Impact of Fontan fenestration on adverse cardiovascular outcomes: a multicenter study

Dib Nabil, MD MSc, Michelle Samuel, MPH, PhD, Sylvie Levesque, MSc, Ali Zaidi, MD, Sarah Cohen, MD, Alexander R. Opotowsky, MD, MMSc, François-Pierre Mongeon, MD SM, Blandine Mondésert, MD, Joseph Kay, MD, Reda Ibrahim, MD, Robert M. Hamilton, MD, Anne Fournier, MD, Susan M. Jameson, LPD, PA-C, Annie Dore, MD, Stephen C. Cook, MD, Scott Cohen, MD, Marie-A Chaix, MD, PhD, Craig S. Broberg, MD, Jamil Aboulhosn, MD, Nancy Poirier, MD, Paul Khairy, MD PhD

PII: S0828-282X(24)00079-5
DOI: https://doi.org/10.1016/j.cjca.2024.01.031
Reference: CJCA 4976
To appear in: Canadian Journal of Cardiology

Received Date: 15 December 2023
Revised Date: 24 January 2024
Accepted Date: 26 January 2024


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier Inc. on behalf of the Canadian Cardiovascular Society.
Outcomes with fenestrated versus non-fenestrated Fontan

Adverse cardiovascular event

Death or cardiac transplant

Atrial arrhythmia

Thromboembolic event

Hazard ratio (95% confidence interval)

Higher risk with no fenestration

Higher risk with fenestration
Impact of Fontan fenestration on adverse cardiovascular outcomes: a multicenter study

Nabil Dib, MD MSc; Michelle Samuel, MPH, PhD; Sylvie Levesque, MSc; Ali Zaidi, MD; Sarah Cohen, MD; Alexander R. Opotowsky MD, MMSc; François-Pierre Mongeon, MD SM; Blandine Mondésert, MD; Joseph Kay, MD; Reda Ibrahim, MD; Robert M Hamilton, MD; Anne Fournier, MD; Susan M. Jameson, LPD, PA-C; Annie Dore, MD; Stephen C Cook, MD; Scott Cohen, MD; Marie-A Chaix, MD, PhD; Craig S. Broberg, MD; Jamil Aboulhosn, MD; Nancy Poirier, MD; Paul Khairy, MD PhD

1Montreal Heart Institute, Université de Montréal, Quebec, Canada; 2Montreal Health Innovations Coordinating Center, Quebec, Canada; 3Nationwide Children’s Hospital, Ohio State University, Columbus, USA; 4Hôpital Marie-Lannelongue, Groupe Hospitalier Saint-Joseph, Le Plessis Robinson, Paris, France; 5Boston Adult Congenital Heart Service, Boston Children’s Hospital and Brigham and Women’s Hospital, Harvard Medical School, Boston, USA; 6The Cincinnati Adult Congenital Heart Disease Program, Cincinnati Children’s Hospital, Cincinnati, Ohio, USA; 7University of Colorado Denver, Aurora, USA; 8The Hospital for Sick Children, University of Toronto, Toronto, Canada; 9Hôpital Sainte-Justine, Université de Montréal, Montreal, Canada; 10Stanford Adult Congenital Heart Program, Lucile Packard Children’s Hospital Stanford and Stanford Health Care, Stanford University School of Medicine, Palo Alto, USA; 11Indiana University Health Medical Center, Indiana, USA; 12The Wisconsin Adult Congenital Heart (WAtCH) Program, Medical College of Wisconsin, Milwaukee, USA; 13Oregon Health and Science University, Portland, USA; 14Ahmanson/UCLA Adult Congenital Heart Program, University of California, Los Angeles, USA

Short title: Fontan fenestration and adverse cardiovascular outcomes

Word count: 5833

Disclosures: The study was funded by an investigator-initiated unrestricted grant from Boehringer Ingelheim. The sponsor had no role in study design, data collection, analysis, interpretation or publication of the findings. The authors have no other relevant relationships to disclose.

Acknowledgments: The authors thank the following: Marie-Claude Villeneuve, MSc (Montreal Health Innovations Coordinating Center); Aynun Naher, MBBS, MS (Oregon Health and Science University); William R. Davidson, Jr., MD, John J. Kelleman, MD, Elizabeth E. Adams, DO, Jennifer Ting, MD and Dena Jefferson RN, BSN, CCRC (Hershey Medical Center); Morgan Hindes (Children's Hospital of Pittsburgh); Ryan Williams and Gwen Derk (University of California, Los Angeles); Michael G. Earing, MD, Jonathan W. Cramer, MD, and Emily Reinhardt, RN (Medical College of Wisconsin)

Correspondence: Dr. Paul Khairy, Montreal Heart Institute, 5000 Belanger St, Montreal, Quebec, Canada, H1T 1C8; Telephone: 514-376-3330; Fax: 514-593-2551; E-mail: paul.khairy@umontreal.ca
STRUCTURED ABSTRACT

**Background:** Fenestrating a Fontan baffle has been associated with improved peri-operative outcomes in patients with univentricular hearts. However, longer-term potential adverse effects remain debated. We sought to assess the impact of a fenestrated Fontan baffle on adverse cardiovascular events including all-cause mortality, cardiac transplantation, atrial arrhythmias, and thromboemboli.

**Methods:** A multicenter North American retrospective cohort study was conducted on patients with a total cavopulmonary connection Fontan baffle, with and without fenestration. All components of the composite outcome were independently adjudicated. Potential static and time-varying confounders were taken into consideration, along with competing risks.

**Results:** A total of 407 patients were followed for 10.4 (7.1-14.4) years, 70.0% of whom had fenestration of their Fontan baffle. The fenestration spontaneously closed or was deliberately sealed in 79.9% of patients a median of 2.0 years after Fontan completion. In multivariable analysis in which a persistent fenestration was modelled as a time-dependent variable, an open fenestration did not confer a higher risk of the composite outcome [hazard ratio 1.18, 95% confidence interval (0.71 to 1.97), P=0.521]. In secondary analyses, an open fenestration was not significantly associated with components of the primary outcome, i.e., mortality or transplantation, atrial arrhythmias, or thromboemboli. However, sensitivity analyses to assess the possible range of error resulting from imprecise dates for spontaneous fenestration closures could not rule-out significant associations between an open fenestration and atrial arrhythmias or thromboemboli.

**Conclusion:** In this multicenter study, no significant association was identified between an open fenestration in the Fontan baffle and major adverse cardiovascular events.

**Key words:** univentricular heart; Fontan; fenestration; atrial arrhythmias; thromboemboli
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AARCC</td>
<td>Alliance for Adult Research in Congenital Cardiology</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>FAT</td>
<td>Focal atrial tachycardia</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IART</td>
<td>Intra-atrial reentrant tachycardia</td>
</tr>
<tr>
<td>MHICC</td>
<td>Montreal Health Innovations Coordinating Center</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>TACTIC</td>
<td>The AntiCoagulation Therapy In Congenital heart disease study</td>
</tr>
</tbody>
</table>
INTRODUCTION

The Fontan procedure has revolutionized the surgical management of the univentricular heart.\(^1\) However, the resulting single ventricle physiology is associated with prevalent long-term complications including arrhythmias, thromboembolic events, Fontan-associated liver disease, and Fontan circulatory failure.\(^2\)-\(^9\) The type of Fontan surgery performed impacts healthspan trajectories, as exemplified by higher rates of arrhythmias and thromboembolic events with atrio-pulmonary compared to total cavopulmonary connections.\(^6\) A common variation of the total cavopulmonary connection Fontan is to fenestrate the baffle so as to mitigate the post-operative rise in systemic venous pressure\(^10\) and increase in ventricular preload.\(^11\) This approach has been associated with improved peri-operative outcomes, with less pleural drainage and a shorter post-operative length of stay.\(^12\) However, the drawbacks created by a right-to-left shunt include some degree of oxygen desaturation and the potential for paradoxical thromboemboli. Longer-term risks remain poorly defined. One study found that fenestrating a Fontan baffle did not impact long-term survival but incurred a higher risk of thromboembolic events.\(^13\) The data collected did not allow for adjustments for potential confounders such as thromboprophylaxis, atrial arrhythmias, and subsequent fenestration closures. We, therefore, conducted a multicenter North American study to evaluate the effect of a fenestrated Fontan baffle on adverse cardiovascular events including all-cause mortality, cardiac transplantation, atrial arrhythmias, and thromboemboli, while taking into account potential static and time-varying confounders.

MATERIAL AND METHODS

**Study design and patient population**

Details of the AntiCoagulation Therapy In Congenital heart disease (TACTIC) study conducted by the Alliance for Adult Research in Congenital Cardiology (AARCC) have previously been
reported. In short, TACTIC is a North American (3 Canadian and 9 USA centers) retrospective cohort study that includes patients with Fontan palliation performed during childhood. Inclusion in the current substudy was limited to those born in June 2011 or earlier who had survived their index surgery, had a total cavopulmonary connection Fontan, and were followed up at the same institution that performed the surgery.

_data collection_

Patients were identified retrospectively at each of the 12 participating institutions through the use of local surgical and medical databases. Time of study entry was defined as the date of Fontan completion. Patients were classified into two groups according to the main exposure variable, i.e., creation of a fenestration at the time of Fontan surgery. Baseline characteristics, recorded at the time of Fontan completion, included age, sex, number and type of previously performed surgical and catheter-based interventions, and comorbidities such as ongoing heart failure, pulmonary and systemic hypertension, and respiratory, renal, hepatic, and endocrine disorders. Pre-operative heart failure was defined as chronic diuretic use or as New York Heart Association (NYHA) functional class III or IV symptoms, independent of medical therapy. Diagnosis of pulmonary arterial hypertension was made in accordance with clinical guidelines available at the time of enrollment.

_outcomes of interest_

The primary outcome was a composite endpoint consisting of all-cause mortality, cardiac transplantation, sustained (>30 seconds) atrial arrhythmia (≥100 beats/min), or thromboembolic event during follow-up. Sustained atrial arrhythmias required documentation by an
electrocardiogram or rhythm strip. Regular atrial arrhythmias were classified as focal atrial
tachycardia (FAT) if well-formed P waves were distinguishable electrocardiographically and
separated by an iso-electric interval.\textsuperscript{16} Otherwise, the regular atrial tachycardia was classified as
intra-atrial re-entrant tachycardia (IART), a term that encompassed all forms of typical and
atypical atrial flutter.\textsuperscript{16} Atrial fibrillation was defined as the absence of well-formed P waves with
undulating baseline atrial deflections of varying amplitude.\textsuperscript{17}

Thromboembolic events were classified as systemic or venous. Systemic thromboemboli
were categorized as cardiac systemic circulation, neurologic, peripheral, or renal.\textsuperscript{14,18-20} Systemic
cardiac thromboemboli included coronary embolism and thrombi within the pulmonary venous
atrium or single ventricle. Neurologic events included transient ischemic attacks and strokes.
Transient ischemic attacks were defined as acute focal deficits lasting <24 hours without
infarction on imaging. Strokes included deficits persisting <24 hours but with confirmatory
imaging, or at least 24 hours with or without confirmatory imaging.\textsuperscript{21} Peripheral emboli were
diagnosed on the basis of the 6 key signs of acute limb ischemia: pain, pallor, paralysis, pulse
deficit, paresthesia, and poikilothermia.\textsuperscript{22} Imaging was required to confirm renal events. Venous
thromboemboli were subdivided into those involving the Fontan pathway or pulmonary arterial
circulation.\textsuperscript{14,19} These complications required documentation by appropriate imaging tests (e.g.,
echocardiography, magnetic resonance imaging, computed tomography, ventilation/perfusion
scan, or angiography).

\textit{Adjudication process and study coordination}

All deaths, cardiac transplantations, thromboembolic events and arrhythmias were adjudicated by
an independent blinded committee consisting of 4 physicians. Discrepancies were reviewed
against case report forms and all other supportive documents required as per protocol, and were
subjected to discussion for final adjudication. The Montreal Health Innovations Coordinating
Center (MHICC) oversaw data collection, integration, and entry and performed regular quality
assurance checks. The authors confirm that patient consent does not apply to this article given the
retrospective nature of the study on de-identified data. Data collection proceeded at each site with
a waiver of consent following local human research ethics board approval and was performed in
accordance with the International Council of Harmonization Tripartite Guidelines for Good
Clinical Practice.

**Statistical analysis**
Continuous variables were expressed as mean ± standard deviation or median and interquartile
range (IQR; 25th to 75th percentile), based on normality of distribution as assessed by Shapiro-
Wilk tests, kurtosis, and skewness. Categorical variables were presented as frequencies and
percentages. Continuous baseline characteristics of patients with and without a fenestrated Fontan
baffle were compared using Student t-tests or Wilcoxon rank sum tests according to whether the
distribution was normal or not. Comparisons of categorical variables were performed using chi-
square or Fisher exact tests, as appropriate. Cumulative incidence curves were plotted for the
combined endpoint and its components (i.e., cardiac transplantation or all-cause death, atrial
arrhythmias, and thromboembolic events). Gray’s tests were used to compare cause-specific
cumulative incidence functions between groups.

Univariable and multivariable regression models were created for the following end-
points: adverse cardiovascular events (primary outcome), cardiac transplantation or all-cause
mortality, atrial arrhythmias, and thromboembolic events. Cox regression models were used for
the first two endpoints. For the latter two endpoints, Fine and Gray subdistribution hazard models
considered cardiac transplantation and death as competing events. For all outcomes, the presence
of an open fenestration was modelled as a time-dependent variable. The analyses, therefore, took
into consideration later fenestration closures, whether spontaneous or by an intervention. In the
Fine and Gray hazard model for thromboembolic events, thromboprophylaxis (anticoagulation
therapy, antiplatelet agent, both, or none) and atrial arrhythmias were also modelled as time-
dependent covariates. Covariates considered in multivariable models were selected on the basis
of substantive knowledge while respecting a minimum of 15 events per variable, with forced
retention of the main exposure variable (i.e., fenestration status). Collinearity between variables
was assessed using correlation matrices and chi-squared tests. Linearity of continuous variables
in multivariable models was tested by including the square of the variable in the model.
Proportional hazards assumptions for fixed covariates were assessed by testing the interaction
between the covariate and the natural logarithm of the time to endpoint.

For all models, two sensitivity analyses were performed to assess the possible range of
error associated with imprecise dates for spontaneous fenestration closures. More specifically, for
patients in whom no imaging study noted that their fenestration had spontaneously closed until
after a cardiovascular event, the first sensitivity analysis (A) considered that all events occurred 1
day prior to closure (maximal risk; last observation carried forward approach) whereas the second
(B) considered that all events occurred 1 day after spontaneous fenestration closure (minimal
risk; next observation carried backward approach). If the subject did not experience the endpoint,
the closure date was set to half the follow-up between imaging studies. The same adjustment
variables retained in the multivariable models were applied to sensitivity analyses. For all
models, basic assumptions were verified prior to analyses. P-values <0.05 were considered to
indicate statistical significance. Analyses were performed with SAS® release 9.4 (SAS Institute
Inc., Cary, NC, USA).
RESULTS

Baseline characteristics

A total of 407 patients were included, 284 (70.0%) of whom had surgical baffle fenestration at the time of Fontan completion. Table 1 summarizes baseline characteristics in the overall cohort and according to whether or not the Fontan baffle was fenestrated. Patients without a fenestration were older at the time of Fontan completion (median 5.3 versus 3.0 years, \( P<0.001 \)) and had a higher oxygen saturation level (mean 92.2% versus 86.9%, \( P<0.001 \)). No statistically significant differences were noted in preoperative comorbidities among the two groups. Although the type of total cavopulmonary connection Fontan (i.e., intracardiac lateral tunnel versus extracardiac conduit) was comparable among the two groups, patients with no fenestration were less likely to have had a Norwood procedure (13.0% versus 33.8%, \( P<0.001 \)) or bidirectional Glenn shunt (67.5% versus 78.5%, \( P=0.018 \)).

Adverse cardiovascular outcomes

Adjudicated events that occurred during a median of 10.4 (IQR 7.1 to 14.4) years after Fontan completion are summarized in Table 2. The incidence of the composite outcome of all-cause mortality, cardiac transplantation, atrial arrhythmia, or thromboembolic event was 2.3 versus 2.0 cases per 100 person-years in patients with and without a surgically created fenestration, respectively. As shown in Figure 1, unadjusted cumulative rates of the composite endpoint 10, 15, and 20 years after Fontan surgery were 20.7%, 29.4% and 61.4% in patients who initially had a fenestration versus 19.1%, 24.8%, and 39.8% in those with no surgical fenestration, \( P=0.280 \).

During follow-up, the fenestration spontaneously closed or was deliberately sealed in 227 of 284 (79.9%) patients at a median of 1.96 (IQR 1.08 to 3.75) years after Fontan completion. In the multivariable regression analysis that modelled an open fenestration as a time-dependent...
presence of a fenestration was not associated with the primary composite outcome [hazard ratio (HR) 1.18, 95% confidence interval (CI; 0.71 to 1.97), \( P=0.521 \)]. As summarized in Table 3, variables significantly associated with the primary outcome were older age at Fontan completion [HR 1.05, 95% CI (1.01 to 1.09), \( P=0.006 \)] and Norwood procedure [HR 1.99, 95% CI (1.20 to 3.32), \( P=0.008 \)]. Sensitivity analyses, summarized in Table 4, likewise revealed no statistically significant association between an open Fontan fenestration and adverse cardiovascular outcomes.

### Cardiac transplantation and death

A total of 18 patients underwent cardiac transplantation (N=9) or died (N=9) during follow-up. There was no significant difference in the proportion of patients who either had cardiac transplantation or died among those who did and did not have their Fontan baffle surgically fenestrated (\( P=0.071 \)). However, as shown in Figure 2A, the unadjusted cumulative incidence rate was higher among patients with a surgically fenestrated Fontan baffle (\( P=0.0164 \)). In the Cox regression model that considered fenestration as a time-dependent variable, presence of an open fenestration was not associated with cardiac transplantation or death [HR 1.23, 95% CI (0.34 to 4.38), \( P=0.755 \)]. Given the limited number of events, multivariable analysis was not performed. Sensitivity analyses, summarized in Table 4, were consistent.

### Atrial arrhythmias

A total of 55 (13.5%) patients had at least one sustained atrial arrhythmia during the course of follow-up, with comparable rates among the two groups (Figure 2B; \( P=0.651 \)). The most common arrhythmia was IART (N=35; 8.6%) followed by FAT (N=13; 3.2%) and atrial
fibrillation (N=9; 2.2%). In the multivariable model presented in Table 5 that considered fenestration as a time-dependent variable, presence of an open fenestration was not significantly associated with atrial arrhythmias [HR 1.62, 95% CI (0.85 to 3.08), P=0.144]. However, the sensitivity analyses summarized in Table 5 indicated that the range of potential error due to inexact dates of spontaneous fenestration closure included the possibility of a significant association between the presence of an open fenestration and atrial arrhythmias [HR 2.05, 95% CI (1.14 to 3.69), P=0.016]. Older age at Fontan completion was independently associated with atrial arrhythmias [HR 1.05, 95% CI (1.01 to 1.10), P=0.022].

Thromboembolic events

A total of 35 patients had 36 thromboembolic events including 16 systemic and 20 in the Fontan/pathway or pulmonary artery. Adjudicated thromboembolic events are summarized in Table 2. The cumulative incidence of thromboembolic events was similar among patients with and without a surgical fenestration (Figure 2C; P=0.736). In the multivariable model that considered fenestration, arrhythmias, and thromboprophylaxis as time-dependent variables (Table 5), the presence of an open fenestration was not significantly associated with thromboembolic events [HR 1.24, 95% CI (0.54 to 2.83), P=0.614]. The only variable independently associated with thromboembolic events was anticoagulation therapy [HR 2.86, 95% CI (1.08 to 7.54), P=0.034]. However, the sensitivity analyses summarized in Table 4 indicated that the range of possible error included a scenario in which the presence of an open fenestration was significantly associated with systemic thromboembolic events [HR 3.46, 95% CI (1.06 to 11.29), P=0.040] but not thromboembolic events within the Fontan pathway/pulmonary arterial circulation.
The main finding of this multicenter retrospective cohort study from AARCC designed to assess the longer-term impact of a fenestrated Fontan baffle is the lack of association between presence of an open fenestration and the primary composite outcome, along with its components, i.e., all-cause mortality or cardiac transplantation, sustained atrial arrhythmia, and thromboembolic event. Every effort was made to adjust for competing risks and key potential confounders, including thromboprophylaxis modelled as a time-varying covariate and subsequent spontaneous or intentional fenestration closure. However, spontaneous fenestration closure is a subclinical event for which exact dates cannot be inferred (i.e., may have closed at any point in the interval between two imaging studies documenting the presence followed by absence of a fenestration). Thus, a degree of error is introduced when modelling presence of an open fenestration as a time-dependent variable. To quantify the potential range of error, sensitivity analyses were performed to estimate maximum and minimum risks that could possibly be attributed to an open fenestration. These analyses revealed that the “worst case” scenarios included the potential for significant associations between an open fenestration and a) atrial arrhythmias [HR 2.05, 95% CI (1.14, 3.69), P=0.016] and b) systemic thromboemboli [HR 3.46, 95% CI (1.06, 11.29), P=0.040]. As such, further studies are required to draw definitive conclusions regarding these two outcomes.

**Death and cardiac transplantation**

Prior reports on the impact of a fenestrated Fontan baffle on death and cardiac transplantation have yielded discordant results, in part reflecting differences in definitions and methodologies. For example, Kotani et al asserted that a persistent fenestration was associated with a higher rate of death or Fontan failure (31% versus 1% at 5 years). However, a persistent fenestration was
defined as one that remained patent one-year post creation. In our TACTIC cohort study, the
median time at which a fenestration was demonstrated to have spontaneously closed was 2 years.
Therefore, not capturing fenestration closures beyond one year carries the potential for a
differential misclassification error that results in over-estimation of the impact of an open
fenestration on adverse outcomes. Concordant with our findings, a meta-analysis and propensity
score-matched analysis reported no difference in long-term mortality associated with a
fenestration. In the TACTIC cohort study, these results were robust to the sensitivity analyses
performed.

**Atrial arrhythmias**

The high arrhythmic burden associated with Fontan surgery is well known. The cumulative
incidence of sustained atrial arrhythmias observed in our cohort, which exceeded 20% by 20
years of follow-up, is consistent with prior reports. One previous study that included 93
patients with a total cavopulmonary connection Fontan, 30 of which were fenestrated, found no
association between fenestration and tachyarrhythmias. This analysis, which was focused on
post-operative mortality and somatic development, did not consider spontaneous closures or other
potential confounders. While the main findings of our TACTIC study support the lack of
association between a fenestrated Fontan baffle and atrial arrhythmias, sensitivity analyses
suggest that these results are inconclusive. Most sustained atrial arrhythmias in patients with total
cavopulmonary connection Fontan palliation occur in the pulmonary venous atrium. Reasons as
to why a fenestrated Fontan baffle could potentially lead to a higher incidence of atrial
arrhythmias remain speculative. Hypotheses include adverse arrhythmogenic atrial remodelling
due to atrial and ventricular volume overload and/or persistent cyanosis, with chronic
subendocardial ischemia resulting from increased blood viscosity and prolonged hypoxia.
independent association between older age at Fontan completion and sustained atrial arrhythmias may reflect the consequences of prolonged cyanosis and single ventricle volume overload on subsequent ventricular function and atrial remodelling.

**Thromboembolic events**

The high rate of thromboembolic complications is likewise well established in patients with Fontan palliation. Nevertheless, numerous issues remain unsettled regarding thromboprophylaxis including the choice of agent and the identification of an appropriate target population beyond those with sustained atrial arrhythmias or previous thromboembolic events. A prior iteration of management guidelines issued a Class I recommendation for anticoagulation in patients with an atrial shunt in the context of Fontan palliation. The need to anticoagulate patients with a fenestrated Fontan baffle was subsequently called into question, with two meta-analyses reporting no difference in thromboembolic events among those with and without fenestrations. In contrast, a study from the Australian and New Zealand Fontan registry reported a modest increase in thromboembolic events in patients with a fenestrated Fontan baffle (16% versus 11% at a median follow-up of 10.6 years, P=0.03). Between-study comparisons are obscured by major differences in definitions of exposures and outcomes, and adjustments for potential confounders. For example, one meta-analysis considered only strokes as opposed to all thromboembolic events. The second reported that a fenestration was paradoxically associated with a 5.9-fold lower risk of stroke (P=0.007), with no difference in thrombosis (P=0.47). Definitions were not provided. The Australian and New Zealand study clearly defined thromboembolic events (systemic, intracardiac, and Fontan conduit). Furthermore, patients with and without fenestrated Fontan baffles were propensity-matched according to age, sex, and additional anatomic and surgical variables. However, not
taking into account subsequent fenestration closures could have a major impact on effect estimates considering that fenestrations were no longer present at the last follow-up visit in 80% of patients enrolled in the current TACTIC study. Moreover, potential confounding effects of thromboprophylaxis and atrial arrhythmias were not directly adjusted for. In the current analysis that addressed these issues, presence of an open fenestration was not significantly associated with thromboemboli.

From a practical perspective, the totality of evidence suggests that fenestrating a Fontan baffle is a reasonable therapeutic option given the demonstrated acute postoperative benefits and the lack of clearly harmful long-term consequences. However, the sensitivity analyses in the current study could not exclude a possible link between an open fenestration and systemic (but not Fontan pathway/pulmonary arterial) thromboemboli. Considering that it is biologically plausible that a persistent right-to-left shunt predisposes to paradoxical systemic thromboemboli, an adequately powered study with systematic serial imaging ideally performed at brief intervals would be required to further elucidate the relationship between a persistent Fontan baffle fenestration and systemic thromboemboli. Additional studies are also required to explore potential center-specific and patient-level modulators of risk.

Limitations

The study is observational and retrospective and is hence subject to associated limitations related to potential unmeasured or unknown confounders and data not captured by medical records. In order to minimize missing data, the study was limited to patients who survived Fontan completion and were followed at the same tertiary center that performed the surgery. These restrictions bear relevance to extrapolations to patients not meeting these inclusion criteria. To maximize internal validity, all eligible patients from multiple participating sites were included.
regardless of their vital status at the time of data collection, information biases were minimized
by implementing a clinical trial-like protocol with multiple levels of quality assurance checks,
and all outcomes were validated and classified by an independent blinded adjudicating
committee. Nevertheless, while all tertiary centers included in the TACTIC study had their own
defined institutional follow-up protocols, the retrospective nature of the study precluded
imposing a uniform outcomes assessment approach across centers. Finally, as the sensitivity
analyses revealed, inexact dates of spontaneous fenestration closure inferred from intermittent
clinical surveillance introduced a potential misclassification error. The possible range of error
includes significant associations between the presence of an open fenestration and both atrial
arrhythmias and systemic thromboembolic events.

CONCLUSION

In conclusion, this large North American multicenter retrospective cohort study that employed
standardized definitions, blinded outcome adjudication, and adjustments for competing risks and
potential confounders found no convincing evidence to support an association between an open
fenestration across the Fontan baffle and major adverse cardiovascular events. Nevertheless,
definitive conclusions could not be drawn with regard to two components of the composite
outcome, i.e., atrial arrhythmias and systemic thromboembolic events. Further studies are
required to address these and other unresolved questions and controversies.
FUNDING SOURCES

Dr. Khairy is supported by the André Chagnon research chair in electrophysiology and congenital heart disease. Dr. Dib is supported by the French Federation of Cardiology (FFC) and ADETEC grants.

DISCLOSURES

The authors have no other relevant relationships to disclose.
REFERENCES


GRAPHICAL ABSTRACT

Outcomes with fenestrated versus non-fenestrated Fontan

- Adverse cardiovascular event
- Death or cardiac transplant
- Atrial arrhythmia
- Thromboembolic event

Hazard ratio (95% confidence interval)

Higher risk with no fenestration
Higher risk with fenestration
FIGURE LEGENDS

Figure 1. Unadjusted cumulative incidence of cardiovascular events (i.e., all-cause mortality, cardiac transplantation, sustained atrial arrhythmia, or thromboembolic event) in patients with and without surgical fenestration of their Fontan baffle.

Figure 2. Unadjusted cumulative incidence of A) death or cardiac transplant, B) atrial arrhythmia, and C) thromboembolic event according to whether the Fontan baffle was fenestrated or not.
### Table 1. Baseline characteristics according to Fontan fenestration status

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All N=407</th>
<th>Fenestration N=284</th>
<th>No fenestration N=123</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Fontan completion, years</td>
<td>3.3 (2.3-5.8)</td>
<td>3.0 (2.2-4.5)</td>
<td>5.3 (3.0-9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>171 (42.0)</td>
<td>123 (43.3)</td>
<td>48 (39.0)</td>
<td>0.421</td>
</tr>
<tr>
<td>Oxygen saturation post-Fontan, %</td>
<td>89.0±7.0</td>
<td>86.9±7.1</td>
<td>92.2±5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure, N (%)</td>
<td>10 (2.6)</td>
<td>8 (3.0)</td>
<td>2 (1.7)</td>
<td>0.730</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension, N (%)</td>
<td>3 (0.8)</td>
<td>1 (0.4)</td>
<td>2 (1.7)</td>
<td>0.216</td>
</tr>
<tr>
<td>Chronic lung disease, N (%)</td>
<td>2 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.9)</td>
<td>0.511</td>
</tr>
<tr>
<td>Thyroid disorder, N (%)</td>
<td>5 (1.3)</td>
<td>3 (1.12)</td>
<td>2 (1.7)</td>
<td>0.639</td>
</tr>
<tr>
<td>Liver cirrhosis, N (%)</td>
<td>1 (0.3)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0.090</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>2 (0.5)</td>
<td>0 (0.0)</td>
<td>2 (1.7)</td>
<td>0.192</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack, N (%)</td>
<td>9 (2.4)</td>
<td>7 (2.6)</td>
<td>2 (1.7)</td>
<td>0.730</td>
</tr>
<tr>
<td>Surgical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic-pulmonary shunts, N (%)</td>
<td>176 (43.2)</td>
<td>117 (41.2)</td>
<td>59 (48.0)</td>
<td>0.206</td>
</tr>
<tr>
<td>Blalock Taussig shunt, N (%)</td>
<td>172 (42.6)</td>
<td>114 (40.1)</td>
<td>58 (47.2)</td>
<td>0.188</td>
</tr>
<tr>
<td>Waterston, N (%)</td>
<td>8 (2.0)</td>
<td>5 (1.8)</td>
<td>3 (2.4)</td>
<td>0.703</td>
</tr>
<tr>
<td>Norwood procedure, N (%)</td>
<td>112 (27.5)</td>
<td>96 (33.8)</td>
<td>16 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary artery banding, N (%)</td>
<td>56 (13.8)</td>
<td>34 (12.0)</td>
<td>22 (17.9)</td>
<td>0.112</td>
</tr>
<tr>
<td>Superior cavopulmonary anastomosis, N (%)</td>
<td>344 (84.5)</td>
<td>246 (86.6)</td>
<td>98 (79.7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Bidirectional Glenn, N (%)</td>
<td>306 (75.2)</td>
<td>223 (78.5)</td>
<td>83 (67.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Hemi-Fontan, N (%)</td>
<td>43 (10.6)</td>
<td>27 (9.5)</td>
<td>16 (13.0)</td>
<td>0.291</td>
</tr>
<tr>
<td>No prior staging procedure, N (%)</td>
<td>23 (5.7)</td>
<td>17 (6.0)</td>
<td>6 (4.9)</td>
<td>0.657</td>
</tr>
<tr>
<td>Fontan type</td>
<td></td>
<td></td>
<td></td>
<td>0.718</td>
</tr>
<tr>
<td>Intracardiac lateral tunnel, N (%)</td>
<td>214 (52.6)</td>
<td>151 (53.2)</td>
<td>63 (51.2)</td>
<td></td>
</tr>
<tr>
<td>Extracardiac conduit, N (%)</td>
<td>193 (47.4)</td>
<td>133 (46.8)</td>
<td>60 (48.8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Adjudicated events during follow-up

<table>
<thead>
<tr>
<th>Event Type</th>
<th>All N=407</th>
<th>Fenestration N=284</th>
<th>No fenestration N=123</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or cardiac transplantation, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, N (%)</td>
<td>18 (4.4)</td>
<td>16 (5.6)</td>
<td>2 (1.6)</td>
<td>0.071</td>
</tr>
<tr>
<td>Cardiac transplantation, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial arrhythmias, N (%)</td>
<td>55 (13.5)</td>
<td>36 (12.7)</td>
<td>19 (15.5)</td>
<td>0.453</td>
</tr>
<tr>
<td>Atrial fibrillation, N (%)</td>
<td>9 (2.2)</td>
<td>6 (2.1)</td>
<td>3 (2.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Focal atrial tachycardia, N (%)</td>
<td>13 (3.2)</td>
<td>8 (2.8)</td>
<td>5 (4.1)</td>
<td>0.511</td>
</tr>
<tr>
<td>Intra-atrial reentrant tachycardia, N (%)</td>
<td>35 (8.6)</td>
<td>23 (8.1)</td>
<td>12 (9.8)</td>
<td>0.584</td>
</tr>
<tr>
<td>Thromboembolic events, N (%)</td>
<td>35 (8.6)</td>
<td>24 (8.5)</td>
<td>11 (8.9)</td>
<td>0.871</td>
</tr>
<tr>
<td>Systemic, N (%)</td>
<td>16 (3.9)</td>
<td>13 (4.6)</td>
<td>3 (2.4)</td>
<td>0.308</td>
</tr>
<tr>
<td>Neurologic, N (%)</td>
<td>8 (2.0)</td>
<td>7 (2.5)</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac systemic circulation, N (%)</td>
<td>6 (1.5)</td>
<td>6 (2.1)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Renal, N (%)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral, N (%)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>Fontan pathway/pulmonary arterial, N (%)</td>
<td>20 (4.9)</td>
<td>12 (4.2)</td>
<td>8 (6.5)</td>
<td>0.329</td>
</tr>
<tr>
<td>Fontan pathway, N (%)</td>
<td>18 (4.4)</td>
<td>10 (3.5)</td>
<td>8 (6.5)</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary arterial circulation, N (%)</td>
<td>2 (0.5)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Follow-up duration, years</td>
<td>10.4 (7.1-14.4)</td>
<td>9.6 (6.5-13.0)</td>
<td>11.9 (8.6-17.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Factors associated with adverse cardiovascular events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable HR (95% CI)</th>
<th>Univariable P-value</th>
<th>Multivariable Adjusted HR (95% CI)</th>
<th>Multivariable P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenestration</td>
<td>1.25 (0.76, 2.06)</td>
<td>0.383</td>
<td>1.18 (0.71, 1.97)</td>
<td>0.521</td>
</tr>
<tr>
<td>Age at Fontan, years</td>
<td>1.02 (0.99, 1.06)</td>
<td>0.167</td>
<td>1.05 (1.01, 1.09)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.27 (0.81, 1.97)</td>
<td>0.296</td>
<td>1.38 (0.85, 2.24)</td>
<td>0.189</td>
</tr>
<tr>
<td>Norwood procedure</td>
<td>1.80 (1.13, 2.88)</td>
<td>0.014</td>
<td>1.99 (1.20, 3.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Extracardiac versus intracardiac Fontan</td>
<td>0.77 (0.48, 1.24)</td>
<td>0.290</td>
<td>0.70 (0.43, 1.14)</td>
<td>0.149</td>
</tr>
<tr>
<td>Blalock-Taussig-Thomas shunt</td>
<td>0.61 (0.39, 0.97)</td>
<td>0.035</td>
<td>0.63 (0.39, 1.01)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

HR denotes hazard ratio; CI, confidence interval.
Table 4. Sensitivity analyses according to A) last observation carried forward and (B) next observation carried backward Fine and Gray Cox regression models

<table>
<thead>
<tr>
<th>Event</th>
<th>Group A sensitivity analyses</th>
<th>Group B sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted HR (95% CI)</strong></td>
<td><strong>P-value</strong></td>
<td><strong>Adjusted HR (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Adverse cardiovascular events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.57 (1.00, 2.46)</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Cardiac transplantation or death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.98 (0.63, 6.20)</td>
<td>0.242</td>
</tr>
<tr>
<td><strong>Atrial arrhythmia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>2.05 (1.14, 3.69)</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Any thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.74 (0.76, 3.96)</td>
<td>0.188</td>
</tr>
<tr>
<td><strong>Systemic thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>3.46 (1.06, 11.29)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Fontan pathway/pulmonary arterial thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.11 (0.38, 3.24)</td>
<td>0.856</td>
</tr>
</tbody>
</table>

HR denotes hazard ratio; CI, confidence interval.

*From multivariable Fine and Gray Cox regression models with same the adjustment variables presented in Tables 3 and 5

†From simple Fine and Gray Cox regression models
Table 5. Factors potentially associated with atrial arrhythmias and thromboembolic events

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial arrhythmia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.62 (0.85, 3.08)</td>
<td>0.144</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.05 (1.01, 1.10)</td>
<td>0.022</td>
</tr>
<tr>
<td>Norwood procedure</td>
<td>1.10 (0.53, 2.29)</td>
<td>0.803</td>
</tr>
<tr>
<td>Extracardiac versus intracardiac Fontan</td>
<td>0.91 (0.49, 1.68)</td>
<td>0.753</td>
</tr>
<tr>
<td><strong>Any thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>1.24 (0.54, 2.83)</td>
<td>0.614</td>
</tr>
<tr>
<td>Thromboprophylaxis</td>
<td></td>
<td>0.083</td>
</tr>
<tr>
<td>Anticoagulation versus none</td>
<td>2.86 (1.08, 7.54)</td>
<td>0.034</td>
</tr>
<tr>
<td>Antiplatelet therapy versus none</td>
<td>0.91 (0.34, 2.46)</td>
<td>0.858</td>
</tr>
<tr>
<td>Combined therapy versus none</td>
<td>2.31 (0.62, 8.60)</td>
<td>0.211</td>
</tr>
<tr>
<td><strong>Systemic thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>2.19 (0.65, 7.31)</td>
<td>0.205</td>
</tr>
<tr>
<td><strong>Fontan pathway/pulmonary arterial thromboembolic event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenestration</td>
<td>0.73 (0.25, 2.12)</td>
<td>0.561</td>
</tr>
</tbody>
</table>

HR denotes hazard ratio; CI, confidence interval.

*From a simple Fine and Gray Cox regression model
FIGURES

Figure 1

[Graph showing cumulative incidence of cardiovascular events over time with two lines representing fenestration and no fenestration conditions.]

Number at risk:
- Fenestration: 284
- No fenestration: 123

Time (years):
- 0
- 5
- 10
- 15
- 20

P = 0.280
Figure 2

A

Cumulative incidence of death or cardiac transplant (%)

P = 0.0164

Number at risk
Fenestration
284
230
131
53
13
No fenestration
123
105
79
41
19

Time (years)

B

Cumulative incidence of atrial arrhythmia (%)

P = 0.651

Number at risk
Fenestration
284
220
118
43
6
No fenestration
123
97
71
35
15

Time (years)

C

Cumulative incidence of thrombembolic event (%)

P = 0.736

Number at risk
Fenestration
284
217
135
50
12
No fenestration
123
102
73
37
18

Time (years)
The graph illustrates the cumulative incidence of cardiovascular events over time for two groups: Fenestration and No fenestration. The cumulative incidence increases with time for both groups, but the lines for fenestrated (blue) and non-fenestrated (red) conditions do not show a statistically significant difference in incidence up to 20 years, with a p-value of 0.280. The number at risk is provided for each group at different time points:

- **Fenestration**: 284 at 0 years, 209 at 5 years, 110 at 10 years, 41 at 15 years, and 6 at 20 years.
- **No fenestration**: 123 at 0 years, 94 at 5 years, 65 at 10 years, 32 at 15 years, and 14 at 20 years.