Published in final edited form as:

Expert Rev Cardiovasc Ther. 2014 June ; 12(6): 703–713. doi:10.1586/14779072.2014.912132.

Pulmonary Arteriovenous Malformations After the Superior Cavopulmonary Shunt: Mechanisms and Clinical Implications

Minoo N. Kavarana, M.D.^{a,b}, Jeffrey A. Jones, PhD^{b,c}, Robert E. Stroud, MS^b, Scott M. Bradley, MD^{a,b}, John S. Ikonomidis, MD, PhD^b, and Rupak Mukherjee, PhD^b

^aDivision of Pediatric Cardiothoracic Surgery, Department of Surgery, Medical University of South Carolina, Charleston, SC

^bDivision of Cardiothoracic Surgery, Department of Surgery, Medical University of South Carolina, Charleston, SC

^cRalph H. Johnson, VA Medical Center, Charleston, SC

Abstract

Children with functional single ventricle heart disease are commonly palliated down a staged clinical pathway toward a Fontan completion procedure (total cavopulmonary connection). The Fontan physiology is fraught with long term complications associated with lower body systemic venous hypertension, eventually resulting in significant morbidity and mortality. The bidirectional Glenn shunt or superior cavopulmonary connection (SCPC) is commonly the transitional stage in single ventricle surgical management and provides excellent palliation. Some studies have demonstrated lower morbidity and mortality with the SCPC when compared with the Fontan. Unfortunately the durability of the SCPC is significantly limited by the development of pulmonary arteriovenous malformations (PAVMs) which have been commonly attributed to the absence of hepatic venous blood flow and the lack of pulsatile flow to the affected lungs. Abnormal angiogenesis has been suggested as a final common pathway to PAVM development. Understanding these fundamental mechanisms through the investigation of angiogenic pathways associated with the pathogenesis of PAVMs would help to develop medical therapies that could prevent or reverse this complication following SCPC. Such therapies could improve the longevity of the SCPC, potentially eliminate or significantly postpone the Fontan completion with its associated complications, and improve long-term survival in children with single ventricle disease.

Keywords

Single ventricle; congenital heart disease; pulmonary arteriovenous malformations; angiogenesis; superior cavopulmonary connection; Fontan operation

Introduction

Standard surgical management of patients with functional single ventricle congenital heart defects, involves a staged approach. This approach begins in the neonatal period with a palliative procedure commonly involving an aortopulmonary shunt, a Norwood procedure, or a pulmonary artery band. This initial stage is commonly followed by a superior cavopulmonary connection (SCPC) later in infancy, culminating in a Fontan procedure between two to three years of age. The development of a connection between the superior vena cava and the right pulmonary artery, or Glenn shunt, was an important clinical breakthrough in the management of cyanotic congenital heart disease.[1,2] The SCPC provides pulmonary blood flow and improves oxygenation without an increased volume load on the ventricle as seen with an aortopulmonary shunt. The SCPC, is commonly performed as a transitional stage, in most palliative single ventricle pathways, and has reduced mortality in patients that were originally advanced directly to a Fontan procedure. [3,4] With careful selection and improved techniques, the Fontan procedure can now be performed with low perioperative mortality and morbidity.[5] However, even after a “perfect Fontan”, persistent high Fontan pathway pressures with subsequently elevated lower body systemic venous pressures limit the durability of this palliative procedure.[6] This results in medium-term morbidity and mortality with atrial arrhythmias,[7] protein losing enteropathy,[8] prolonged pleural effusions,[9] and a fairly high attrition rate as these children reach adolescence.[10] In addition, patients with the Fontan circulation are only able to increase their cardiac output and exercise capacity by increasing their heart rate and oxygen extraction as their stroke volume is limited by the pulmonary vascular bed.[11] Therefore, in spite of higher oxygen saturations following the Fontan when compared with the SCPC, these children have a limited exercise capacity secondary to their inability to increase cardiac output beyond a certain threshold.[12] Thus, patients with single ventricle physiology, particularly patients with risk factors for a Fontan procedure, seem to tolerate a SCPC better, with lower perioperative morbidity and mortality.[13-15]

However, the durability and longevity of the SCPC is complicated by the development of hypoxia and cyanosis secondary to the formation of pulmonary arteriovenous malformations (PAVMs) in a large proportion of patients.[16] Evaluation of patients with contrast echocardiography following a SCPC has demonstrated the early demonstration of right-to-left shunting through the lungs almost universally, resulting in the progressive development of cyanosis, hypoxia, and exercise intolerance.[17-19]

The development and progression of arteriovenous malformations have been attributed to abnormalities in angiogenesis.[20] For example, in a clinical study, Jabbour and colleagues reported that a higher proliferation rate in endothelial cells isolated from cerebral arteriovenous malformations was associated with increased levels of vascular endothelial growth factor (VEGF)-A and VEGF receptors [21]. Recent findings from clinical and experimental studies have implicated similar pro-angiogenic processes to be operative in PAVM development in the post-SCPC setting [22]. Accordingly, the present review focuses on the current understanding of the role of angiogenesis and its modulators in the development of PAVMs.

Etiology & Pathology

The originally described classic Glenn shunt or unidirectional SCPC is constructed by performing an end-to-end anastomosis of the superior vena cava (SVC) to the proximal right pulmonary artery.[2] This shunt diverts all SVC blood flow to the right lung and venous return from the inferior vena cava (IVC), which contains hepatic effluent, continues to flow through the heart to the left lung. In contrast, the bidirectional SCPC, directs SVC blood to both lungs that results in both lungs receiving venous blood devoid of hepatic effluent (Figure 1). Although PAVMs were originally seen most commonly in the right lung bases of patients who had undergone the classic Glenn shunt,[16] they have been demonstrated almost universally in both forms of SCPC.[17] In the absence of PAVMs excellent long-term durability has been demonstrated upto thirty years.[23]

PAVMs are thin-walled vascular malformations that are located pleurally or subpleurally, and may range from microscopic telangiectasia's to 1-5 cm in size.[24] Morphologic studies of PAVMs in the lungs of lambs following a Glenn shunt using novel vascular corrosion casts demonstrated multiple abnormal tortuous vessels, a minimum of 15 μ m in size, connecting the pulmonary arteries to the pulmonary veins, and bypassing the pulmonary alveolar beds .[25] .

PAVMs may be classified as simple, with a single feeding segmental artery and a single draining vein, or complex, with two or more feeding arteries or draining veins.[19,26] Eighty to ninety percent of PAVMs are simple, while the rest are classified as complex.[19] There are two basic elements that characterize these malformations: vascular channels lined by endothelium and a scant connective tissue stroma.[27]

Patients with PAVMs may be entirely asymptomatic, suggesting a smaller physiologic burden of intrapulmonary right-left shunt in which oxygenation is not significantly affected. However, advanced stages of PAVM formation may present with hypoxemia, cyanosis, cerebral embolization and brain abscesses.

Pathogenesis : Proposed Hypotheses

Based on these observations, multiple theories regarding the development of PAVMs following an SCPC have been proposed. An early theory was that non-pulsatile flow to the right lung stimulated the development of PAVMs.[28] Nevertheless, a theory suggesting non-pulsatile flow as the sole etiologic factor fails to explain PAVMs in patients with two-ventricle physiology with liver failure from cirrhosis and the hepato-pulmonary syndrome (HPS).[29] Another theory proposed that PAVMs formed secondary to a discrepancy in flow distribution, with increased flow going to the lung bases versus the apices, due to gravitational forces. However, over time PAVMs have been observed in all lung segments. [30]

There is some evidence that the liver may play an important role in the development of PAVMs. The presence of PAVMs in the right lung devoid of hepatic venous flow following the classic SCPC supports this hypothesis (Figure 2).[31] The most convincing clinical evidence of the liver's role in PAVM formation comes from patients with the heterotaxy / polysplenia syndrome and interrupted IVC who have undergone a Kawashima procedure

which involves creation of a SCPC with lower body venous blood returning to the SVC via the azygos vein. In this instance, hepatic venous blood is diverted away from both lungs and bilateral PAVMs are seen with progressive cyanosis.[18] Multiple reports have now demonstrated the complete resolution of hypoxemia and PAVMs following connection of the hepatic veins to the pulmonary arteries.[32,33] This strong correlation of the heterotaxy-polysplenia syndrome with PAVM formation following a SCPC suggests a genetic influence. A recent study found an increased prevalence of PAVMs in patients with the Abernethy syndrome which is characterized by congenital portosystemic venous connections, thus further supporting a genetic basis. [34]

Another scenario that supports the hepatic factor hypothesis is the persistence of unilateral PAVMs after Fontan completion due to unilateral hepatic venous flow from caval offset. Surgical strategies that have been effective in resolving PAVMs in this setting are revision of the Fontan connection to eliminate hepatic venous streaming[35] and provision of hepatic venous blood to the pulmonary arteries through a systemic arterio-venous fistula.[36] A clinical example of the liver's role in PAVM formation in the non-cardiac surgery setting comes from patients with end stage liver disease, such as cirrhosis, that have progressive cyanosis from intrapulmonary shunting.[29,37,38] HPS, which is caused by a derangement of liver function, alters the constituents of hepatic venous effluent creating a clinical scenario similar to that after a SCPC.[29] Further, the PAVMs associated with these conditions closely resemble the angiographic and histological picture of PAVMs seen after SCPC. Complete resolution of these PAVMs is seen with restored liver function following liver transplantation.[37,38] Nevertheless, the fact that persistence of PAVMs has been reported even after Fontan completion despite restoration of balanced hepatic venous flow suggests the involvement of a "non hepatic" factor, which may include a loss of pulsatile flow.[39] Although abnormal liver function does explain the HPS observed in end-stage liver disease the patients that developed PAVMs following a Fontan procedure were noted to have biochemical liver function tests in the normal range with the abdominal computed tomography (CT) demonstrating no abnormal findings in the liver except mild hepatosplenomegaly.[37]

Systemic veno-venous collaterals have been known to develop following a SCPC.[40] These collaterals are associated with an abnormal superior vena caval connection, pulmonary artery distortion, increased pressure in the superior vena cava, increased pulmonary artery pressure, and most significantly, with an increased trans-pulmonary gradient. The majority of patients without the above risk factors did not develop these veno-venous collaterals. Further, none of the patients with veno-venous collaterals developed PAVMs,[40] thus reducing the likelihood of increased venous pressure as a trigger for PAVM development.

Therefore, we now have indirect, but compelling, clinical evidence that two major etiologic factors contribute to the development of PAVMs: the lack of hepatic venous effluent directly perfusing the pulmonary arteries, and /or the loss of pulsatile pulmonary blood flow. [18,41,42]

Diagnosis

Traditionally the diagnosis of PAVMs has been made by right heart catheterization and pulmonary angiography, as depicted in Figure 3.[43] However, contrast echocardiography performed with agitated saline has been found to be more sensitive than angiography.[44] In a patient without PAVMs, the bubble contrast is lost in passage through the pulmonary capillaries, and therefore no bubbles are observed in the left atrium. On the other hand, bubbles seen in the left atrium within three to five cardiac cycles of their injection into the pulmonary arterial circulation indicates rapid transit through larger caliber blood vessels due to arteriovenous shunting.[45]

The advantage of echocardiography in comparison with angiography is its non-invasiveness and high sensitivity. A study in 29 patients that had undergone a SCPC demonstrated a 60% prevalence of PAVMs detected by contrast echocardiography.[45] However, it is possible that echocardiography may be too sensitive and may detect clinically non-significant lesions.[46] Computed tomography[47] and magnetic resonance imaging[48] are newer imaging modalities in this setting. These modalities have both been used to document the progression or regression of PAVMs following treatment in the adult population, but not in children with univentricular physiology following a SCPC.

Treatment

The treatment of PAVMs depends on the clinical setting within which they develop. Embolization may be successful with isolated or large PAVMs and is commonly used to treat isolated PAVMs. However, embolization therapy is rarely feasible after a SCPC as the disease usually presents in the diffuse form. This form does not respond well to embolization and most often the surgical redirection of hepatic venous blood flow to the pulmonary arterial circulation is required to effectively treat and often eliminate PAVMs. [18,49] Patients who have undergone a SCPC and develop PAVMs have shown complete resolution following Fontan completion, by redirecting hepatic venous effluent toward the lungs.[33] On the other hand, persistence of PAVMs has been observed even following redirection of hepatic venous flow to the lungs and PAVMs have been shown to develop even after completion Fontan procedures.[49] Some of these patients may have caval offset with streaming of pulmonary venous effluent away from the diseased lung and demonstrate resolution with redirection of hepatic venous flow toward the lung with PAVMs.[35] Other surgical techniques that have been used to treat refractory PAVMs following a SCPC involve the creation of brachio-cephalic arteriovenous fistulae which have been shown to effectively improve cyanosis in these patients likely from the re-introduction of hepatic venous blood into the pulmonary circulation. [36] Refractory PAVMs following a Fontan have also been successfully treated by a heart-single lung transplant with regression of PAVMs in the native lung.[50] In non-cardiac surgery patients with liver failure, liver transplantation after HPS have resulted in complete resolution of cyanosis, hypoxia and PAVMs.

These clinical findings provide indirect evidence of the requirement for adequate liver function and the liver's role in the pathogenesis of PAVMs.[37] While angiogenic pathways have been recognized in many normal and pathologic physiologic processes including

arterio-venous malformations,[20,21,31] there are currently no established molecular mechanisms that have been linked to PAVM formation. The lack of understanding of molecular mechanisms may explain the absence of non-surgical, non-invasive, treatment(s) for PAVMs.

Molecular mechanisms and the role of angiogenesis in PAVM development

It is well recognized that many physiological processes, such as tissue development and repair, are dependent on angiogenesis (Figure 4).[31] Angiogenesis is normally tightly controlled and regulated in order to provide adequate blood flow to meet the demands of specific tissues. Endothelial cells must first break through the basement membrane, a process which occurs in response to signals from tissue requiring increased blood supply, by recruiting proteinases and local myofibroblasts [31]. Proliferation follows shortly after and is controlled by a variety of different inhibitors and activators.[31] The new blood vessels supply growing tissues with oxygen, hormones, growth factors and nutrients, required for optimal function and growth.

While angiogenesis is highly regulated by a complex network of biological molecules, there are multiple clinical examples of abnormal angiogenesis. One of the most well studied examples of pathological angiogenesis occurs with tumor formation.[51] Tumor growth requires new vessel formation; when angiogenesis is reduced, a dramatic decrease in tumor growth and metastasis has been reported.[31] Many chemotherapeutic drugs attempt to block or downregulate angiogenesis in order to prevent tumors from growing and spreading. The development of PAVMs has been, therefore, intuitively associated with an alteration in the angiogenic balance towards a pro-angiogenic milieu in the pulmonary vasculature.[20] PAVMs may develop following a SCPC secondary to the absence of anti-angiogenic factors present in hepatic venous blood, which would normally inhibit vascular proliferation. Conversely, the liver may be responsible for the degradation of angiogenic factors, which in the setting of liver dysfunction, may result in excessive uncontrolled angiogenesis in the pulmonary vascular network.

Therefore, the lack of, or alteration in, the constituents of hepatic venous blood perfusing the lungs along with non-pulsatile blood flow experienced following the creation of a SCPC may together influence angiogenic pathways, which then result in PAVM formation. Clinical evidence exists that a major etiologic factor in the development of PAVMs occurs when hepatic venous effluent does not perfuse the pulmonary arteries directly.[18,41,42]

The liver is known to produce collagen XVIII and plasminogen, which are precursors to potent angiogenesis inhibitors. Collagen XVIII and plasminogen are produced in large quantities by the liver and are secreted into hepatic venous effluent. [31,52,53] Here subsequent action by proteolytic enzymes cleaves these precursors into the angiogenesis inhibitors endostatin and angiostatin, respectively. The first four domains of plasminogen yield fragments that are angiogenesis inhibitors, one of which is a 38-kd peptide called angiostatin.[54] These fragments that inhibit angiogenesis are generated by cleavage of plasminogen by extracellular matrix metalloproteinases (MMP), specifically MMP3 (stromelysin), MMP7 (matrilysin), and MMP9 (gelatinase B) and metallo-elastase.[55,56] One study demonstrated that MMP-7 and MMP-9 hydrolyzed human plasminogen to

generate angiostatin molecules, and thus, regulate angiogenesis.[57] Cleaving human plasminogen with MMP-3 has generated a similar angiostatin-like fragment.[55]

Endostatin is a 20-kd fragment of collagen XVIII that has been found to inhibit angiogenesis and tumor growth in mice and endothelial cell proliferation *in vitro*. [58] Production of these inhibitors varies in liver disease with their release orchestrated and finely regulated by the expression of specific proteinases.[52] Exclusion of these substances from the pulmonary arterial circulation would result in vascular proliferation that would normally be tightly regulated.[31] PAVMs have also been observed following development of HPS using a well-established common bile duct ligation (CBDL) model in rats.[59] The authors evaluated the impact of rats treated with anti-angiogenesis factors. They used intramuscular angiostatin and endostatin adenoviral constructs and pentoxifyline, a tumor necrosis factor (TNF)- α inhibitor to inhibit angiogenesis. They found significantly reduced PAVMs in animals treated with anti-angiogenic factors, associated with a reduction in VEGF-A levels and a decrease in phosphorylation of VEGFR-2. They concluded that treatment of CBDL animals with these anti-angiogenic agents down-regulated angiogenesis and activation of VEGF-A-mediated angiogenic pathways and improved the HPS.

A recent clinical study evaluated endostatin levels in patients that had undergone a bidirectional SCPC and showed a significant decrease in plasma endostatin levels with an increase in its precursor collagen XVIII within 24 hours postoperatively.[22] In contrast, patients undergoing a Fontan procedure or biventricular repair of congenital heart defects, these changes were not apparent.[22] They suggested that the decrease in endostatin was not caused by the decreased production of collagen XVIII by the liver but rather by an aberration in the cleavage of the precursor likely from the absence of first pass metabolism in the lungs (Figure 2).[22] At this time the specific influence the liver has on pulmonary vascular metabolism is unknown. However the pathways involved with endostatin release by MMP, elastase and cathepsin activity have been established.[60-62] This clinical study further strengthens the hypothesis that the reduction or absence of an angiogenesis inhibitor permits uncontrolled angiogenesis and PAVM formation in the lungs of patients following a bidirectional SCPC.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by multisystem vascular dysplasia's with a high incidence of PAVMs. Mutations in endoglin, a TGF- β binding protein, have been identified with abnormal angiogenesis demonstrated in patients with HHT.[63] TGF- β is a potent angiogenic factor which mediates vascular remodeling through control of extracellular matrix production by the endothelial cells and smooth muscle cells.[64] The process of angiogenesis is regulated by interactions between the extracellular matrix, smooth muscle cells and endothelial cells which may be stimulated by TGF- β or inhibited by its β 1 isoform.[64] The effect of selective inhibition of the TGF- β receptor has already demonstrated significant inhibition of tumor proliferation and angiogenesis and may prove to be a valuable therapeutic agent for certain cancers.[65] Through a similar pathway, selective inhibition of TGF- β may prove to be a novel therapeutic tool to prevent or treat cyanotic children who have developed PAVMs following a SCPC.

Since PAVMs are a form of abnormal angiogenesis (Figure 4A), VEGF and its receptor were evaluated in lung specimens from 13 children after SCPC at the time of the Fontan procedure and were compared with 6 control subjects.[20] These biopsies showed a significantly increased expression of both VEGF and its receptor, suggesting that VEGF may be a mediator of angiogenesis in patients with SCPC.[20] The major shortcoming of this study was that it failed to control the influence of hypoxia on VEGF expression. While other cyanotic congenital heart disease subjects with chronic hypoxia do demonstrate increased serum levels of VEGF, it is not known whether they have elevated levels in their lung tissue.[51,66]

The identification of these factors and their inhibitors which are well established modulators of pro and anti-angiogenic pathways and their interactions with each other can be only studied through reliable animal models. This will then help to identify and isolate the fundamental mechanisms responsible for PAVM development.

Previous Research and Current Animal models

Although extensive mechanistic studies regarding PAVM development are lacking, several past studies have attempted to simulate and evaluate PAVM formation and progression in animals. A study in lambs showed that intrapulmonary shunting could be detected in normal fetal and neonatal lungs by contrast echocardiography, but not after one month of life.[67] These findings suggest that PAVMs may represent re-opening of pre-existing embryonic vascular channels that close during normal development of the lung.[68]

A unilateral SCPC model of a SVC to right pulmonary artery (RPA) connection was developed in sheep.[69] Pulmonary arteriovenous shunting was detectable by bubble contrast echocardiography in all animals by 8 weeks. Evaluation of lung biopsies demonstrated an increase in expression of type 1 and type 2 angiotensin II receptors, suggesting their involvement in the pathological vascular remodeling that occurs after SCPCs.[69] The same group studying the same model demonstrated a suppression of pulmonary angiotensin converting enzyme after a SCPC.[70] In a rat model of unilateral SCPC, the presence of PAVMs was documented at 11 months postoperatively in the lung devoid of hepatic venous perfusion.[71] This study showed a time-dependent increase in microvessel density in the shunted lung.[71] The limitations of this model are the prolonged postoperative course required to develop PAVMs, the small animal model which may not be clinically relevant, and the existence of a left SVC which could be a confounding source of hepatic venous blood.

A rabbit model of SCPC studied a SVC to RPA shunt and demonstrated the lack of hypoxic pulmonary vasoconstriction in animals with no hepatic venous flow.[72] A follow up study by the same group using a similar model compared complete absence of hepatic venous effluent to the right lung versus partial maintenance of hepatic flow to the right lung.[73] They found that the animals that had even a small amount of hepatic venous flow to the right lung continued to demonstrate hypoxic pulmonary vasoconstriction, which strongly suggests that hepatic venous effluent regulates pulmonary vascular physiology.[73]

A porcine model of a unidirectional Glenn was developed and PAVM formation demonstrated by 6 weeks.[74] This study demonstrated that the pulmonary artery endothelial cells (PAEC) converted to a “proangiogenic” phenotype with PAVM formation (Figure 4B). These phenotypic differences in the PAECs from lungs with PAVMs included increased proliferation, tubule formation, and gene expression of proangiogenic factors such as angiopoietin-1 and TIE2 pathway.[74] Another group developed a porcine model of a bidirectional SCPC in which the RPA was ligated or banded.[75] They demonstrated that residual antegrade pulsatile flow following a SCPC prevented PAVM formation.[75] These two studies evaluating porcine models of PAVMs following a SCPC support the hypothesis that one – or both – of two major etiologic factors stimulate PAVM development through modulation of angiogenic pathways.

A role for altered oxidative stress in the development of PAVMs has been suggested.[76] HIF-1 is known to be induced by hypoxia or ischemia.[77] Three groups were compared in an ovine model: SCPC, PA banding, and sham surgery with 30 minutes of RPA occlusion. The SCPC and PA banded cohorts had an increase in expression of oxidative stress genes; HIF-1 and HO-1 compared to the sham cohort. This suggested that PAVMs may result from hypoxia and increased oxidative stress. However, there were no differences in gene expression of these markers demonstrated in a porcine model of PAVMs.[74] While hypoxia may indeed play a role in PAVM development in true single ventricle physiology clinically, this may not be demonstrable in the currently established SCPC animal models, which do not have significant hypoxemia in the post-SCPC setting. A potential explanation for these findings is that all animal models studied to date use SCPC within the context of two-ventricle physiology where normal cellular and tissue oxygenation may be maintained,. Therefore, the lack of significant hypoxia in these models fails to precisely recapitulate the clinical SCPC scenario and may not adequately address the role of oxidative stress as an etiologic mechanism of PAVM formation.

Both, experimentally in animal models, and clinically, antegrade pulsatile flow has been shown to reverse or retard the formation of PAVMs following SCPC.[75,78] These findings taken together support the hypothesis that the absence of hepatic venous blood flow and the lack of pulsatility act in concert to modify various angiogenesis pathways to stimulate PAVM development.

Conclusions and Future Directions

Although the Fontan procedure provides short-term relief of cyanosis and symptoms, it is now known to lead the patient and physician down an inexorable path of late complications refractory to any medical or surgical treatment. Improving the durability and longevity of the SCPC could delay or potentially eliminate the need for the Fontan procedure. PAVMs which are a form of aberrant angiogenesis limit the long-term durability and potential of the SCPC. Associations between a few key angiogenic pathways and PAVMs have been detected.

Further investigation of the role some of these proteinases play in preventing the abnormal angiogenesis that result in PAVMs, or in maintaining angiogenic “homeostasis”, may shed more light on the development of better therapeutic options for this debilitating condition. It

is possible that the MMPs can act as “angiostatin-converting” enzymes. The specificity, efficiency, detailed cleavage sites, and biological activity of these angiogenesis-inhibitor fragments remain to be determined.[57] The efficiency of these proteinases in the production of angiostatin-like fragments may in turn be subject to other regulatory factors, such as their rate of inactivation by endogenous inhibitors. TGF- β signaling and its receptors play a pivotal role in the control of angiogenesis and provide an additional biologic pathway, which may be modulated to attenuate and target PAVMs.[64] The promotion of angiogenesis through the well established angiopoietin-1/TIE2 pathway and its association with PAVM development following SCPC creation provides another mechanism through which medical therapies for PAVMs may be investigated.[74]

Identification of these fundamental molecular mechanisms and pathways linked to the hepatic regulation of pulmonary vascular development may help develop alternative therapeutic options and improve long-term quality of life for children with single ventricle physiology.

Expert Commentary

In the current era the Fontan completion is and will remain the final stage in the surgical palliation of children with single ventricle disease. A large proportion of these patients will continue to present with late complications of systemic venous hypertension. Among these patients, a large majority are not heart transplant candidates, and ineffective medical therapy does little to retard the steady decline these patients experience until death. The patients that do qualify for heart transplant often tend to be in an extremely high-risk category. In the absence of PAVMs the SCPC does provide better exercise capacity with less morbidity and mortality than the Fontan. Determination of the key mechanisms orchestrating this angiogenic process would help to elucidate therapeutic targets to prevent or reverse PAVM formation.

Five-year view

Many centers are now seeing failing Fontan patients often as young adults with progressive complications of systemic venous hypertension. Sadly, many of these patients are not eligible for heart transplantation and die from progressive cyanosis, liver failure and heart failure. The recognition of the need for better palliation for children with single ventricle disease makes it imperative that we determine alternative surgical pathways. Past clinical and experimental studies have established the utility of the SCPC and identified PAVM formation as the major limitation to its long-term durability. It is therefore important to investigate the mechanisms of PAVM development and methods to inhibit or reverse them. There are a few groups developing animal models of SCPC with PAVMs for this reason. Preliminary angiogenic pathways, biomolecules and their receptors associated with PAVM formation have been identified. Further focus and study of the safety and efficacy of these factors in preventing and reversing PAVMs need to be established in animal models of SCPC. An observational clinical study has already identified lower levels of an angiogenesis inhibitor, endostatin in patients following a SCPC.[22] Additional mechanistic studies will likely determine the role of key angiogenic molecules critical to PAVM development in the

setting of SCPC. These findings will promote the development of novel drugs and therapeutic agents used to prevent or treat PAVMs.

References

1. Glenn WW, Patino JF. Circulatory by-pass of the right heart. I. Preliminary observations on the direct delivery of vena caval blood into the pulmonary arterial circulation; azygos vein-pulmonary artery shunt. *Yale J Biol Med*. 1954; 27(3):147–151. [PubMed: 13226952]
2. Glenn WW. Circulatory bypass of the right side of the heart. IV. Shunt between superior vena cava and distal right pulmonary artery; report of clinical application. *N Engl J Med*. 1958; 259(3):117–120. [PubMed: 13566431]
3. Castaneda AR. From Glenn to Fontan. A continuing evolution. *Circulation*. 1992; 86(5 Suppl):II80–84. [PubMed: 1424039]
4. Jonas RA. Indications and timing for the bidirectional Glenn shunt versus the fenestrated Fontan circulation. *J Thorac Cardiovasc Surg*. 1994; 108(3):522–524. [PubMed: 7521499]
5. Hirsch JC, Goldberg C, Bove EL, et al. Fontan operation in the current era: a 15-year single institution experience. *Ann Surg*. 2008; 248(3):402–410. [PubMed: 18791360]
6. Fontan F, Kirklin JW, Fernandez G, et al. Outcome after a "perfect" Fontan operation. *Circulation*. 1990; 81(5):1520–1536. [PubMed: 2331765]
7. Stephenson EA, Lu M, Berul CI, et al. Arrhythmias in a contemporary fontan cohort: prevalence and clinical associations in a multicenter cross-sectional study. *J Am Coll Cardiol*. 56(11):890–896. [PubMed: 20813285]
8. Silvilairat S, Cabalka AK, Cetta F, Grogan M, Hagler DJ, O'Leary PW. Protein-losing enteropathy after the Fontan operation: associations and predictors of clinical outcome. *Congenit Heart Dis*. 2008; 3(4):262–268. [PubMed: 18715460]
9. Mascio CE, Austin EH 3rd. Pleural effusions following the Fontan procedure. Current opinion in pulmonary medicine. 2010; 16(4):362–366. [PubMed: 20410822]
10. Khairy P, Fernandes SM, Mayer JE Jr. et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation*. 2008; 117(1):85–92. [PubMed: 18071068]
11. Gewillig MH, Lundstrom UR, Bull C, Wyse RK, Deanfield JE. Exercise responses in patients with congenital heart disease after Fontan repair: patterns and determinants of performance. *J Am Coll Cardiol*. 1990; 15(6):1424–1432. [PubMed: 2329245]
12. Paridon SM, Mitchell PD, Colan SD, et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. *J Am Coll Cardiol*. 2008; 52(2):99–107. [PubMed: 18598887]
13. Bridges ND, Jonas RA, Mayer JE, Flanagan MF, Keane JF, Castaneda AR. Bidirectional cavopulmonary anastomosis as interim palliation for high-risk Fontan candidates. Early results. *Circulation*. 1990; 82(5 Suppl):IV170–176. [PubMed: 1699686]
14. Yeh T Jr. Williams WG, McCrindle BW, et al. Equivalent survival following cavopulmonary shunt: with or without the Fontan procedure. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 1999; 16(2):111–116. [PubMed: 10485406]
15. Day RW, Etheridge SP, Veasy LG, et al. Single ventricle palliation: greater risk of complications with the Fontan procedure than with the bidirectional Glenn procedure alone. *International journal of cardiology*. 2006; 106(2):201–210. [PubMed: 16321693]
16. McFaul RC, Tajik AJ, Mair DD, Danielson GK, Seward JB. Development of pulmonary arteriovenous shunt after superior vena cava-right pulmonary artery (Glenn) anastomosis. Report of four cases. *Circulation*. 1977; 55(1):212–216. [PubMed: 830212]
17. Vettukattil JJ, Slavik Z, Lamb RK, et al. Intrapulmonary arteriovenous shunting may be a universal phenomenon in patients with the superior cavopulmonary anastomosis: a radionuclide study. *Heart*. 2000; 83(4):425–428. [PubMed: 10722543]

18. Srivastava D, Preminger T, Lock JE, et al. Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. *Circulation*. 1995; 92(5): 1217–1222. [PubMed: 7648668]
19. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med*. 1998; 158(2):643–661. [PubMed: 9700146]
20. Starnes SL, Duncan BW, Kneebone JM, et al. Angiogenic proteins in the lungs of children after cavopulmonary anastomosis. *J Thorac Cardiovasc Surg*. 2001; 122(3):518–523. [PubMed: 11547304]
21. Jabbour MN, Elder JB, Samuelson CG, et al. Aberrant angiogenic characteristics of human brain arteriovenous malformation endothelial cells. *Neurosurgery*. 2009; 64(1):139–146. discussion 146–138. [PubMed: 19145162]
22. Field-Ridley A, Heljasvaara R, Pihlajaniemi T, et al. Endostatin, an inhibitor of angiogenesis, decreases after bidirectional superior cavopulmonary anastomosis. *Pediatr Cardiol*. 2013; 34(2): 291–295. [PubMed: 22961274]
23. Kopf GS, Laks H, Stansel HC, Hellenbrand WE, Kleinman CS, Talner NS. Thirty-year follow-up of superior vena cava-pulmonary artery (Glenn) shunts. *J Thorac Cardiovasc Surg*. 1990; 100(5): 662–670. discussion 670–661. [PubMed: 1700228]
24. Boshier LH Jr, Blake DA, Byrd BR. An analysis of the pathologic anatomy of pulmonary arteriovenous aneurysms with particular reference to the applicability of local excision. *Surgery*. 1959; 45(1):91–104. [PubMed: 13624986]
25. McMullan DM, Reddy VM, Gottliebson WM, et al. Morphological studies of pulmonary arteriovenous shunting in a lamb model of superior cavopulmonary anastomosis. *Pediatric cardiology*. 2008; 29(4):706–712. [PubMed: 18043856]
26. White RI Jr, Mitchell SE, Barth KH, et al. Angioarchitecture of pulmonary arteriovenous malformations: an important consideration before embolotherapy. *AJR Am J Roentgenol*. 1983; 140(4):681–686. [PubMed: 6601370]
27. Sloan RD, Cooley RN. Congenital pulmonary arteriovenous aneurysm. *Am J Roentgenol Radium Ther Nucl Med*. 1953; 70(2):183–210.
28. Marianeschi SM, McElhinney DB, Reddy VM. Pulmonary arteriovenous malformations in and out of the setting of congenital heart disease. *Ann Thorac Surg*. 1998; 66(2):688–691. [PubMed: 9725455]
29. Laberge JM, Brandt ML, Lebecque P, et al. Reversal of cirrhosis-related pulmonary shunting in two children by orthotopic liver transplantation. *Transplantation*. 1992; 53(5):1135–1138. [PubMed: 1585477]
30. Kawashima Y. Cavopulmonary shunt and pulmonary arteriovenous malformations. *The Annals of thoracic surgery*. 1997; 63(4):930–932. [PubMed: 9124964]
31. Clement B, Musso O, Lietard J, Theret N. Homeostatic control of angiogenesis: A newly identified function of the liver? *Hepatology*. 1999; 29(3):621–623. [PubMed: 10051458]
32. Knight WB, Mee RB. A cure for pulmonary arteriovenous fistulas? *Ann Thorac Surg*. 1995; 59(4): 999–1001. [PubMed: 7695433]
33. Shah MJ, Rychik J, Fogel MA, Murphy JD, Jacobs ML. Pulmonary AV malformations after superior cavopulmonary connection: resolution after inclusion of hepatic veins in the pulmonary circulation. *Ann Thorac Surg*. 1997; 63(4):960–963. [PubMed: 9124971]
34. McElhinney DB, Marx GR, Newburger JW. Congenital portosystemic venous connections and other abdominal venous abnormalities in patients with polysplenia and functionally univentricular heart disease: a case series and literature review. *Congenit Heart Dis*. 2011; 6(1):28–40. [PubMed: 21269410]
35. McElhinney DB, Marx GR, Marshall AC, Mayer JE, Del Nido PJ. Cavopulmonary pathway modification in patients with heterotaxy and newly diagnosed or persistent pulmonary arteriovenous malformations after a modified Fontan operation. *J Thorac Cardiovasc Surg*. 2011; 141(6):1362–1370. e1361. [PubMed: 21146835]
36. Hickey EJ, Alghamdi AA, Elmi M, et al. Systemic arteriovenous fistulae for end-stage cyanosis after cavopulmonary connection: a useful bridge to transplantation. *J Thorac Cardiovasc Surg*. 2010; 139(1):128–134. e121. [PubMed: 19922957]

37. Stoller JK, Lange PA, Westveer MK, Carey WD, Vogt D, Henderson JM. Prevalence and reversibility of the hepatopulmonary syndrome after liver transplantation. The Cleveland Clinic experience. *West J Med.* 1995; 163(2):133–138. [PubMed: 7571560]
38. Stoller JK, Moodie D, Schiavone WA, et al. Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis after liver transplantation. *Hepatology.* 1990; 11(1):54–58. [PubMed: 2295472]
39. Kwon BS, Bae EJ, Kim GB, Noh CI, Choi JY, Yun YS. Development of bilateral diffuse pulmonary arteriovenous fistula after Fontan procedure: is there nonhepatic factor? *Ann Thorac Surg.* 2009; 88(2):677–680. [PubMed: 19632446]
40. Magee AG, McCrindle BW, Mawson J, Benson LN, Williams WG, Freedom RM. Systemic venous collateral development after the bidirectional cavopulmonary anastomosis. Prevalence and predictors. *Journal of the American College of Cardiology.* 1998; 32(2):502–508. [PubMed: 9708483]
41. Lamberti JJ, Spicer RL, Waldman JD, et al. The bidirectional cavopulmonary shunt. *J Thorac Cardiovasc Surg.* 1990; 100(1):22–29. discussion 29–30. [PubMed: 1694938]
42. Moore JW, Kirby WC, Madden WA, Gaither NS. Development of pulmonary arteriovenous malformations after modified Fontan operations. *J Thorac Cardiovasc Surg.* 1989; 98(6):1045–1050. [PubMed: 2586119]
43. Dines DE, Seward JB, Bernatz PE. Pulmonary arteriovenous fistulas. *Mayo Clinic proceedings.* Mayo Clinic. 1983; 58(3):176–181.
44. Chang RK, Alejos JC, Atkinson D, et al. Bubble contrast echocardiography in detecting pulmonary arteriovenous shunting in children with univentricular heart after cavopulmonary anastomosis. *J Am Coll Cardiol.* 1999; 33(7):2052–2058. [PubMed: 10362213]
45. Bernstein HS, Brook MM, Silverman NH, Bristow J. Development of pulmonary arteriovenous fistulae in children after cavopulmonary shunt. *Circulation.* 1995; 92(9 Suppl):II309–314. [PubMed: 7586429]
46. Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook MM. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. *The American journal of cardiology.* 2002; 89(3):281–285. [PubMed: 11809429]
47. Remy J, Remy-Jardin M, Wattinne L, Deffontaine C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. *Radiology.* 1992; 182(3):809–816. [PubMed: 1535899]
48. Silverman JM, Julien PJ, Herfkens RJ, Pelc NJ. Magnetic resonance imaging evaluation of pulmonary vascular malformations. *Chest.* 1994; 106(5):1333–1338. [PubMed: 7956380]
49. McElhinney DB, Kreutzer J, Lang P, Mayer JE Jr, del Nido PJ, Lock JE. Incorporation of the hepatic veins into the cavopulmonary circulation in patients with heterotaxy and pulmonary arteriovenous malformations after a Kawashima procedure. *The Annals of thoracic surgery.* 2005; 80(5):1597–1603. [PubMed: 16242423]
50. Mott AR, Spray TL, Bridges ND. Heart/single-lung transplant for a "failed Fontan" with pulmonary A-V malformation. *The Annals of thoracic surgery.* 1999; 67(3):841–843. [PubMed: 10215245]
51. Waleh NS, Brody MD, Knapp MA, et al. Mapping of the vascular endothelial growth factor-producing hypoxic cells in multicellular tumor spheroids using a hypoxia-specific marker. *Cancer Res.* 1995; 55(24):6222–6226. [PubMed: 8521417]
52. Musso O, Rehn M, Saarela J, et al. Collagen XVIII is localized in sinusoids and basement membrane zones and expressed by hepatocytes and activated stellate cells in fibrotic human liver. *Hepatology.* 1998; 28(1):98–107. [PubMed: 9657102]
53. Raum D, Marcus D, Alper CA, Levey R, Taylor PD, Starzl TE. Synthesis of human plasminogen by the liver. *Science.* 1980; 208(4447):1036–1037. [PubMed: 6990488]
54. Gately S, Twardowski P, Stack MS, et al. The mechanism of cancer-mediated conversion of plasminogen to the angiogenesis inhibitor angiostatin. *Proc Natl Acad Sci U S A.* 1997; 94(20):10868–10872. [PubMed: 9380726]

55. Lijnen HR, Uguw F, Bini A, Collen D. Generation of an angiostatin-like fragment from plasminogen by stromelysin-1 (MMP-3). *Biochemistry*. 1998; 37(14):4699–4702. [PubMed: 9548733]
56. Dong Z, Kumar R, Yang X, Fidler IJ. Macrophage-derived metalloelastase is responsible for the generation of angiostatin in Lewis lung carcinoma. *Cell*. 1997; 88(6):801–810. [PubMed: 9118223]
57. Patterson BC, Sang QA. Angiostatin-converting enzyme activities of human matrilysin (MMP-7) and gelatinase B/type IV collagenase (MMP-9). *The Journal of biological chemistry*. 1997; 272(46):28823–28825. [PubMed: 9360944]
58. O'Reilly MS, Boehm T, Shing Y, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell*. 1997; 88(2):277–285. [PubMed: 9008168]
59. Zhang J, Luo B, Tang L, et al. Pulmonary angiogenesis in a rat model of hepatopulmonary syndrome. *Gastroenterology*. 2009; 136(3):1070–1080. [PubMed: 19109954]
60. Felbor U, Dreier L, Bryant RA, Ploegh HL, Olsen BR, Mothes W. Secreted cathepsin L generates endostatin from collagen XVIII. *EMBO J*. 2000; 19(6):1187–1194. [PubMed: 10716919]
61. Ferreras M, Felbor U, Lenhard T, Olsen BR, Delaisse J. Generation and degradation of human endostatin proteins by various proteinases. *FEBS Lett*. 2000; 486(3):247–251. [PubMed: 11119712]
62. Zatterstrom UK, Felbor U, Fukai N, Olsen BR. Collagen XVIII/endostatin structure and functional role in angiogenesis. *Cell Struct Funct*. 2000; 25(2):97–101. [PubMed: 10885579]
63. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet*. 1994; 8(4):345–351. [PubMed: 7894484]
64. Basson CT, Kocher O, Basson MD, Asis A, Madri JA. Differential modulation of vascular cell integrin and extracellular matrix expression in vitro by TGF-beta 1 correlates with reciprocal effects on cell migration. *Journal of cellular physiology*. 1992; 153(1):118–128. [PubMed: 1522126]
65. Wan X, Li ZG, Yingling JM, et al. Effect of transforming growth factor beta (TGF-beta) receptor I kinase inhibitor on prostate cancer bone growth. *Bone*. 2011
66. Starnes SL, Duncan BW, Kneebone JM, et al. Vascular endothelial growth factor and basic fibroblast growth factor in children with cyanotic congenital heart disease. *J Thorac Cardiovasc Surg*. 2000; 119(3):534–539. [PubMed: 10694614]
67. McMullan DM, Hanley FL, Cohen GA, Portman MA, Riemer RK. Pulmonary arteriovenous shunting in the normal fetal lung. *J Am Coll Cardiol*. 2004; 44(7):1497–1500. [PubMed: 15464334]
68. Pandurangi UM, Shah MJ, Murali R, Cherian KM. Rapid onset of pulmonary arteriovenous malformations after cavopulmonary anastomosis. *Ann Thorac Surg*. 1999; 68(1):237–239. [PubMed: 10421150]
69. Malhotra SP, Reddy VM, Thelitz S, et al. Cavopulmonary anastomosis induces pulmonary expression of the angiotensin II receptor family. *J Thorac Cardiovasc Surg*. 2002; 123(4):655–660. [PubMed: 11986592]
70. Malhotra SP, Riemer RK, Thelitz S, He YP, Hanley FL, Reddy VM. Superior cavopulmonary anastomosis suppresses the activity and expression of pulmonary angiotensin-converting enzyme. *J Thorac Cardiovasc Surg*. 2001; 122(3):464–469. [PubMed: 11547295]
71. Starnes SL, Duncan BW, Fraga CH, et al. Rat model of pulmonary arteriovenous malformations after right superior cavopulmonary anastomosis. *American journal of physiology. Heart and circulatory physiology*. 2002; 283(5):H2151–2156. [PubMed: 12384493]
72. Ikai A, Shirai M, Nishimura K, et al. Hypoxic pulmonary vasoconstriction disappears in a rabbit model of cavopulmonary shunt. *J Thorac Cardiovasc Surg*. 2004; 127(5):1450–1457. [PubMed: 15116007]
73. Ikai A, Shirai M, Nishimura K, et al. Maintenance of pulmonary vasculature tone by blood derived from the inferior vena cava in a rabbit model of cavopulmonary shunt. *J Thorac Cardiovasc Surg*. 2005; 129(1):199–206. [PubMed: 15632843]

74. Kavarana MN, Mukherjee R, Eckhouse SR, et al. Pulmonary artery endothelial cell phenotypic alterations in a large animal model of pulmonary arteriovenous malformations after the Glenn shunt. *Ann Thorac Surg.* 2013; 96(4):1442–1449. [PubMed: 23968766]
75. Henaine R, Vergnat M, Mercier O, et al. Hemodynamics and arteriovenous malformations in cavopulmonary anastomosis: the case for residual antegrade pulsatile flow. *J Thorac Cardiovasc Surg.* 2013; 146(6):1359–1365. [PubMed: 23490250]
76. Malhotra SP, Reddy VM, Thelitz S, et al. The role of oxidative stress in the development of pulmonary arteriovenous malformations after cavopulmonary anastomosis. *J Thorac Cardiovasc Surg.* 2002; 124(3):479–485. [PubMed: 12202863]
77. Semenza GL. HIF-1 and human disease: one highly involved factor. *Genes & development.* 2000; 14(16):1983–1991. [PubMed: 10950862]
78. Gerelli S, Boulitrop C, Van Steenberghe M, et al. Bidirectional cavopulmonary shunt with additional pulmonary blood flow: a failed or successful strategy? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2012; 42(3):513–519. [PubMed: 22368190]

Key Issues

- Children with single ventricle disease undergo standard staged surgical palliation comprising Norwood, superior cavopulmonary connection (SCPC, a.k.a. Glenn shunt), and culminating with a Fontan procedure. Unfortunately, Fontan physiology is fraught with medium-term and long-term complications related to lower body systemic venous hypertension and – in the absence of complications, such as development of pulmonary arteriovenous malformations (PAVMs) – it may be clinically beneficial to leave children with the SCPC.
- The development – and progression – of PAVMs after the SCPC results in progressive hypoxia and cyanosis.
- Two major theories that may explain the etiology of PAVMs: 1. the absence of hepatic venous effluent in the venous return to the lung receiving blood through the SCPC, and 2. lack of pulsatile flow to the lungs directly receiving venous blood.
- PAVMs likely form due to aberrant angiogenesis. Key angiogenic factors and pathways have been associated with PAVM development in animal models of SCPC.
- Identifying mechanistic (cause-effect) roles for these angiogenic pathways in PAVM development could lead to the development of therapies to prevent or reverse PAVMs and improve the durability of the SCPC.
- Potential benefits of targeted therapy could include the delaying and/or elimination of the Fontan procedure, which may lead to improvement in the quality of life and longevity of children with single ventricle congenital heart disease.

Figure 1.

Role of the liver in the development of pulmonary arteriovenous malformations (PAVMs) after superior cavopulmonary connection (SCPC): Isolation of the lungs from hepatic venous return results in a reduced exposure to angiogenesis inhibitors, increased expression of pro-angiogenic substances and PAVM development. VEGF: Vascular endothelial growth factor, which is an angiogenic factor.

“Reprinted from: Pulmonary arteriovenous malformations after cavopulmonary anastomosis, Vol 76, Author(s): Brian W. Duncan, MD, Shailesh Desai, PhD, Pages No.1759-1766, Copyright (2003), with permission from Elsevier: License number 2845581266282, date: Feb 10, 2012.

Figure 2.

Schematic comparing hepatic venous flow before and after the superior cavopulmonary connection (Glenn shunt). A. In the normal circulation, deoxygenated venous return (blue lines) from the superior vena cava (SVC) and the inferior vena cava (IVC, which contains hepatic effluent – indicated as green “stars”) mix in the right heart before being pumped through to both lungs. The oxygenated blood (red lines) is then returned to the left heart for systemic distribution. B. As depicted schematically for a unidirectional Glenn shunt, venous return from the SVC is redirected to the right lung, bypassing the right heart. This diversion of flow causes the right lung to receive steady (non-pulsatile) flow that is devoid of the hepatic effluent. Initially, normal oxygenation of blood occurs. C. However, with the development of PAVMs as late sequelae to the Glenn, where venous blood is shunted through low resistance conduits and does not get oxygenated, cyanosis can become manifest (purple line).

Figure 3.

An angiogram showing diffuse PAVMs of the right lung 8 months after a SCPC (arrow).

“Reprinted from: Pulmonary arteriovenous malformations after cavopulmonary anastomosis, Vol 76, Author(s): Brian W. Duncan, MD, Shailesh Desai, PhD, Pages No. 1759-1766, Copyright (2003), with permission from Elsevier: License number 2845581266282, date: Feb 10, 2012. Fig 1. Selective injection of right lower lobe pulmonary artery in a patient with diffuse PAVMs.

Figure 4.

A. Angiogenic and anti-angiogenic factors that potentially contribute to angiogenesis culminating in PAVM formation in the setting of SCPC. The angiogenic factors, angiopoietin-1, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)- β , matrix metalloproteinases (MMPs), and receptors for angiopoietin-1 (TIE-2), hypoxia inducible factor (HIF)-1 α , and heme oxygenase (HO)-1 have been reported to be increased in the setting of SCPC. Conversely, the abundance of anti-angiogenic factors (angiostatin and endostatin) are reduced culminating in a strong angiogenic signal. B. Paracrine signaling between the endothelial and smooth muscle cells as well as signaling from circulating factors likely culminate in PAVM formation. For example, angiopoietin-1 can be synthesized and released from the smooth muscle cells, which would then bind to TIE-2 receptors that are found predominantly on the endothelial cells. This paracrine signaling loop may be evoked through changes in the biomechanical forces and biochemical milieu that occur following the SCPC.