The Challenges of the Fontan Circulation

Aortopulmonary Collateral Flow: Natural Adaptation or Harmful Development?

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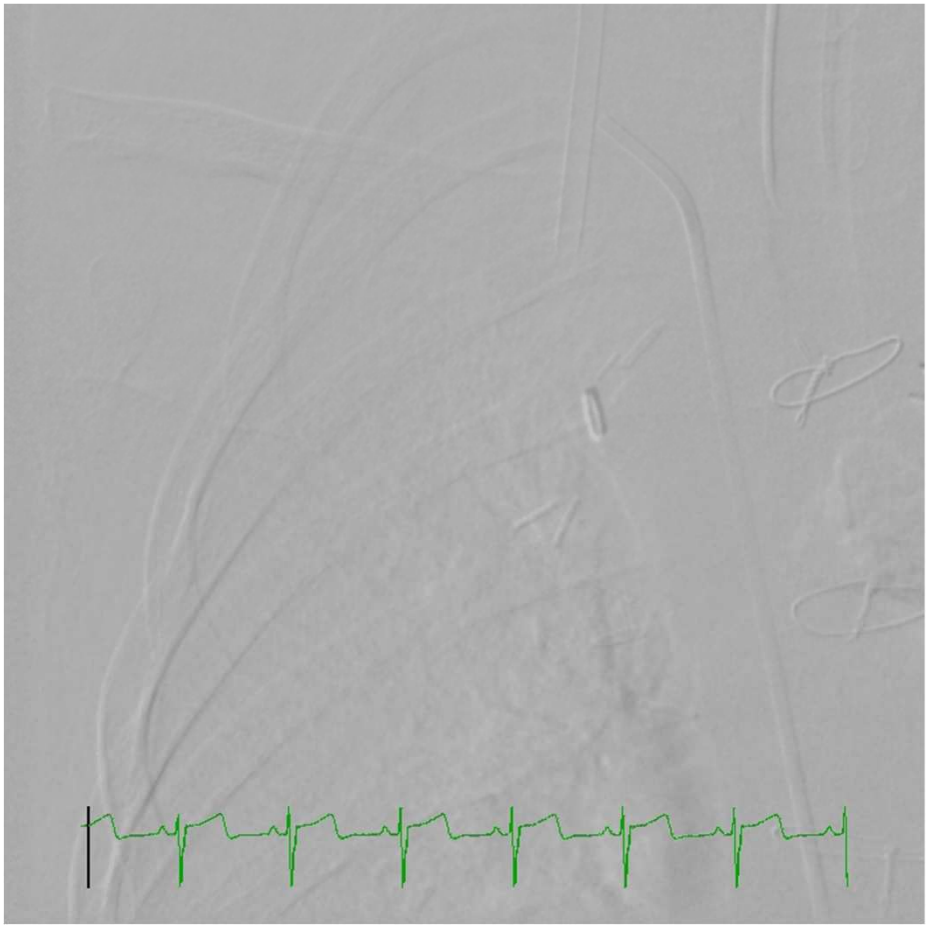
Collaterals



Do collaterals matter?

Extent of Aortopulmonary Collateral Blood Flow as a Risk Factor for Fontan Operations

Factors Influencing Perioperative Morbidity During Palliation of the Univentricular Heart

Congenital Heart Disease

Aortopulmonary collateral vessels and prolonged pleural effusions after modified Fontan procedures

Importance of Acquired Systemic-to-Pulmonary Collaterals in the Fontan Operation

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Background. Children with chronic cyanotic heart disease often develop systemic-to-pulmonary collateral arteries that can be deleterious at the time of a Fontan procedure due to excessive pulmonary blood flow. We therefore occlude all significant collaterals during cardiac catheterization.

Methods. From June 1993 to May 1998, 93 children aged 1.5 to 15.8 years (median 2.5 years) underwent a fenestrated lateral tunnel Fontan procedure. Eighty-nine (96%) had a previous bidirectional Glenn anastomosis, including 31 (33%) with a Norwood procedure.

Results. Preoperatively, 33 children (35%) required occlusion of 1 to 11 (mean 3.6) collateral vessels. Two of the three perioperative deaths (operative survival 97%) were due to excessive pulmonary blood flow from unrecognized collaterals in one and uncontrollable collaterals in the other. Postoperatively, 19 children (20%) required coil occlusion of 1 to 21 (mean 5.6) collaterals for elevated pulmonary artery pressures, heart failure, or prolonged chest tube drainage. Duration of inotropic support, postoperative ventilation, intensive care unit stay, and postoperative hospitalization were all significantly longer in the patients who had postoperative occlusion of collaterals. On follow-up of 2 to 67 months (mean 35 months), there have been four late deaths (two infections, two heart failures). 6 patients underwent successful cardiac transplantation for refractory heart failure. All 8 patients with ventricular failure required occlusion of significant collaterals postoperatively.

Conclusions. Hemodynamically significant collaterals are not uncommon in Fontan candidates, and aggressive control can result in good operative and medium-term survival. After the Fontan, significant collaterals may be a marker for eventual cardiac failure because 8 of 18 patients requiring postoperative coils went on to transplantation or died of heart failure.

(Ann Thorac Surg 1999;68:969–75)

The Fontan procedure with its various modifications currently is the treatment of choice for children with single-ventricle physiology. Advances over the past decade have improved both early and late outcomes despite the application of this procedure to patients with increasingly complex anatomy [1].

These children with long-standing cyanotic heart disease can develop systemic-to-pulmonary artery collateral vessels [2–6]. Some studies have shown that patients with these abnormal vessels have prolonged pleural effusions after the Fontan procedure [7, 8] and can even have a higher mortality [9]. With this in mind, since June 1993, we have aggressively searched for these collaterals and attempted to occlude all significant collaterals at the time of cardiac catheterization. This paper reviews the results of this policy in 93 consecutive children undergoing a Fontan procedure.

Patients and Methods

From June 1993 to May 1998, 93 consecutive children underwent a modified Fontan procedure by a single surgeon (K.R.K.). Ages at time of operation ranged from 1.5 to 15.8 years (mean 3.3 ± 2.3 years, median 2.5 years). The principal underlying diagnoses are shown in Table 1. Thirty-one children (33%) had undergone a Norwood procedure in infancy. Fourteen children had previous pulmonary artery banding, including 6 with repair of an aortic coarctation. A previous Blalock-Taussig or central shunt had been performed in 44 patients (47%), excluding the children with a Norwood procedure. Eighty-nine (96%) had a previous bidirectional Glenn anastomosis at 1.2 ± 1.4 years of age (median 9.7 months). The time interval from the bidirectional Glenn anastomosis to the Fontan procedure was 1.7 ± 0.7 years (range 3 months to 4.4 years). All four children without a previous bidirectional Glenn anastomosis were older at the time of the modified Fontan procedure (range 6.5 to 15.8 years).

Cardiac Catheterization

All children had preoperative hemodynamic investigation by cardiac catheterization with angiography. Attempts were made to identify significant systemic-to-pulmonary artery collaterals by aortogram as well as selective injections into the internal mammary, intercostal, bronchial, and chest wall arteries as necessary. Five criteria were used to determine if a systemic to pulmonary collateral artery was significant. First was direct opacification of a pulmonary artery segment with con-

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HARM

Aortopulmonary Collateral Flow in the Fontan Patient: Does It Matter?

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Catheterization and Cardiovascular Interventions 65:427–433 (2005)

PEDIATRIC AND CONGENITAL HEART DISEASE

Original Studies

Transcatheter Occlusion of Aortopulmonary Shunts During Single-Ventricle Surgical Palliation

D. Scott Lim,[1]* MD, Joseph N. Graziano,[2] MD, FSCAI, Albert P. Rocchini,[2] MD, and Thomas R. Lloyd,[2] MD, FSCAI

Development of aortopulmonary collaterals during the course of surgical palliation for single-ventricular anatomy has been linked to adverse outcomes following Fontan palliation. We investigated the hemodynamic significance of aortopulmonary collaterals during preaurgical cardiac catheterization of patients with single-ventricle surgically palliated anatomy. Thermal indicator dilution studies were performed to determine degree of shunt. A total of 52 patients were studied and the data were analyzed. Measurements by thermal indicator dilution correlated significantly with qualitative angiographic grading of aortopulmonary collaterals. However, the hemodynamic significance of these aortopulmonary collaterals, as measured by thermal indicator dilution, did not correlate with postoperative outcome variables. This study demonstrated that thermal indicator dilution measurement holds promise for hemodynamically quantifying the significance of aortopulmonary shunts in surgically palliated single-ventricular patients. However, the degree of recirculation from aortopulmonary collaterals does not correlate with outcome after Fontan surgery in this patient cohort.

Key words: aortopulmonary collaterals; Fontan; coil embolization

INTRODUCTION

Since the first reports of surgical palliation for a single-ventricular anatomy by Fontan et al. [1,2] in 1971, multiple subsequent studies have documented the improvement in surgical technique as well as outcomes following surgical palliation [3–6]. However, significant morbidity following surgical palliation continues to persist in a subgroup of patients, and further studies have investigated different factors contributing to that morbidity [5,7]. As a consequence of surgical palliation of single-ventricular anatomy, significant aortopulmonary collateral vessels can develop [8] and have been described in nearly 85% of such patients [7]. These aortopulmonary collaterals have been implicated in adverse surgical outcomes [9]. Previously, only qualitative assessment by angiography of the degree of shunt from aortopulmonary collaterals has been performed [8]. Additionally, because of the concern of adverse effects of these aorta pulmonary collaterals on the post-Fontan physiology, the procedure of transcatheter coil occlusion of these collaterals has evolved [10–12].

Despite the lack of significant physiologic data to determine the efficacy of coil occlusion of aortopulmonary collaterals, this practice has become frequent in many institutions [7,13,14]. Therefore, the hypotheses of this present study were threefold: that the technique of thermal indicator dilution could be used to quantify small shunts caused by aortopulmonary collateral circulation; that the degree of this shunt would correlate with clinical outcome after the Fontan surgery; and that transcatheter coil occlusion of these collaterals would affect clinical outcome after surgery.

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NO EFFECT

Incidence and Implications of Systemic to Pulmonary Collaterals After Bidirectional Cavopulmonary Anastomosis

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Background. Systemic to pulmonary arterial collaterals often develop after bidirectional cavopulmonary anastomosis (BCPA). It has been proposed that such collaterals may be related to perioperative outcome and duration of effusions after the modified Fontan procedure. However, the incidence and significance of collaterals after BCPA remain uncertain.

Methods. To evaluate risk factors for, and significance of, such collaterals, we reviewed angiographic and clinical data for all 76 patients who underwent BCPA between January 1990 and June 1996 and had follow-up catheterization during or before 1997.

Results. The median age at BCPA was 10 months, and the median duration from BCPA to follow-up catheterization was 18 months. Arterial collaterals were detected on follow-up catheterization in 45 patients (59%). Factors associated with collateral development included a prior right-sided systemic-to-pulmonary arterial shunt, lower pre-BCPA end-diastolic ventricular pressure and pulmonary vascular resistance, and use and duration of cardiopulmonary bypass during the BCPA operation. Fourteen of the 45 patients (30%) underwent coil embolization of the collaterals. Forty-three patients have undergone extracardiac conduit Fontan, with 1 early and 1 late death. Collaterals were present in 22 of these patients, 7 of whom underwent pre-Fontan embolization. The duration from BCPA to Fontan was longer in patients with collaterals, but these patients were not more likely to have prolonged effusions than those without, and the duration of tube thoracostomy was significantly shorter in patients with collaterals. Embolization of collaterals did not affect the duration of effusions.

Conclusions. Systemic-to-pulmonary arterial collaterals are common after BCPA. In contrast to prior reports, collaterals were not associated with a higher incidence of prolonged effusions after the Fontan procedure in our experience, and did not correlate with poor outcome.

(Ann Thorac Surg 2000;69:1222–8)

A bidirectional cavopulmonary anastomosis (BCPA) has become a standard component of the staged palliation of functionally univentricular heart disease at many centers [1, 2]. The principle of BCPA is to provide a controlled low pressure source of pulmonary blood flow that has growth potential and relieves the volume load on a functionally univentricular heart [3]. Although a cavopulmonary shunt is believed to confer a number of benefits to patients undergoing staged palliation of univentricular heart disease, patients with a pulmonary circulation dependent on a BCPA can develop various problems [4–8], including systemic-to-pulmonary collateral arteries [8]. In this setting, systemic-to-pulmonary arterial collaterals are of unknown physiologic and clinical significance [7, 10–13]. We reviewed our recent experience in order to characterize the incidence of systemic-to-pulmonary collateral arteries after BCPA, factors associated with their development, their clinical significance, and the role of transcatheter embolization in their management.

Patients and Methods

Patients and Previous Procedures

Seventy-six patients who had a bidirectional superior cavopulmonary anastomosis performed at our institution between January 1990 and June 1996, underwent cardiac catheterization and angiography before and after BCPA (follow-up angiography in 1997 or before), and had both angiograms available for review. Diagnoses are summarized in Table 1. BCPA was the first surgical procedure performed in 16 patients, while the remaining 60 had undergone 1 (n = 44) or more (n = 16) prior procedures. In 45 patients (59%), 1 (n = 39) or more (n = 6) systemic-to-pulmonary artery shunts had been performed previously, and connected to the right pulmonary artery in 35 patients, the left pulmonary artery in 13, and the central pulmonary artery (central shunt) in 8. Three patients had previously undergone a classic Glenn shunt.

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BENEFIT?

Practice variation

Practice variability and outcomes of coil embolization of aortopulmonary collaterals before fontan completion: A report from the Pediatric Heart Network Fontan Cross-Sectional Study

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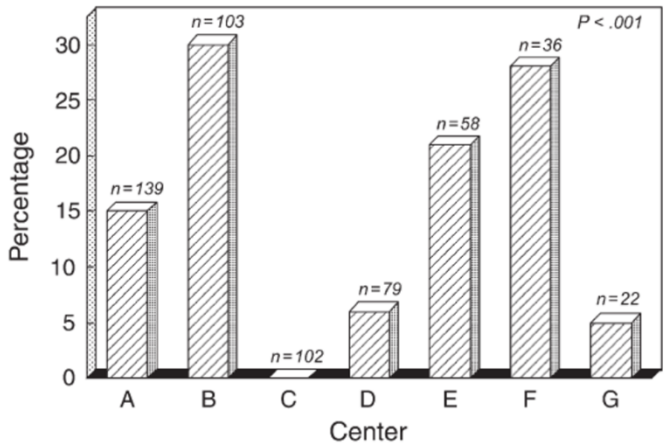
Background The practice of coiling aortopulmonary collaterals (APCs) before Fontan completion is controversial, and published data are limited. We sought to compare outcomes in subjects with and without pre-Fontan coil embolization of APCs using the Pediatric Heart Network Fontan Cross-Sectional Study database which enrolled survivors of prior Fontan palliation.

Methods We compared hospital length of stay after Fontan in 80 subjects who underwent APC coiling with 459 subjects who did not. Secondary outcomes included post-Fontan complications and assessment of health status and ventricular performance at cross-sectional evaluation (mean 8.6 ± 3.4 years after Fontan).

Results Centers varied markedly in frequency of pre-Fontan APC coiling (range 0%-30% of subjects, $P < .001$). The coil group was older at Fontan ($P = .004$) and more likely to have single right ventricular morphology ($P = .054$) and pre-Fontan atrioventricular valve regurgitation ($P = .03$). The coil group underwent Fontan surgery more recently ($P < .001$), was more likely to have a prior superior cavopulmonary anastomosis ($P < .001$), and more likely to undergo extracardiac Fontan connection ($P < .001$) and surgical fenestration ($P < .001$). In multivariable analyses, APC coiling was not associated with length of stay (hazard ratio for remaining in-hospital 0.91, 95% CI 0.70-1.18, $P = .48$) or postoperative complications, except more post-Fontan catheter interventions (hazard ratio 1.74, 95% CI 1.04-2.91, $P = .03$), primarily additional APC coils. The groups had similar outcomes at cross-sectional evaluation.

Conclusion Management of APCs before Fontan shows marked practice variation. We did not find an association between pre-Fontan coiling of APCs and shorter postoperative hospital stay or with better late outcomes. Prospective studies of this practice are needed. (Am Heart J 2011;162:125-30.)

Figure 1



- No association between practice of pre-Fontan embolization and post-op LOS or late outcomes

Some clarity, maybe?

Aortopulmonary Collaterals After Bidirectional Cavopulmonary Connection or Fontan Completion

Quantification With MRI

Lars Grosse-Wortmann, MD; Abdulmajeed Al-Otay, MD; Shi-Joon Yoo, MD

Background—Aortopulmonary collaterals (APCs) have been associated with increased morbidity after the Fontan operation. We aimed to quantify APC flow after bidirectional cavopulmonary connections and Fontan completions, using phase-contrast MRI, and to identify risk factors for the development of APCs.

Methods and Results—APC blood flow was quantifiable in 24 of 36 retrospectively analyzed MRI studies. Sixteen studies were performed after the bidirectional cavopulmonary connections (group A) and 8 after the Fontan operation (group B). APC blood flow was calculated by subtracting the blood flow volume through the pulmonary arteries from that through the pulmonary veins. The ratio of pulmonary to systemic blood flow (Qp/Qs) was 0.93±0.26 in group A and 1.27±0.16 in group B. APC flow was 1.42 (0.58 to 3.83) L/min/m^2 and 0.82 (0.50 to 1.81) L/min/m^2 in groups A and B, respectively. The mean inaccuracies corresponded to 7.9±14.5% and 7.1±13.6% of ascending aortic flow in groups A and B, respectively. Qp/Qs was negatively correlated with a younger age at the time of the bidirectional cavopulmonary connections operation (r=0.62, P=0.01) and positively correlated with the age at the time of the Fontan completion (r=0.81, P=0.01). Patients with a previous right-sided modified Blalock-Taussig shunt had more collateral flow to the right lung than those without.

Conclusions—APC blood flow can be noninvasively measured in bidirectional cavopulmonary connections and Fontan patients, using MRI in the majority of patients and results in a significant left-to-right shunt. (***Circ Cardiovasc Imaging*. 2009;2:219-225.**)

Key Words: collateral circulation ■ Fontan procedure ■ MRI

Whereas there is general agreement that aortopulmonary collaterals (APCs; Figure 1) develop frequently with a bidirectional cavopulmonary connections (BCPC) or Fontan circulation, controversy persists regarding their hemodynamic and clinical consequences.[1–5] Some investigators have found them to be associated with prolonged pleural effusions and even an increased mortality rate after the Fontan operation, whereas others could not confirm a deleterious effect.[2,4]

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Clinical Perspective on p 225

The contradicting nature of these reports may be related to the difficulty in assessing the magnitude of blood flow through collaterals angiographically.[1] Conventional angiographic grading of APCs is neither objective nor quantitative as the extent of visualization of the APCs varies widely according to where, how fast, and how much contrast medium is injected.[1,6] Ichikawa et al[3] and Bradley et al[6] quantified the blood flow through APCs during cardiopulmonary bypass at the time of the Fontan operation by measuring the amount of blood returning to the left atrium and relating it to the pump flow delivered via the aortic cannula. This approach, although of academic value in elucidating the magnitude and risk factors for APCs, is not helpful in the patients' clinical management before the Fontan operation and does not allow for follow-up after the operation. Furthermore, it requires intracardiac access, which is not otherwise necessary when extracardiac modifications or catheter laboratory completions of the Fontan procedure are performed. Inuzuka et al[7] recently used nuclear imaging in combination with catheterization to quantify APC flow in BCPC patients. To date, no noninvasive and readily applicable method has been proposed to quantify APC blood flow in patients with functionally single ventricles, except for in a case report, using MRI.[8] (Figure 1) It is conceptually possible to quantify APC blood flow by subtracting the pulmonary arterial from the pulmonary venous blood flow volume.[8–10] MRI is the gold standard for the quantification of arterial flow volumes,[10,11] and it has recently been shown that pulmonary venous flow volumes can be measured accurately using phase-contrast MRI.[12]

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Noninvasive Quantification of Systemic-to-Pulmonary Collateral Flow

A Major Source of Inefficiency in Patients With Superior Cavopulmonary Connections

Kevin K. Whitehead, MD, PhD; Matthew J. Gillespie, MD; Matthew A. Harris, MD; Mark A. Fogel, MD; Jonathan J. Rome, MD

Background—Systemic-to-pulmonary collateral flow (SPCF) is common in single-ventricle patients with superior cavopulmonary connections (SCPC). Because no validated method to quantify SPCF exists, neither its hemodynamic burden nor its clinical impact can be systematically evaluated. We hypothesize that (1) the difference in total ascending aortic (Ao) and caval flow (superior vena cava [SVC]+inferior vena cava [IVC]) and (2) the difference between pulmonary vein and pulmonary artery flow (PV−PA) provide 2 independent estimators of SPCF.

Methods and Results—We measured Ao, SVC, IVC, right (RPA) and left (LPA) PA, and left (LPV) and right (RPV) PV flows in 17 patients with SCPC during routine cardiac MRI studies using through-plane phase-contrast velocity mapping. Two independent measures of SPCF were obtained: model 1, Ao−(SVC+IVC); and model 2, (LPV−LPA)+(RPV−RPA). Values were normalized to body surface area, Ao, and PV, and comparisons were made using linear regression and Bland-Altman analysis. SPCF ranged from 0.2 to 1.4 L/min for model 1 and 0.2 to 1.6 L/min for model 2, for an average indexed SPCF of 0.5 to 2.8 L/min/m^2: 11% to 53% (mean, 37%) of Ao and 19% to 77% (mean, 54%) of PV. The mean difference between model 1 and model 2 was 0.01 L/min (P=0.40; 2-SD range, −0.45 to 0.47 L/min).

Conclusions—We present a noninvasive method for SPCF quantification in patients with SCPC. It should provide an important clinical tool in treating these patients. Furthermore, we show that SPCF is a significant hemodynamic burden in many patients with bidirectional Glenn shunt physiology. Future investigations will allow objective study of the impact of collateral flow on outcome. (***Circ Cardiovasc Imaging*. 2009;2:405-411.**)

Key Words: single ventricle ■ collateral circulation ■ MRI ■ blood flow ■ superior cavopulmonary connection

It has long been recognized that single-ventricle patients with cavopulmonary anastomoses are susceptible to development of systemic-to-pulmonary collateral flow (SPCF).[1,2] There has been much investigation and speculation into the etiology of these collaterals. Cyanosis, pleural effusion, and decreased pulmonary blood flow have all been implicated in the development of collateral flow to the lungs.[2,3]

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Controversy exists over the prevalence of collateral flow and more importantly, the significance of these collaterals. Some investigations have shown that the presence of significant SPCF is a risk factor for pleural effusion, poor outcomes, and heart failure.[1,3,4] However, other investigators have failed to show a difference in outcome based on the amount of collateral flow.[5] Some studies have demonstrated increased prevalence of collaterals in superior cavopulmonary connections (SCPC) compared with total cavopulmonary anastomoses.[2] Collateral flow is potentially a significant source of power loss, and other research has suggested that collateral flow results in additional power loss in the Fontan pathway by transferring kinetic energy to the distal pulmonary vasculature and causing competitive flow losses.[6]

One of the major obstacles to investigating the importance of SPCF in single-ventricle physiology has been the inability to accurately quantify this flow. These collaterals have been classically identified and then graded qualitatively by angiography.[2] However, the validity of the grading systems has never been verified. When a decision is made to coil collaterals thought to be hemodynamically significant, there is no good method of assessing the effect of the procedure.

One potential method to quantify collateral flow involves the use of MRI, using through-plane phase-contrast velocity mapping (PC-MRI), a technique that has been validated in multiple in vitro and clinical investigations.[7–10] We recently published flow data obtained from PC-MRI velocity mapping

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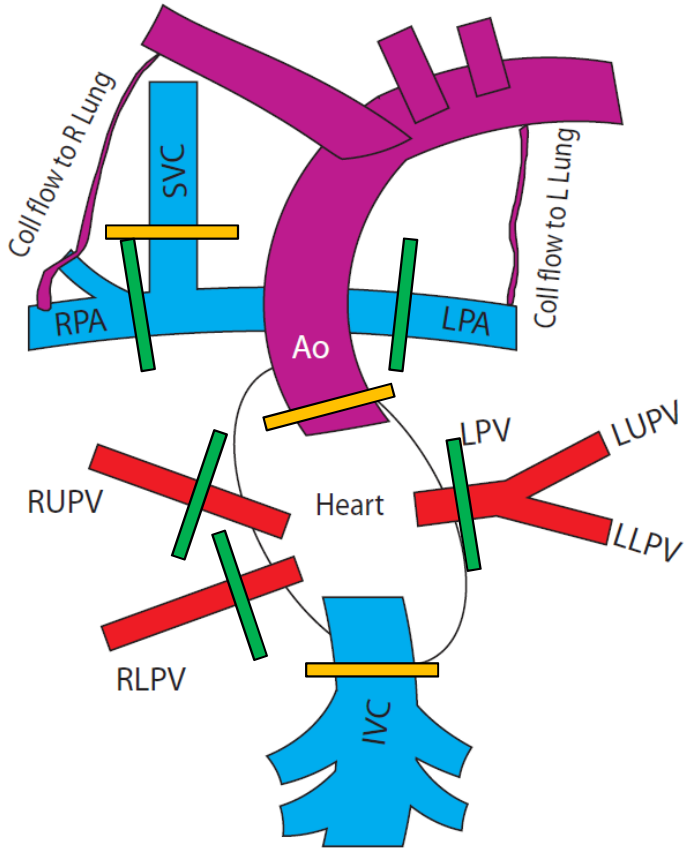
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.108.832113

Stage 2 physiology



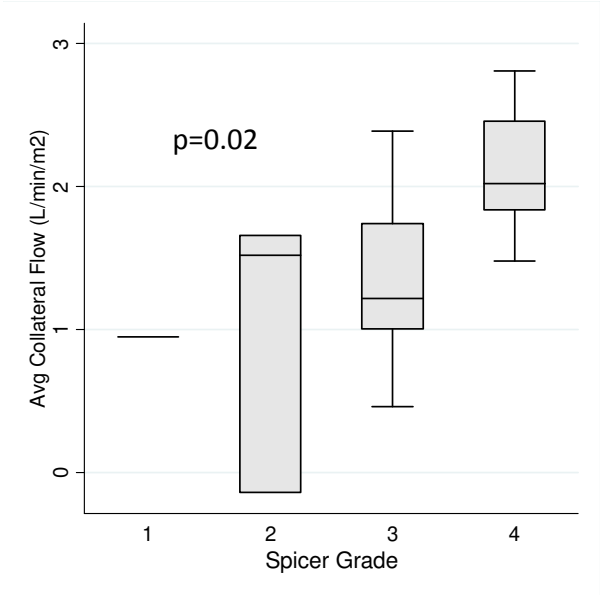
$$Q_{coll\_syst} = Q_{Ao} - (Q_{SVC} + Q_{IVC})$$

$$Q_{coll\_pulm} = (Q_{RPV} + Q_{LPV}) - (Q_{RPA} + Q_{LPA})$$

$$Q_{coll} = (Q_{coll\_syst} + Q_{coll\_pulm}) / 2$$

The new gold standard?

- Physiologic
- Non-invasive
- Fully quantitative



Spicer Grading

Table I. Aortopulmonary collateral vessels

Grade	*Number* ..... *Size*	*Pulmonary opacification*
1	Few ..... Small	-
2	Multiple ..... Small or Few ..... Large	-
3	Multiple ..... Small or Few ..... Large	+
4	Multiple ..... Large	+

Few, ≤3; *small*, <1 mm; +, present.

Am Heart J 1996;131:1164-8

Outline

- Natural adaptation?
  - Risk factors for CollF
  - “Natural” history of CollF
  - Investigating mechanistic basis
- Harmful development?
  - Hemodynamic importance
  - Associations with post-Fontan outcomes
  - Role of collateral embolization

Natural adaptation?

Risk factors for collateral flow

Risk Factors

ORIGINAL ARTICLE

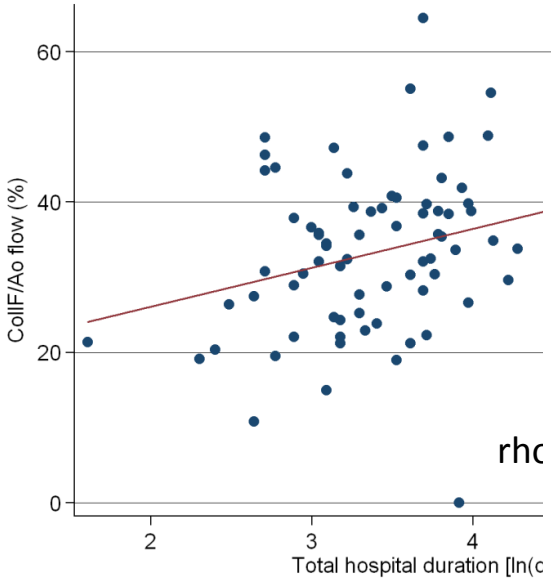
Factors associated with systemic to pulmonary arterial collateral flow in single ventricle patients with superior cavopulmonary connections

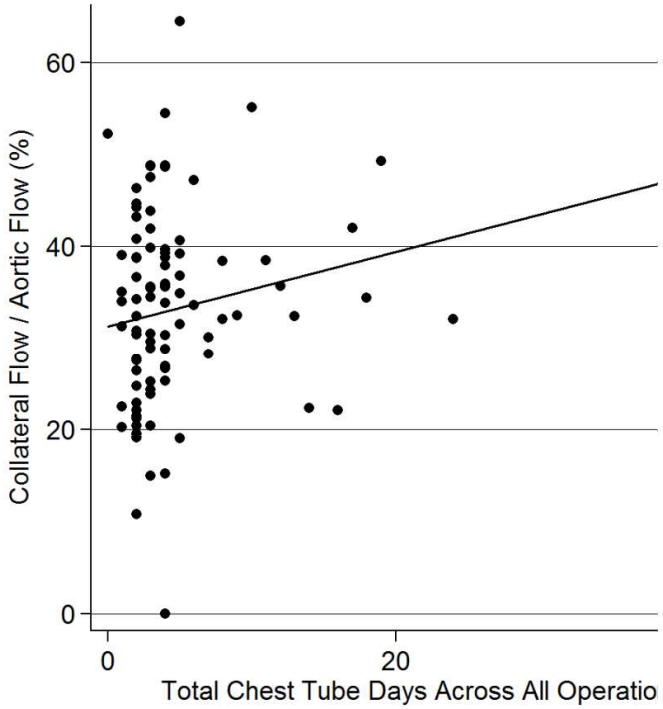
Andrew C Glatz,[1,2,3] Neil Harrison,[1] Adam J Small,[1] Yoav Dori,[1,2] Matthew J Gillespie,[1,2] Matthew A Harris,[1,2,4] Mark A Fogel,[1,2,4] Jonathan J Rome,[1,2] Kevin K Whitehead[1,2,4]

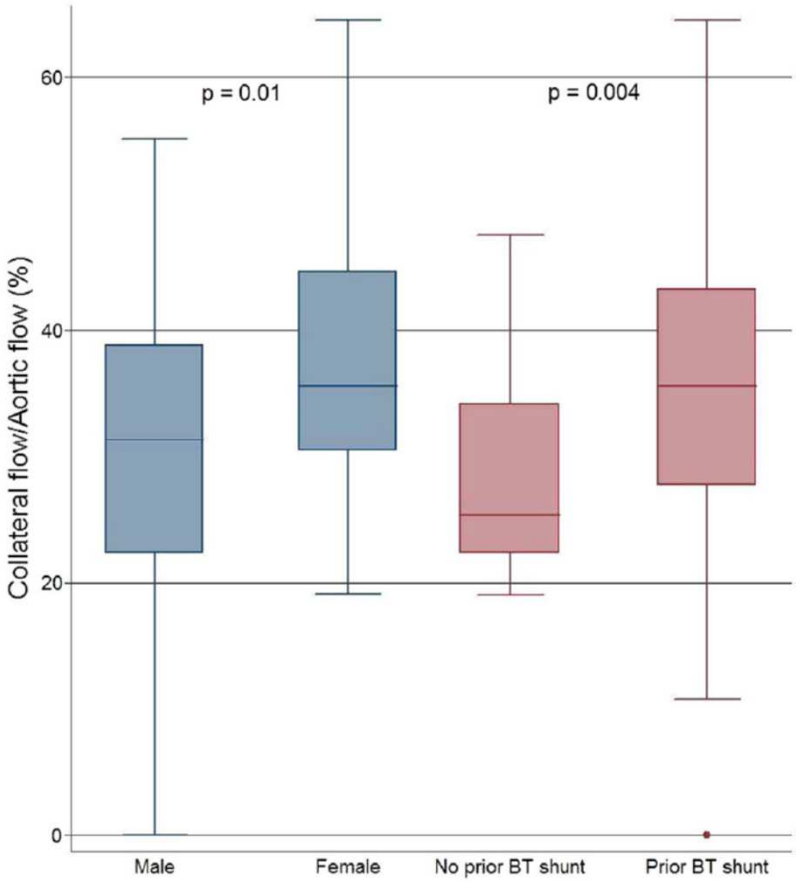
To cite: Glatz AC, Harrison N, Small AJ, *et al*. *Heart* 2015;**101**: 1813–1818.

- AIM: to identify factors associated with CollF as measured by CMR in a large cross-section of Glenn patients
- Detailed retrospective review of all events from birth to time of study CMR for all Glenn patients who had CollF quantified by CMR
- Tested associations between candidate risk factors and CollF as measured by CMR

Results, Glenn patients (n=96)







Conclusions

- Among superior CPC patients, CollF is associated with:
  - Indicators of peri-operative morbidity and pleural inflammation
  - History of prior BT shunt
  - Being female
- These data support hypotheses:
  - Perioperative morbidity and pleural inflammation play a role in CollF development
  - There are likely important factors (genetic, etc) influencing CollF development that are poorly understood

Natural adaptation?

"Natural" history of collateral flow

“Natural” history of collateral flow

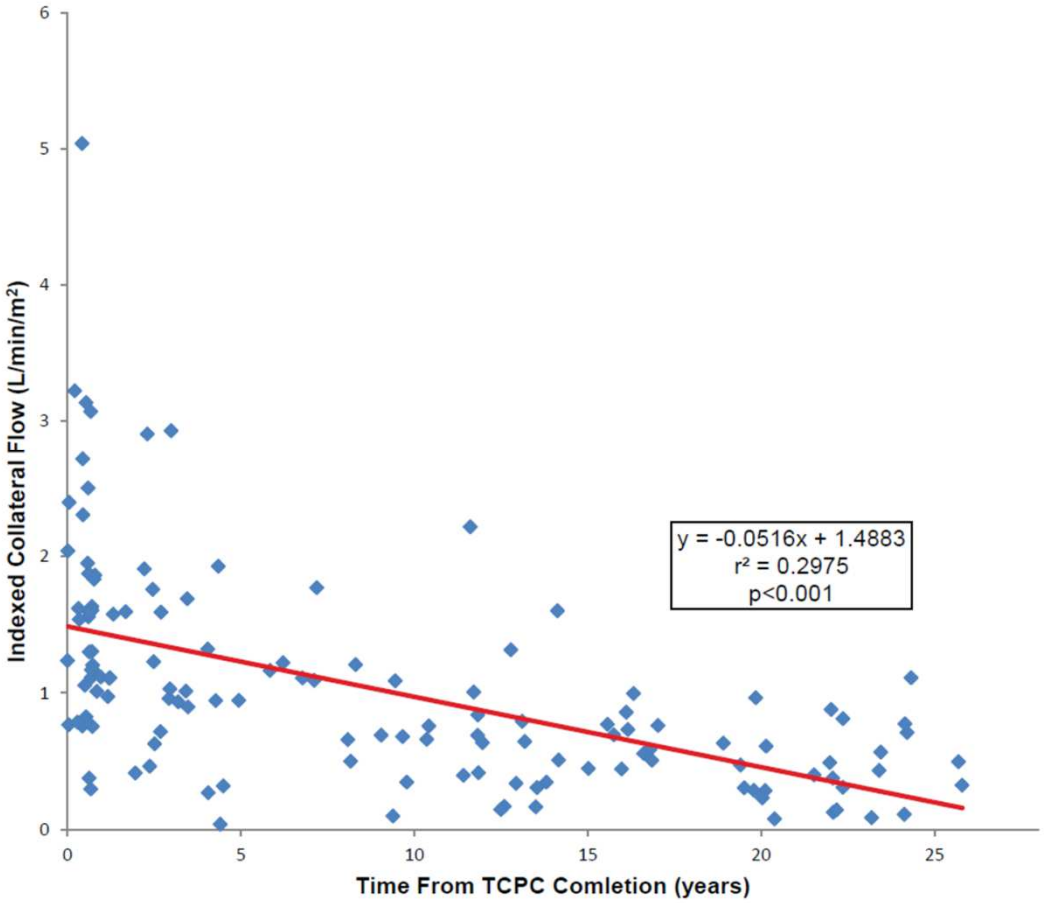
Status of Systemic to Pulmonary Arterial Collateral Flow After the Fontan Procedure

Kevin K. Whitehead, MD, PhD*, Matthew A. Harris, MD, Andrew C. Glatz, MD, Matthew J. Gillespie, MD, Michael V. DiMaria, MD, Neil E. Harrison, MD, Yoav Dori, MD, PhD, Marc S. Keller, MD, Jonathan J. Rome, MD, and Mark A. Fogel, MD

(Am J Cardiol 2015;115:1739–1745)

- Description of CollF in a large cross-section of Glenn and Fontan patients, including a subset with longitudinal data
- 250 CMR studies in 219 single ventricle patients
- 115 Glenn, 135 Fontan, 31 patients with studies both before and after Fontan
  - 18 controls

“Natural” history late after Fontan



Results, serial data

	SCPC	TCPC	p-value
n	31	31	
Age (years)	2.9±1.3	4.0±1.3	
Time from TCPC (years)	-0.37±0.5	0.62±0.3	
Q_{Ao} (L/min/m^2)	4.6±0.7	4.4±1.0	p=0.13
Q_{coll} (L/min/m^2)	1.5±0.7	1.7±1.0	p=0.09
Q_{coll}/Q_{Ao} x100 (%)	31±13	37±17	p=0.02
Q_{coll}/Q_P x100 (%)	45±17	41±18	p=0.15
Q_P (L/min/m^2)	3.2±0.7	4.0±1.0	p<0.001
Q_S (L/min/m^2)	3.2±0.7	2.8±0.8	p=0.002
Q_{PA} (L/min/m^2)	1.7±0.6	2.2±0.8	p<0.001
Q_P / Q_S	1.1±0.4	1.5±0.6	p<0.001
Right to Left Shunt (L/min/m^2)	1.5±0.5	0.5±0.4	p<0.001

Natural adaptation?

Investigating mechanistic basis

Mechanistic approach

- "*Determining the molecular signals involved in the growth and development of systemic-pulmonary arterial collateral vessels in children with single ventricle heart disease*"
- Collaboration with Carlo Bartoli MD PhD, University of Pennsylvania
- Supported in part by:
  - Congenital Heart Disease Coalition
  - Big Hearts to Little Hearts

Mechanistic approach

- Von Willebrand factor (vWF) major regulatory role in angiogenesis through VEGF pathway
  - Degradation of vWF into multimers by protease, ADAMTS-13, produced by hepatic stellate cells
  - Influenced by blood flow conditions
  - Angiodysplasia observed in patients with non-pulsatile ventricular assist devices
- Hypothesis: Glenn patients have abnormal circulating vWF profiles putting them at risk for angiodysplasia

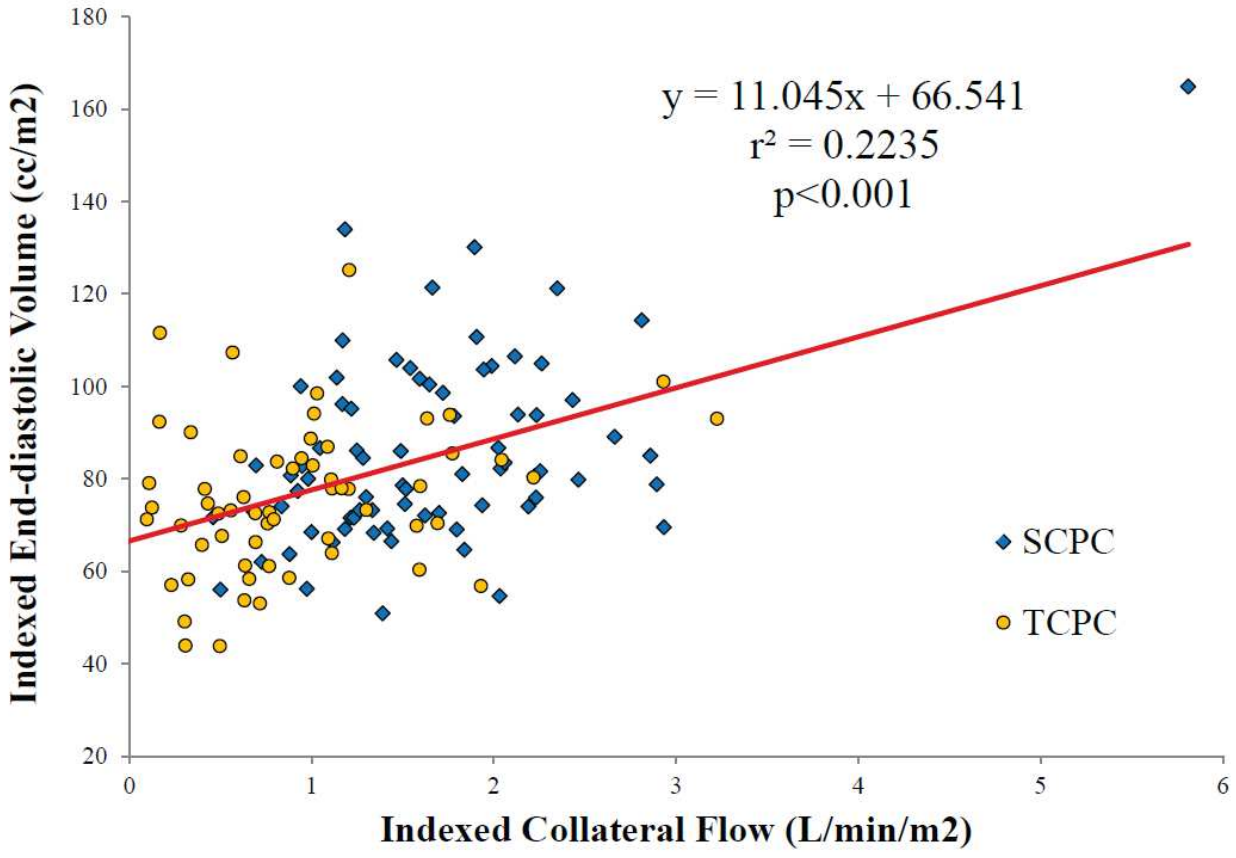
Mechanistic approach

- Study objectives:
  - From various blood compartments of Glenn patients, characterize:
    - vWF multimer profile
    - ADAMTS-13 activity
    - Platelet activity
    - Profile of other angiogenic signaling molecules
  - Correlate angiogenic profiles with:
    - Collateral flow as measured by CMR
    - Hemodynamics at catheterization
    - Clinical outcomes following Fontan

Harmful development?

Hemodynamic importance

Collaterals as a volume load



Collaterals and the Fick principle

Circulation
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Accuracy of Conventional Oximetry for Flow Estimation in Patients With Superior Cavopulmonary Connection: A Comparison With Phase-Contrast Cardiac MRI

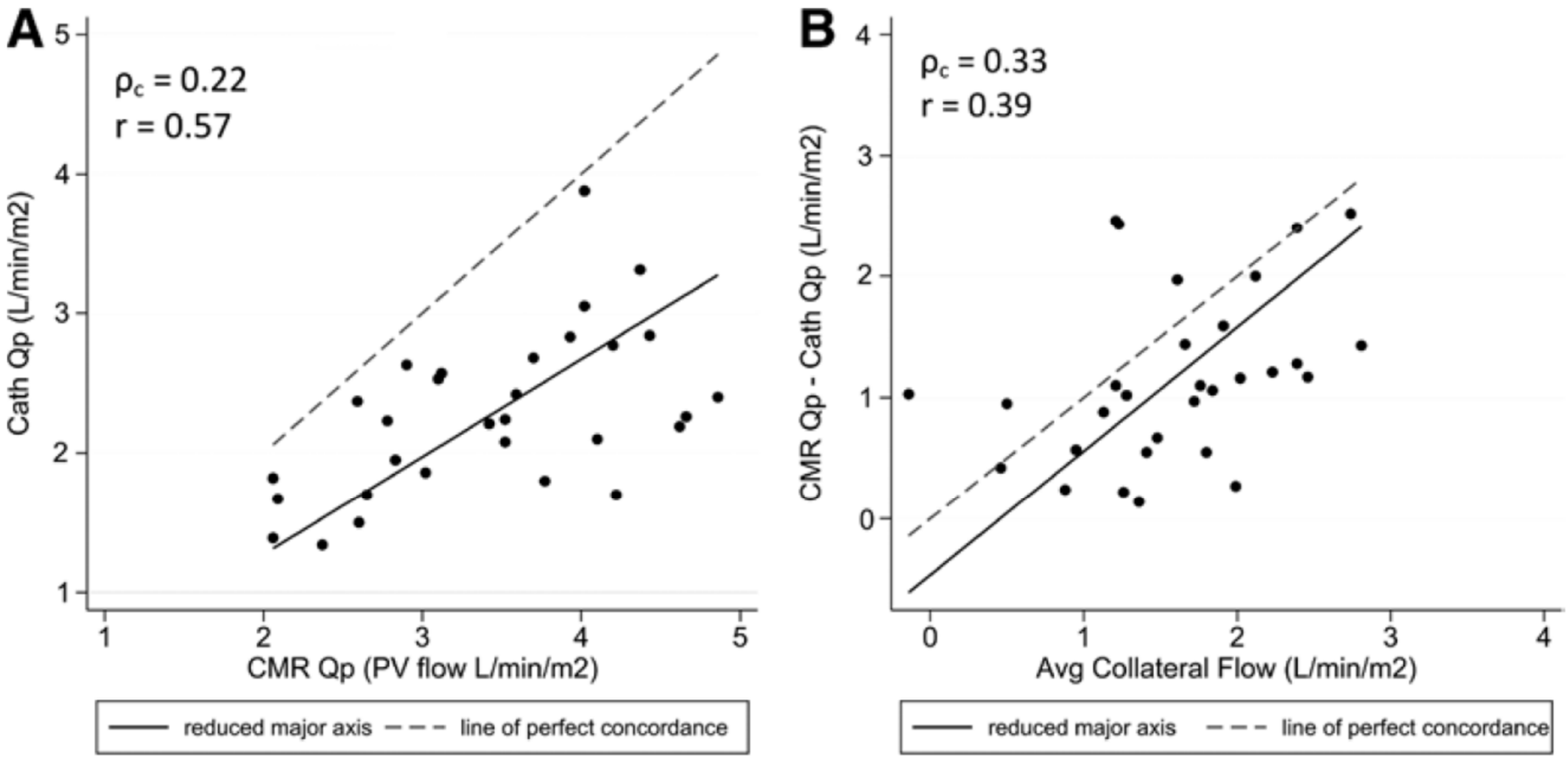
Tacy E. Downing, Kevin K. Whitehead, Yoav Dori, Matthew J. Gillespie, Matthew A. Harris, Mark A. Fogel, Jonathan J. Rome and Andrew C. Glatz

Circ Cardiovasc Imaging. 2013;6:943-949; originally published online October 4, 2013;
doi: 10.1161/CIRCIMAGING.113.000496
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

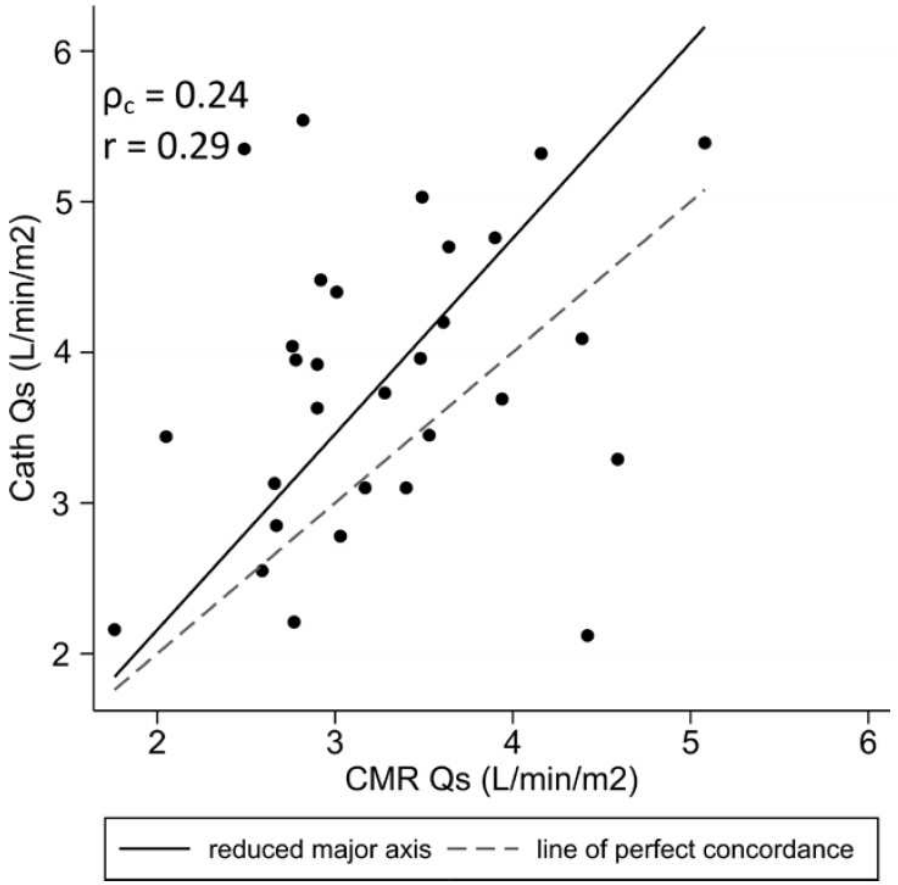
Print ISSN: 1941-9651. Online ISSN: 1942-0080

- 30 Glenn patients with combined MRI/cath
- Compared MRI and cath-measures of flows

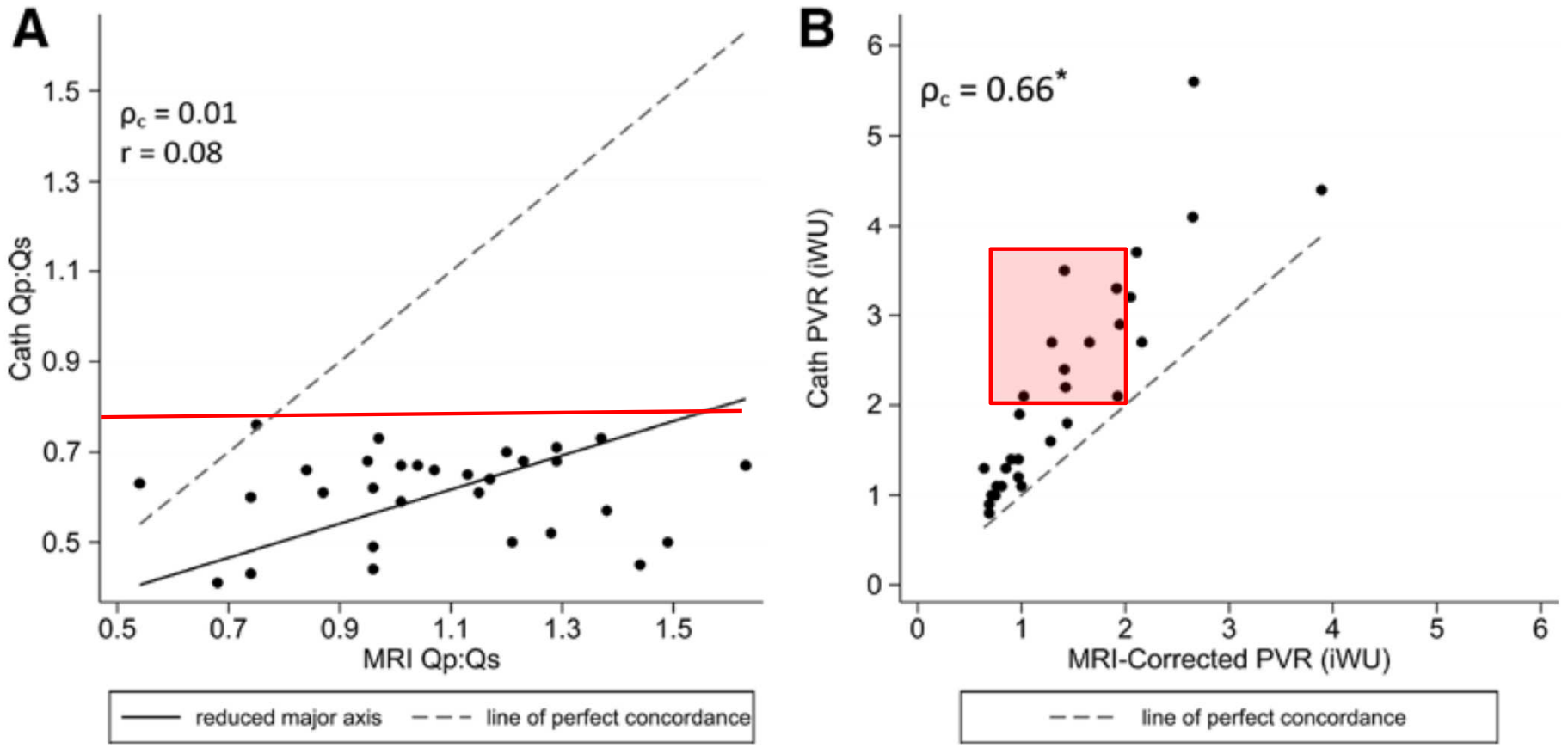
Cath underestimates Q_P



Cath overestimates Q_S



Cath underestimates Q_P:Q_S and overestimates PVR



Harmful development?

Associations with post-Fontan outcomes

Collaterals and outcomes

Circulation
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JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

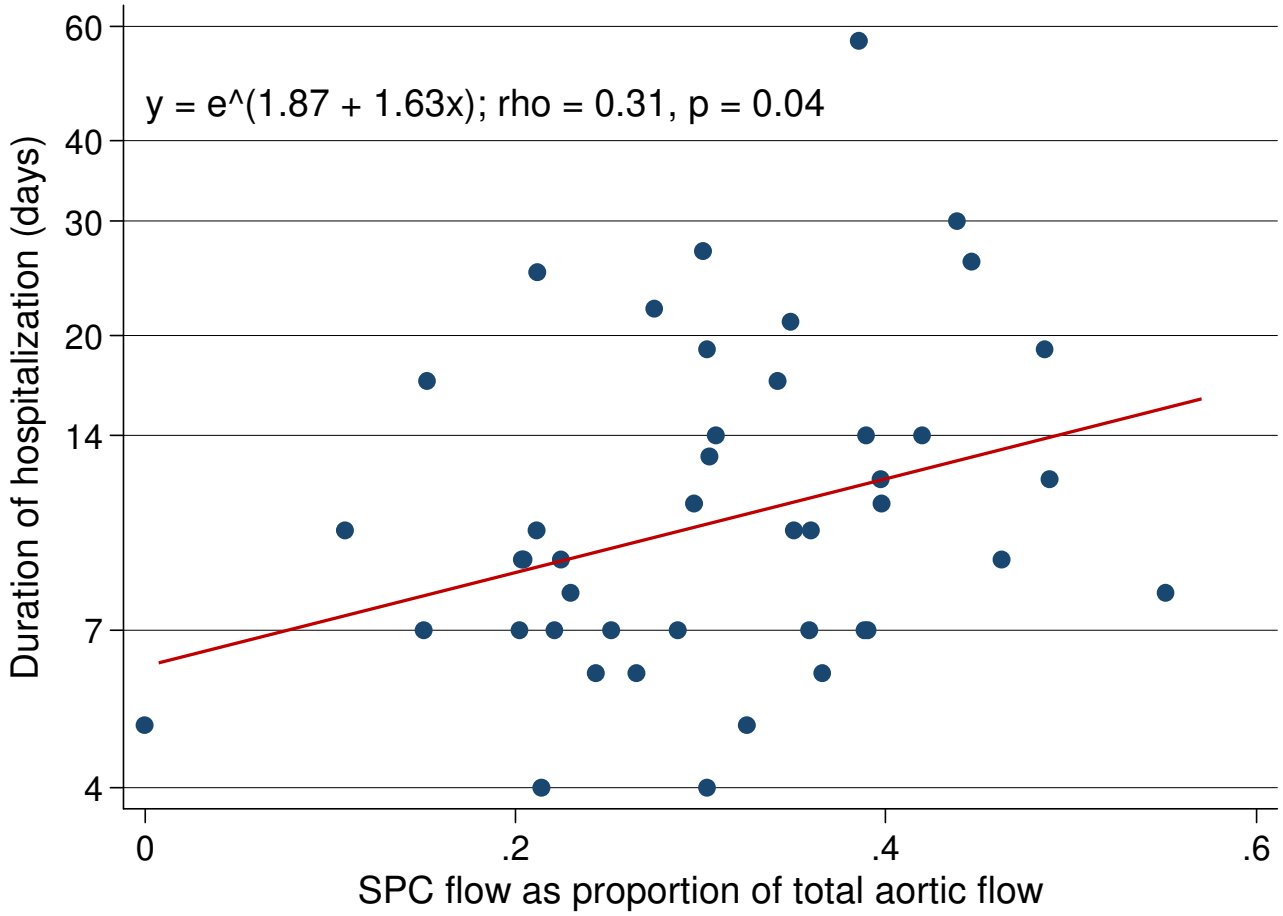
Systemic-to-Pulmonary Collateral Flow, as Measured by Cardiac Magnetic Resonance Imaging, Is Associated With Acute Post-Fontan Clinical Outcomes

Andrew C. Glatz, Jonathan J. Rome, Adam J. Small, Matthew J. Gillespie, Yoav Dori, Matthew A. Harris, Marc S. Keller, Mark A. Fogel and Kevin K. Whitehead

Circ Cardiovasc Imaging 2012;5;218-225; originally published online January 6, 2012;
DOI: 10.1161/CIRCIMAGING.111.966986

- Retrospective review of 44 patients who had surgical Fontan completion between May 1, 2008 and September 30, 2010 who also had a CMR performed prior to the operation

Collaterals and outcomes



Collaterals and outcomes

	Chest tube ≥ 10d		Hospitalization ≥ 7d		Hospitalization ≥ 14d	
	OR*	p	OR*	p	OR*	p
Q_{coll}	22.7 (2.2,239)	**0.009**	9.2 (1.4,61)	**0.02**	1.46 (0.6,3.3)	0.4
Q_{coll}/Q_{Ao}	1.24 (1.06,1.4)	**0.007**	1.09 (1,1.2)	**0.048**	1.06 (0.99,1.14)	0.1
Q_{coll}/Q_{PV}	1.18 (1.05,1.34)	**0.006**	1.07 (1,1.14)	**0.048**	1.04 (0.98,1.09)	0.17

*From logistic regression, adjusted for presence of a fenestration and Fontan type (extra-cardiac conduit v. intra-atrial lateral tunnel); Q_{coll} = systemic-pulmonary collateral flow; Q_{Ao} = aortic flow; Q_{PV} = pulmonary venous flow

Collaterals and outcomes

Aortopulmonary collateral flow volume affects early postoperative outcome after Fontan completion: A multimodality study

Lars Grosse-Wortmann, MD,[a,b] Christian Drolet, MD,[a] Andreea Dragulescu, MD, PhD,[a] Yasuhiro Kotani, MD,[a] Rajiv Chaturvedi, MD,[a] Kyong-Jin Lee, MD,[a] Luc Mertens, MD, PhD,[a] Katherine Taylor, MD,[a] Gustavo La Rotta, MD,[a] Glen van Arsdell, MD,[a] Andrew Redington, MD,[a] and Shi-Joon Yoo, MD, PhD[a,b]

JTCVS 2012;144:1329-36

- 24 patients with CollF measured by CMR prior to Fontan
- Significant correlations between CollF and: duration of pleural drainage and hospital LOS

ORIGINAL ARTICLE

Systemic to pulmonary collateral blood flow influences early outcomes following the total cavopulmonary connection

Tobias Odenwald,[1] Michael A Quail,[1] Alessandro Giardini,[2] Sachin Khambadkone,[2] Marina Hughes,[1] Oliver Tann,[1] Tain-Yen Hsia,[2] Vivek Muthurangu,[1] Andrew M Taylor[1]

Heart 2012;98:934-40

- 41 patients with CollF measured by CMR prior to Fontan
- Significant correlations between CollF and: chest drain volume, chest drain duration, and ICU and hospital LOS

Harmful development?

Role of collateral embolization

Efficacy of embolization

Circulation
Cardiovascular Interventions

American Heart Association®

Acute Effects of Embolizing Systemic-to-Pulmonary Arterial Collaterals on Blood Flow in Patients With Superior Cavopulmonary Connections: A Pilot Study

Yoav Dori, Andrew C. Glatz, Brian D. Hanna, Matthew J. Gillespie, Matthew A. Harris, Marc S. Keller, Mark A. Fogel, Jonathan J. Rome and Kevin K. Whitehead

Circ Cardiovasc Interv. 2013;6:101-106; originally published online January 15, 2013;
doi: 10.1161/CIRCINTERVENTIONS.112.972265
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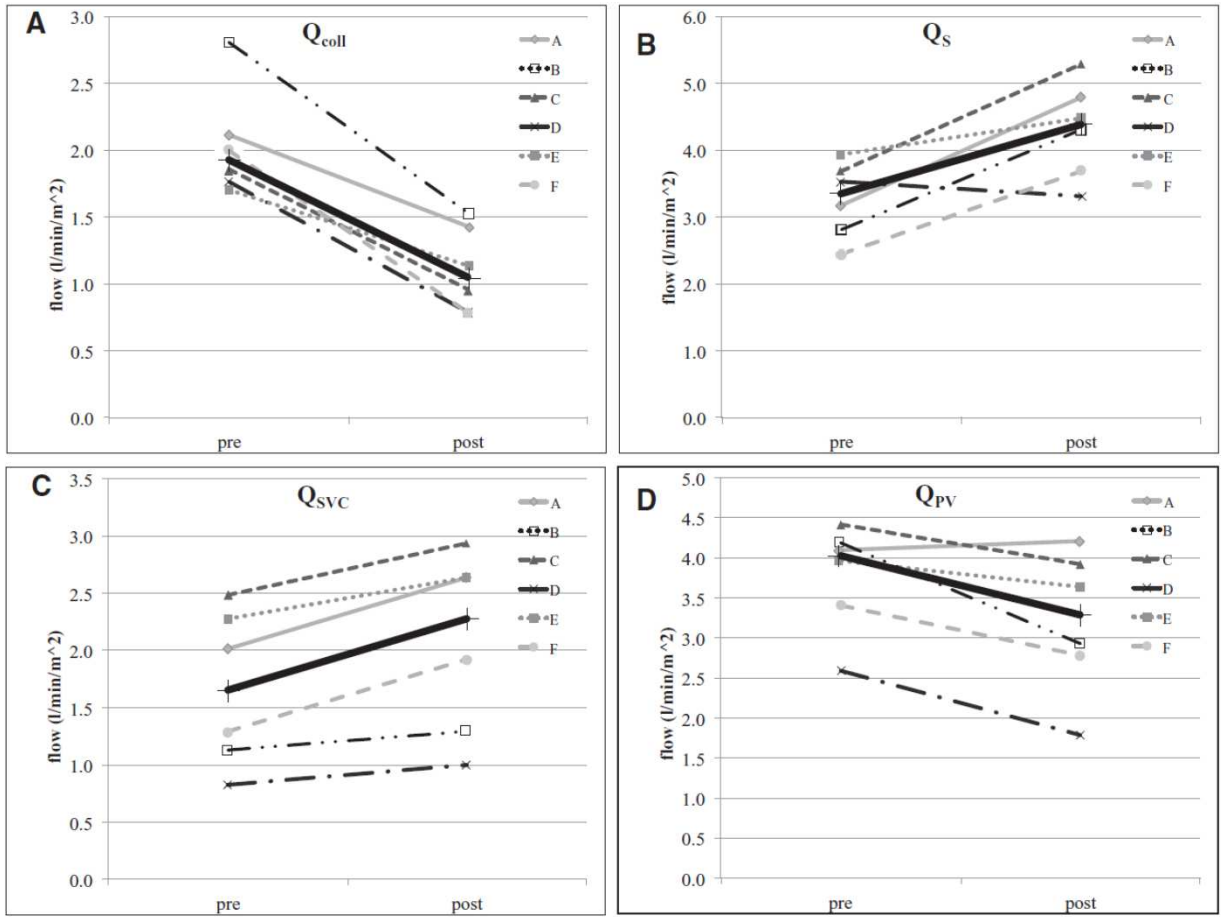
Print ISSN: 1941-7640. Online ISSN: 1941-7632

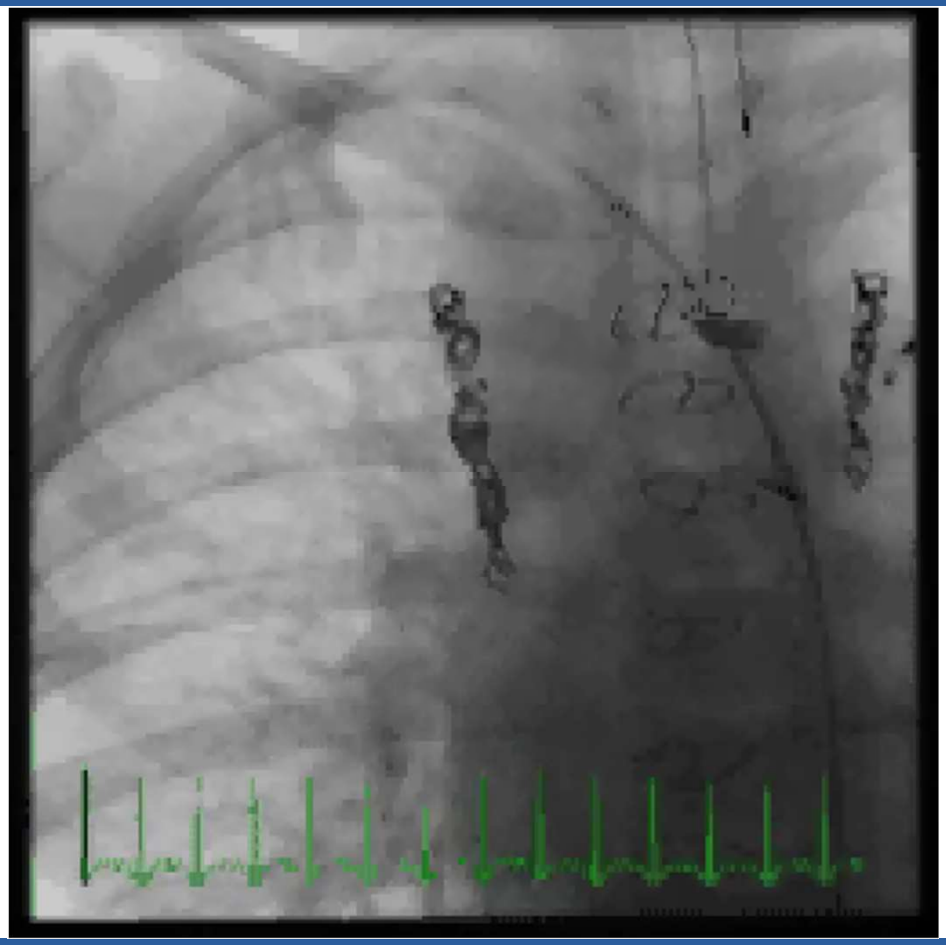
- 6 Glenn patients with CMR immediately before and after embolization

Acute efficacy of embolization



Durability

- Has not been reliably demonstrated
- Anecdotally, not necessarily…



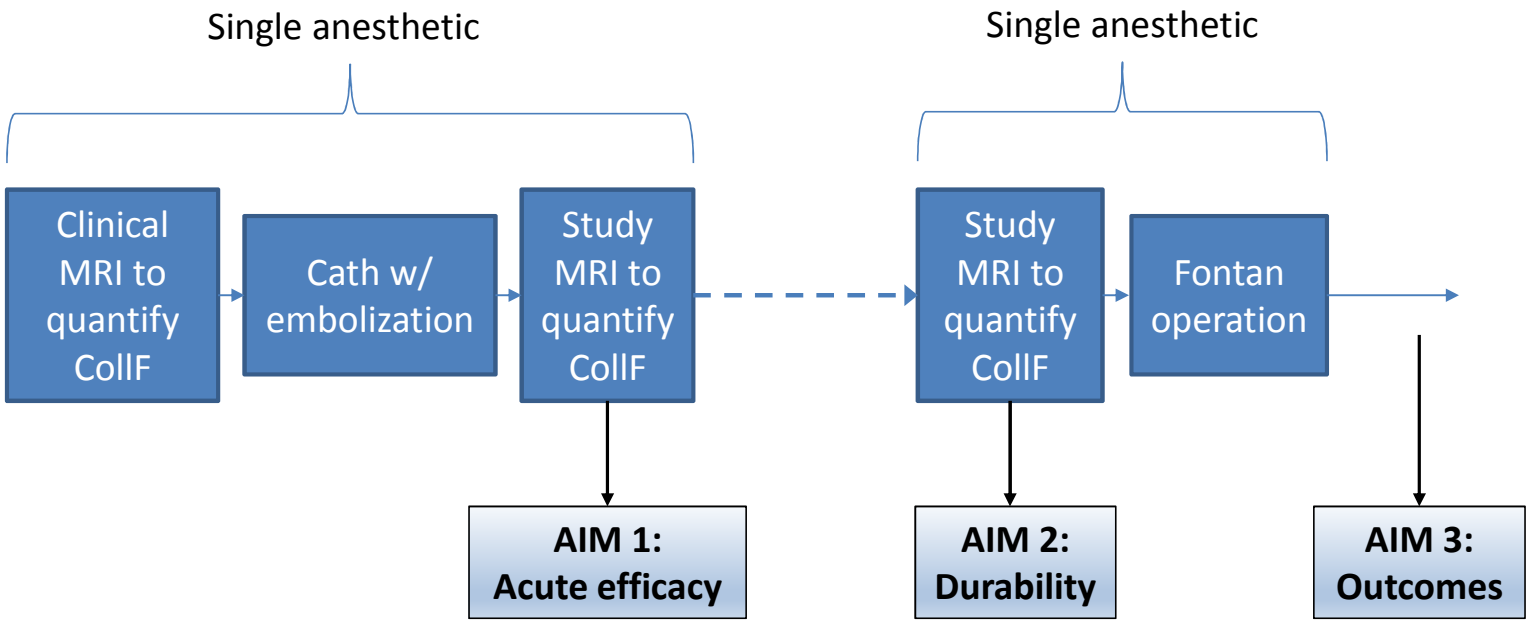
Outcomes

- Clinically relevant outcomes are “dirty”
- Short-term outcomes are easiest target
  - Duration of effusions, length of stay
- Effect on longer-term outcomes is more complicated
  - Associations demonstrated between post-Fontan duration of effusions/LOS and longer-term mortality
    - Hirsch et al., *Ann Surg* 2008;248(3):402-10
    - Downing et al., presented at *AATS 2015*

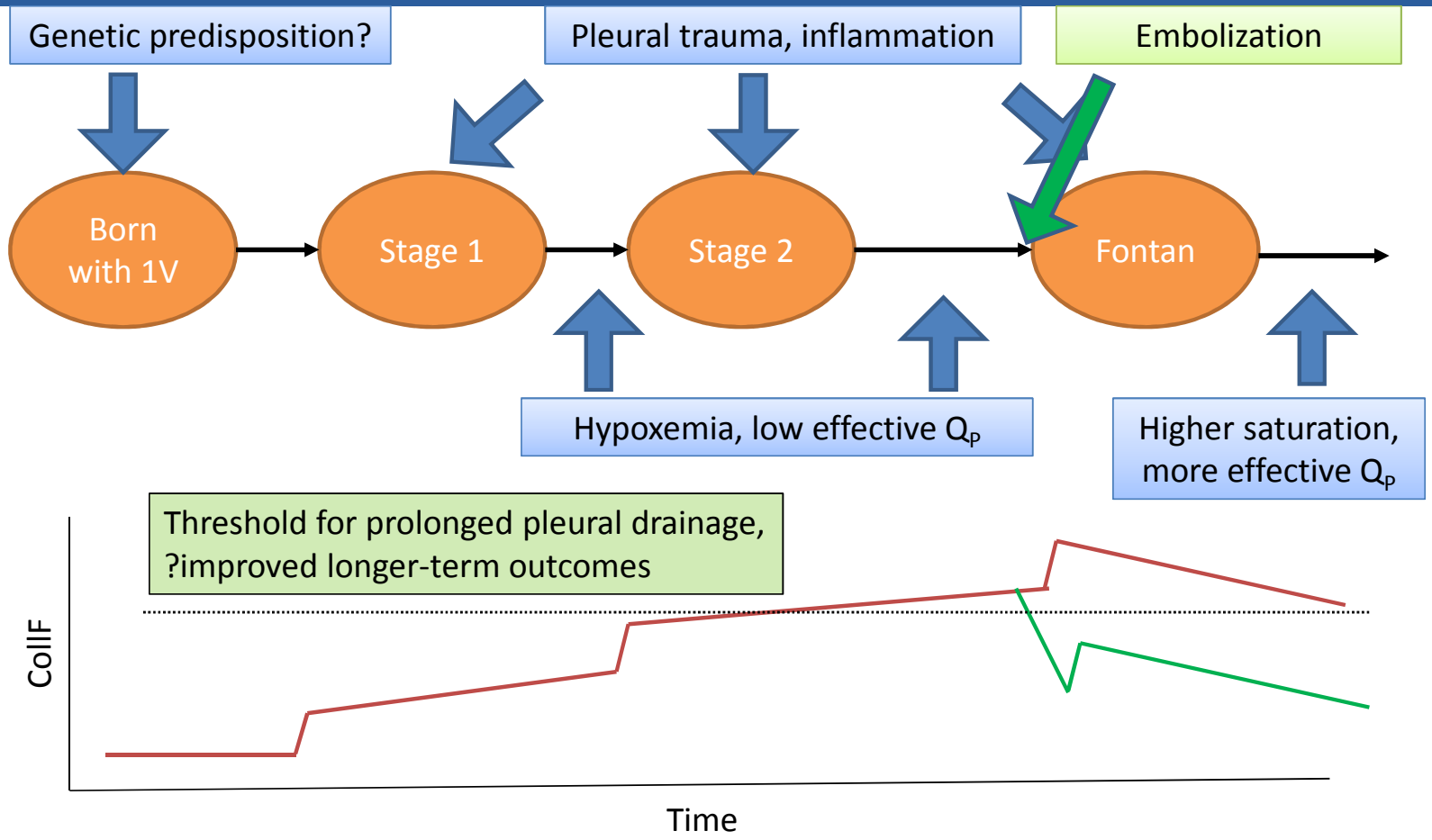
Children's Heart Foundation study

- Prospective observational study
- Specific Aims:
  - *Specific Aim 1: To determine the acute efficacy of SPC embolization on reducing collateral flow in Glenn patients as measured by CMR.*
  - *Specific Aim 2: To determine the durability of reduction in SPC flow after embolization.*
  - *Specific Aim 3: To determine the effect of SPC embolization on acute post-Fontan clinical outcomes.*

Study design



Conceptual Model



Conclusions

- With CMR, we now have a way to objectively study collateral flow
- Collaterals are ubiquitous in single ventricle patients
  - Natural adaption to the physiology and surgical course imposed upon them
- Variability is not well understood
  - Genetic, angiogenic signaling pathways?
- Collateral flow can have a significant hemodynamic impact
- Collateral flow may affect short term post-Fontan outcomes
  - May be a modifiable risk factor
- Ongoing prospective studies may help clarify role of embolization

The original question

- Natural adaptation?

YES!

- Or harmful development?

YES!

Thank you

Results, Glenn patients (n=96)

Table 2a. Correlation between potential risk factors and CollF measures						
Risk factor	CollF		CollF / Ao flow		CollF / PV flow	
	rho	p	rho	p	rho	p
Total ventilator days	0.24	**0.03**	0.29	**0.008**	0.37	**0.0007**
Total ICU days	0.23	**0.04**	0.29	**0.008**	0.39	**0.0003**
Total hospital days	0.25	**0.02**	0.33	**0.002**	0.39	**0.0003**
Total chest tube days	0.21	**0.04**	0.24	**0.02**	0.2	**0.05**
O_2 sat at Stage 2 discharge	0.22	**0.04**	0.19	*0.06*	0.06	0.57

- No associations found with hemoglobin, pulmonary artery size, pre-Stage 2 cath variables, or Stage 2 surgical support times.

Results, cross-sectional data

	SCPC	TCPC	p (SCPC vs. TCPC)	Controls	p (SCPC vs. Ctrl)	p (TCPC vs. Ctrl)
n	115	135		18		
Age (years)	2.6±1.2	12.2±8.8	<0.001	10.1±7.4	<0.001	1.0
BSA (m^2)	0.53±0.10	1.16±0.51	<0.001	1.05±0.49	<0.001	1.0
Q_{Ao} (L/min/m^2)	4.85±1.1	3.61±1.0	<0.001	3.9±0.9	0.007	1.0
Q_{coll} (L/min/m^2)	1.64±0.8	1.03±0.8	<0.001	0.21±0.27	<0.001	<0.001
$100xQ_{coll}/Q_{Ao}$ (%)	34%±12%	26%±15%	<0.001	5%±6%	<0.001	<0.001
$100xQ_{coll}/Q_P$ (%)	48%±17%	29%±17%	<0.001	5%±5%	<0.001	<0.001
Q_P (L/min/m^2)	3.4±0.9	3.3±0.8	1.0	4.1±1.0	0.006	0.005
Q_S (L/min/m^2)	3.2±0.9	2.6±0.6	<0.001	3.7±0.8	0.11	<0.001
Q_{PA} (L/min/m^2)	1.7±0.6	2.3±0.6	<0.001	3.9±0.9	<0.001	<0.001
Q_P / Q_S	1.10±0.3	1.31±0.40	<0.001	1.13±0.2	1.0	0.20

Collaterals and outcomes