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Are dynamic measurements of central venous pressure in Fontan circulation during exercise or volume loading superior to resting measurements?

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Abstract

Background: The main objective measure to assess the health of the Fontan circulation is the pressure measurement of the superior vena cava or pulmonary arteries. We reviewed the literature for benefits of measuring resting pressure in the Fontan circuit and explored whether dynamic measurement by volume loading or exercise has the potential to refine this diagnostic tool. *Methods:* PubMed was searched for articles showing a relationship between resting post-operative central venous pressure or pulmonary artery pressure and Fontan failure. Relationships between post-operative central venous pressure or pulmonary artery pressure and volume loading changes, such as during exercise or volume loading during cardiac catheterization, were also queried. *Results:* A total of 44 articles mentioned relationships between resting central venous pressure or pulmonary artery pressure and Fontan failure. Only 26 included an analysis between the variables and only seven of those articles found pressure to be predictive of Fontan failure. Ten articles examined the relationship between exercise or volume loading and outcomes and demonstrated a large individual variation of pressures under these dynamic conditions. *Conclusions:* Based on current literature, there is not a lot of strong evidence to show that elevated resting central venous pressure or pulmonary artery pressure is predictive of Fontan failure. Some individuals experience dramatic increases in central venous pressure or pulmonary artery pressure under increased loading conditions with exercise or bolus fluid infusion, while others experience increases closer to that of a healthy control population. Further studies are needed to examine whether more dynamic and continuous monitoring of systemic venous pressures might better predict outcomes in patients with Fontan circulation.

Today, we are still unable to predict which one of our patients with a Fontan circulation will succumb or suffer from severe complications. It is estimated that only 61% of patients will survive to age 50,[1] and the literature reports that heart transplantation, plastic bronchitis and protein-losing enteropathy may be experienced by up to 4, 14, and 24% of patients, respectively, in the years following Fontan.[1–3] Yet, in a recent study in Australia and New Zealand, one-third of deceased patients were found to have had a follow-up visit within 2 years of their demise without any report of clinical deterioration in that time.[4] We still struggle to identify the optimal time at which we should refer patients for heart transplantation. And, at the time when the outcomes of protein-losing enteropathy have vastly improved, we are still unable to distinguish those patients who will have a sustainable recovery and for those whom protein-losing enteropathy is the sign of an unremittable deterioration.

Our difficulty in assessing the clinical status of our patients with Fontan circulation stems from our inability to objectively assess the "Health" of a Fontan circulation. Today we base our judgments on peripheral indices of health such as the exercise capacity, the amount of liver fibrosis, and the severity of the reported symptoms of right-sided heart failure such as decreased exercise capacity, ascites, and peripheral oedema. The main objective measure at our disposal, the measurement of the pressure in the Fontan circulation, in the superior vena cava or the pulmonary arteries, seems to elude its potential to guide us as it largely fails to correlate with adverse outcomes.[5]

We, therefore, reviewed the current literature to assess the relationship of resting Fontan pressure with outcomes related to Fontan failure. Additionally, we explored the relationship between dynamic Fontan pressure measurement and outcomes.

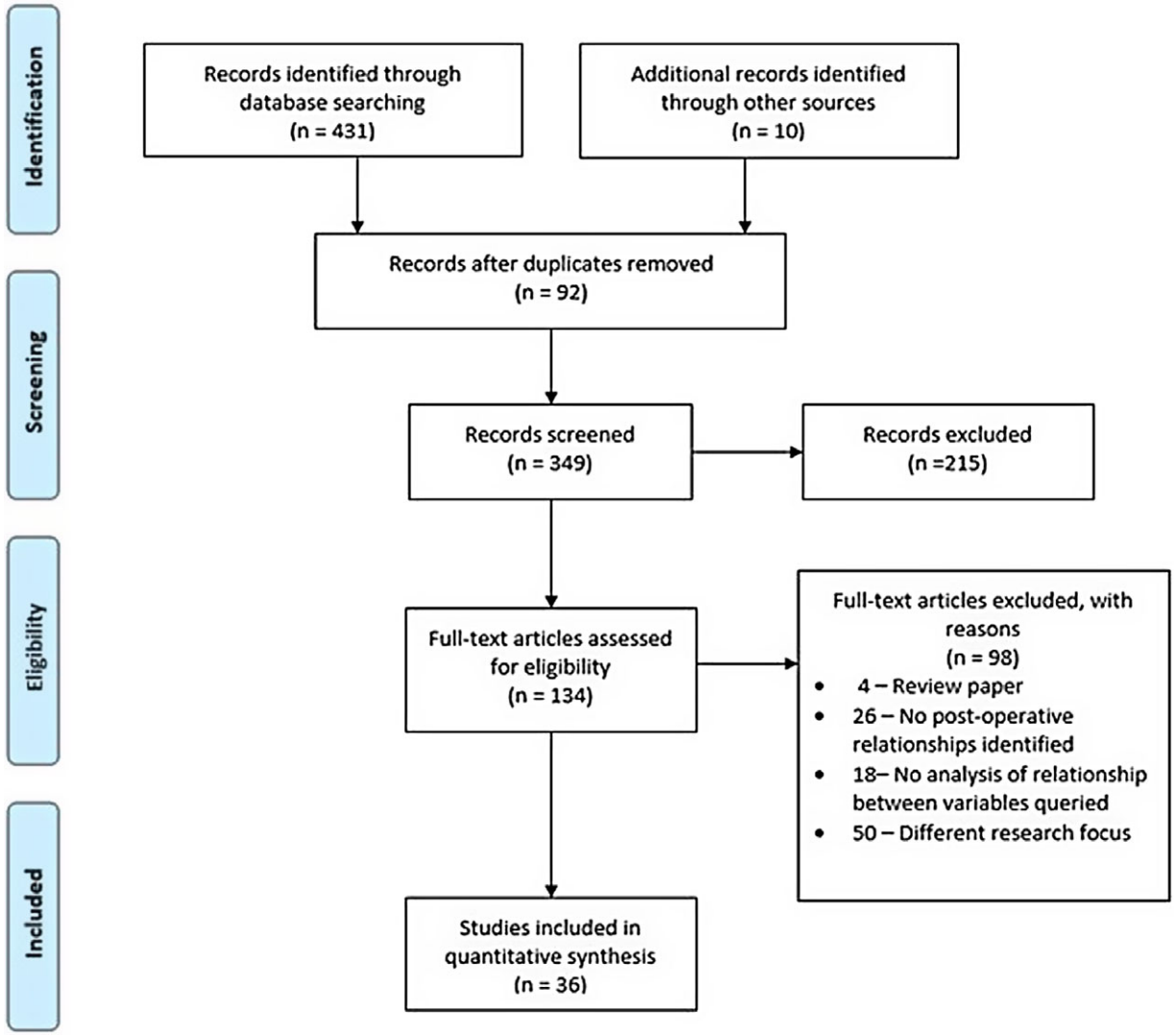

Figure 1. PRISMA flow diagram of systematic process used to select articles.

Materials and methods

The PubMed database was used to search for appropriate articles pertaining to the relationship between (1) measurements of elevated resting systemic pressures obtained after a Fontan completion and Fontan failure and (2) exercise or volume load on systemic pressure measurements in patients with Fontan circulation. Systemic pressures were defined as central venous pressure or pulmonary artery pressure. Fontan failure was identified as death, transplantation, protein-losing enteropathy, plastic bronchitis, or Fontan-associated liver disease. Studies were considered eligible if they showed an analysis between post-operative resting central venous pressure or pulmonary artery pressure and markers of Fontan failure or between exercise or volume load on the heart and measured central venous pressure or pulmonary artery pressure following a Fontan operation. A full list of search terms can be found in Supplementary Table S1. Additional articles were identified in our review and were screened for inclusion. All articles from 1976 to January 2023 were included. Non-human and non-English articles were excluded. Articles were excluded if subjects had not reached Fontan completion. Case reports and review papers were also excluded.

Results

An initial search in PubMed produced 431 articles, with an additional 10 identified through references cited in the original search, giving a total of 441 articles to be reviewed for eligibility (Fig. 1). Of those that mentioned Fontan failure, 44 studies identified a relationship between post-Fontan resting systemic pressures and events related to Fontan failure, however, only 26 produced an analysis and were included in the final review. All but 2[6,7] of the 26 studies that presented an analysis between systemic venous pressure and Fontan failure were retrospective (Table 1). Only 10 articles correlated exercise or volume loading to outcomes.

Elevated central venous pressure/pulmonary artery pressure and risk of mortality or heart transplantation

Nine studies[6,8–14] examined the relationship between elevated central venous pressure or pulmonary artery pressure and death or transplantation with only three clearly identifying that elevated pressures were predictive of premature death[12,13,15] and only one showing that higher pulmonary artery pressure was predictive of need for heart transplantation.[6]

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Table 1. Effects of central venous pressure/pulmonary artery pressure on Fontan failure.

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
Myers, 1990	R	Thirty-eight patients with Fontan circulation	Fontan completed between 1978–1989; Patient ages at time of Fontan ranged from 7 months to 23 years. Follow-up time ranged from 1 month to 8.4 years	PAP and Death	Post-operative Mean PAP measured in survivors (14.25 mm Hg) versus non-survivors (12.29 mm Hg) was nonsignificant.
Feldt, 1996	R	Forty-one patients with PLE	Fontan completed between 1973–1987; PLE onset mean 3.7 years (Range 2 months–9 years); 30% developed PLE after 5 years post-Fontan	PAP and PLE	Univariate analysis found no significant risk of developing PLE amongst patients with "normal" Mean PAP (< 30 mm Hg) versus "abnormal" Mean PAP (≥ 30 mm Hg)
Mertens, 1998	R	One hundred fourteen patients with PLE	Fontan completed between 1975–1995; Mean age at PLE onset was 2.7 years (Range 1 month–16.4 years)	PAP and PLE	77 of 114 patients underwent cardiac catheterisation after PLE diagnosed, mean PAP: 16.3 ± 6.1 mm Hg (Range 6 – 40)
Mitchell, 2004	R	Fifteen patients (14 with a failed Fontan circulation, 1 with Kawashima circulation) all with Htx	Mean time interval post-Fontan to Htx was 7.4 ± 6.2 years	PAP and Htx	Paired analysis showed pre-Htx mean PAP was 17.0 ± 3.7 mm Hg compared to post-Htx mean PAP, 19.7 ± 3.3 mm Hg, p = 0.064; Mean PAP measured in 9 late Fontan failure patients (> 1 year failure post-Fontan), mean PAP in pre-Htx was 17.0 ± 3.4 mm Hg versus in post-Htx, 20.6 ± 2.5 mm Hg, p = 0.057.
Lin, 2006	R	Nine patients with PLE	Fontan completed between 1985 and 2005; mean time interval Post-Fontan to PLE was 4.8 years (Range 1.2–9.7 years)	PAP and PLE	Hemodynamics after PLE was assessed in 6 patients, mean PAP was 22.3 ± 6.4 mmHg (Range 16 – 33 mmHg)
Ohuchi, 2012	R	Eighteen "excellent" versus 43 "non-excellent" Fontan survivors	Fontan completed between 1979–1998; Serial hemodynamic assessments performed before Fontan and 1, 5, 10, 15 and ≥ 20 years post-Fontan	CVP and death	"Excellent" Fontan survivors were free from unscheduled hospitalisations, major complications (including death, PLE, PB, among other events), and failing hemodynamics (including CVP ≥ 16 mm Hg); "Non-excellent" survivors had significantly higher CVP (p = 0.024).
Ohuchi, 2013	R	Twenty-six patients with PLE compared to 56 "excellent" Fontan group (without failing Fontan circulation, defined as having CVP ≥ 16 mm Hg, among other findings)	Last Follow-up recorded in 2010; Cardiac catheterisation performed before Fontan and 1, 5, 10, 15 and ≥ 20 years post-Fontan	CVP and PLE	CVP was higher in PLE group than in "excellent" group (P = 0.0001), but pressure decreased in chronic phase (P = 0.01). Odds ratio for the development of PLE was 3.49 in patients with CVP ≥ 12 mm Hg, p = 0.003)
Avitabile, 2014	R	Fourteen patients with PB	Time of PB diagnosis post-Fontan ranged from 9 days to 15 years. Cardiac catheterisation performed within 6 months of PB onset.	CVP and PB	Median pressure in Fontan baffle was measured in 13 patients with PB: 15.5 mm Hg (Range 10-28)
John, 2014	R	Forty-two patients with PLE	Fontan completed between 1992–2010; Mean age at Fontan was 10.1 ± 10.8 years; PLE mean diagnosis time post-Fontan was 8.4 years ± 14.2 years	CVP and PLE	2 groups (Fontan Pressure ≤ 15 mm Hg vs > 15 mm Hg) reviewed, Group with pressure ≤ 15 mm Hg had greater survival 10 years post PLE diagnosis (p = 0.03)
Mori, 2016	R	Eighteen adult patients experiencing serious adverse event versus 42 patients without a serious adverse event	Mean time from Fontan to Catheterisation follow-up with patients "with serious adverse events" was 22.2 ± 4.9 years, and "without serious adverse events" was 22.4 ± 5.6 years, p = 0.9; Serious adverse event was defined as death, Htx or listing for Htx.	CVP and serious adverse event	Mean CVP in patients "with serious adverse events" was 18.6 ± 6.5 mm Hg versus 16.1 ± 4.3 mm Hg in patients "without serious adverse events," *p* = 0.03; Cox proportional Hazard analysis showed a nonsignificant probability for risk of death/Htx for every 1 mm Hg increase in CVP.

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Table 1. (*Continued*)

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
Ohuchi, 2017	R	Three hindred eighty-seven patients with Fontan circulation in early group versus 161 patients in late group	Fontan completed between 1979–2014; post-operative serial cardiac catheterizations performed every 5 years; Early group defined as 6 months – 5 years post-Fontan; Late group defined as ≥ 15 years post-Fontan	CVP and death	Mean CVP in Early group was 11 ± 2.8 mm Hg versus in Late group was 9.8 ± 2.6 mm Hg. Univariate analysis looked at predictors for 5-year mortality in early and late survivors and revealed increased mortality for every 1 mm Hg increased in pressure in the early group (Hazard Ratio of 1.46, $p < 0.0001$) and in late group (Hazard ratio of 1.38, $p = 0.0002$); Multivariate analysis was not performed; Log relative hazard graphs did not show significant differences in CVP and mortality between the early and late groups.
Ono, 2018	R	Twenty-eight patients with Fontan circulation and 14 patients with BVR, all diagnoses with PLE	Age of repair in BVR versus Fontan group was 4.2 ± 1.2 versus 5.4 ± 0.9 years, $p = 0.46$; Mean age at PLE diagnosis in BVR versus Fontan was 18.5 ± 2.6 versus 13.4 ± 1.8, $p = 0.14$; Mean time from repair to PLE onset in BVR versus Fontan group was 14.2 ± 2.0 versus 8.2 ± 1.4 years, $p = 0.02$	CVP and PLE	CVP significantly lower in BVR group at first catheterisation following repair with a time range of 2 to 84 months (6.8 ± 4.6 versus 11.8 ± 2.3, $p < 0.001$); No difference in CVP between the groups at onset of PLE (13.5 ± 0.8 versus 12.8 ± 0.5, $p = 0.47$)
Song, 2018	R	Twenty-six patients with Fontan circulation undergoing catheterisation and hepatic evaluation	Median age at time of evaluation was 13 years (Range 10–35); Median time from Fontan to follow-up was 10.5 years (Range 4–17); Liver dysfunction was defined as changes seen on liver ultrasonography, liver CT and/or transient elastography.	PAP and liver dysfunction	Mean PAP at the time of evaluation was 12.8 ± 2.3 mm Hg; On Liver CT, mean PAP was significantly higher in the Liver Cirrhosis group (14.50 ± 2.73 mm Hg) versus in the Chronic Parenchymal Liver Disease group (12.07 ± 1.75 mm Hg), $p = 0.046$; No significant association of PAP and liver fibrosis seen via ultrasonography or transient elastography.
Bradley, 2019	P	Six adult patients with NYHA-FIII or greater and at least 1 hospitalisation in past year for acute compensated heart failure implanted with invasive hemodynamic monitoring using CardioMEMs™ heart failure system	Mean age at time of implantation was 30 ± 7 years measured once a day for a 12-month period; Exercise testing completed at baseline and at 6–month clinic visit.	PAP and Htx; Exercise and PAP	Mean Fontan pressure measured at baseline (16 ± 5 mm Hg); Mean PAP measured during heart failure-mediated events was 18.2 ± 6.6 mm Hg (Range 6-40 mm Hg) and was higher when compared to those without an event ($p < 0.0001$). Higher mean PAP was associated with greater odds (OR 1.17 [1.09, 1.25], $p < 0.0001$) of having a heart failure-mediated event, defined as clinical status or treatment change due to worsening heart failure including cardiac medication change, hospital admission, paracentesis or Htx listing change; No significant change in mean PAP with exercise; Figures 1 and 2 show varied slopes of each patient during average monthly mean PAP readings and during 12 minutes of exercise, respectively.

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Table 1. (*Continued*)

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
de Lange, 2019	R	Sixty-two patients with Fontan circulation undergoing routine CMR with T1 mapping in the liver	Mean age at Fontan was 3.3 ± 0.9 years; Mean age at time of post-Fontan CMR was 11.4 ± 4.4 year; Time from CMR to CVP measurement was 1719 ± 183 days.	CVP and CMR markers suggestive of liver fibrosis	Mean CVP was 10.9 ± 0.8 mm Hg; Markers suggestive of liver fibrosis were not associated with CVP (no p value presented).
Nakatsuka, 2019	P	Sixteen patients with Fontan circulation who underwent catheterisation and abdominal ultrasound with Doppler waveform of the hepatic vein	Mean age at Fontan was 4.1 ± 4.5 years; Mean age at catheterizations was 15.6 ± 11.3 years; Mean time post-Fontan to catheterisation was 11.4 ± 7.9 years; Hepatic vein waveform is used to categorise staging of liver fibrosis.	CVP and hepatic vein waveforms suggestive of liver fibrosis	Mean CVP of 13.4 ± 3.5 mm Hg was not associated with liver fibrosis as measured by hepatic vein waveform, $p = 0.323$.
Oka, 2020	R	Ninety-one patients who were followed at least 3 years post-Fontan	Mean age at Fontan was 2.3 ± 1.4 years; Mean follow-up post-Fontan was 8.7 ± 4.7 years	CVP and FALD	Post-operative Mean PAP was 11.7 ± 2.7 mm Hg. Univariate analysis revealed that post-Fontan PAP was not a predictor for FALD, $p = 0.310$.
Patel, 2020	R	Sixty-three patients with Fontan circulation who underwent surveillance catheterisation	Mean age at Fontan was 14.6 ± 3 years; Mean time post-Fontan to catheterisation was 11.3 ± 3.1 years.	CVP and liver fibrosis	Mean Fontan pressure was 11.8 ± 2.1 mm Hg and univariate analysis revealed it was not a predictor of advanced liver fibrosis, $p = 0.965$.
Schleiger, 2020	R	One hundred twenty-nine patients with Fontan circulation grouped by "Fontan failure" ($n = 21$) versus "no Fontan failure" ($n = 108$)	Median age at Fontan of Total cohort was 3.6 years (IQR, 2.5); Median time from Fontan to follow-up date in failure group versus no failure group was 9.6 years (IQR, 8.6) versus 23.1 years (IQR, 7), $p < 0.001$; Fontan failure was defined as Severely compromised NYHA status without improvement for ≥ 6 months, ≥ 2 hospitalisations as a result of clinical deterioration in last 12 months, active PLE or PB without remission for 6 months, or impaired CPET	PAP and Fontan failure; PAP and FALD severity	Significant difference in median PAP in Fontan failure group, 15 mm Hg (IQR, 6.3) versus no Fontan failure group, 11 mm Hg (IQR, 3), $p < 0.001$; Significant association between advanced FALD and higher PAP, $p = 0.006$.
Schleiger, 2020	R	One hundred forty-five patients with Fontan circulation underwent hepatic assessment	Median age at Fontan was 3.5 years (IQR, 3.3); Median time from Fontan to follow-up was 10.3 years (IQR, 14.7)	PAP and FALD	Median PAP was 12 mm Hg (IQR, 4); Median PAP was significantly higher in patients with liver cirrhosis, $p = 0.008$; Median PAP not associated with FALD incidence
Sethasathien, 2020	R	One hundred seventeen patients with Fontan circulation	Median age of repair was 5.7 years	PAP and death	Multivariate cox regression analysis revealed post-operative mean PAP ≥ 23 mm Hg to be predictor of early mortality (less than 30 days after Fontan), Hazard Ratio 23.2, $p = 0.004$.
Sethasathien, 2020	R	Eighty patients with Fontan circulation grouped by "FALD" ($n = 21$) and "no FALD" ($n = 29$)	Median age at Fontan was 5.7 years (Range 2.4–17.2); Median time from Fontan to follow-up was 5.5 years (Range 1-21.7)	PAP and FALD	Mean PAP was significantly higher in the FALD group (15 ± 3 mm Hg) versus in the no FALD group (13 ± 3 mm Hg), $p = 0.01$; PAP was not found to be an independent predictor of FALD.
Rodriquez, 2021	R	Nine Patients with Fontan circulation were referred for Htx	Age range was 10–19 years at the time of Htx	CVP and Htx	Mean CVP measured pre-Htx (18.8 ± 2.2) and post-Htx (9.3 ± 3.0), $p < 0.0004$. Figure 2 shows varied slopes of patients before and after Htx.

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Table 1. (*Continued*)

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
Hansen, 2022	R	One hundred seventy patients with Fontan circulation	Median follow-up post-Fontan was 10.2 years (Range 6.5–15.2). FALD severity was graded using the Liver Disease Score (0–10) that counted liver abnormalities on routine ultrasound and blood testing.	PAP and FALD	Median PAP of patients with Liver disease score of 0–4 versus 5–10 was 10 mm Hg (Range 9–12) versus 13 mm Hg (11–15), $p < 0.001$. Multivariate analysis revealed that higher CVP was a risk factor for having more advanced FALD (Odds ratio 1.6), $p < 0.001$.
Inai, 2022	R	One thousand one hundred seventeen perioperative survivors of Fontan from nine institutions in Japan	All Fontan operations completed before 2011; Median age of repair was 3.6 years; Median time from Fontan to catheterisation was 1 year.	CVP and death	Multivariable analysis revealed that CVP ≥ 16 mm Hg was an independent predictor of death (Hazard Ratio with 95% Confidence Interval: 2.3 [1.3–3.9]), $p = 0.003$
Inuzuka, 2023	R	One thousand one hundred seventeen perioperative survivors of Fontan from nine institutions in Japan	All Fontan operations completed before 2011; Median age of repair was 3.4 years (IQR, 2.3–6.3); Median time from Fontan to catheterisation was 1 year (IQR, 0.58–1.6); Median follow-up post-Fontan was 10.3 years (IQR, 7.3–16.4).	CVP and FALD	Mean CVP of patients with FALD was 13.7 ± 3.1 mm Hg and without FALD was 12.7 ± 3.0 mm Hg, $p = 0.011$; Multivariable analysis revealed CVP increase of 3 mm Hg was independent predictor of FALD (Hazard Ratio with 95% Confidence Interval: 1.28 [1.01 to 1.63]), $p = 0.042$.

BVR = biventricular repair; CMR = cardiac magnetic resonance; CPET = cardiopulmonary exercise test; CT = computed tomography; CVP = central venous pressure; FALD = Fontan-associated liver disease; Htx = heart transplantation; NYHA-FIII = New York heart association functional class, PAP = pulmonary artery pressure, PLE = protein-losing enteropathy; PB = plastic bronchitis; P = prospective; R = retrospective.

In 2017, Ohuchi et al were the first to show the predictive impact of higher central venous pressure on outcomes when measured early (6 months to 5 years post-Fontan), and late (≥ 15 years post-Fontan). Univariate analysis showed an increased risk of late mortality for every 1 mm Hg increase in central venous pressure in the group investigated early (hazard ratio of 1.46, $p < 0.001$) as well as investigated late (hazard ratio of 1.38, $p = 0.0002$).[12] Subsequently, Sethasathien et al used multivariate cox regression to show that early post-operative elevated pulmonary artery pressure ≥ 23 mm Hg were predictive of mortality within 30 days of Fontan operation (hazard ratio of 23.2, $p = 0.004$).[13] More recently, Inai et al performed a multi-institutional study involving nine centres in Japan and found that central venous pressure ≥ 16 mm Hg, measured a median of one year after Fontan completion, was an independent predictor of death in the following 2 decades (hazard ratio of 2.3, $p = 0.003$).[15] The only study to find a predictive relationship between elevated central venous pressure and heart transplantation was performed by Bradley et al in 2019. This group looked at six patients with clinical deterioration who were hospitalised at least once for acutely decompensated heart failure and who had a CardioMEMS™ (Abbot, Chicago, IL, US), an implantable hemodynamic monitor inserted. They found that having higher mean pulmonary artery pressure was associated with greater odds of developing a heart failure-mediated event (odds ratio of 1.17, $p < 0.0001$).[6] This article also assessed changes in PAP during 10 one-minute exercise intervals and identified a great variability in the changes observed with exercise. Having variations greater than 4 mm Hg was predictive of worse outcomes.[6]

Another two studies pointed to better outcomes in patients with lower central venous pressure.[10,11] In a group of 60 patients catheterised two decades after Fontan, Mori et al found a slightly higher central venous pressure in those who subsequently died or were transplanted, but time-related analysis could not identify any correlation.[11] In 2012, Ohuchi et al tried to define the characteristics of patients who were in "excellent" condition, defined as not having a re-hospitalization or adverse hemodynamics. The group of patients with excellent status had lower central venous pressure over serial catheterisation performed at 1, 5, 10, and 15 years, but the average of those differences was around 1–2 mm Hg and they considered having a central venous pressure over 16 mmHg to be adverse hemodynamics, precluding any predictive analysis.[10]

Another indirect evidence of the lack of adequacy of measuring central venous pressure as an index of the health of the Fontan circulation is brought by a study by Mitchell et al who assessed the hemodynamics of patients before and after heart transplantation.[9] This work revealed that, in patients undergoing heart transplantation for late Fontan failure, the pulmonary vascular resistance is elevated above normal, but this fact could only be unveiled early after transplantation as the transpulmonary gradient increased by 8 mmHg early after transplantation ($p = 0.0004$ by paired analysis). Interestingly, the average PA pressure pre-transplantation was 17 mm Hg.[9] On the other hand, Rodriguez et al revealed that mean central venous pressure decreased significantly by 9 mm Hg post-transplantation ($p < 0.004$).[14]

Finally, of the nine studies reviewed, the first article to examine relationships between systemic pressure and death was performed in 1990 by Myers et al.[8] This study, however, found no significance between post-operative mean pulmonary artery pressure in survivors and non-survivors.

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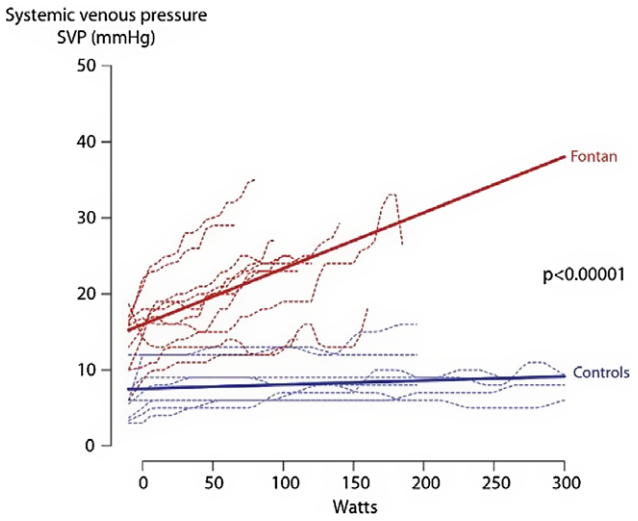

Figure 2. Individual systemic venous pressure responses during exercise in Fontan patients and controls. In Fontan, the systemic venous pressure change (in mm Hg) relative to power output is described by: 15.97 + 0.073 x watts. In control, the systemic venous pressure change (in mm Hg) relative to power output is described by: 7.52 + 0.005 x watts ($p < 0.0001$). Reprinted from The American Journal of Cardiology, Volume 117 Issue 10, D. Navaratnam, S. Fitzsimmons, M. Grocott, H. B. Rossiter, Y. Emmanuel, G. Diller, T. Gordon-Walker, S. Jack, N. Sheron, J. Pappachan, J. N. Pratap, J. J. Vettukattil, and G. Veldtman. Exercise-induced systemic venous hypertension in the Fontan circulation. Pages 1667–1671 (2016), with permission from Elsevier.

Elevated central venous pressure/pulmonary artery pressure and protein-losing enteropathy

Of the 6[3,16–20] studies that analysed relationships between central venous pressure or pulmonary artery pressure and protein-losing enteropathy, only one positively identified elevated central venous pressure to be a risk factor for developing protein-losing enteropathy.[16]

In a series of 26 patients with protein-losing enteropathy out of a cohort of 354 patients, Ohuchi et al demonstrated that central venous pressure measured one year post-operatively was an independent predictor of developing protein-losing enteropathy, with a 39 times greater risk of developing protein-losing enteropathy if central venous pressure was ≥ 12 mm Hg (Odds ratio of 3.49, $p = 0.003$).[16]

Contrastingly, a historical series was performed by the Mayo Clinic in 1996, where Feldt et al compared 42 patients developing protein-losing enteropathy to the remaining 385 patients of their cohort.[3] Central venous pressure was measured at serial intervals after Fontan completion but was not a predictor of having protein-losing enteropathy when analysed as a continuous variable. The average pressure of those having protein-losing enteropathy was 19 mm Hg at the time of diagnosis.[3]

The remaining studies observed elevated systemic pressures in patients who were already diagnosed with protein-losing enteropathy. In a series of 42 patients from the Mayo Clinic, John et al analyzed the impact of having a pressure above or below 15 mm Hg at the time of diagnosis of protein-losing enteropathy and demonstrated that patients with pressures < 15 mm Hg had greater survival ($p = 0.03$).[17] Ono et al found no difference in mean post-operative central venous pressure between patients with protein-losing enteropathy who underwent Fontan versus biventricular repair ($p = 0.47$).[18] In a seminal multi-centric study of 114 patients, Mertens et al identified that the mean PA pressure at the time of diagnosis of protein-losing enteropathy was 16 mm Hg,[19] and in another smaller study of 6 patients with protein-losing enteropathy, the mean PA pressure was 22 mm Hg at diagnosis.[20] No correlations were presented in the latter two studies.

Effects of elevated central venous pressure/pulmonary artery pressure and plastic bronchitis

One study examined the central venous pressure in patients with plastic bronchitis and reported that their median pressure within the Fontan baffle was 16 mm Hg (Range 10–28).[21] This study only consisted of 14 patients diagnosed with plastic bronchitis, 13 of which had a Fontan completion, and thus no correlations were reported in the results.

Elevated central venous pressure/pulmonary artery pressure and Fontan-associated liver disease

Of the 10 articles[7,22–30] that identified a relationship between elevated systemic venous pressures and symptoms related to liver failure, only two[29,30] showed a predictive relationship.

At a median follow up of 10.2 years post-Fontan, Hansen et al reviewed the relationship of pulmonary artery pressure and liver disease score and found that both times since Fontan (odds ratio of 1.2, $p < 0.01$) and higher central venous pressure (odds ratio of 1.6, $p < 0.001$) were predictors of advanced Fontan-associated liver disease.[29] Inuzuka et al reviewed data from 1117 perioperative survivors of Fontan across nine institutions in Japan with and without Fontan-associated liver disease.[30] Central venous pressure, measured at an average of one year after Fontan completion, was significantly higher in the Fontan-associated liver disease group ($p = 0.011$). By Cox regression, higher central venous pressure (by 3 mm Hg increases) was an independent predictor of Fontan-associated liver disease (hazard ratio of 1.28, $p = 0.042$).[30] Three additional studies, however, revealed that systemic venous pressures were not predictive of Fontan-associated liver disease, although pressures measured in these studies were no higher than 15 mm Hg[24,25,28]

Additional contrasting evidence was reported in two different studies performed by Schleiger and colleagues. This group initially described the incidence and severity of Fontan-associated liver disease. First, they looked at 21 patients with Fontan failure compared to 108 patients without failure and found that those with higher pulmonary artery pressure had advanced Fontan-associated liver disease ($p = 0.006$).[26] In a subsequent study, they found that pulmonary artery pressure was significantly higher in patients with liver cirrhosis ($p = 0.08$), but that it was no longer associated with incidence of Fontan-associated liver disease.[27]

The three[7,22,23] remaining studies that assessed systemic venous pressures and liver failure used imaging and biomarkers that were indicative of liver fibrosis and disease, however, all three studies showed no significant associations between central venous pressure and pulmonary artery pressure and liver dysfunction.

Exercise and central venous pressure/pulmonary artery pressure

Two retrospectives[31,32] and three prospective studies[33–35] were included (Table 2).

All of the studies that were reviewed looked at central venous pressure or pulmonary artery pressure measurements during various exercise stress tests. In an earlier study, Goldstein et al. measured pulmonary artery pressure during exercise in the supine position and found that it increased significantly in six patients

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Table 2. Effects of exercise on central venous pressure/PAP measurements.

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
Goldstein, 2010	P	Six patients with Fontan circulation completed exercise in supine position	Mean age 13.6 ± 6.2 years	Exercise and PAP	Mean PAP at rest was 15.5 ± 2.1 mm Hg versus 24.7 ± 5.1 at peak exercise ($p = 0.001$)
Navaratnam, 2016	P	Ten patients with Fontan circulation completed exercise on electromagnetically braked cycle for 8–12 minutes.	Mean age 26.4 years (Range 19–31 years)	Exercise and SVP	SVP measured in Fontan compared to controls; SVP increase significant in Fontan group during exercise. ($p < 0.00001$); Figure 1 illustrates wide range of slopes for SVP versus power output (watts) across patients.
Claessen, 2019	P	Twenty Healthy control versus 10 patients with Fontan completed supine ergometer exercises	Mean age of controls: 35 ± 11 years versus mean age of Fontan: 20 ± 4 years, $p < 0.0001$	Exercise and PAP	Mean PAP measured at baseline in controls: 13 ± 3 mm Hg versus mean PAP in Fontan: 9 ± 3 mm Hg, $p = 0.007$; Mean PAP measured during exercise in controls: 27 ± 7 mm Hg versus mean PAP in Fontan: 21 ± 5 mm Hg, $p = 0.022$
Asagai, 2020	R	Thirty-four patients with Fontan circulation completed hand ergometer exercises	Mean time post-Fontan 12.7 years (Range 2.9–25.4 years)	Exercise and CVP	Mean Rest CVP 11 mm Hg (Range 7–18) versus Mean Exercise CVP 19 mm Hg (Range 11–28); Figure 1 illustrates wide range of scatterplot values of CVP at exercise versus CVP at rest across patients ($r = 0.54$, $p = <0.001$)
Egbe, 2020	R	Twenty-ninr symptomatic adult patients with Fontan circulation undergoing invasive hemodynamic exercise testing	Mean age at time of Fontan was 5 ± 3 years; Mean age at time of study was 29 ± 6 years. Pulmonary Vascular Resistance was defined as slope of mean PAP in relation to cardiac output (mean PAP/CO) during supine cycle ergometry exercises with 20 W increases every 2 minutes. Abnormal slope measured as mean PAP/CO > 3 mm Hg/l*min.	Exercise and CVP	Abnormal mean PAP/CO slope had higher CVP at rest (16 ± 3 mm Hg) compared to normal mean PAP/CO slope (12 ± 2 mm Hg), $p = 0.002$. Abnormal mean PAP/CO slope had higher CVP at 20 W (24 ± 5 mm Hg) compared to normal mean PAP/CO slope (16 ± 3 mm Hg), $p < 0.001$. Abnormal mean PAP/CO slope had higher CVP at peak exercise (29 ± 7 mm Hg) compared to normal mean PAP/CO slope (19 ± 5 mm Hg), $p < 0.001$).

CO = cardiac output; CVP = central venous pressure; PAP = pulmonary artery pressure; P = prospective; R = retrospective; SVPs = systemic venous pressures; W = watts.

with Fontan circulation. Mean pulmonary artery pressure increased from 16 mm Hg at rest to 25 mm Hg at peak exercise ($p = 0.001$).[33] Another study by Claessen et al measured mean pulmonary artery pressure during supine ergometer exercises in healthy controls versus patients with Fontan circulation. Mean pulmonary artery pressure was higher in the control groups at baseline and during exercise. The mean PA pressure in patients with a Fontan increased from 9 to 21 mm Hg.[35] Most notably, Navaratnam et al. showed in the initial figure of their manuscript that there is a wide variation in systemic venous pressures between controls and patients with a Fontan circulation with even a minimal amount of exercise.[34] Exercise in this study consisted of patients completing 8–12 minutes on an electromagnetically braked bicycle. In patients with normal biventricular circulation, there was an increase in central venous pressure of 5–10 mmHg with exercise while these elevations were significantly more pronounced in patients with Fontan circulation. The slope of increase in venous pressure from even a minimal amount of exercise varied greatly in the small set of patients that were tested, with some of the patients having central venous pressure increasing to a level up to 35 mmHg.[34] (Fig. 2) A retrospective study by Asagai et al examined central venous pressure changes before and during hand ergometer exercises. They also found great variations between patients in terms of the size of increase of PA pressures at exercise and identified some correlation between having an elevated PA pressure on exercise and some biological parameters.[31] In a detailed analysis of hemodynamic parameters during exercise in 29 symptomatic patients with Fontan circulation, Egbe et al determined that a constructed "vascular reserve index," extracted from the change during exercise in the ratio between pulmonary artery pressures and cardiac output, was able to better define pulmonary vascular function. They found that pulmonary vascular reserve was impaired in these patients during exercise, even when patients had a normal vascular resistance at baseline, and that these limitations in reserve during exercise were associated with end-organ dysfunction. Thus, this index might be best used to assess the health of the pulmonary vascular bed and to prevent the eventual end-organ damage of patients with a Fontan circulation.[32]

Volume loading and central venous pressure/pulmonary artery pressure

Four prospective studies[36–39] and one retrospective study[40] investigating the impact of volume loading on central venous pressure measurements were found. (Table 3) In 2015, the team from Leuven studied 28 patients with Fontan circulation having 32 catheterisation studies. They showed a significant difference ($p < 0.05$) in mean venous pressure before (14.6 ± 2.8 mm Hg, Range 10–21) and after intravascular volume loading of 15cc/Kg of 0.9% NaCl (18.3 ± 3.3 mm Hg, Range 2–19), with clear variation in individual responses to the volume challenge. They concluded that pressure

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Table 3. Effects of volume loading on central venous pressure/PAP measurements.

Author, date published	Type of study	Patient population	Assessment data and defined diagnosis criteria	Variables analysed	Outcomes observed
De Mey, 2015	P	Twenty-eight patients with Fontan circulation underwent volume challenge (15cc/Kg of 0.9% NaCl) during catheterisation	Fontan completed between 2005 – 2011; Mean time post-Fontan 5.6 ± 4.8 years (Range 0.2–18.3)	Volume challenge and MVP	MVP at baseline 14.6 ± 2.8 mm Hg (Range 10–21) versus MVP during volume challenge 18.3 ± 3.3 mm Hg (Range 2–19), $p < 0.05$; Table 2 reports varied individual MVP following volume challenge.
Averin, 2016	P	Fourty-six patients with Fontan circulation (16 with ODD and 30 without ODD) underwent RVE (15 mL/kg of 0.9% NaCl) during cardiac catheterisation	Mean time post-Fontan 10.8 years (IQR 5.1–17.8)	RVE and Mean Fontan circuit pressure	Mean Fontan circuit pressure increased between baseline 12.4 ± 2.2 mm Hg and RVE, 15.2 ± 2.5, $p < 0.001$
Kim, 2018	P	Forty patients with Fontan circulation versus 29 controls with BVR underwent volume loading by angiography (0.4 mg/kg of indocyanine green contrast medium)	Mean age in Fontan group 9.8 ± 7.8 years versus BVR group 5.4 ± 4.2 years ($p < 0.01$)	Volume loading and CVP	Mean CVP in Fontan group 10.2 ± 3.1 mm Hg versus in BVR group 6.2 ± 3.4 mm Hg ($p < 0.0001$); Figure 1 shows comparison of wide range of CVP changes between baseline and Post-angiography in Fontan versus control groups.
Möller, 2022	P	Thirty-eight patients with Fontan circulation underwent RVE (5 mL of 0.9% saline/kg body weight at room temperature)	Median age at Fontan was 2 years (IQR, 1–11); Median age at time of RVE was 16.6 years (IQR, 15.4–17.9); Median time post-Fontan to RVE was 14.4 years (IQR, 6-16.7)	RVE and CVP	Mean CVP before versus after RVE was 13.2 ± 3.4 and 16.7 ± 3.4 mm Hg, $p < 0.001$. Figure 3 depicts individual patient changes in CVP during RVE
Peck, 2023	R	Eighty-nine Patients with Fontan circulation underwent RVE (15 mL/kg saline), grouped by "ODD" (n = 28) versus "no ODD" (n = 61)	Median age at Fontan in no ODD group was 3.6 years (IQR, 3.1–4.6) versus in ODD group was 3.7 years (IQR, 2.7–4.8), $p = 0.9$; Median time from Fontan to follow-up in no ODD group was 8.4 years (IQR, 3.3–13.6) versus in ODD group was 16.3 years (IQR, 9.2–23.8), $P = 0.001$; ODD was defined as baseline EDP < 15 mm Hg and post-RVE EDP ≥ 15 mm Hg and adverse outcomes were defined as death, VAD placement, Htx, cerebral incident, PLE, PB, haemoptysis, and hospitalisation for one of the following: heart failure, arrhythmia, thrombus, pleural effusion or seizure	RVE and Fontan pressure and adverse outcomes	No significant difference between Median baseline versus post-RVE Fontan pressure in ODD group 12 mm Hg (IQR, 11–14) versus no ODD 13 mm Hg (IQR, 12–15), $p = 0.18$; Univariate analysis revealed increases in Baseline Fontan pressure (per 1 mm Hg) was not a predictor for Post-RVE EDP (Spearman correlation coefficient was 0.20, $p = 0.06$)

BVR = biventricular repair; CVP = central venous pressure; EDP = end-diastolic pressure; MVP = mean venous pressure; ODD = occult diastolic dysfunction; P = prospective; RVE = rapid volume expansion; R = retrospective; VAD = ventricular assist device.

changes in response to volume increases can be helpful in differentiating between cardiac and pulmonary limitations.[36] A similar study by Möller et al. found a significant increase in mean central venous pressure following rapid volume expansion (5 mL of 0.9% saline/kg of body weight at room temperature) ($p < 0.001$) and this study also illustrated variable slopes in patients' pressure responses to volume expansion.[39]

One hospital in particular has implemented a ventricular stress test protocol using rapid volume expansion as part of standard clinical care in patients undergoing cardiac catheterisation. In their initial reports following this implemented protocol, Averin et al found that mean Fontan circuit pressure, as well as ventricular end-diastolic pressure, increases significantly following ventricular volume load (15 mL/kg of 0.9% NaCl). Mean pressures increased from 12.4 ± 2.2 mm Hg at rest to 15.2 ± 2.5 ($p < 0.001$) following volume loading. When looking closely at the slopes of the ventricular end-diastolic pressure in each patient, those who initially had a systemic ventricle end-diastolic pressure less than 15 mm Hg that increased above 15 mm Hg after volume loading were labelled as having occult diastolic dysfunction.[37] This group later reviewed 28 patients with occult diastolic dysfunction and 61 without occult diastolic dysfunction and demonstrated that occult diastolic dysfunction was associated with late adverse outcomes related to Fontan failure (Fig. 3). Interestingly, central venous pressure pressures at baseline were not different in those with or without occult diastolic dysfunction.[40]

A Japanese study demonstrated that in response to volume load by angiography (0.4 mg/kg of indocyanine green contrast medium), central venous pressure increased more in patients with a Fontan circulation than in patients with a biventricular circulation (10.2 ± 3.1 mm Hg versus 6.2 ± 3.4 mm Hg, $p < 0.0001$).[38]

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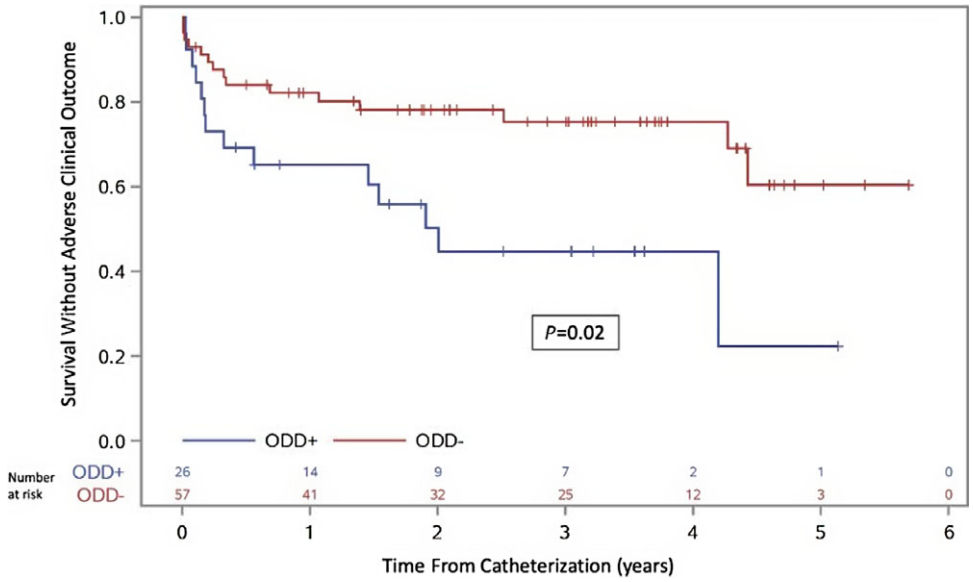

Figure 3. Freedom from adverse clinical outcomes, stratified by occult diastolic dysfunction. Kaplan–Meier survival curve demonstrating freedom from adverse clinical outcomes, stratified by the presence (blue) or absence (red) of occult diastolic dysfunction. Occult diastolic dysfunction indicates occult diastolic dysfunction. Reprinted from Journal of the American Heart Association, Volume 12, Issue 1, D. Peck, K. Averin, P. Khoury, G. Veldhuis, T. Alsaied, A. M. Lubert, R. Hirsch, W. M. Whiteside, G. Veldtman, B. H. Goldstein. Occult diastolic dysfunction and adverse clinical outcomes in adolescents and young adults with fontan circulation. Page e026508 (2022), with permission from Wiley Blackwell.

Discussion

Fifty years after the description of the Fontan operation, there seem to be only 26 studies that closely investigate the relationship between elevated resting central venous or pulmonary pressures after Fontan completion and adverse outcomes. Of those, seven[6,12,13,15,16,29,30] articles showed the predictive impact of elevated venous pressures on Fontan failure, five[3,11,24,25,28] showed no predictive impact, and another 14[7–10,14,17–23,26,27] looked at the relationships between variables, with only 5[10,14,17,26,27] of those showing a significant association. Only two studies[13,15] showing a positive relationship between elevated pressures and mortality could identify a cut-off value that would be of clinical relevance. Inai et al found that central venous pressure ≥ 16 mm Hg was an independent predictor of death, but only in patients with a median follow-up time of 1 year.[15] Sethasathien et al found that a mean pulmonary artery pressure ≥ 23 mm Hg is predictive of mortality, but this was measured within 30 days of Fontan operation.[13] Ohuchi et al identified a cut-off value of 12 mm Hg to predict 3 times increased risk of protein-losing enteropathy.[16] That value may not be discriminant enough for us to neither make predictions nor change treatment course, as there is a subset of our healthy asymptomatic patients that are reported to have values above this cut-off.[41] Another study showed that patients with protein-losing enteropathy who had PA pressures above 15 mm Hg had a higher risk of late death.[17] The pressure cut-off values in all other studies showing a positive association were only analysed as continuous variables. With nine studies[6,10,14,16,17,26,27,29,30] showing significantly higher central venous pressure pressures in patients with worse outcomes, it is undeniable that the central venous and pulmonary pressures of our patients will rise during failure of the Fontan circulation. There are multiple possible reasons for these observations, for example, vasoplegia related to anaesthesia, hypovolemia induced by fasting, the supine position and changes induced by medications may all explain what is happening during this phenomenon.

Despite our need to have an objective way to assess the health of the Fontan circulation of our patients, the most significant value collected is providing us only a vague impression rather than a clear indication of a pathological phenomenon. It has been postulated that dynamic testing of these pressures under exercise condition or with bolus of volume testing may be more sensitive to detect patients with early stages of the failure of the Fontan circulation. The seven studies investigating this hypothesis seem to point to a great variation in the slope of increase of these central pressures under these conditions. We suspect that patients with a steeper slope of increase in systemic pressure will correlate with worst function of the Fontan circulation. No studies have yet been able to clearly identify a relationship betwen this steeper slope of increase and subsequent adverse outcomes and should be addressed in future work.

Continuous monitoring of these pressures may ultimately be useful in the future but remain fraught with technical difficulties at this stage.[6,42,43] Other non-invasive continuous monitoring devices that measure peripheral venous pressures have been introduced, but only a few studies have actually shown that these pressures are comparable to central venous pressure or pulmonary artery pressure.[44,45]

While we are limited by the number of studies that are reported on this topic, and by the low yield of patients that are reported on in these few studies, it is important to highlight the need to report more results on this topic. In this regard, the articles presented in this review vary dramatically in the number of patients analysed, and therefore it may be unfair to compare significant predictions made from articles with thousands of patients to nonsignificant results from smaller population samples. It is also important to note that in reporting on resting systemic venous pressures, there are many factors that are confounding the associations between systemic pressure and adverse outcomes. General anaesthesia during cardiac catheterisation, for example, interferes with the hemodynamics of the patient and will be responsible for an

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underestimate of the pressures of these patients.[46,47] These patients usually arrive volume depleted after fasting since at least the previous night, which will affect the hemodynamics measured during catheterizations. The concomitant use of contrast agents and medications will also interfere with the measurement of these resting pressures.

In conclusion, while it has been shown in some studies that Fontan failure is associated with elevation of the central venous pressure, the observed resting catheterisation measurements in the literature fail to provide us with useful cut-off values above which long-term adverse outcomes could be predicted. Current studies showing central venous pressure or pulmonary artery pressure changes during exercise or volume loading identify a vast array of differences in the slopes of venous pressure changes between patients. Further studies are needed to prospectively investigate whether more dynamic measurement of central venous pressure and pulmonary artery pressure in patients with a Fontan circulation would allow us to better identify the health status of these patients and better predict their outcomes. These novel investigations could potentially unmask the patients who have occult diastolic dysfunction or increasing pulmonary vascular resistance, identify patients who will have a worse outcome after an episode of protein-losing enteropathy, and may better delineate at what stage a patient should be introduced to more intensive heart failure medications or even heart transplantation.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123003797.

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