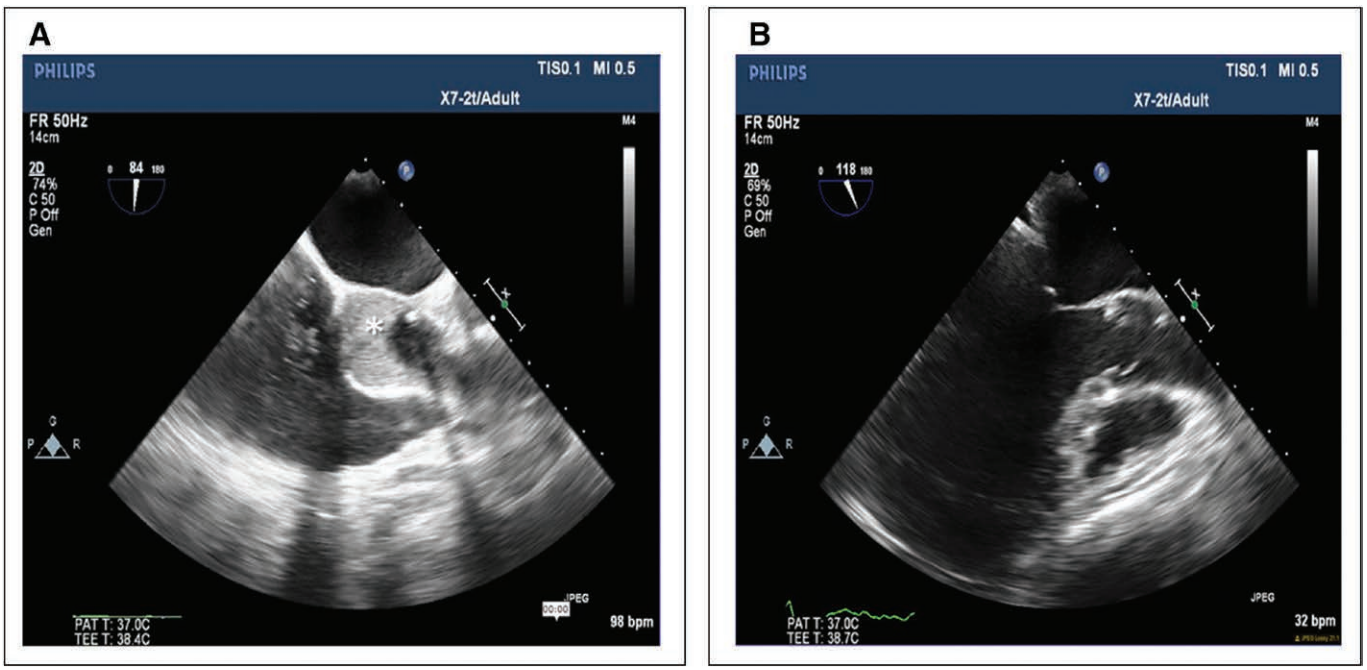

Figure 2. A, Transoesophageal echocardiogram, modified mid-oesophageal short axis view. Echo contrast is seen in the aortic root (*). The aortic valve is not opening throughout the cardiac cycle. **B**, After inotropic therapy and reduction of veno-arterial extracorporeal membrane oxygenation flow, resumption of systolic aortic valve opening and disappearance of echo contrast were observed within 3 min. bpm = beats/min, G = general, P = penetration (imaging characteristics), PAT = patient, R = resolution, TEE = transoesophageal echocardiography.

patient remained hemodynamically and electrically unstable, requiring high doses of catecholamines and repeated defibrillation. Veno-arterial ECMO was installed followed by coronary angiography revealing advanced three-vessel coronary artery disease. A later performed TEE was suggestive for thrombotic material in the ascending aorta and showed a nonejecting heart. Following correction of severe metabolic acidosis, resumption of systolic aortic valve opening was documented. The clinical course was unfavorable, and the patient died due to severe hypoxic brain injury including persistent myoclonic status.

CASE 6

A 71-year-old female with epigastric pain for 6 hours was transferred from a regional hospital with a lateral ST-segment elevation myocardial infarction. During transfer, she suffered cardiac arrest and arrived under ongoing mechanical CPR using the LUCAS system (Physio-Control Inc., Lund, Sweden). In the ED, the patient had ROSC with an initially stable rhythm but required inotropic support. Coronary angiography showed occlusion of the left main coronary artery. After percutaneous revascularization, circulation remained insufficient despite high dose inotropes, and femoral veno-arterial ECMO was initiated. Hemodynamic instability persisted due to intra-abdominal blood loss from a liver laceration caused by CPR with the LUCAS system. After surgical control of the liver bleeding, low-dose heparin infusion was started. TEE showed a nonejecting heart and thrombotic material in the aortic valve cusps. Cardiac function did not recover, and the patient remained in persistent shock despite veno-arterial ECMO whereupon therapy was aborted.

DISCUSSION

The reported cases illustrate the development of aortic root thrombosis during femoral veno-arterial ECMO support for profound cardiogenic shock. So far, aortic root thrombus formation in the setting of femoral veno-arterial ECMO has only been described in five patients (for a synthesis, see **Supplementary Table 1**, Supplemental Digital Content 7, http://links.lww.com/CCM/D175) (9). In all cases, we observed an absent ejection of blood across the nonopening aortic valve into the aorta, a state we refer to as "nonejecting heart." Echocardiographic signs of absent blood flow, sedimentation, and thrombus formation in the aortic root were observed in all cases. Application of UFH did not prevent the phenomenon, what argues that it is a distinct entity different to the well-known ventricular thrombus typically seen in large myocardial infarction. More so, we hypothesize that in all cases, the mechanism was based on the loss of contractility and subsequent blood stasis in the aortic root. This is supported by animal models which described an increase in LV afterload and a prolonged closure of the aortic valve under peripheral veno-arterial ECMO. Our observation and interpretation are line with the previously published cases (9), where there are nine cases with intracardiac thrombus formation and five patients with thrombus in the aortic root during ECMO, but only in one patient, both entities were present. Nevertheless, optimal anticoagulation therapy remains crucial to prevent other ECMO-associated complications (11, 12).

The reasons for developing a nonejecting heart during femoral veno-arterial ECMO are manifold. Severe LV myocardial dysfunction seems to be a prerequisite and can be caused by acute inflammation (case 1), intoxication (case 2), severe metabolic disturbance (case 5), and most commonly, acute ischemia due to coronary heart disease (cases 3–6). Besides LV dysfunction, the status of no LV ejection is aggravated by afterload elevation through inverted blood flow in the aortic arch and descending aorta during femoral veno-arterial ECMO favoring blood stasis and blood sedimentation in the aortic root. This in turn causes a vicious circle with reduced coronary blood flow and further impairment of LV function (13–16). Besides contractile reserves, LV loading conditions are critical to maintain forward flow across the aortic valve (17, 18). Initiation of femoral veno-arterial ECMO immediately lowers LV preload but elevates LV afterload (13, 19, 20). Furthermore, hypovolemia as in case 6 and systemic inflammatory response syndrome reduce preload. LV filling may additionally be impaired in patients with local pericardial hematoma or pericardial effusion (case 4) and patients with progressive right ventricular (RV) failure, for example, due to pulmonary embolism, RV infarction or inadequately high intrathoracic pressure under mechanical ventilation (11, 12, 21–23).

Within minutes after persistent nonopening of the aortic valve, blood stasis and sedimentation in the aortic root can be observed. This phenomenon seems to be reversible once the aortic valve reopens (case 3). Absent ejection and the observation of spontaneous echo contrast do not equal the presence of clinically relevant thrombus. However, spontaneous echo contrast increases the risk for intracardiac thrombi and strokes (24). In cases 2 and 3, intermittent stasis and spontaneous echo contrast in the aortic root were documented without resulting embolic complications and full clinical recovery of the patients. The length of a nonejecting phase likely affects the risk of actual thrombus formation, and even rare sporadic LV strokes with small ejected volumes may prevent the progression from the phenomenon of echo contrast to the presence of clinically relevant thrombotic material in the aortic root (**Supplementary Table 2**, Supplemental Digital Content 8, http://links.lww.com/CCM/D176). On the other hand, even a single LV forward stroke volume across the aortic valve can cause devastating embolic complications once actual thrombotic material is present in the aortic cusps.

In situations with undetectable pulsatile flow in the peripheral arterial blood pressure tracing, we recommend to continue treatment based on the presented algorithm (**Fig. 3**). This algorithm was developed based on the experience with the herein reported cases at our institution and is since then implemented in clinical practice. Immediate echocardiography is necessary to confirm a persistently closed aortic valve and to evaluate for the presence of aortic root thrombi. With no signs of thrombotic material, measures to regain pulsatile flow across the aortic valve should be taken by correcting possible hypovolemia, rhythm disturbances, or pericardial filling restraints and

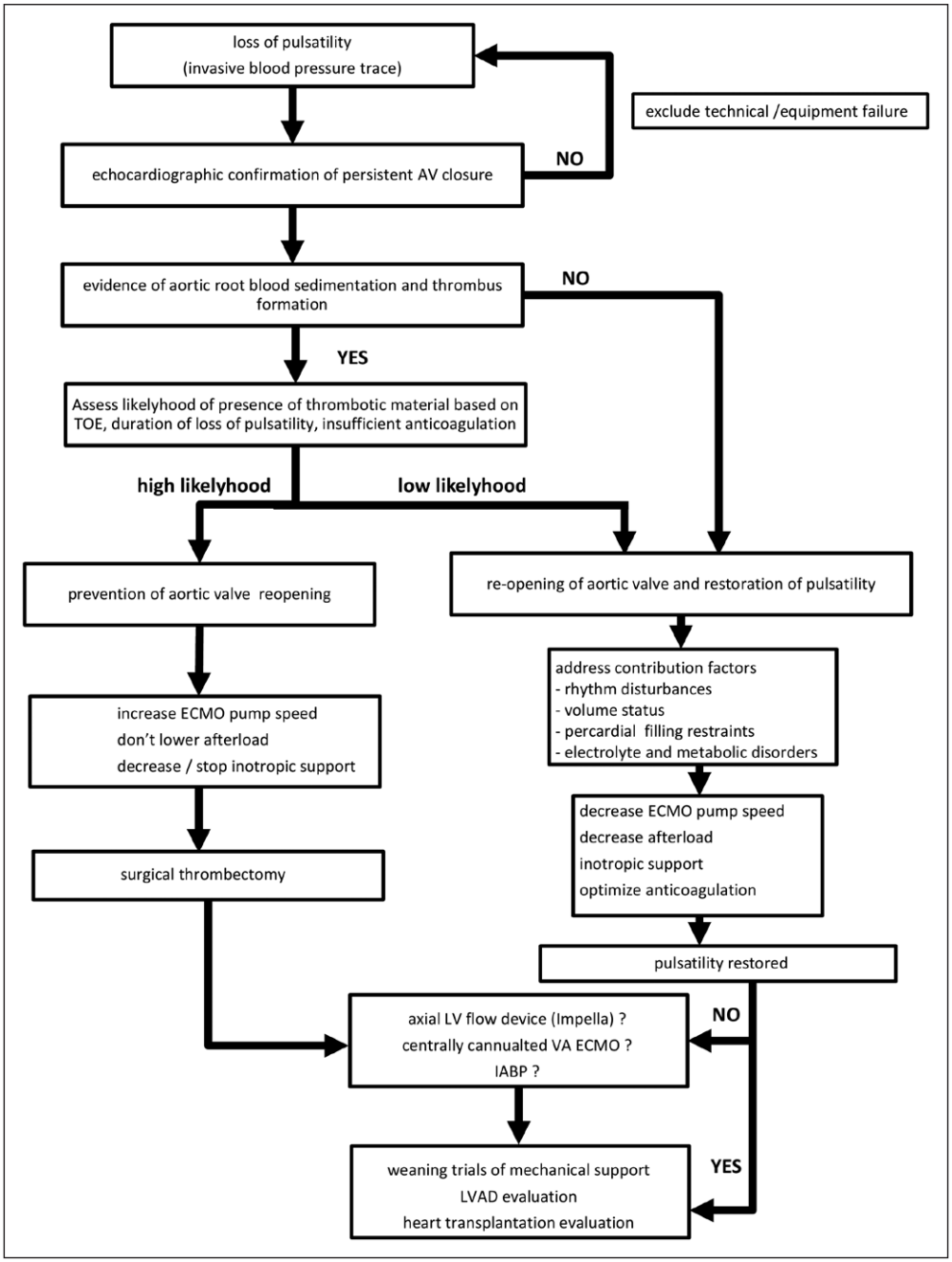

Figure 3. Flowchart depicting an algorithm to detect and treat the state of a nonejecting during femoral veno-arterial extracorporeal membrane oxygenation (VA ECMO) support. In situations with undetectable pulsatile flow in the peripheral arterial blood pressure tracing, we recommend to immediate echocardiography to confirm a persistently closed aortic valve (AV) and to evaluate the presence of thrombus. With no signs of thrombotic material, measures to regain pulsatile should be taken. The strategy to restore pulsatile flow encompasses the reduction of femoral VA ECMO flow to the absolute minimum needed to maintain vital organ perfusion (oxygen saturation in the venous ECMO cannula of 60% is advisable, repetitively check lactate level), inotropic and possibly afterload reducing drugs. Weaning of femoral VA ECMO support is of paramount importance. If ongoing mechanical circulatory support is needed, switching to a centrally cannulated VA ECMO or to a left axial flow device like the Impella (CP/5.0) are valuable treatment options. If peripheral VA ECMO needs to be left in place, the additional implantation of a left axial flow pumps (Impella 2.5/CP) will enhance left ventricle (LV) unloading and provide flow in the ascending aorta (25). In case of high suspicion for aortic root thrombosis, the treatment strategy must urgently be individualized to the patients' general condition and prognosis in a multidisciplinary approach. The decision to either aim for AV reopening or to suppress pulsatile flow depends on the time of lost pulsatility, the size and location of the possible thrombus. In selected cases, urgent heart transplantation or the implantation of a permanent LV assist device may be treatment options. CP = cardiac power, IABP = intra-aortic balloon pump, LVAD = left ventricular assist device, TOE = transesophageal echocardiography.

by addressing and optimizing pump speed, LV contractility and loading conditions besides optimizing anticoagulation (Fig. 3). The strategy to restore pulsatile flow encompasses the reduction of femoral veno-arterial ECMO flow to the absolute minimum needed to maintain vital organ perfusion (oxygen saturation in the venous ECMO cannula of 60% is advisable, repetitively check lactate level), inotropic, and possibly additional afterload reducing drugs. Weaning of femoral veno-arterial ECMO support is of paramount importance. If ongoing mechanical circulatory support is needed, switching to a centrally cannulated veno-arterial ECMO or to a left axial flow device like the Impella (CP/5.0; Abiomed, Inc., Danvers, MA) could be treatment options. If peripheral venoarterial ECMO needs to be left in place, the additional implantation of a left axial flow pumps (Impella 2.5/CP) will enhance LV unloading and provide flow in the ascending aorta (25). Another option is the insertion of an IABP in addition to peripheral venoarterial ECMO support, but only if aortic valve opening can be demonstrated with echocardiography. We strongly discourage from inserting a transseptal left atrial drainage catheter, an atrial septostomy or a TandemHeart (Cardiac Assist, Inc.; Pittsburgh, PA), as these interventions will likely enhance the nonejecting status by volume/preload reduction in the left atrium.

In case of high suspicion for aortic root thrombosis, the treatment strategy must urgently be individualized to the patients' general condition and prognosis in

a multidisciplinary approach. The decision to either aim for aortic valve reopening or to suppress pulsatile flow depends on the time of lost pulsatility, the size and location of the possible thrombus, complicating factors as pericardial effusion and rhythm disturbances, and most importantly the underlying disease and general prognosis of the patient (26–29). Hence, clear-cut echocardiographic distinction between thrombus in formation (with potentially already present microthrombi) and firm thrombus is often impossible. Treatment decisions in such cases should be made by experienced physicians based on multidisciplinary discussion. If one aims for surgical thrombectomy, high ECMO pump speeds are advised to prevent aortic valve opening until urgent surgery. In selected cases, urgent heart transplantation or the implantation of a permanent LV assist device may be treatment options.

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