A Preoperative Estimate of Central Venous Pressure Is Associated with Early Fontan Failure

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Glossary of Abbreviations

AUC = Area under curve

BCPC = Bidirectional cavopulmonary connection

CMR = Cardiac magnetic resonance imaging

CVP = Central venous pressure

EDV = end-diastolic volume

ESV = end-systolic volume

EF = Ejection fraction

EFF = Early Fontan Failure

ICU = Intensive care unit

OR = Odds ratio

PVR = Pulmonary vascular resistance

Q_p = Pulmonary blood flow

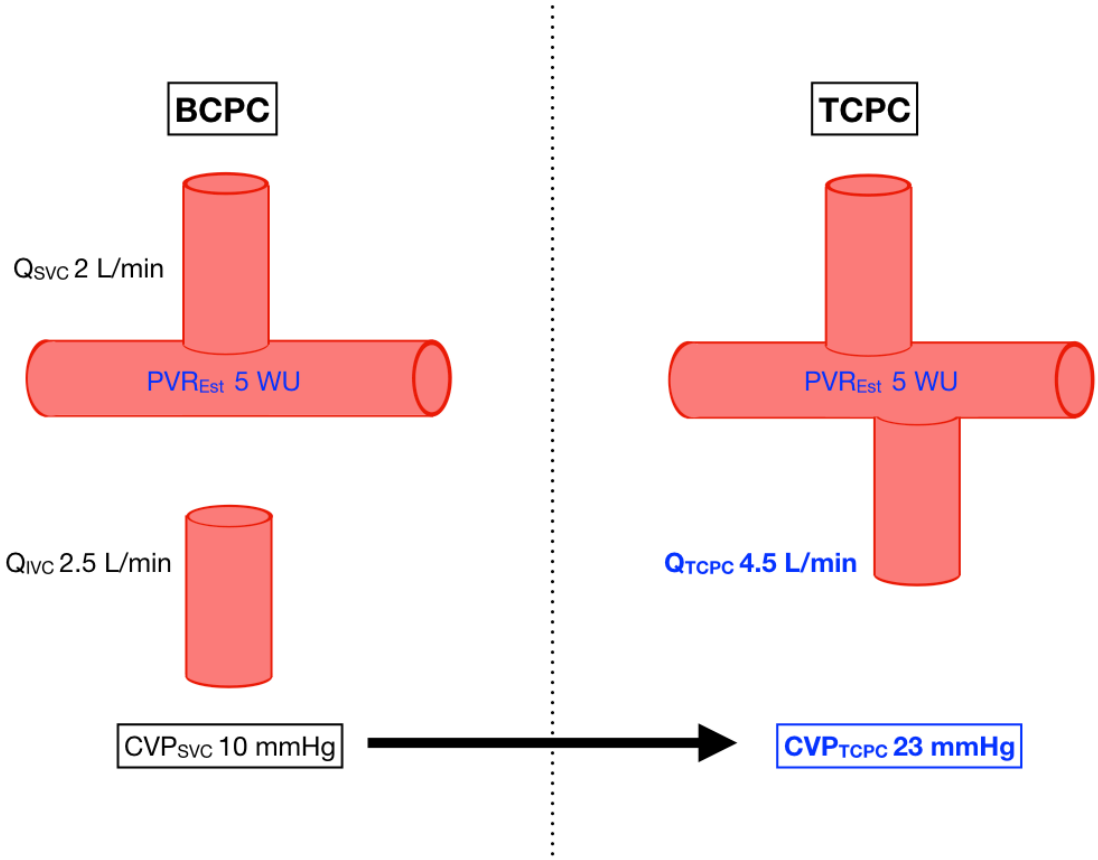
ROC = Receiver operating characteristics

SPC = Systemic to pulmonary collaterals

SV = Stroke Volume

TCPC = Total cavopulmonary connection

43 **Central Picture**



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45 CVP_{TCPC} is calculated as the product of estimated PVR and the assumed TCPC flow.

Central Message

An estimate of the central venous pressure following total cavoplulmonary connection can be calculated from pre-operative Glenn data is associated with increased risk of early Fontan failure.

Perspective

Early Fontan failure is an infrequent but serious postoperative complication which may result in death or necessitate Fontan takedown or emergency fenestration. Estimated central venous pressure may help clinicians select patients for mitigation strategies (e.g. elective fenestration); a process currently hampered by a lack of clinically useful biomarkers.

Abstract

Word Count: 242

Objective

Early Fontan Failure (EFF) is a serious complication following total cavopulmonary connection (TCPC), characterised by high central venous pressure (CVP), low cardiac output and resistance to medical therapy. This study aimed to estimate post-operative CVP in TCPC patients (CVP_{TCPC}) using data routinely collected during pre-operative assessment. We sought to determine if this metric correlated with measured post-operative CVP and if it was associated with EFF.

Methods

In this retrospective study, CVP_{TCPC} was estimated in 131 patients undergoing pre-TCPC assessment by cardiac magnetic resonance imaging and CVP measurement under general anaesthesia. Post-operative CVP during the first 24hours in ICU (CVP_{ICU}) was collected from electronic patient records in a subset of patients. EFF was defined as death, transplantation, TCPC takedown or emergency fenestration within the first 30days.

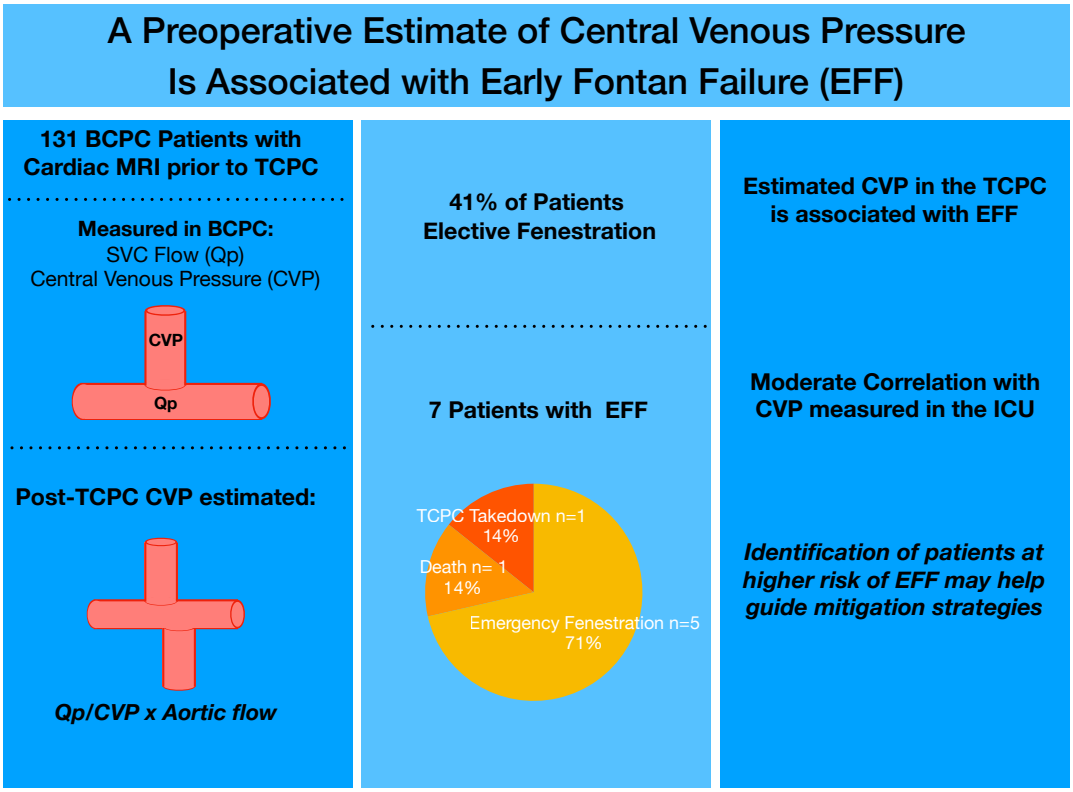
Results

Estimated CVP_{TCPC} correlated significantly with CVP_{ICU} ($r=0.26$, $p=0.03$), particularly in patients without a fenestration ($r=0.45$, $p=0.01$). CVP_{TCPC} was significantly associated with EFF (Odds Ratio [OR] 1.1 (1.01-1.21), $p=0.03$). A threshold of CVP_{TCPC} ≥33mmHg was found to have the highest specificity (90%) and sensitivity (58%) for identifying EFF (area under receiver operating curve, AUC = 0.73), OR 12.4 (2.5-62.3), $p=0.002$. This association was stronger in patients with single SVCs.

Conclusions

Estimated CVP_{TCPC} is an easily calculated metric combining pre-operative pressure and flow data. Higher CVP_{TCPC} is associated with an increased risk of EFF and is correlated with directly measured post-TCPC pressure. Identification of patients at risk of EFF has the potential to guide risk mitigation strategies.

Graphical Abstract



In this study, CMR was performed in bidirectional superior cavopulmonary connection (BCPC) patients undergoing pre-operative assessment for total cavopulmonary connection (TCPC). Using routinely collected data: pulmonary blood flow (Qp), central venous pressure (CVP) and aortic flow (Qs). We calculated a metric which attempts to estimate how much central venous pressure would increase should the TCPC be completed; if all systemic flow is directed to the lungs. Given that early Fontan failure (EFF) is associated with high post-operative CVP, we investigated whether this metric was associated with EFF events, and also if it correlated to directly measured CVP in the TCPC during the ICU stay. Our study demonstrates an association between estimated TCPC pressure and EFF and also a moderate correlation with CVP measured in the ICU.

Introduction

Early Fontan failure (EFF) is a malignant haemodynamic state which occurs in the early post-operative period following total-cavopulmonary connection (TCPC). EFF is primarily characterised by high central venous pressure (CVP), as well as low cardiac output and resistance to medical therapy. Importantly, EFF may result in death, take-down of the TCPC, emergency fenestration or cardiac transplantation. [1, 2]

It is recognized that mean CVP rises linearly with both pulmonary blood flow (Q_p) and pulmonary vascular resistance (PVR) in patients with cavo-pulmonary connections. Thus, the transition from the bidirectional cavopulmonary connection (BCPC) to the TCPC must result in increased CVP, due to the increase in Q_p. Patients who experience large rises in CVP may be at increased risk of EFF.

Unfortunately, pre-operative biomarkers for EFF are lacking. [3, 4] Given the pathophysiology of EFF, identification of a postoperative high CVP phenotype would be desirable to both to inform surgical risk and guide mitigation strategies (e.g. elective fenestration).

One possibility is to use pressure and flow data, routinely acquired in the pre-operative BCPC state, to derive an estimate of CVP following TCPC completion.

In this study we aimed to i) estimate CVP in the immediate TCPC post-operative period using data routinely collected during pre-operative cardiovascular magnetic resonance (CMR) and ii) determine the association, if any, with CVP measured in ICU and iii) assess if metrics were associated with EFF.

Methods

Study population

The study cohort included all children between April 2005 and September 2017 who underwent elective pre-TCPC CMR assessment in whom a complete CMR flow and CVP dataset were available:131 patients from a total population of 147. Demographic and clinical details were obtained from the medical record.

All patients subsequently underwent an extracardiac TCPC with or without elective fenestration. The decision to electively fenestrate the TCPC conduit was made by consensus of the cardiology and cardiac surgical staff at the time of case discussion, based on clinically available data. This did not include the investigational estimated TCPC pressure. The cardiac surgical team may also have decided to fenestrate based on intra-operative data, including high TCPC pressure.

Informed consent for the use of imaging data was obtained from all parents or guardians of the patients included in this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local committee of the UK national research ethics service (06/Q0508/124).

CMR protocol

All CMR studies were undertaken on a 1.5 T MR scanner (Avanto; Siemens Medical Systems, Erlangen, Germany) with the patient under general anaesthetic as is our institutional policy for all pre-TCPC CMR exams. Ventilator parameters were adjusted to keep end-tidal carbon

dioxide between 3.5 - 5.5 kPa and supplemental oxygen was given as required to maintain oxygen saturations (SpO_2) at the usual pre-anaesthetic value for the patient.

Flow Imaging

Through-plane quantitative flow data was acquired using retrospectively gated, velocity encoded, phase contrast magnetic resonance. Images were either acquired using a free breathing Cartesian sequence with 3 signal averages or a spiral sequence acquired during a short apnoeic period of 5-8 seconds. The spirals sequence has previously been validated against free breathing Cartesian phase contrast magnetic resonance with good agreement. [5] Data was acquired in the following positions: SVC close to pulmonary artery anastomosis, IVC at diaphragm level, pulmonary trunk (if present), proximal branch PAs, proximal pulmonary veins and ascending aorta. Vessels were segmented using a semi-automatic vessel edge detection algorithm (OsiriX; OsiriX Foundation, Switzerland) with manual operator correction. The following calculations was made using flow data: Systemic-to-pulmonary collateral flow proportion = (total pulmonary venous return - total PA flow) / total pulmonary venous return, expressed as a percentage.[6]

Ventricular Volume and Function

Ventricular volumes were assessed using a retrospectively gated multi-slice short-axis steady state free precession cine sequence. [7] Slices were acquired separately, in an apnoeic period of 5-10 seconds. Manual segmentation quantified end diastolic and systolic volumes (EDV and ESV) of the functionally single ventricle using an in-house plug-in for OsiriX. Stroke volume (SV) and ejection fraction (EF) were calculated from the volumetric data. Atrioventricular valve regurgitation (AVVR) was calculated from flow and volumetric data.

Anatomical assessment

Arterial and venous anatomy were assessed using gadolinium-enhanced MRA as previously described. [8] Two consecutive angiograms were acquired within a single 20-30 second period of apnoea. The first angiogram provided systemic arterial anatomy and the second angiogram provided second-pass contrast enhancement of venous and PA anatomy. Systemic venous decompressing collaterals from SVC territory to IVC territory were visualised using late-phase 3D MRA. These collaterals were graded by severity as previously described.[3]

Measurement of central venous pressure during pre-operative CMR

Following CMR data acquisition, a right internal jugular venous line (Abbocath-T, 22G, Venisystems) was sited aseptically, under ultrasound guidance. [9] The mean central venous pressure (CVP_{BCPC}) was transduced after careful flushing and zeroing, under the same conditions as the CMR, at passive end expiration. Following measurement, the cannula was removed and the site dressed.

Pressure-Flow Metrics

Pressure and flow data were used to calculate the following metrics (Figure Legends *Figure 1*, Video 1):

1. A simple estimate of pulmonary vascular resistance (PVR_{EST}) that neglects left atrial pressure, calculated by dividing CVP at time of BCPC by Q_P (SVC flow or SVC flow + native PA flow):

$$PVR_{EST} = CVP_{BCPC}/Q_P$$

2. An estimate of CVP following completion of the TCPC (CVP_{TCPC}) assuming post-TCPC pulmonary artery flow will equal aortic flow, Q_{Ao}:

$$CVP_{TCPC} = PVR_{EST} \times Q_{Ao}$$

Sensitivity Analysis to alternative method of measuring systemic flow

Estimated CVP_{TCPC} is calculated using aortic flow which necessarily includes systemic to pulmonary collateral flow (SPC). We also performed a sensitivity analysis using CVP_{TCPC} which excludes SPC flow (substituting Aorta flow with SVC+IVC (or descending aorta) flow).

Predetermined outcome measures

Post-operative ICU electronic records were available for patients from 2012 onwards (n=70). In this group, the mean of hourly CVP in the 24hrs after TCPC (CVP_{ICU}) was recorded for comparison to pre-operative CMR measures.

Early outcome was evaluated in two ways:

i) Length of hospital stay (measured from the day of TCPC surgery until the day of discharge from hospital to home)

ii) Composite early outcome of need for emergency fenestration, emergency TCPC takedown or early death (<30 days post TCPC).

Medium term outcome was evaluated as:

i) Death or transplantation at any time during follow-up.

Statistics

STATA 13.1 and Graphpad Prism 5f were used for statistical analysis and Figures. Data were examined for normality and where appropriate, non-normally distributed variables were log transformed to ensure normal distribution prior to analysis. Descriptive statistics are expressed

as mean (±95% confidence interval) when normally distributed, and median (IQR) when non-normally distributed, unless specified. Proportions are expressed as percentages. Data were examined for normality using the Shapiro-Wilk test, and where appropriate, non-normally distributed variables were transformed prior to analysis. Median regression analysis was used to assess the relationship between hospital stay and covariates.

We used logistic regression analysis to assess the relationship between EFF and clinical parameters. Multivariable logistic regression analysis was used to assess independent relationships (and control for confounding) between EFF and associated covariates. Covariates with a $p<0.1$ were eligible for inclusion in the multivariable model. Non-parametric receiver operating characteristics (ROC) analysis was performed. The area under the resulting ROC curve was computed using the trapezoidal rule. The area under the receiver operating characteristics curve (AUC) was used to identify the threshold of CVP_{TCPC} with the greatest classification accuracy. The threshold was derived using the methodology of Liu *et al.* which optimizes the product of sensitivity and specificity.[10] Kaplan Meier survival analysis was used to assess the relationship between covariates and medium outcome.

Results

Demographics

CMR and central venous pressure (CVP_{BCPC}) data were obtained in 131 patients (80 male) prior to TCPC completion under general anaesthesia. Patient characteristics for the study cohort are described in Table 1. There were no significant differences between the study cohort and the 16 excluded patients in terms of age, sex, cardiac morphology, cardiac output, ejection fraction, length of hospital stay or EFF. Of the patients who had CMR, 6/131 underwent subsequent diagnostic or interventional catheterization to further investigate the hemodynamics before proceeding to TCPC. The decision to perform additional catheterization was made by the multi-disciplinary team following discussion of clinical data including CMR, echocardiography and clinical status.

The median age at CMR was 3.2years (IQR 2.8-3.8years) and age at TCPC completion 3.8 (IQR 3.2-4.4years), mean interval 6.7months (SD 5.5months). TCPC completion is performed in our institution using an extra-cardiac conduit and the TCPC was electively fenestrated in 41% of patients. Median CVP_{TCPC} was 23.6mmHg (IQR 18.1-28.4 [range 5.2-48]). There were no differences in CVP_{TCPC} between patients who did or did not have elective fenestration (23.0 vs 23.8mmHg, p=0.9).

In the sample of 70 patients with electronic ICU records. 11% (8/70) underwent operation room extubation and 91% (64/70) of patients were extubated with 24 hours. The median time of extubation was 6 hours after admission to ICU.

Relationship to ICU Pressure

Post-operative ICU electronic records were available in 70 patients. Estimated CVP_{TCPC} correlated significantly with CVP_{ICU} (r=0.26, p=0.03), particularly in patients without a fenestration (n=33, r=0.45, p=0.01), Figure 2. However, CVP_{TCPC} significantly overestimated CVP_{ICU} (15±3 vs 22±7mmHg). In patients with a time interval between CMR and ICU measurement less than 1 year (90%), the strength and significance of the correlation was higher (r=0.31, p=0.01).

Relationship to clinical parameters

There was no association between CVP_{TCPC} and patient age at CMR, age at BCPC or sex. Patients with higher oxygen saturations at the time of CMR had lower estimated CVP_{TCPC} (Beta -0.19, p=0.047). CVP_{TCPC} was higher in patients with HLHS (27 vs 22mmHg, p<0.005), in whom there was a higher PVR_{Est} (6.1 vs 5.1WU index, p=0.01).

Outcome

Early Fontan failure

EFF occurred in 7/131 patients: Emergency fenestration only – 5 (one of whom previously had an elective fenestration), Emergency takedown – 1 (patient also had emergency fenestration), Death -1 (patient also had emergency takedown) (Table 2).

CVP_{TCPC} was significantly associated with EFF (Odds Ratio [OR] 1.1 (1.01-1.21), p=0.03). A threshold of CVP_{TCPC} ≥33mmHg was found to have the highest specificity (90%) and sensitivity (57%) for identifying EFF (area under receiver operating curve, AUC = 0.73 [confidence interval 0.53-0.92]), OR 12.4 (2.5-62.3), p=0.002, Figure 3A.

The relationship between CVP_{TCPC} and EFF was stronger in patients with a single SVC (n=115, OR 1.15 [1.03-1.28], p=0.01). In this group, a CVP_{TCPC} threshold of ≥33mmHg was also found to have the highest specificity (90%) and sensitivity (80%) for EFF (AUC=0.85 [confidence interval 0.67-1.0]), OR 36.0 (3.7-351), p=0.002, Figure 3B.

Except for the severity of systemic veno-venous collateral grade (p=0.04), there was no other univariable associations between EFF and conventional pre-operative CMR and demographic variables (including: CVP_{BCPC}, ventricular volumes, ejection fraction, PVR_{EST}, hypoplastic left heart syndrome, azygos vein diameter, SPC flow, Pre-operative SpO2, age at TCPC, age at BCPC and sex (Table 3).

Medium Term Outcome

During mean follow-up of 6.8years (SD 3.2years), 4 patients died (1 <30days and 3 >30days) and 1 patient underwent cardiac transplantation. 7 patients were lost to followup. There were significant univariable associations between medium term adverse outcomes and CVP_{TCPC} and veno-venous collateral grade (Table 3). CVP >=33mmHg was significantly associated with time to event, Log-rank test (p=0.001) (Figure *4*). However, in our series, the covariate with strongest association with decreased transplant-free survival was the prior occurrence of EFF, OR 164 (13.8-1943), p<0.005.

Hospital Stay

Using median regression analysis, hospital stay was associated with: CVP_{ICU}, CVP_{TCPC} >=33mmHg, and the severity of offloading veno-venous collaterals. On multivariable analysis only CVP_{TCPC} >=33mmHg was independently associated with hospital stay (Table 4).

Sensitivity Analyses

Alternative method of measuring systemic flow

Estimated CVP_{TCPC} calculated by excluding SPC flow was significantly lower than with SPC flow included: 18 vs 24mmHg, $p<0.05$. Calculated in this manner, there remained an equally significant association with EFF (OR 1.2 (1.01-1.36), p=0.03). However, there was no significant correlation with CVP_{ICU} for the group (r=0.1, p=0.4) and only a trend to correlation in patients without fenestration (r=0.35, p=0.06)

Patients who underwent Cardiac Catheterisation

Given our practice of reserving cardiac catheterisation as a second-line investigation, patients who underwent cardiac catheterisation may have a different baseline risk of EFF. Excluding this group (n=125) did not significantly change the association between CVP_{TCPC} and EFF (OR 1.1 (1.03-1.25), p=0.01).

Discussion

With the evolution of surgical and perioperative management of the TCPC, biomarkers from previous eras may no longer prove robust. In this study we have shown that a novel estimated pressure metric, CVP_{TCPC}, can be calculated from pre-operative data and that it is associated with early Fontan failure, hospital stay and is moderately correlated with directly measured post-operative pressure from ICU, Figure 5.

Although EFF has decreased in incidence in published series, it is still an important clinical event.[4] In this study we have used a conventional definition based on objective clinical events and investigated typical pre-operative risk factors. CVP_{TCPC} may perform well as a predictive biomarker in our series because it is closely related to the haemodynamic hallmark of the condition – high CVP.

Our analysis showed a reasonable correlation between measured CVP_{ICU} and estimated CVP_{TCPC}. However, there was a significant bias of approximately 7mmHg and there are several possible causes of this discrepancy. One possible reason was that patients were mechanically ventilated for CMR, but were predominately extubated and spontaneously breathing while in ICU (median time of extubation was 6 hours after arrival to ICU). It is well recognized that positive pressure ventilation increases PVR. Consequently, using PVR measured during CMR may result in overestimation of the CVP in spontaneously breathing post-TCPC patients. Studies have also shown that cardiac index is lower in TCPC versus Glenn patients, probably as a consequence of higher SaO_2 in the TCPC circulation.[11] Thus, using the pre-TCPC cardiac output in the estimation of CVP_{TCPC} could be another important cause of the observed positive bias. Causes of variation between CVP_{TCPC} and CVP_{ICU} (but not necessarily bias) include: CVP modifying therapies used in ICU (IV fluids, sedation, inotropes and diuretics), the time

interval between CMR and the TCPC and the fact that CVP_{TCPC} is a spot measurement in contrast to CVP_{ICU}, which is an average of measurements taken over an extended time frame. Even though there is a bias, CVP_{TCPC} does predict EFF and is therefore is potentially useful clinical measure. However, CVP_{TCPC} and CVP_{ICU} are not interchangeable and this must be taken into account if CVP_{TCPC} were to be used clinically.

The fact that CVP_{TCPC} is associated with EFF, even when its constituent components (Qs and PVR) don't, suggest its importance as an integrator of deleterious haemodynamics. The stronger relationship between CVP_{TCPC} and clinical outcome in patients with single SVC is interesting and may be because accurate measurement of CVP_{BCPC} in patients with bilateral SVCs is more difficult due to asymmetric SVC size or pulmonary artery narrowing between the bilateral Glenn anastomoses. Nevertheless, the diagnostic accuracy in the entire group remains satisfactory. In our sensitivity analysis, we used SVC and IVC or descending aorta flow as an alternative to aortic flow. We found that this approach had similar prognostic significance to using aortic flow, but the correlation with ICU pressure was reduced.

These data suggest that it may be possible to CVP_{TCPC} identify patients at increased risk of EFF. Such a metric could be used to improve peri- and immediate post-operative care, for example it could be used to better select patients who require elective fenestration. There is currently a lack of consensus regarding routine fenestration; whilst it may reduce post-operative CVP, it comes at the expense of increased systemic desaturation and a possible increased risk of systemic thromboembolism.[12-15] Thus, a metric that helps identify patients who could benefit from fenestration would be beneficial. However, significant further validation is required before CVP_{TCPC} could be used for this purpose.

Whilst not the primary aim of this study, there was an association between CVP_{TCPC} and death or transplantation in the medium term. This finding suggests that CVP_{TCPC} has some capacity to assess longer term risk. However, this association appears to be mediated almost entirely via its association with EFF, because in our study, the majority of deaths occurred in patients with prior EFF.

Our group has previously shown the importance of qualitative assessment of decompressing veno-venous collaterals for early and late TCPC failure.[3] Collaterals facilitate decompression of the BCPC, allowing for normalisation of CVP (which explains the lack of association between BCPC CVP and outcome); however after TCPC completion, this route of decompression is no longer possible, and consequently PA pressure becomes elevated. The calculation of CVP_{TCPC} provides an actual estimate of the rise of pressure as consequence of TCPC completion. Elevated CVP_{TCPC} and decompressing collaterals may therefore identify patients with an adverse pulmonary vasculature; in such patients, it is possible that cardiac catheterisation could be used to identify reversible causes (PA obstruction or elevated PVR) prior to TCPC completion.

Limitations

This is a retrospective study from a single centre, which may limit generalisation of the study findings, insofar as our patient population and practice differ. However, our clinical practice will be broadly similar to many institutions. Nevertheless, one advantage of the retrospective design is that CVP_{TCPC} was not used during multidisciplinary meetings to guide decision making, and therefore will not have influenced clinical outcomes, such as the rate of EFF, decision to defer TCPC, or fenestration.

Our method of pre-operative clinical evaluation does not involve routine cardiac catheterization, therefore we are not able to evaluate the relationship of elevated end-diastolic pressure (independently of CVP) in our dataset.

Given marked practice variation in pre-operative assessment for TCPC completion, it is recommended that a prospective comparative study of CMR and cardiac catheterization be undertaken. In the absence of a direct comparison (ideally randomized controlled trial), we cannot exclude the possibility that performing a cardiac catheterization could provide comparable data to CMR.

Conclusion

CVP_{TCPC} is easily calculated at the time of pre-TCPC assessment by combining pressure and flow data. Although there is a significant bias between estimated and measured CVP, higher CVP_{TCPC} is associated with an increased risk of EFF events. Thus, this metric could be used to inform important clinical decisions such as pre-emptive TCPC fenestration. However, further larger multi-centre prospective studies are required to validate this metric, especially in centres who undertake routine TCPC fenestration.

Contributors: Each author has contributed significantly to the submitted work. MQ conceived the design of the study. The data collection, analysis and interpretation of the data was undertaken by MQ, IC, SS, MH and VM. The drafting of the manuscript and its revision was completed by MQ and VM. Each has read and approved the manuscript as written, and there are no conflicts of interest to disclose. None of the paper's contents have been published previously and it is not under consideration elsewhere.

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426 *Patient consent for publication:* Not required.

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428 *Ethics approval:* This study was approved by the local research ethics committee.

429

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432 *Data availability statement:* Data are available on reasonable request.

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Figure Legends

Figure 1. Diagrammatic presentation of methodology for calculating CVP_{TCPC}. This approach attempts to estimate the change in CVP should all systemic flow be directed to the pulmonary arteries following TCPC completion. A. At bidirectional total cavopulmonary connection (BCPC) stage, Superior vena cave (SVC) flow and central venous pressure (CVP_{SVC}) are measured to calculate an estimate of pulmonary vascular resistance (PVR) which neglects distal atrial pressure. B. An estimate of the pressure following total cavopulmonary connection (CVP_{TCPC}) is calculated using the product of PVR and the assumed TCPC flow, either: aortic flow or SVC + IVC flow. In this way, the BCPC central venous pressure is scaled in proportion to the anticipated flow in the TCPC circulation.

Figure 2 Scatter plot of average central venous pressure measured in ICU over 24hours (CVP_{ICU}) and estimated CVP at the time of total cavo-pulmonary connection (CVP_{TCPC}). Patients with fenestrated TCPC are shown in blue, compared with non-fenestrated in red.

Figure 3 Receiver operating characteristic curves (ROC) for estimated central venous pressure (CVP_{TCPC}) and early TCPC failure. A: All patients, AUC 0.73 (CI 0.53-0.92). Sensitivity 0.67 and specificity 0.90 at cut-point 33mmHg (OR 18.8, p=0.001). B: Patients with single SVC, AUC 0.85 (CI 0.67-1.0), Sensitivity 0.80 and specificity 0.90 at cut-point 33mmHg (OR 36, p=0.002). Cut-points: Red squares

Figure 4 Kaplan Meier survival curves plotting freedom from death or transplantation grouped according to high CVP_{TCPC} >=33mmHg (Red) or low CVP_{TCPC} <33mmHg (blue). Log-rank test (p=0.001).

Figure 5 Graphical Abstract: In this study, CMR was performed in bidirectional superior cavopulmonary connection (BCPC) patients undergoing pre-operative assessment for total cavopulmonary connection (TCPC). Using routinely collected data: pulmonary blood flow (Qp), central venous pressure (CVP) and aortic flow (Qs). We calculated a metric which attempts to estimate how much central venous pressure would increase should the TCPC be completed; if all systemic flow is directed to the lungs. Given that early Fontan failure (EFF) is associated with high post-operative CVP, we investigated whether this metric was associated with EFF events, and also if it correlated to directly measured CVP in the TCPC during the ICU stay. Our study demonstrates an association between estimated TCPC pressure and EFF and also a moderate correlation with CVP measured in the ICU.

Video Legend

Video 1 Animation of methodology for estimating post-TCPC CVP. In this patient, central venous pressure (CVP) measured in the Glenn is 10mmHg and the SVC flow is 2L/min. The estimated PVR, neglecting atrial pressure is $5mmHg.L^{-1}.min^{-1}$. The total flow through the TCPC circuit after completion is estimated as 4.5L/min (aortic flow or SVC+descending aorta

or IVC flow). The estimated TCPC pressure is given as the product of flow and resistance, 22.5mmHg.

523

524 Table 1 Patient demographics in the study cohort, n=131

Parameter	**Median (IQR) or Number (%)**
Male	80 (61%)
Age at BCPC (years)	0.5 (0.3-1.0)
Age at CMR (years)	3.2 (2.8-3.8)
Age at TCPC (years)	3.8 (3.2-4.4)
Weight at CMR (kg)	13.7 (12.8-15.5)
SpO_2 at CMR (%)	85 (80-87)
Cardiac catheterisation following CMR	6 (4.5%)
Hypoplastic left heart syndrome	48 (36%)
Damus Kaye Stansel	68 (52%)
Preserved native PA flow	17 (13%)
Isomerism of left or right atrial appendage	4 (3%)
Bilateral SVC	15 (11%)
End diastolic volume (ml)	57 (47-64)
End systolic volume (ml)	24 (19-29
Cardiac Output (L/min)	3.3 (2.9-3.9)
Ejection Fraction (%)	56 (52-63)
AV valve regurgitant fraction (%)	5 (0-10)
Systemic-pulmonary flow proportion of pulmonary venous return (%)	32 (25-43)
Severity of decompressing Venous Collaterals	
Grade 1	72 (55%)
Grade 2	23 (18%)
Grade 3	36 (27%)
CVP (mmHg)	11 (10-13)
Pulmonary vascular resistance index: (CVP / total pulmonary artery flow index)	5.2 (4.0-6.3)
Coarctation ratio (isthmus/diaphragm Ao)	1.0 (0.94-1.1)
Nakata index	208 (152-256)
McGoon ratio	2.0 (1.7- 2.3)
Diameter of azygos (mm)	3.5 (2.8-4.3)

ICU LOS (days)	2 (0-4)
Hospital LOS (days)	13 (10-20)
ICU 24hr CVP (mmHg)	15 (14-18)
Post-operative time of extubation (<24hrs)	64 (91%)
Elective fenestration at TCPC	54 (41%)
Early Fontan Failure	7 (5%)
Death	1 (14%)
TCPC Takedown	1 (14%)
Emergency Fenestration only	5 (71%)

Key to abbreviations: BCPC = bidirectional superior cavo-pulmonary connection, CMR = Cardiovascular magnetic resonance, TCPC = Total cavo-pulmonary connection, PA = pulmonary artery, AV valve = Atrioventricular valve, CVP = Central Venous Pressure, ICU = Intensive Care Unit, LOS = Length of Stay

Table 2 Early and medium-term clinical Outcome data for patients. EF: Ejection Fraction (%), CVP: Central Venous pressure, ICU:Intensive care unit, CPB: cardiopulmonary bypass.

Case	Follow-up (months	EF (%)	Estimated TCPC CVP	ICU CVP	CPB Time	Elective Fenestration	Emergency Fenestration	Takedown	Early Death	Late Death	Late Transplantation
1	0.9	51	36.0	-	159	Yes	No	Yes	Yes	-	-
2	9.5	63	39.9	-	78	No	Yes			Yes	
3	15.0	67	34.1	-	84	No	Yes			Yes	
4	65.8	52	27.2	-	97	Yes	No				Yes
5	88.4	58	36.3	17.4	115	No	Yes				
6	0.1	60	23.2	18.6	136	No	Yes	Yes			
7	3.8	51	22.0	20.2	97	No	Yes			Yes	
8	19.6	48	22.5	22.9	245*	Yes	Yes				

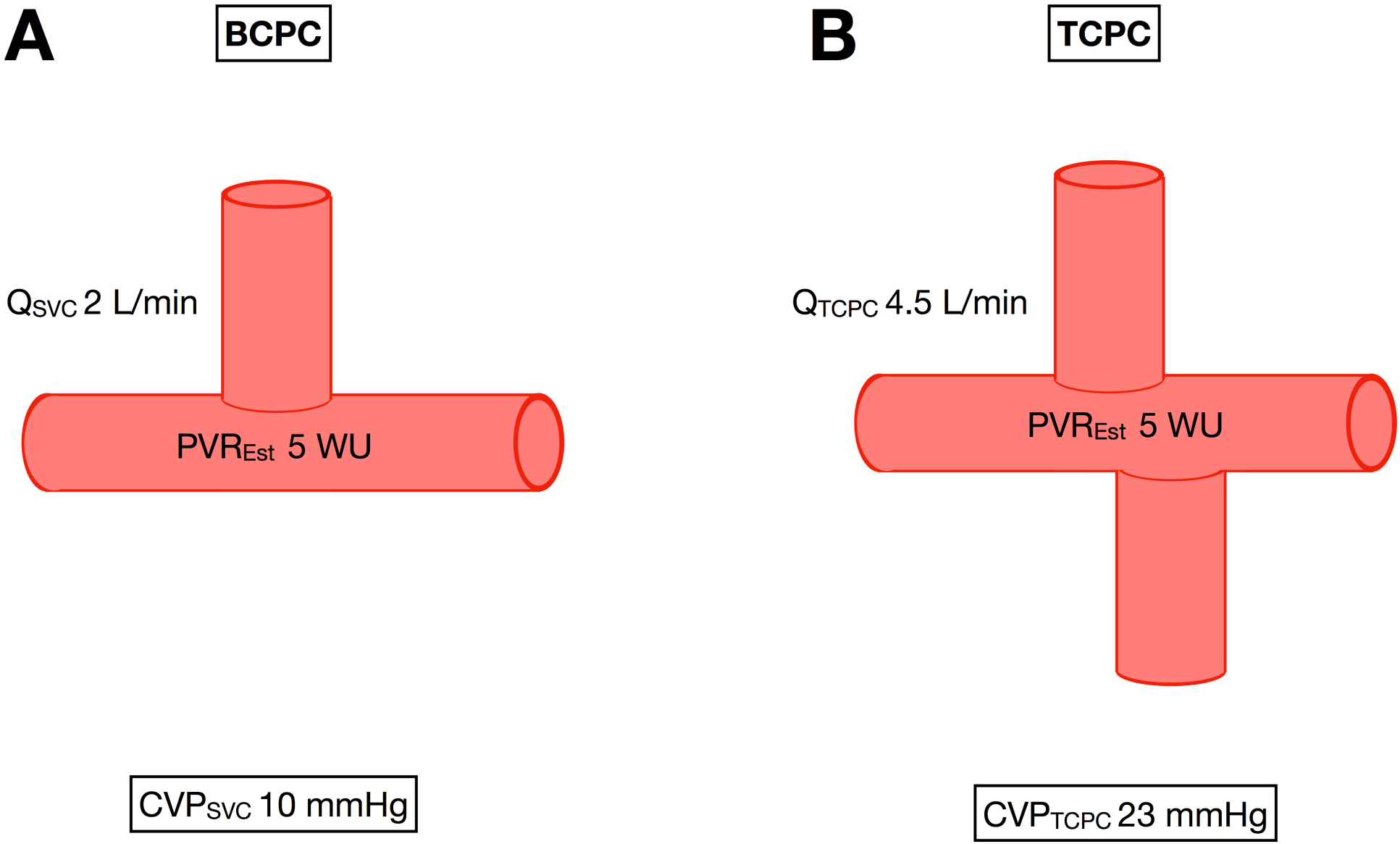
*Additional procedures: atrial septectomy and closure of pulmonary valve.

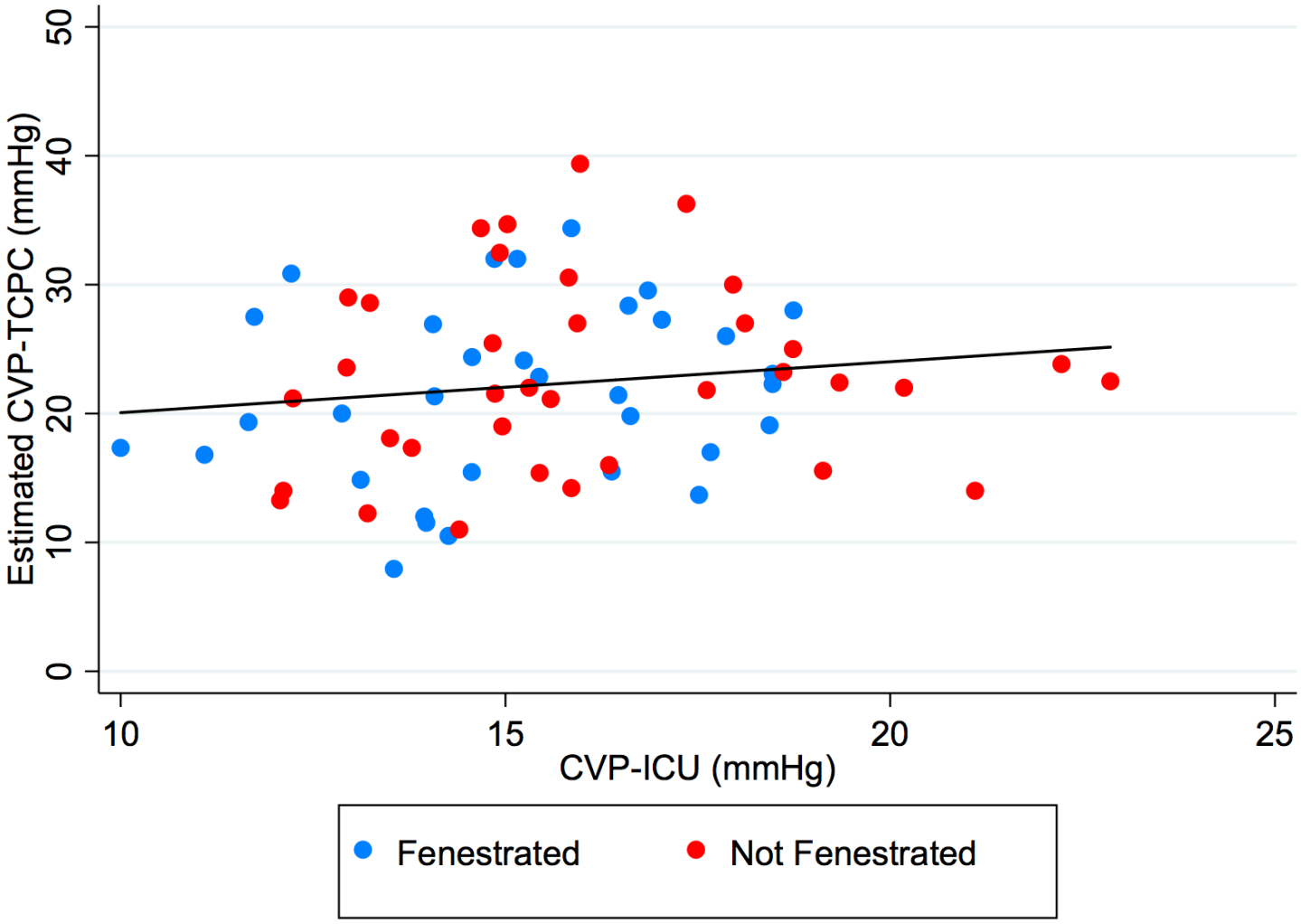
Table 3 Univariable analysis of association between clinical outcome and covaratiariates. CVP: central venous pressure, BCPC: bidirectional superior cavopulmonary connection, TCPC: total cavopulmonary connection ICU:intensive care unit, PVR: pulmonary vascular resistance, SPC:systemic to pulmonary collaterals, SpO_2: Oxygen saturations.

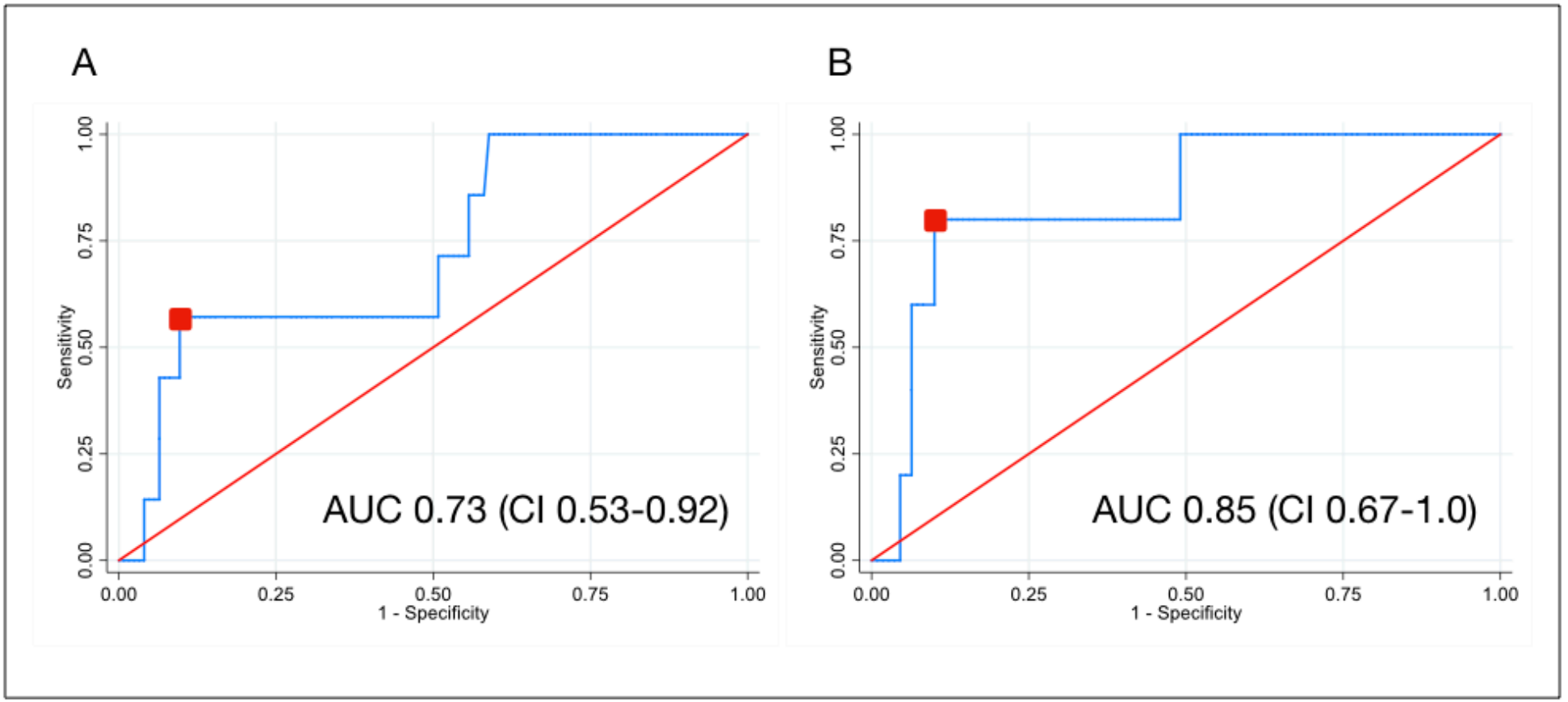
	EFF		*Death-Transplantation*	
Variable	*OR*	*Significance*	*OR*	*Significance*
Estimated CVP_{TCPC} >=33mmHg	12.4 (2.50-62.3)	**0.002**	13.0 (1.99-95.3)	**0.007**
Estimated CVP_{TCPC} (mmHg)	1.10 (1.01-1.21)	**0.03**	1.11 (1.01-1.24)	**0.04**
CVP_{BCPC} (mmHg)	1.18 (0.90-1.51)	0.2	1.23 (0.91-1.66)	0.2
Veno-Venous Collateral Grade (1-3)	2.63 (1.02-6.78)	**0.04**	6.15 (1.08-34.8)	**0.04**
Ejection Fraction (%)	1.00 (0.90-1.10)	0.9	0.99 (0.88-1.12)	0.9
End diastolic volume index (ml/m^2)	1.01 (0.97-1.05)	0.7	0.99 (0.95-1.04)	0.8
PVR Estimate ($woods\ units.m^2$)	1.20 (0.88-1.62)	0.2	1.26 (0.9-1.77)	0.2
Azygos Diameter (mm)	1.36 (0.79-2.36)	0.3	1.55 (0.84-2.86)	0.2
Hypoplastic Left Heart Syndrome	0.83 (0.38-1.82)	0.6	0.52 (0.18-1.45)	0.2
Systemic-Pulmonary Collaterals (%)	22.7 (0.08-6421)	0.3	6.38 (0.01-3572)	0.6
Pre-TCPC SpO_2 (%)	0.96 (0.82-1.12)	0.6	0.99 (0.83-1.19)	1.0
Age at BCPC (year)	0.88 (0.34-2.31)	0.8	0.94 (0.32-2.71)	0.9
Age at TCPC (year)	0.67 (0.29-1.55)	0.3	1.13 (0.6-2.13)	0.7
Sex (male)	1.63 (0.30-8.75)	0.6	2.63 (0.29-24.2)	0.4
Early Fontan Failure	-	-	164 (13.8-1943)	**<0.005**

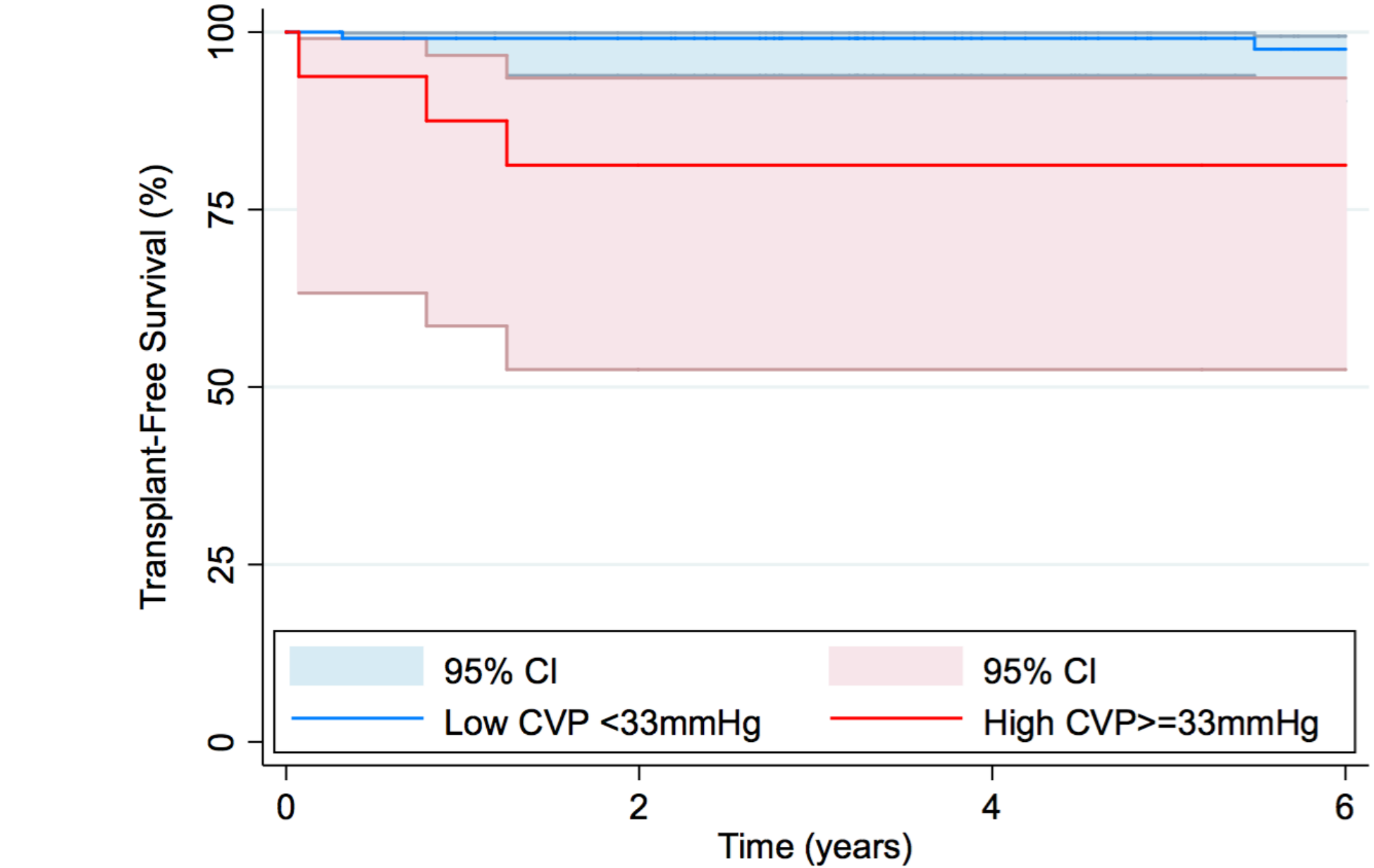
Table 4 Univariable and multivariable median regression analysis between hospital stay and exploratory variables. CVP: central venous pressure, BCPC: bidirectional superior cavopulmonary connection, TCPC: total cavopulmonary connection ICU:intensive care unit, PVR: pulmonary vascular resistance, SPC:systemic to pulmonary collaterals

	Univariable		*multivariable*	
Variable	*Coefficient*	*Significance*	*Coefficient*	*Significance*
CVP_{ICU}	1.01	**0.04**		
Estimated CVP_{TCPC}	0.15	0.2		
Estimated CVP_{TCPC} >=33mmHg	12	**<0.005**	13	**<0.005**
CVP_{BCPC}	$2x10^{-16}$	1.0		
PVR_{EST}	0.24	0.4		
Severity of decompressing Venous Collaterals	3.5	**0.005**	2	0.08
SPC Flow	8.9	0.1		
End-diastolic volume	-0.01	0.8		
Ejection Fraction	0	1.0		
Hypoplastic Left Heart Syndrome	-1.5	0.1		


A
BCPC
Q_{SVC} 2 L/min
PVR_{Est} 5 WU
CVP_{SVC} 10 mmHg
B
TCPC
Q_{TCPC} 4.5 L/min
PVR_{Est} 5 WU
CVP_{TCPC} 23 mmHg


Estimated CVP-TCPC (mmHg)
0
10
20
30
40
50
10
15
20
25
CVP-ICU (mmHg)
Fenestrated
Not Fenestrated


A
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
AUC 0.73 (CI 0.53-0.92)
B
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
AUC 0.85 (CI 0.67-1.0)



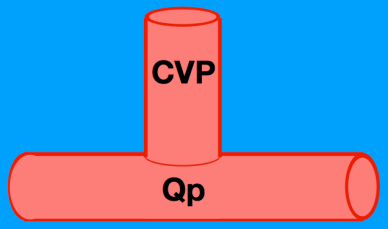
Number at risk

Low CVP	115	105	78	59
High CVP	16	12	12	11

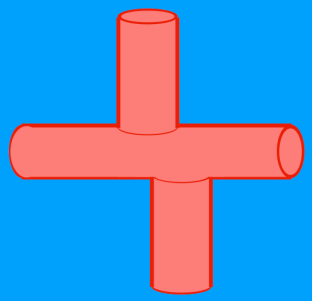
A Preoperative Estimate of Central Venous Pressure Is Associated with Early Fontan Failure (EFF)

131 BCPC Patients with Cardiac MRI prior to TCPC

Measured in BCPC:
SVC Flow (Qp)
Central Venous Pressure (CVP)



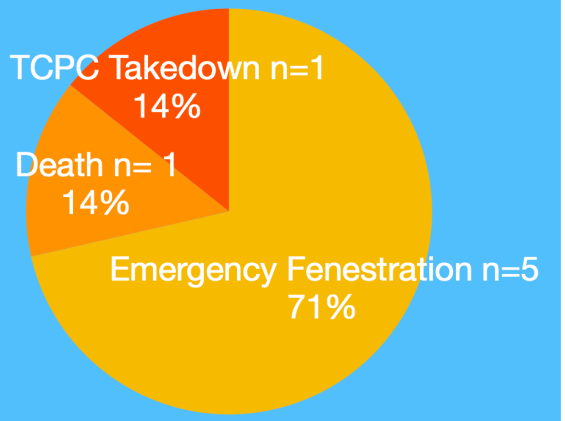
Post-TCPC CVP estimated:



Qp/CVP x Aortic flow

41% of Patients Elective Fenestration

7 Patients with EFF



Estimated CVP in the TCPC is associated with EFF

Moderate Correlation with CVP measured in the ICU

Identification of patients at higher risk of EFF may help guide mitigation strategies