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ORIGINAL ARTICLE

Echocardiographic and Ultrasonographic Parameters Associated with Protein-losing Enteropathy in Patients with Fontan Physiology: a Systematic Review with Meta-analysis

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Abstract

Background: Fontan circulation can be associated with significant morbidity, especially Protein-Losing Enteropathy (PLE). Echocardiographic parameters can provide valuable diagnostic information about a patient's risk of developing PLE after Fontan surgery.

Objectives: To describe echocardiographic/ultrasonographic parameters associated with PLE in patients after Fontan surgery through a systematic review with meta-analysis.

Methods: A literature search was performed in electronic databases to identify relevant studies about echocardiographic parameters and PLE prediction in children after Fontan surgery. The search terms used were: "echocardiography", "ultrasonography", "Fontan," and "protein-losing enteropathy". A $p < 0.05$ was considered statistically significant.

Results: A total of 653 abstracts were obtained from electronic databases and bibliographic references. From these, six articles met criteria to be included in the qualitative analysis and three in the quantitative (meta-analysis). The resistance index in the superior mesenteric artery was described in three studies, and the quantitative analysis showed statistical significance ($p < 0.001$). Other echocardiographic and ultrasonographic parameters were also described, albeit in single studies not allowing a meta-analysis.

Conclusion: This systematic review with meta-analysis identified echocardiographic and ultrasonographic parameters related to PLE in patients with Fontan physiology. Vascular ultrasonography seems to play a prominent role in this aspect, but additional studies are needed to increase the degree of evidence.

Keywords: Fontan Procedure/methods; Ultrasonics/methods; Echocardiography/methods; Protein – Losing Enteropathies.

Introduction

Fontan circulation was described as the final stage of palliation for congenital heart disease with univentricular physiology.[1] In this circulation, blood from the superior and inferior vena cava is bypassed to the pulmonary circulation, so that the dominant ventricle is responsible for systemic circulation. Since its description, this technique has increased the survival and quality of life of patients with univentricular physiology.[2,3]

However, this type of circulation may be associated with significant morbidity.[4] That is because the patient is predisposed to a chronic low output, with increased central venous pressure and congestive heart failure.[5] These conditions can lead to pleural and pericardial effusion, gastrointestinal dysfunction, and protein-losing enteropathy (PLE).[6]

PLE is a severe condition derived from chronic venous hypertension leading to inflammation, tumor necrosis factor release, and consequent changes in the enterocyte membrane's composition. Related complications from this condition are hypoalbuminemia, hypocalcemia, hypogammaglobulinemia, and hypercoagulable states.[6] PLE affects up to 10% of patients after Fontan

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surgery[7] and can have mortality rates up to 60%.[8] Thus, identifying patients at higher risk of developing PLE after Fontan operation is essential because it can impact on their management.

The use of diagnostic imaging methods is vital for the management of congenital heart diseases. Among them, the echocardiogram gained special prominence for its ability to provide anatomical and hemodynamic information, in addition to being less invasive. As such, identifying echocardiographic or ultrasonographic parameters that can provide information on the risk of a patient presenting PLE or could present PLE at the moment after Fontan surgery can be of paramount importance.

Therefore, this study aims to describe echocardiographic or ultrasonographic parameters associated with PLE in patients after Fontan surgery through a systematic review of the literature with meta-analysis.

Methodology

Literature search

A literature search was performed in electronic databases (Medline/Pubmed, Scopus, Web of Science, Scielo, and LILACS) throughout May 2020 to identify relevant studies on echocardiographic parameters in the prediction of PLE in children after Fontan surgery. The search terms used were: "echocardiography", "ultrasonography", "Fontan" and "protein-losing enteropathy". Details on the search strategy can be seen in the supplementary Table 1. Only articles in English, Portuguese, or Spanish were included in this review. No restrictions were applied regarding the year of publication or sample size. A search for additional studies not presented in the electronic databases was carried out by investigating references and studies that cited the articles found in the initial search.

Studies selection

Studies were included in the analysis when they met the following criteria: 1) studies in patients after the Fontan operation, 2) cohort, cross-sectional or case-control studies, and 3) the study investigated echocardiographic or ultrasonographic parameters associated with PLE. Abstracts of congress or academic research in the gray literature were not included.

Data extraction

Two investigators (Mourato, MF and Mourato, FA) extracted the data independently (Mourato, FA made the search strategy. Both authors analyzed each title/abstract of all articles to select those that would go to a full-text evaluation. Both authors analyzed the full

Table 1 – studies main characteristics

First author	Publication year	Study Design	Main findings from echocardiography/ultrasonographic parameters	Quality Assessment
Du Bois	2018	Cohort	A higher celiac artery resistance index is associated with future PLE after Fontan surgery.	GOOD
Ostrow	2006	Cross-sectional	The superior mesenteric to celiac artery flow ratio is associated with present PLE after Fontan surgery.	GOOD
Rychik	2002	Cross-sectional	The superior mesenteric artery resistance index is associated with present PLE after Fontan surgery.	FAIR
González	2015	Cohort	Patients with higher systolic pressure in the pulmonary artery are at higher risk of developing future PLE after Fontan surgery.	FAIR
Silvilairat	2008	Case-control	Smaller shortening fractions are associated with present PLE after Fontan surgery.	FAIR
Mortezaeian	2020	Cross-sectional	Patients with PLE showed lower left ventricle ejection fraction.	FAIR

Legend: PLE - protein-losing enteropathy.

text to select those that would go to qualitative and quantitative analysis). Discrepancies were resolved by consensus between these authors after discussion of previously determined inclusion criteria. The following data were collected from the selected articles: first author name, year of publication, study design, sample size (divided into with PLE, without PLE, and future PLE), and the average age of the sample when submitted to an echocardiogram/ultrasonography. The echocardiographic/ultrasonographic parameter used in each study was described in the Results section. When two or more studies offered information on the same echocardiographic/ultrasonographic parameter, quantitative analysis (meta-analysis) was performed.

Study quality

The quality of the studies was assessed using the Quality Assessment Tool from the National Institute of Health (NIH).[9] Studies were classified as Good, Fair, or Poor quality by two investigators (Mourato, MF and Mourato FA) and discrepancies were resolved by consensus.

Data standardization

Continuous data were expressed as mean ± standard deviation (SD). For studies that described the interquartile ranges, the mean was estimated by the formula [minimum + maximum + 2 (median)]/4 and the SD was calculated as (maximum-minimum)/4 (in groups with $n \leq 70$) or (maximum-minimum)/6 (in groups with $n > 70$).[10]

Statistical analysis

Non-categorical data included in the quantitative analysis had their combined effect estimated with the difference of means with a 95% confidence interval (CI). When the mean difference assumes a negative value, it means that the group without PLE has higher values in that variable. An $I^2 > 50\%$ was adopted as an indicator of high heterogeneity (in such cases, the random model was used for interpretation). When a parameter was present in more than three articles, meta-regression was performed considering the average age when performing the echocardiogram/ultrasonography as a modulating factor. A $p < 0.05$ was considered significant. OpenMetaAnalyst software was used.[11]

Results

Literature search and included studies

Initially, 653 abstracts were obtained from electronic databases and bibliographic references. The initial review of these articles identified 31 candidates for full-text analysis. Of these, 25 were excluded, totaling six articles for qualitative analysis. From these six articles, it was possible to include three for quantitative analysis (meta-analysis). Figure 1 shows the article selection process. Table 1 shows the main characteristics of the selected studies.

Parameters of present PLE

Three echocardiographic parameters (peak systolic wave velocity of the superior mesenteric artery, peak diastolic wave velocity of the superior mesenteric artery, and resistance index of the superior mesenteric artery) were present in more than one study.

The peak systolic and diastolic wave velocities of the superior mesenteric artery were present in two studies,[12,13] but the joint analysis of the data did not allow for a distinction between the groups. More information on this analysis can be seen in supplementary Figures 1 and 2.

The analysis of the superior mesenteric artery resistance index (SMAR), calculated according to Pourcelot, was present in three studies.[12–14] The quantitative analysis demonstrates statistical significance with $p < 0.001$ (Figure 2). Therefore, when meta-regression was performed using the patient's age at the time of the echocardiogram as a modulating factor, the difference in means between the groups still was not significant ($p = 0.253$), as shown in Figure 3. Additionally, one of the studies[13] included patients with PLE or plastic bronchitis in the same group and the separation between them was not possible with the available data.

One echocardiographic/ultrasonographic parameter (the ratio between flow in the superior mesenteric artery and celiac artery) was present in only one study.[14]

Ostrow et al.,[14] described the ratio between the flow of the superior mesenteric artery and the celiac artery. In this study, patients with PLE had a lower ratio (0.23 ± 0.1) as compared to patients without PLE (0.34 ± 0.18) with $p = 0.03$.[12]

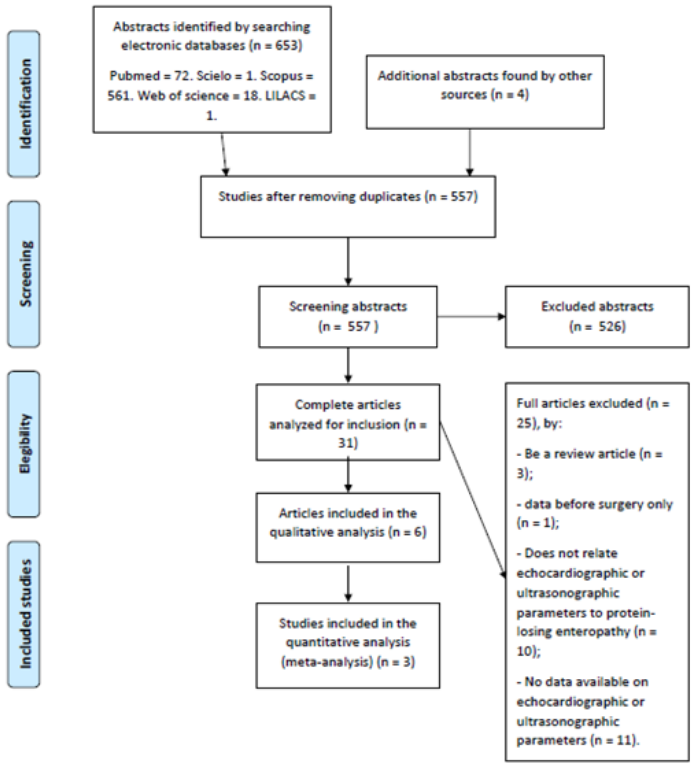

Figure 1 – Articles selection process.

Additionally, a study conducted by Mortezaeian et al.,[15] showed that patients with PLE had a lower left ventricular ejection fraction (35.00 ±15.18) than patients without PLE (49.04±5.48).[15] Another one showed that the fractional area change in different echocardiographic sections was significantly lower in patients with PLE after Fontan in a case-control study. In this study, the biplane variation was 50% vs. 56% (p <0.001), on the short axis it was 50% vs. 57% (p <0.001), and apical was 49% vs. 59% (p = 0.01) in patients with PLE and without PLE, respectively.[16]

More details on these studies can be seen in Table 2.

Predictors parameters of future PLE

Two echocardiographic/ultrasonographic parameters (celiac artery resistance index and estimated systolic pressure in the pulmonary artery) were described in only one study each.

The resistance of the celiac artery index (RCA) was described by Du Bois et al.,[13] comparing patients who would develop PLE or plastic bronchitis after Fontan and patients who would not have either one. The median of this index in patients who would develop PLE was 0.9 (with a maximum and minimum value of 0.8 and 0.9, respectively), while in patients who would not develop PLE it was 0.8 (maximum and minimum value of 0.6 and 0.9, respectively) with p = 0.01.[13]

The estimated pulmonary artery systolic pressure between 12 and 15 mmHg has been described as a risk factor for the development of PLE after Fontan surgery in a sample of Mexican patients, even after assessment with confounding factors, with p <0.01.[17]

Discussion

The increasing survival of patients with Fontan circulation brings an increase in their risks of developing adverse events, such as PLE. These patients are usually submitted to several echocardiographic exams throughout their lives; accordingly, the use of parameters derived from this exam for diagnosis or prediction of adverse events may have a substantial impact on guiding their therapeutic approach. In this systematic review, the

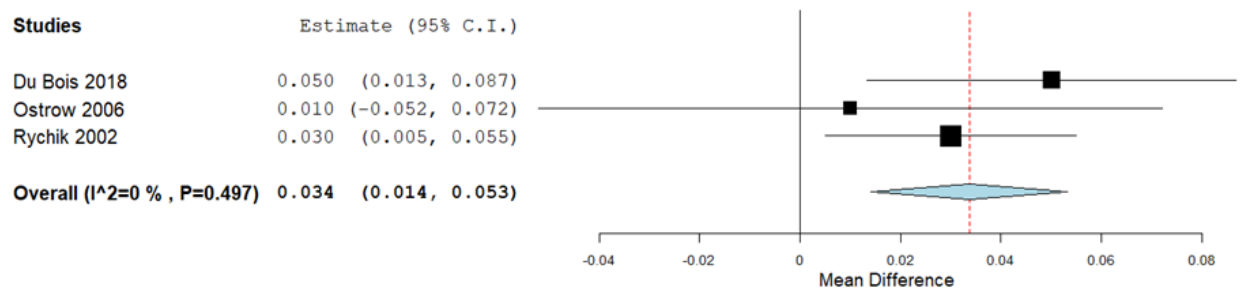

Figure 2 – Superior mesenteric artery resistance index (SMAR) quantitative analysis.

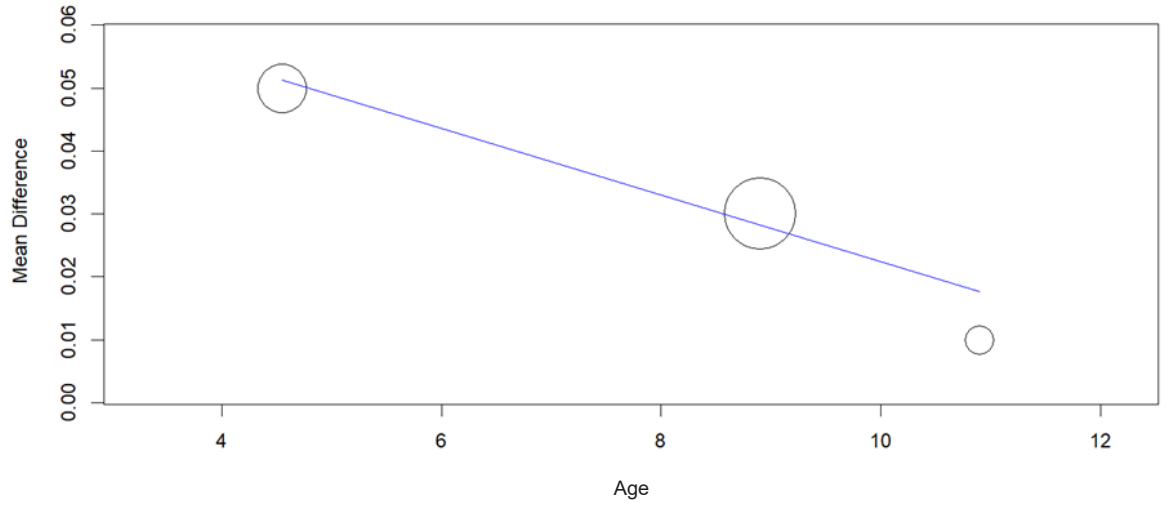

Figure 3 – meta-regression analysis of the SMAR index mean difference between patients with and without PLE and their age

Table 2: Main data from the selected studies

First author	Publication year	Fontan patients with future ple	Fontan patients with present ple	Fontan patients without ple	Mean age at echocardiogram / ultrasonography	Female patients (%)
Du Bois	2018	6*	8*	91	4.26	40
Ostrow	2006	-	7	54	10.9	-
Rychic	2002	-	13	27	8.9	-
González	2015	11	-	31	15 (median)	48
Silvilairat	2008	-	44	472	18 (median)	43
Mortezaeian	2020	-	4	73	-	42

*Legend: PLE - protein-losing enteropathy. *- This group also included patients with plastic bronchitis.*

main echocardiographic findings associated with PLE in patients after the Fontan operation were described. In this analysis, we divided these parameters into two: parameters in the presence of PLE and parameters of future PLE.

Among the parameters in the presence of PLE, SMAR has been more often described in the literature and tended to be higher in patients who presented PLE. Patients after Fontan surgery have a lower cardiac output, on average 2.4 L/min/m².[18] Of these, those who evolve with PLE have even lower rates of 1.5 - 2.0 L/min/m².[18] The state of low cardiac output leads to higher peripheral vascular resistance and, consequently, to vasoconstriction of the mesenteric circulation.[18] The low mesenteric flow promotes the release of inflammatory cytokines that alter the enterocyte cell membrane, increasing intestinal permeability and promoting protein loss.[18,19] Thus, an increased mesenteric vascular resistance may be found in PLE.

In this context, Ryckik et al.,[18] calculated the SMAR index in patients without Fontan circulation, with Fontan circulation but no PLE, and with Fontan circulation and PLE.[12] In their study, the control group had the lowest index value (0.74 ± 0.08). Patients with Fontan physiology had higher indices, being (0.88 ± 0.05) in those without PLE, and the highest (0.91 ± 0.03) in those with PLE ($p < 0.001$). Subsequently, two studies also show a tendency for a higher index in patients with Fontan and PLE circulation, but without statistical significance.[11,12] The combined analysis of data from these articles (Figure 2) shows statistical relevance ($p < 0.001$). Thus, there is evidence that leads to crediting the SMAR index as a potential parameter. Nonetheless, we must view this finding with caution, because in one study[13], it was not possible to distinguish patients with PLE from plastic bronchitis. For instance, one problem with the use of the SMAR index is its proximity between the two Fontan groups, besides the fact that the majority of patients with Fontan circulation have indices greater than usual (defined as a SMAR index between 0.75 and 0.917). This fact may make it hard to find specific cutoff points for PLE in these patients.

The ratio between the flow of the superior mesenteric artery and the celiac artery was lower in patients with PLE.[14] Thus, the analysis of the mesenteric vascularization can be individualized, as the resistance in the celiac artery is generally low in normal circulatory physiology, but may vary in patients with Fontan circulation. This analysis might lead to a better assessment of the distribution of the mesenteric flow and, consequently, the determination of a higher risk of PLE.[14] It is worth noting that this study also evaluated the SMAR, but no significant difference was observed between the groups.

Additionally, PLE after the Fontan operation usually occurs in two peaks, one earlier (in childhood) - which usually responds to therapy - and another later in life, which tends not to.[6] It should be noted that the studies reviewed here included data from different age groups, with echocardiographic parameters based on SMAR being derived from younger patients (Table 1). These different parameters may reflect different mechanisms leading to PLE, with one more linked to poor mesenteric perfusion and the other involving additional hemodynamic changes that contribute to subsequent failure of the Fontan circulation. The prevalence of one or the other could be influenced by age. With this in mind, we performed a meta-regression analysis of the SMAR index mean difference between patients with and without PLE and their age; however, it showed no statistical significance (Figure 3).

Parameters of future PLE were found only in single studies. They are the celiac artery resistance index, estimated systolic pressure in the pulmonary artery, and change in the fractional area.

Low cardiac output leads to peripheral vasoconstriction. It may explain the fact that the RCA index, measured at the site of origin of three arteries responsible for the vascularization of a large part of the abdominal organs, was higher in patients with PLE.[13] However, despite the statistical significance, such finding has limitations. The difference between the groups described by Du Bois et al.,[13] was exceedingly small, like SMAR, and the analysis also included patients with plastic bronchitis (that is, the group was not homogeneous for PLE only).

Fontan physiology is characterized by high pressures and congestion of the venous system, which is ultimately influenced by the impedance of the pulmonary vessels.[5,20] Therefore, flow is directed by the pressure difference between the systemic and pulmonary systems, and small hemodynamic changes (such as an increase in pulmonary pressure) can impair the blood flow.[6,21] Furthermore, myocardial dysfunction, which leads to a reduction in cardiac output, is associated with a higher chance of Fontan circulation failure and the development of PLE.[6]

In this context, in a retrospective Mexican evaluation, it was shown that patients with Fontan circulation and PLE tend to have higher values of pulmonary systolic pressure (between 12-15 mmHg), with a risk ratio of 2.6 ($p = 0.01$).[17] In another case-control study, it was shown that minor changes in the fractional area were associated with PLE since this measure is related to systolic function.[16]

Also, a lower left ejection fraction was correlated with the presence of PLE in patients after Fontan surgery.[15] Therefore, echocardiographic changes in pulmonary pressure and systolic function may be associated with PLE as well.

It is worth noting that the parameters obtained in other procedures can also predict the risk of PLE. An example is an increase in central venous pressure (CVP) in the postoperative period of Fontan surgery.[22] This is likely to occur because CVP leads to more significant venous congestion, altering the intestinal lymphatic drainage, thus leading to PLE. Another hemodynamic aspect that can predict the development of PLE is low pulmonary compliance, even when corrected by other hemodynamic variables.[23] Likewise, low pulmonary compliance is related to more extended pleural effusion periods, yet another risk factor for the onset of PLE.[24]

Finally, this study has some limitations. The majority of the described parameters were present in only one study, not allowing a meta-analysis and reducing the quality of evidence presented (although the majority of the selected studies presented a Fair to Good qualification in the Quality Assessment Tool). Some clinical and surgical aspects of PLE in Fontan patients were not explored due to the lack of information about them in the selected studies (correlation of the parameters with fenestrated tunnel, for example). However, such limitations are a consequence of scarce literature on the topic .

Conclusion

This systematic review with meta-analysis demonstrated the echocardiographic/ultrasound parameters related to the presence and predictors of future PLE in patients with Fontan physiology. The SMAR index was the most frequently described in the literature and showed statistical significance after quantitative assessment. Other indexes, such as the ratio of the flow between the superior mesenteric artery and the celiac artery, may, at least in theory, present better results. Other echocardiographic findings, such as increased pulmonary systolic pressure and measures related to systolic function, are correlated with PLE, but only in single studies.

Author contributions

Conception and design of the research: Mourato MF. Acquisition of data: Mourato MF, Mourato FA. Analysis and interpretation of the data: Mourato FA. Statistical analysis: Mourato FA. Writing of the manuscript: Mourato MF. Critical revision of the manuscript for intellectual content: Neves JR, Mattos SS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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