Cardiac and Hemodynamic Manifestations of Hereditary Hemorrhagic Telangiectasia

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Abstract

The autosomal dominant trait hereditary hemorrhagic telangiectasia (HHT) causes multiorgan dysplastic lesions of the vasculature that can activate multiple physiological cascades leading to a broad array of cardiovascular diseases. Up to 78% of patients with HHT develop hepatic arteriovenous malformations (AVMs), which cause a hyperdynamic circulatory state secondary to hepatic/portal shunting. This condition can eventually progress to high-output cardiac failure (HOCF) with continued peripheral tissue hypoxemia. Treatment for HOCF is often limited to supportive measures (diuretics and treatment of anemia); however, recent studies using systemic bevacizumab have shown promise by substantially reducing the cardiac index. In the context of liver AVMs and high cardiac output, the pulmonary vasculature can also experience high flow. Without adequate dilation of pulmonary vessels, post-capillary pulmonary hypertension can develop. Another form of pulmonary hypertension observed in HHT, pulmonary arterial hypertension, is caused by HHT-related mutations in *ENG* and *ACVRL1* causing congestive arteriopathy. Post-capillary pathogenesis is addressed by reducing the high-output state, whereas the pre-capillary state is treated with supportive mechanisms (diuretics, oxygen) and agents targeting pulmonary vasoreactivity: endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors. If either form of pulmonary hypertension is left untreated or proves refractory and progresses, the common hemodynamic complication is right heart failure. Targeted right heart therapies involve similar strategies to those of pulmonary arterial hypertension, with several experimental approaches under study. In this review, we describe in detail the mechanisms of pathogenesis, diagnosis, and treatment of the hemodynamic complications and associated cardiovascular diseases that may arise in patients with HHT.

Keywords
- arteriovenous malformations
- high-output cardiac failure
- right heart failure
- hereditary hemorrhagic telangiectasia
- pulmonary hypertension
- angiodysplastic lesions
- atrial fibrillation

Hereditary hemorrhagic telangiectasia (HHT), also called Osler–Weber–Rendu syndrome, is an inherited autosomal dominant systemic fibrovascular dysplasia that affects 1 in 5,000 people. It is frequently caused by mutations in the endoglin (*ENG*) and activin A receptor-like type 1 (*ACVRL1*/*ALK1*) genes.[1] Typical manifestations are recurrent epistaxis, gastrointestinal bleeding, and iron deficiency anemia secondary to mucocutaneous telangiectasias. The condition can also

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lead to visceral angiodysplastic lesions within the pulmonary, cerebral, and hepatic circulations, causing a wide range of serious end-organ complications. These complications include high-output cardiac failure (HOCF), pulmonary arteriovenous malformations (AVMs), liver AVMs, cerebral arteriovenous fistulas, and stroke.[2–4] Initial screening for HHT typically involves the four Curaçao criteria (epistaxis, telangiectasia, visceral AVMs, and having a first-degree relative with HHT). The diagnosis of HHT is considered definite if at least three criteria are present.[5]

Treating patients with HHT is challenging because of the multisystemic nature of the disease. Since there is a higher risk of cardiovascular disorders associated with visceral AVMs,[3] these complications are encountered frequently by specialists at HHT treatment centers. Understanding the pathophysiological cascade leading to heart disease in affected patients can improve our approach to treating these patients. In this article, we review the cardiovascular and hemodynamic manifestations of HHT and their treatments.

Arteriovenous Malformations

Many of the visceral complications observed in HHT arise from AVMs.[6] The basic structure of an AVM is a macrovascular shunt connecting arterial blood flow to the venous outflow without a normal intervening capillary bed.[7] Cho et al[8] subclassified AVMs based on their angioarchitecture. Type I, an arteriovenous fistula, is a direct connection between an artery and one or more veins. Type II, an AVM or fistula, has numerous arteries connected to a single outflow vein. Type III, an AVM or nidus-type AVM, has a complex tangle of small-sized abnormal blood vessels (nidus) with several feeding arteries and draining veins. Without intervening capillaries, each of these vascular structures can develop into a low-resistance outlet in their local circulation, leading to pathologically high arterial flow rates and increased venous pressures, often with a complete lack of parallel capillary perfusion due to arterial steal. These hemodynamic changes initiate the pathological cascades that lead to end-organ disease in HHT, as discussed in detail below.[7,9]

Hepatic Disease and Left Heart Pathologies

Presentation and Clinical Characteristics

Liver involvement in patients with HHT is characterized by diffuse type III AVMs that give rise to three types of shunting: arteriovenous (hepatic artery to hepatic vein), arterioportal (hepatic artery to portal vein), and portovenous (portal vein to hepatic vein) (►**Fig. 1**).[2,10,11] Although these three types of shunting likely occur concomitantly, usually one type predominates functionally. The predominant shunt type may change over time.[10] Initial estimates of hepatic involvement frequency in patients with HHT were reported by two retrospective studies in a range from 8 to 31%.[12,13] Recent large, prospective studies, in which Doppler ultrasonography or multislice computed tomography (CT) has been performed systematically in HHT-affected patients, have shown a higher prevalence of 41[14] to 78%.[11,15,16]

Most patients with hepatic involvement of their diseases are asymptomatic. In a study by Ravard et al,[17] among HHT patients with hepatic manifestations shown on helical CT, 74% were asymptomatic. When patients are symptomatic, however, the sequelae can cause severe complications. HOCF, in particular, has been linked to increased morbidity in HHT.[2,11,18,19] The pathogenesis of HOCF involves shunting of oxygenated blood directly from the hepatic artery to the hepatic veins, thereby bypassing the liver and decreasing effective hepatic perfusion. The resultant increased oxygen demand coupled with decreased systemic vascular resistance activates the sympathetic nervous system and the

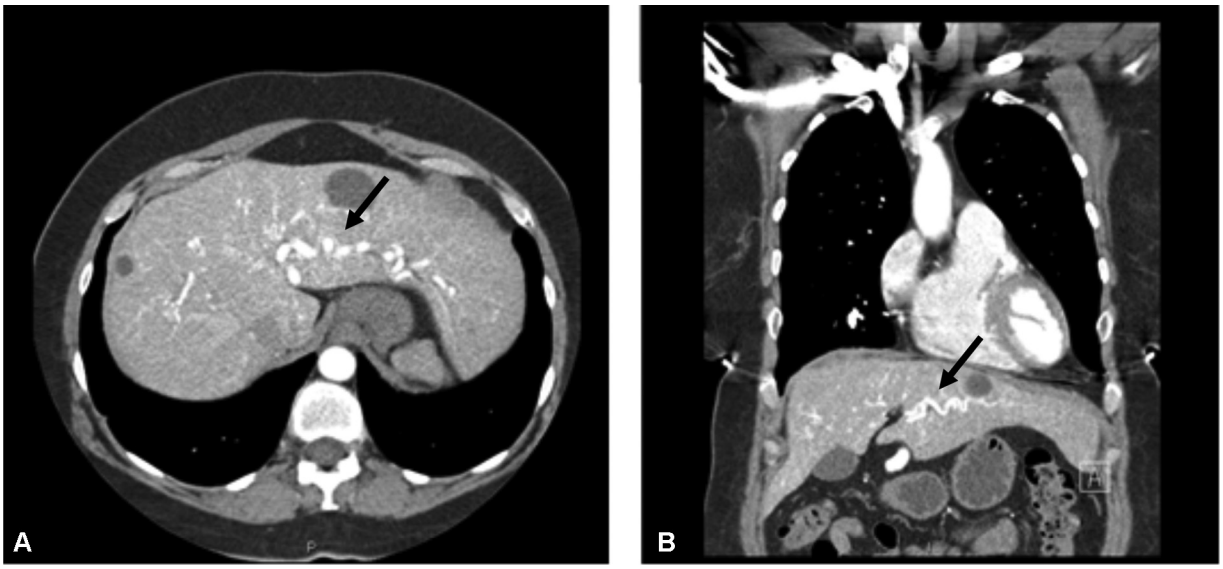

Fig. 1 Computed tomography angiograms in (**A**) the axial liver and (**B**) coronal windows showing hepatic arterioportal vascular shunting secondary to hepatic arteriovenous malformations in the setting of HHT. The arrows point to the arteriovenous malformation. Hepatic arteriovenous malformations decrease effective hepatic perfusion, leading to a hyperdynamic circulatory state and eventually high-output cardiac failure.

renin–angiotensin–aldosterone axis, causing greater cardiac output. Over time, the increased venous return, right atrial pressure, pulmonary artery pressure, and left ventricular end-diastolic volume cause left ventricular dilatation and eventual cardiac failure.[18,20,21]

Clinically, HOCF in this setting is characterized by orthopnea, ascites, shortness of breath, exertional dyspnea, and/or edema.[11] Prior studies[22,23] have found that the condition is also associated with the increased severity of epistaxis and transfusion requirements. Symptoms can be exacerbated during pregnancy, and pregnancy in women with HHT is considered high risk. The physiological adaptations that occur during pregnancy, particularly in the second and third trimesters (e.g., decrease in peripheral vascular resistance and increase in cardiac output by nearly 50%), exacerbate existing shunting lesions and put patients at increased risk of severe complications.[24]

Treatment of HOCF

Treatment options for HOCF in patients with HHT have been limited to supportive care (diuretics and treatment of anemia), with orthotopic liver transplantation being the only definitive treatment to reverse the hyperdynamic circulation and high-output state.[25] In the largest series of 40 patients undergoing orthotopic liver transplantation, Lerut et al[26] reported that the 5- and 10-year survival rates were higher than 80%. In another study of 13 patients from France, the 5-year patient and graft survival rates were 92%.[27] More recently, a study of transplantation outcomes among 24 patients in the United States found an 86% survival after a median follow-up of 4 years.[28]

Despite the excellent survival rates after transplantation, orthotopic liver transplantation is typically reserved for patients with intractable heart failure, intractable portal hypertension, or ischemic biliary necrosis. This is because of the substantial risks of surgery and chronic immunosuppression, which include transplant rejection, bleeding, infection, and biliary complications.[29] Furthermore, a long-term evaluation of graft status after liver transplantation in patients with HHT[30] found disease recurrence in 9 of 14 patients. Typical vascular lesions, including telangiectasias, were found via liver biopsy in five patients. The median interval between transplantation and diagnosis of recurrence was 10.6 years (range, 6.2–15.3 years). The risk of recurrence increased over time: the estimated cumulative risk was 48% at 15 years.[30]

Hepatic artery embolization has also been utilized for HOCF in HHT, frequently improving heart failure and portal hypertension.[31,32] However, the benefit was usually transient, with high rates of severe complications (hepatic necrosis, cholangitis, and cholecystitis) and death.[31,32] As a result, this procedure has been largely abandoned as a frontline treatment option. Currently, embolization is offered only to patients with intractable heart failure or portal hypertension who are not candidates for transplantation, after exclusion of those who are at extremely high risk of complications, including those with cirrhosis, severe biliary disease, and portovenous shunts.[1,25]

More recently, a humanized anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, has shown promising outcomes among adults with HHT, severe liver involvement, and high cardiac index.[1,25] In a phase II trial[1] assessing treatment response in 23 patients, 6 patients had a complete normalization of their cardiac index and 15 patients had a partial response at 6-month follow-up. Blinded cardiac index at 6 months (mean, 4.1 L/min/m^2; 95% confidence interval: 3.8–4.3 L/min/m^2) was significantly lower than that at the beginning of treatment (mean, 5.0 L/min/m^2; 95% confidence interval: 4.7–5.3 L/min/m^2).[1]

Pulmonary Disease and Right Heart Pathologies

Pulmonary Hypertension in HHT

In the context of HHT in association with liver AVMs and high cardiac output, the pulmonary vasculature experiences high blood flow. Without adequate dilation of these vessels, the high venous flow is driven to the left atrium and combines with left ventricular failure to elevate the left atrial pressure and, thus, the pulmonary capillary wedge pressure. Over time, the backward transmission of the elevated left atrial pressure to the pulmonary venous system can lead to the development of pulmonary venous hypertension, also known as post-capillary pulmonary hypertension.[2,33] The condition can progress to cause left atrial fibrillation, secondary to left atrial enlargement from the high left-sided filling, and severe anemia. The loss of atrial contraction with the onset of atrial fibrillation further impairs ventricular filling and exacerbates volume and pressure overload in the pulmonary circulation.[2,33,34] Treating post-capillary pulmonary hypertension focuses on the management of the high-output state through the procedures described earlier and with the addition of antihypertensives, antiarrhythmic agents, and digoxin as needed.[35,36]

Another form of pulmonary hypertension that has been described more frequently in studies of patients with HHT is pre-capillary pulmonary arterial hypertension (PAH).[37–41] PAH occurs less frequently than post-capillary pulmonary hypertension and is caused by HHT-related gene mutations in *ENG* or *ACVRL1*. Both genes encode proteins that cooperate in the transforming growth factor-β/activin receptor-like kinase 1 signaling pathway, which is involved in angiogenesis. These mutations result in arteriopathy characterized by intimal hyperplasia, medial hypertrophy, in situ thrombosis, and plexiform lesions. An obliterative pulmonary vasculopathy, this condition predominantly affects small pulmonary arterioles to increase vascular resistance and pressures at the level of the pulmonary arterial system alone.[36,42,43]

Current treatment guidelines include supportive therapy (diuretics, oxygen, and digoxin) and PAH-specific medications. The latter consists of endothelin-1 receptor antagonists, phosphodiesterase inhibitors, and prostacyclins.[44] Two case reports have described the successful treatment of HHT-associated PAH patients with the endothelin-1 receptor antagonist bosentan.[44,45] Bosentan use improved symptoms, decreased

mean pulmonary arterial pressure (mPAP), and increased the cardiac index without increasing shunt volume. More recently, the first case was described of HHT-associated PAH successfully treated with sildenafil (phosphodiesterase-5 inhibitor).[46] Another study[47] reported a combination of tadalafil (phosphodiesterase-5 inhibitor) and ambrisentan (endothelin-1 receptor antagonist) used to treat a patient with severe HHT-associated PAH, but the treatment was unsuccessful. Twelve months after initiating therapy, the patient developed right heart failure with deteriorating pulmonary hemodynamics (mPAP, 90 mm Hg; cardiac index, 1.88 L/min/m^2). She died of right heart failure 12 months after initiating therapy. In a systematic review of 23 patients with HHT-associated PAH treated with calcium channel blockers for acute pulmonary vasodilation, Girerd et al[38] found minimal pulmonary vasoreactivity, a prognostic sign of poor response to therapy.

Right heart catheterization remains the "gold standard" for diagnosing and differentiating between high-output pulmonary hypertension and PAH. In PAH, the mPAP is typically higher with an increase in pulmonary vascular resistance (PVR) and transpulmonary gradient due to arteriopathy. Furthermore, cardiac output and pulmonary artery wedge pressure are typically normal or decreased. In contrast, in high-output pulmonary hypertension, there is only a moderate increase in mPAP, normal PVR, elevated pulmonary artery wedge pressure, and increased cardiac output.[33,36,48]

Right Heart Failure

The common hemodynamic complication for both forms of pulmonary hypertension is right heart failure. Pulmonary load is an important determinant of right ventricular (RV) systolic function, and the RV adapts to increasing volume and pressure overload in the pulmonary circulation by increasing contractility and hypertrophy. In most patients, these compensatory mechanisms are insufficient, and RV dysfunction results, leading to RV dilatation, decreased systolic function, and subsequent failure.[49]

Targeted right heart therapy optimizes RV preload, afterload, and contractility. Amelioration of the primary drivers for RV failure reduces further RV insults and enables reverse remodeling of the right heart. Preload optimization and afterload reduction are achieved through similar treatment strategies as those used in treating PAH, as described earlier in the text.[33,36,48] Recent investigations have studied agents that have been beneficial in left heart failure with decreased ejection fraction. One study[50] reported that continuous low-dose treatment with bisoprolol, a cardioselective β blocker, delayed the progression of right heart failure in mice with induced pulmonary hypertension. Another study[51] found that adrenergic receptor blockade using carvedilol reversed RV remodeling and improved RV function in rats with pulmonary hypertension. However, these beneficial effects may be mitigated in patients with severe PAH. This is because these patients often have a substantially reduced contractile reserve, which is the ability of the ventricle to respond to physiologic stress by increasing contractility to improve systolic output, as measured by ejection fraction and stroke volume.[52] For patients with severe PAH in whom RV contractile reserve has been diminished, the ability of the right ventricle to enhance systolic function to counter the elevated afterload from the pulmonary circulation is severely limited. Other novel treatment strategies, including angiotensin-converting enzyme, angiotensin or aldosterone blockade, myosin activators, implantable defibrillators, and RV assist device implantation, have not been investigated comprehensively in patients with right heart failure syndrome associated with pulmonary hypertension.[49]

Pulmonary AVMs

Pulmonary AVMs in HHT are typically arteriovenous fistulas (types I and II AVMs) (►**Fig. 2**). Without an interposed nidus, these fistulous malformations have lower resistance and higher flow than type III AVMs. Therefore, these malformations create a more pronounced hemodynamic effect associated with their pulmonary right-to-left shunting.[7] The presence of pulmonary AVMs in the setting of pulmonary hypertension or PAH has both clinical and therapeutic ramifications, which are described below. These ramifications become important when considering that approximately 50 to 80% of patients presenting with pulmonary AVMs are eventually diagnosed with HHT.[53,54] Furthermore, some studies have shown that approximately 15 to 60% of patients with an underlying diagnosis of HHT have pulmonary AVMs, depending on the imaging modality used.[25,35,55,56]

Agitated saline echocardiography (ASE) is the most common screening test for patients who may have pulmonary AVMs, with a sensitivity of up to 98.6%.[57,58] In an ASE, an air–saline mixture is briskly agitated between syringes to create a solution of microbubbles. This solution is injected into the antecubital vein while conducting a transthoracic echo (TTE) such that the microbubbles will be visualized on the right side of the heart on TTE. Normally, these microbubbles dissipate as they enter the pulmonary circulation and become trapped in the pulmonary capillary beds. If the bubbles appear on the left side of the heart, the study is considered positive for shunting. The timing of the bubble appearance is important with respect to the cardiac cycle to determine the level at which shunting is occurring. If they are visualized within one to two cardiac cycles from appearing in the right heart, it is suggestive of an intracardiac shunt, such as a patent foramen ovale. If they appear at or after the third cardiac cycle, their appearance is likely due to an intrapulmonary shunt such as an AVM.[57,58]

The presence of pulmonary AVMs in patients with PAH could have a protective effect on the PAH by providing a low-resistance vascular bed, thereby reducing RV afterload. However, the progression of PAH can predispose patients to enlargement and subsequent rupture of the pulmonary AVM. This most commonly occurs in patients who have thin-walled AVMs and in pregnant patients, who have hormonal changes to their pulmonary AVM walls and increased circulating blood volume.[53] Pulmonary AVMs are commonly subpleural, so rupture can result in hemoptysis or hemothorax.[53,59]

Because pulmonary AVMs can unload the RV, special considerations exist when treating pulmonary AVMs with

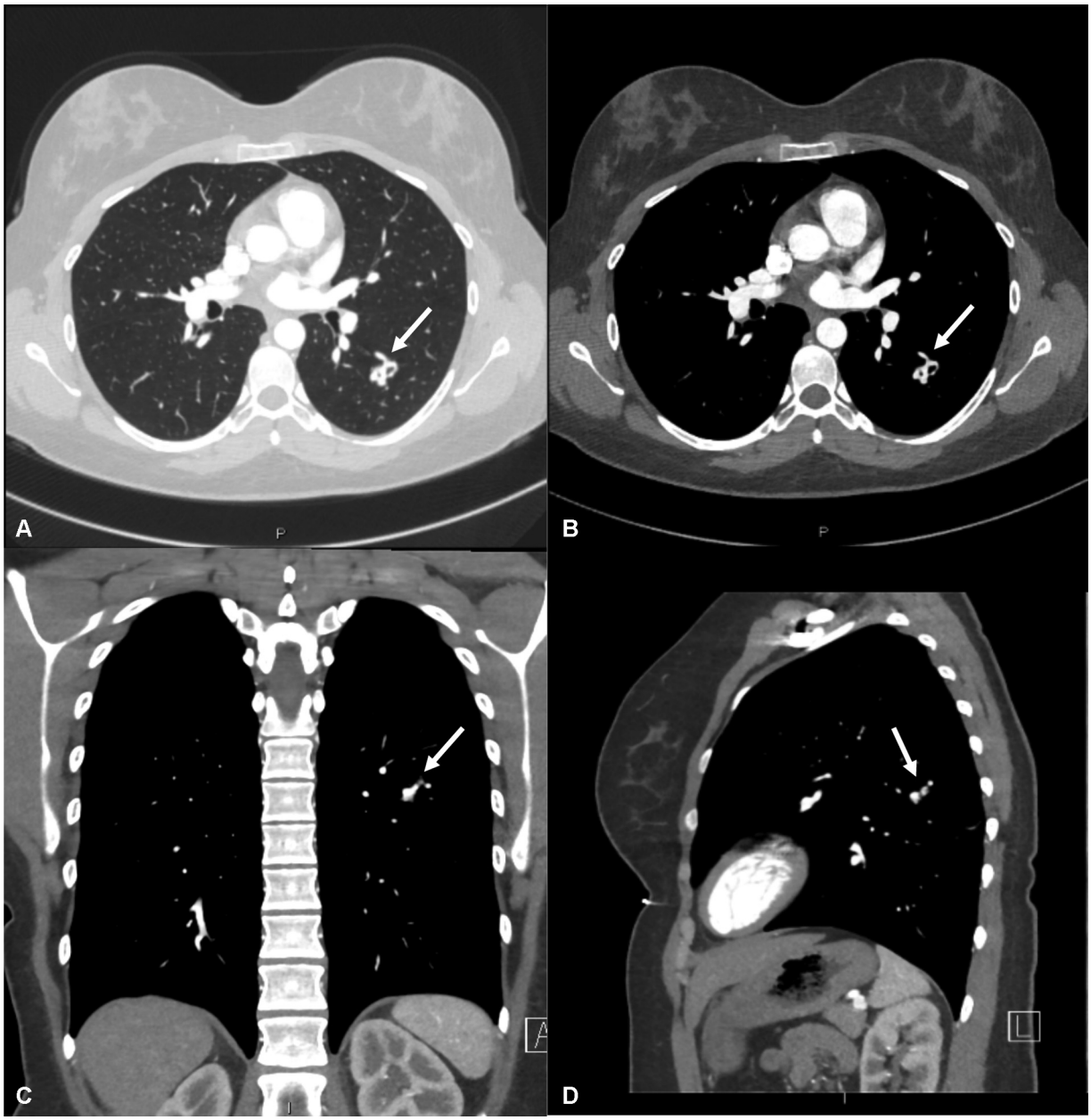

Fig. 2 Computed tomography angiograms of the chest showing pulmonary arteriovenous malformation in the superior segment of the left lower lobe using (**A**) axial bone, (**B**) mediastinal, (**C**) coronal, and (**D**) sagittal windows. The arrows point to the arteriovenous malformation.

embolization in patients with PAH. The procedure would theoretically lead to an increase in pulmonary arterial pressures and RV afterload, predisposing patients to right heart failure. Despite this possibility, the extent to which embolization might contribute to the progression of pulmonary or cardiovascular disease is unknown, with studies showing mixed results.[60–62] Shovlin et al[61] studied 143 patients with pulmonary AVMs and found no significant elevation in mPAP or right heart failure after embolization. These findings may be attributed to the decrease in cardiac output after embolization secondary to increased PVR rather than the effects of directly occluding the pulmonary AVMs.[60] However, it should be noted that patients with PAH were not included in the report.[33,61] Thus, it will be critical to identify patients with low cardiac output and reduced RV function whose RV function may worsen after embolization. To this point, a case report[63] described a male infant with PAH in the setting of HHT who later developed pulmonary AVMs. The development of these pulmonary AVMs was associated with a reduction in mPAP and improvement in PVR.[63]

Conclusion

Advancements in our understanding of HHT, including its diagnosis and treatment, have underscored the importance of cardiovascular disease in this setting. These complications include HOCF, atrial fibrillation, RV enlargement and systolic dysfunction, and hyperdynamic states, including pre-capillary and post-capillary pulmonary hypertension (►**Fig. 3**).

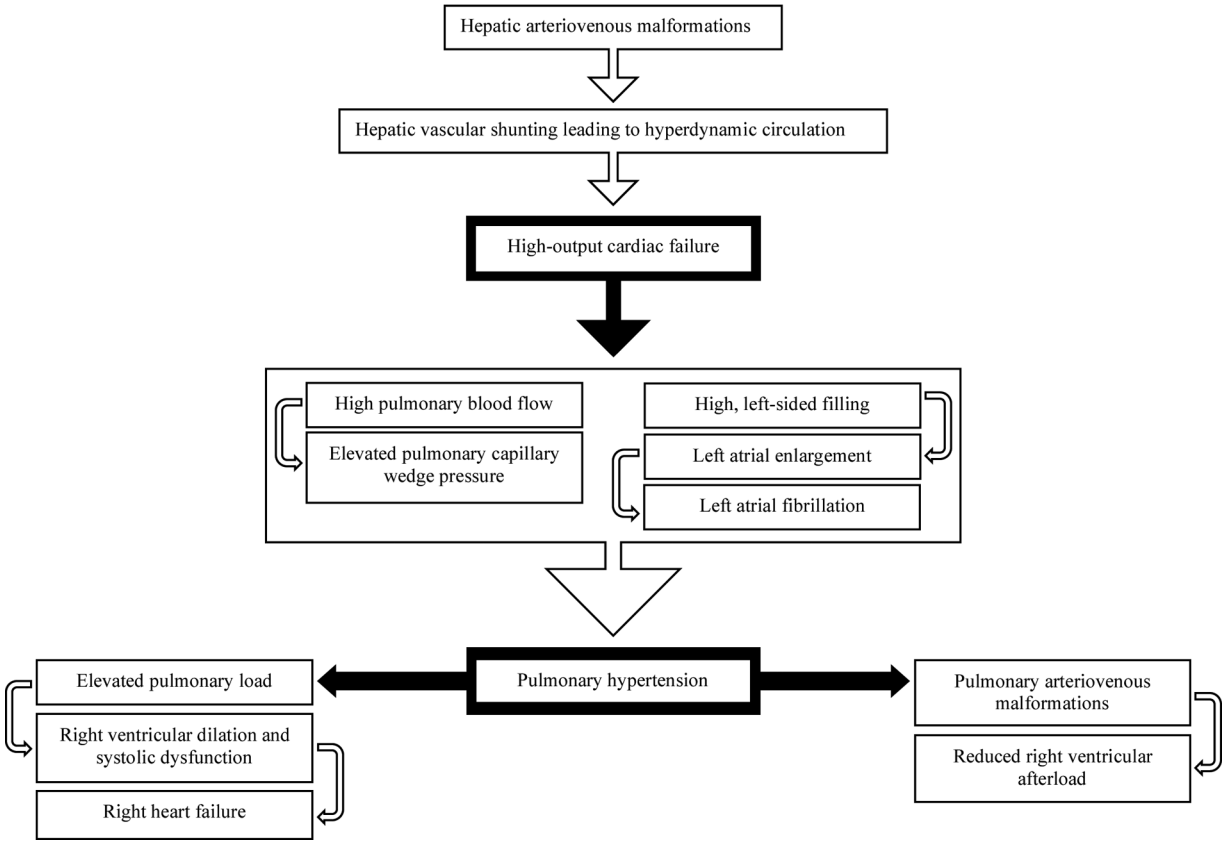

Fig. 3 Schematic diagram for the progression of cardiovascular disease in patients with HHT and liver arteriovenous malformations with the demonstration of cardioprotection arising from secondary development of pulmonary arteriovenous malformations.

Many investigations have sought to characterize and develop treatments for these manifestations. Certain treatments have shown promising results, including the novel targeted anti-angiogenic agent bevacizumab in the treatment of HOCF. However, effective and safe treatment approaches for other cardiac diseases, including right heart failure, have yet to be discovered. As such, more research is required to advance the outcomes of patients with cardiac involvement in HHT. Furthermore, this review highlights the multisystemic nature of HHT and the importance of specialists who treat these patients and lead HHT centers of excellence, to closely coordinate their care with other specialties, such as vascular surgery, cardiologists, pulmonologists, and hepatologists. With additional research to advance therapies and a clinical model of combined expertise, the quality of care that HHT patients receive can be improved.

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Conflicts of Interest
None declared.

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