Cardiology in the Young

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Angiographic tool to detect pulmonary arteriovenous malformations in single ventricle physiology

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Original Article

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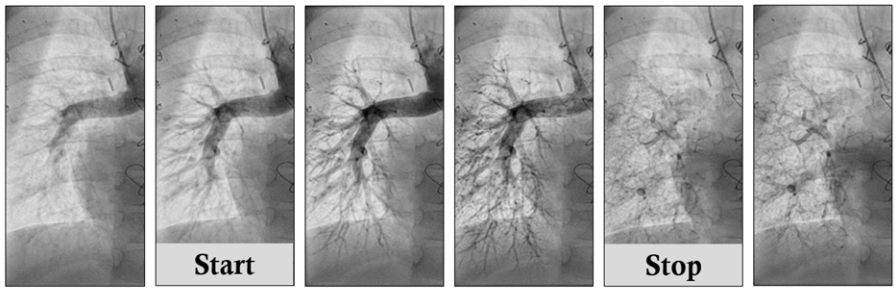
Abstract

Objective: Individuals with single ventricle physiology who are palliated with superior cavopulmonary anastomosis (Glenn surgery) may develop pulmonary arteriovenous malformations. The traditional tools for pulmonary arteriovenous malformation diagnosis are often of limited diagnostic utility in this patient population. We sought to measure the pulmonary capillary transit time to determine its value as a tool to identify pulmonary arteriovenous malformations in patients with single ventricle physiology. *Methods:* We defined the angiographic pulmonary capillary transit time as the number of cardiac cycles required for transit of contrast from the distal pulmonary arteries to the pulmonary veins. Patients were retrospectively recruited from a single quaternary North American paediatric centre, and angiographic and clinical data were reviewed. Pulmonary capillary transit time was calculated in 20 control patients and compared to 20 single ventricle patients at the pre-Glenn, Glenn, and Fontan surgical stages (which were compared with a linear-mixed model). Correlation (Pearson) between pulmonary capillary transit time and haemodynamic and injection parameters was assessed using angiograms from 84 Glenn patients. Five independent observers calculated pulmonary capillary transit time to measure reproducibility (intraclass correlation coefficient). *Results:* Mean pulmonary capillary transit time was 3.3 cardiac cycles in the control population, and 3.5, 2.4, and 3.5 in the pre-Glenn, Glenn, and Fontan stages, respectively. Pulmonary capillary transit time in the Glenn population did not correlate with injection conditions. Intraclass correlation coefficient was 0.87. *Conclusions:* Pulmonary angiography can be used to calculate the pulmonary capillary transit time, which is reproducible between observers. Pulmonary capillary transit time accelerates in the Glenn stage, correlating with absence of direct hepatopulmonary venous flow.

Pulmonary arteriovenous malformations frequently develop after superior cavopulmonary anastomosis (Glenn surgery).[1–4] Remarkably, these pulmonary arteriovenous malformations can resolve after total cavopulmonary anastomosis (Fontan completion), which has led to the "hepatic factor" hypothesis: the liver makes an unknown substance that maintains the normal vascular architecture of the lungs.[3,5] To maintain normal function, this factor must travel quickly from the liver, through the heart, and to the lungs (critically, without traversing the systemic capillaries)—which we term "direct hepatopulmonary blood flow." Surgical and interventional strategies to restore direct flow of hepatic venous blood to affected lungs have been successful to resolve pulmonary arteriovenous malformations.[6–9] However, while all non-pulsatile Glenn patients lose direct flow of "hepatic factor" to their lungs, not all Glenn patients develop clinically significant pulmonary arteriovenous malformations.[10]

Pulmonary arteriovenous malformation screening of Glenn patients is fraught with technical difficulty. Intracardiac mixing prevents use of peripheral arterial oxygen saturation or the partial pressure of dissolved oxygen. Direct measurement of oxygen saturation from the pulmonary veins is not always technically feasible. Additionally, the common screening modality (peripherally injected bubble contrast echocardiography) is prone to false positives and unable to detect capillary recruitment or proliferation of small calibre vessels.[11–14] Meanwhile, the confirmatory test used in patients with hereditary haemorrhagic telangiectasia (CT) has a spatial resolution of 0.15 mm, which may not be able to detect shunts that are due to diffuse microvascular dilation, to a diameter of 0.10 mm.



$$\text{Pulmonary Capillary Transit Time (\# cardiac cyles)} = \text{Transit Time (sec)} \times \frac{\text{Heart Rate}}{60\ \text{sec}}$$

Figure 1. Definition of the pulmonary capillary transit time. Pulmonary capillary transit time is defined as the number of cardiac cycles taken for contrast to traverse the pulmonary capillary bed. This is calculated by using either the number of frames (of the angiogram) or in seconds. Calculation of the transit time starts when the contrast reaches the distal major branches of the pulmonary arteries, and stops when the first visible contrast is present in the pulmonary veins.

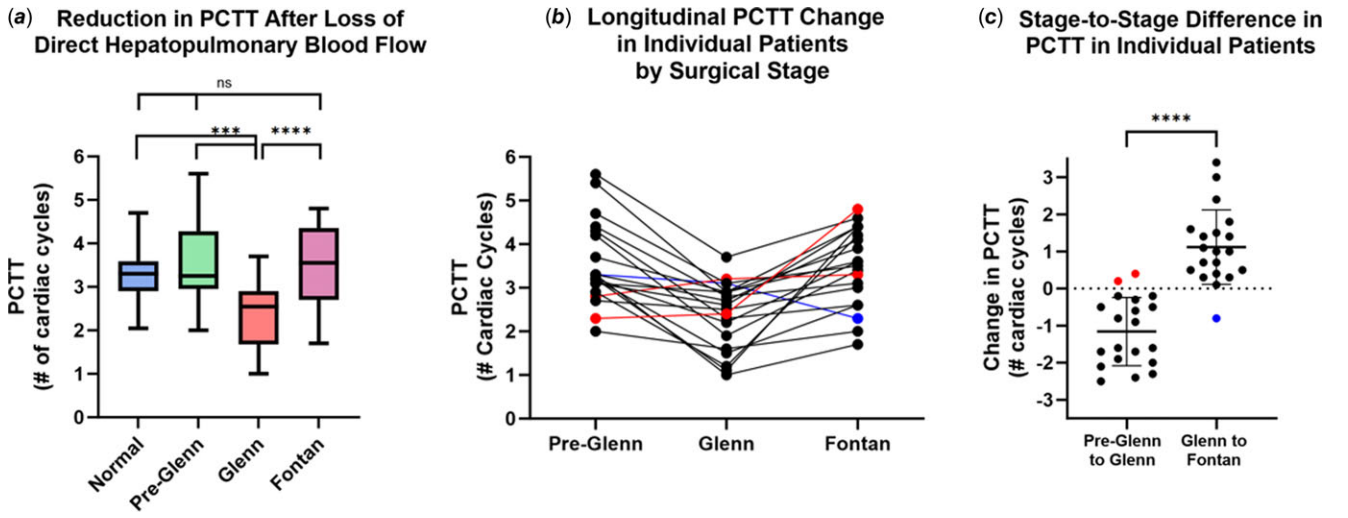


Figure 2. Loss of direct hepatopulmonary blood flow leads to reversible acceleration of pulmonary capillary transit time (PCTT). (***a***) There is no significant difference in the PCTT between patients with normal cardiopulmonary vascular connections and single ventricle patients in the Pre-Glenn or Fontan stage. However, the PCTT in patients with Glenn anatomy is significantly accelerated. (***b***) Tracking individual patients (from A) through each surgical stage shows accelerated PCTT in the Glenn that reverts to normal after restoration of direct hepatopulmonary blood flow. Two patients whose PCTT did not decrease from Pre-Glenn to Glenn are highlighted in red, and one patient whose PCTT did not increase from Glenn to Fontan is highlighted in blue. (***c***) Stage-to-stage difference for the individual patients shown in (B).

In light of these unresolved issues with the current tools for detection, and cognizant of the importance of detection for prognosis and clinical management, we sought to develop a screening tool that could detect changes in the pulmonary microvascular architecture. We used pulmonary angiography to define a pulmonary capillary transit time, tracking the flow of contrast through the normal pulmonary vasculature or through the shortcuts that pulmonary arteriovenous malformations provide. This pulmonary capillary transit time tool, applied to single ventricle patients with Glenn anatomy, was studied to determine pulmonary vascular changes that may occur in the absence of direct hepatopulmonary venous flow.

Materials and methods

Study Cohort

Single ventricle patients who underwent clinically indicated cardiac catheterisation including a pulmonary artery angiogram at our institution between February 2021 and February 2023 were included in the study. For these patients, both current and prior angiograms were reviewed. Baseline clinical and catheterisation data (haemodynamic measurements, blood gases, and injection parameters) for all patients were analysed, in accordance with UTSW IRB 2020-0047.

A group of twenty patients with biventricular circulation and normal hepatopulmonary blood flow served as controls (pulmonary artery stenosis, n = 11; pulmonary valve stenosis, n = 9). Twenty patients with univentricular hearts and pulmonary angiograms available from all three surgical stages were selected for longitudinal analysis.

Angiograms from eighty-four Glenn-stage patients (including the 20 from the prior stage-to-stage analysis) were utilised to evaluate for correlation between pulmonary capillary transit time and injection conditions, haemodynamic measurements, or additional clinical factors. Pulmonary capillary transit times for this group were calculated by the lead author. From this group, twenty sequentially enrolled angiograms were evaluated by the lead author as well as four paediatric interventional cardiologists (YA, TZ, SR, AD) to measure the reproducibility of the visually calculated pulmonary capillary transit time.

Definition of pulmonary capillary transit time

We defined pulmonary capillary transit time as the number of cardiac cycles between initial opacification of the distal pulmonary

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arteries to the earliest opacification of the major pulmonary veins (Fig. 1). The degree of opacification was not taken into account. All patients were sedated and mechanically ventilated as part of the procedure, and angiographic technique was at the discretion of the attending cardiologist. However, angiograms were only selected for analysis if the contrast was injected centrally, not in a distal pulmonary artery (Supplementary Table S1). Consequently, there is a short delay between the start of injection and the start of the pulmonary capillary transit time. In the Fontan cases wherein one lung had preferential flow of contrast from the superior vena cava, separate injections in the superior vena cava and Fontan conduit were used to calculate pulmonary capillary transit time for each individual lung.

Cardiac cycle time was obtained from simultaneous electrocardiogram recordings. When simultaneous electrocardiogram was not available, direct observation of the motion of the cardiac silhouette was used (average of five cardiac cycles; frame rate of the angiogram divided by number of frames per beat, multiplied by 60 to obtain beats per minute). Pulmonary capillary transit time was calculated for left and right lungs separately, and the average was then used for subsequent grouping and analysis.

Statistical analysis

Descriptive statistics (i.e., mean, standard deviation, median, min, and max) were employed for summarising demographic, haemodynamic, and clinical variables. The two-sample t test was used to compare continuous variables. Analysis of variance was used to compare the continuous variables between several groups with Tukey Honestly Significant Difference being the multiple comparison adjustment method. The relationships between pulmonary capillary transit time and injection pressure, dose, rate, and rise were investigated by the Pearson correlation coefficient. For comparing the pulmonary capillary transit time in the longitudinal analysis, a linear-mixed model was used to incorporate the correlation between repeated measurements from the same patient. Intraclass correlation coefficient based on the two-way random effects model was used to investigate the agreement between the five readers. The p values for pairwise intraclass correlation coefficient were not adjusted. The level of significance was set at 5%. All the analyses were conducted using SPSS v29 (IBM Corp., Armonk, NY), GraphPad Prism 10.0.0 (Dotmatics, La Jolla, CA), or SAS 9.4 (SAS Inc., Cary, NC).

Results

Pulmonary capillary transit time is accelerated during the Glenn stage

The clinical characteristics of our Glenn cohort are listed in Table 1. We found that the mean pulmonary capillary transit time of the control group (with normal cardiopulmonary vascular connections and biventricular hearts) was 3.25 (95% CI 2.9–3.6) cardiac cycles. Similar to the control group, the mean pulmonary capillary transit time of the pre-Glenn and the Fontan groups were 3.53 and 3.48 cardiac cycles, respectively (Fig. 2a). However, the mean pulmonary capillary transit time of the Glenn patients was 2.37 (95% CI 2.01–2.73) cardiac cycles, significantly faster than all other individual groups ($p < 0.001$). A detailed comparison of clinical characteristics at each stage is available in Supplementary Table S2.

Table 1. Study cohort characteristics

		n (%)
Sex	Male	54 (64)
	Female	30 (36)
Functional ventricle	Right	60 (71.4)
	Left	24 (28.6)
Major cardiac defect	HLHS	33 (39.3)
	DORV	16 (19.0)
	AVCD	11 (13.1)
	TA	10 (11.9)
	PA	8 (9.5)
	DILV	6 (7.1)
Visceral situs	Solitus	69 (82.1)
	Inversus	1 (1.2)
	Right Isomerism	6 (7.1)
	Left Isomerism	8 (9.5)
Initial palliation	Sano	28 (33.3)
	BTTS	21 (25.0)
	PDA Stent	13 (15.5)
	PA Band	11 (13.1)
	None	11 (13.1)
Glenn sidedness	Right	67 (79.8)
	Left	9 (10.7)
	Bilateral	8 (9.5)
Antegrade pulmonary blood flow	No	78 (92.9)
	Yes	6 (7.1)
Pulmonary arterioplasty during Glenn	No	40 (47.6)
	Yes	44 (52.4)

HLHS = Hypoplastic Left Heart Syndrome; DORV = Double Outlet Right Ventricle; AVCD = Atrioventricular Canal Defect; TA = Tricuspid Atresia; PA = Pulmonary Atresia; DILV = Double Inlet Left Ventricle; BTTS = Blaylock Taussig Thomas Shunt; PDA = patent ductus arteriosus; PA = pulmonary artery.
Among 84 glenn patients recruited to the study, the majority were male, situs solitus, and with a single right ventricle. Initial palliation procedures were variable.

When individual patients were analysed longitudinally, we found that 90% (18/20) of patients had a faster pulmonary capillary transit time in the Glenn stage, compared to the pre-Glenn stage (Fig. 2b,c). Using a linear-mixed model, incorporating the correlation between repeated measurements from the same patient, we found that there is a significant decrease from pre-Glenn to Glenn ($p < 0.0001$) and a significant increase from Glenn to Fontan ($p = 0.0002$) (Table 2).

In our Glenn patients, there was no association between pulmonary capillary transit time and either injection pressure, contrast dose, rate of injection, or rate of rise (Supplementary Figure S1). Additionally, there was no association between pulmonary capillary transit time and catheter size ($p = .55$) or catheter type ($p = .24$) (Supplementary Figure S2). Similarly, in the Glenn cohort, neither peak pulmonary artery pressure, mean pulmonary artery pressure, transpulmonary gradient, or ventricular end-diastolic pressure correlated with pulmonary capillary transit time (Table 3). Five independent reviewers calculated

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Table 2. Transit time acceleration in the Glenn stage

		Estimated Difference (ED)	Standard Error of ED	p value
Pre-Glenn	Glenn	1.1598	0.2065	<0.0001
Pre-Glenn	Fontan	0.0524	0.2594	0.9778
Glenn	Fontan	− 1.1074	0.2224	0.0002

Using a linear-mixed model, the longitudinal analysis of pulmonary capillary transit time in single ventricle palliation reveals a statistically significant acceleration during the Glenn stage.

pulmonary capillary transit time for twenty Glenn angiograms, which yielded an intraclass correlation coefficient of 0.87 (95% CI 0.7–0.95, $p < 0.001$), indicating good agreement between viewers (Supplementary Table S3).

Discussion

This study provides the first published evidence that the pulmonary capillary transit time varies with the stage of single ventricle palliation. Our results validate the traditional teaching that, in the absence of pulmonary arteriovenous malformations, contrast takes at least three cardiac cycles to travel through the pulmonary capillary bed. In 90% of patients, pulmonary capillary transit time accelerates in the Glenn stage. The pre-Glenn data presented in our study provides evidence that the pulmonary vasculature was in fact normal prior to the changes that occur in the Glenn stage. The acceleration of pulmonary capillary transit correlates with the absence of direct hepatopulmonary venous flow in this surgical stage.

Pulmonary arteriovenous malformation detection is difficult and subject to variable limitations in the Glenn population. Diagnostic modalities of pulmonary arteriovenous malformation detection may be understood as attempts either to *visualise the lesion* (CT, MRI, or pulmonary angiography) or to *detect the effects* of pulmonary arteriovenous shunting (pulmonary venous desaturation, contrast echocardiography, 99mTc macroaggregated albumin scan). The pulmonary capillary transit time represents a combination of these two strategies, as we visualise an effect of pulmonary arteriovenous shunting.

Peripherally injected contrast echocardiography remains the standard screening method for pulmonary arteriovenous malformations in patients with normal, fully septated hearts.[15] Contrast echocardiography has been used previously to show reversibility of pulmonary arteriovenous malformations after reintroduction of hepatopulmonary venous flow, by comparing patients in the Glenn and Fontan stages.[5] Work in Fontan patients, however, has shown that the significant majority of Fontan patients have a positive contrast echocardiogram.[12] We suspect that their remarkably high positive rate is affected by the use of a distally placed end-hole catheter for bubble contrast injection (applying direct force to either deform bubbles so that they can pass through the pulmonary capillaries, or simply reduce the time spent in the capillary bed, where collapse occurs). However, their work does highlight the need for a new diagnostic modality that can track changes secondary to presence or absence of hepatic factor.

While our work is the first to quantify transit time as a pulmonary arteriovenous malformation detection method in paediatric cardiology, a single study in adult patients with hepatopulmonary syndrome defines a similar "pulmonary transit time" (time in seconds from initial injection and opacification of the main pulmonary artery to that of the left atrium).[16] Intriguingly, they report a diagnostic utility comparable to contrast echocardiography. However, they include in their transit time the portion that takes place in the large arteries, and—critically—do not index to the cardiac cycle, thereby preventing application of their methods to paediatric patients with single ventricle heart disease and highly variable heart rate.

By requiring a central (rather than peripheral) injection site, we reduce the likelihood of falsely accelerating the pulmonary capillary transit time. By not starting the transit time until contrast reaches the distal pulmonary vessels, we focus analysis on the intraparenchymal pulmonary arteriovenous malformations. Indeed, in *ex vivo* studies of isolated, perfused lungs, the distal capillary bed was shown to be responsible for the major variations in pulmonary transit time.[17]

In a regional analysis of individual lung lobes, transit time (using MRI) has been shown to reflect changes in regional pulmonary vascular resistance.[18] The fact that whole lung pulmonary capillary transit time does not correlate with pulmonary vascular resistance or transpulmonary gradient is likely due to the limited ability to pick up the subtle regional drops in pulmonary vascular resistance that would result from pulmonary arteriovenous malformations.

While visual calculation of the pulmonary capillary transit time is reliable and fast, we plan to develop an automated analysis for further ease of application. We anticipate that machine learning coupled with shadow tracking will prove effective against a background of respiratory and cardiac motion. Quantification of MR or CT-derived transit times will also be helpful, especially as their use increases for pre-Glenn evaluation.[19,20] Finally, as more data is gathered, we hope to use pulmonary capillary transit time as a measure to predict outcomes secondary to the myriad pulmonary vascular changes after the Glenn and Fontan surgeries.

Limitations

For clinical application, a direct comparison between our pulmonary capillary transit time and bubble contrast echocardiography will be necessary. Due to the variability of both anatomy and clinical management, collaboration with other centres will be necessary to power discovery of the patient-specific factors that increase risk of pulmonary arteriovenous malformation development.

Conclusions

Pulmonary capillary transit time is a simple, rapid, and reproducible method to assess changes in the pulmonary vascular architecture. Our results confirm the traditional teaching that the contrast takes at least three cardiac cycles to traverse the normal pulmonary vasculature. Our longitudinal study of pulmonary capillary transit time in single ventricle patients reinforces the

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Table 3. Relation of pulmonary capillary transit time (PCTT) and patient-specific factors during the Glenn stage

		Mean Value		Correlation With PCTT	
		N	Mean ± SD	r	p value
Demographics	Age (Years)	84	3.8 ± 1.5	0.026	0.816
	Age at Glenn	84	0.6 ± 0.6	−0.16	0.141
	Time Since Glenn	84	3.2 ± 1.5	0.094	0.396
	Age at Fontan	47	4.5 ± 1.3	−0.074	0.619
	Time Spent as Glenn	47	4.0 ± 1.3	−0.0004	0.998
Physical parameters	Height (cm)	84	94.4 ± 17.5	0.1	0.354
	Weight (kg)	84	15.9 ± 10.5	0.013	0.905
	BSA (m ^ 2)	84	0.6 ± 0.2	0.062	0.577
	VO2 (mL/kg/min)	84	159.5 ± 26.1	0.042	0.703
Catheterisation haemodynamics	Heart Rate	84	88.8 ± 14.9	0.19	0.091
	Peak PA Pressure	84	13.5 ± 2.7	−0.11	0.308
	Trough PA pressure	84	12.4 ± 2.5	−0.027	0.808
	Delta PA Pressure	84	1.2 ± 1.3	−0.18	0.096
	Mean PA pressure	84	12.7 ± 2.4	−0.078	0.480
	Mean PV or PCW Pressure	84	8.9 ± 1.8	−0.11	0.318
	TPG	84	3.8 ± 1.5	0.0087	0.937
	Ventricular EDP	84	9.0 ± 2.0	−0.085	0.440
Fick calculation of flows/resistances	Qp (mL/min)	73	2.7 ± 0.7	−0.16	0.186
	Qs (mL/min)	77	4.5 ± 2.5	−0.053	0.648
	Qp:Qs	73	0.6 ± 0.2	0.035	0.768
	PVR (Woods units)	71	1.7 ± 0.6	0.16	0.177
	SVR (Woods units)	72	12.6 ± 4.8	0.09	0.450
PV O2 Sat	Minimum PV Sat	68	94.4 ± 7.4	0.37	0.002
Femoral artery blood gas	Femoral artery pH	84	7.3 ± 0.0	0.063	0.570
	PCO2	84	41.7 ± 5.0	−0.016	0.882
	PO2	84	52.6 ± 6.9	0.21	0.054
	O2 sat	84	83.7 ± 5.9	0.24	0.028
	Base Excess	84	−3.8 ± 3.2	0.06	0.586
	HCO3 (mEq/L)	84	22.1 ± 2.8	0.06	0.588
	Haemoglobin (g/dL)	84	14.8 ± 1.8	0.011	0.918
Contrast injection parameters	Catheter Size (French)	84	5 ± 0.6	−0.032	0.771
	Dose (mL)	84	11.1 ± 3.3	−0.065	0.557
	Rate (mL/sec)	69	13.7 ± 2.8	−0.17	0.156
	Rise (sec)	69	0.1 ± 0.3	−0.029	0.811
	Pressure (PSI)	69	430.8 ± 162.6	−0.18	0.145

PA = pulmonary artery; PV = pulmonary vein; PCW = pulmonary capillary wedge; Qp = pulmonary blood flow; Qs = systemic blood flow; PVR = pulmonary vascular resistance (Woods units); SVR = systemic vascular resistance (Woods units); RUPV = right upper PV; RLPV = right lower PV; LUPV = left upper PV; LLPV = left lower PV.
Basic physical parameters, angiographic and haemodynamic conditions, and readouts of successful alveolar gas exchange were examined using Pearson correlation for their relation to the PCTT. Parameters were highlighted in red if there was a significant correlation with PCTT. All pressure measurements are in mm Hg.

hepatic factor hypothesis and shows a measurable effect of hepatic factor loss in even "normal" Glenn patients.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124000933.

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Competing interests. None.

Ethical standard. The authors assert that this work complies with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the University of Texas Southwestern Independent Review Board, UTSW IRB 2020-0047.

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