

[Original article]

Can a volume challenge pinpoint the limiting factor in a Fontan circulation?

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Objective It is difficult to indicate whether the limitation in a failing Fontan circulation lies within the pulmonary vasculature or the heart. Such differentiation is crucial to direct adequate therapy. This study was set out to determine if a volume challenge could identify the limiting factor.

Methods and study population Thirty-two catheterizations in 28 patients with a Fontan circulation were included. Pressures and oxygen saturations were measured before and after volume challenge (NaCl 0.9%; 15 cc/Kg). The changes in data were grouped based on the location of the major pressure increase. Ventricular function was measured in the resting state.

Results The majority of the patients showed an increase in aortic oxygen saturation, mixed venous oxygen saturation, systolic, pulmonary and systemic venous pressures. The arterio-venous oxygen gradient decreased, suggesting an increase in cardiac output. Different patterns in pressure changes were observed. Most (n = 17) showed a similar increase of ventricular end-diastolic pressure and mean venous pressure (MVP); some (n = 7) showed a lower increase of MVP, suggesting pulmonary reserve and recruitment; others (n = 8) showed a significant higher increase in MVP, suggesting increased pulmonary vascular resistance. All volume challenge was well tolerated.

Conclusion Most patients were preload-responsive. The pressure changes following volume load showed patterns with a potential of differentiating between patients with a major pulmonary or cardiac limiting factor.

Keywords *Fontan – total cavopulmonary connection – circuit failure – volume challenge.*

INTRODUCTION

In 1971 Fontan and Baudet reported the first successful right-sided cardiac bypass in a patient with a single functional ventricle¹. Nowadays, the preparation from birth onwards and the operative techniques have been modified to the extent that a spectacular improvement of the early survival²⁻⁴ and a reduction in preoperative and late complications are obtained⁵⁻⁹. The focus

of follow-up of patients with a Fontan circulation has now shifted to the long-term effects.

In a Fontan circuit the mechanisms controlling cardiac output differ significantly¹⁰. The late failure of the Fontan circulation is due to congestion and/or low cardiac output. This can be caused by a ventricular or pulmonary dysfunction. Pulmonary vascular resistance is proven to be a major determinant of preload reserve and circulatory output in Fontan circuits^{11,12}. Any therapeutic strategy is only successful if directed to the limiting factor in the circulation¹³.

It is important to differentiate between patients whose major limiting factor is localised in the lungs and patients with a more important cardiac limiting factor. Differentiation is difficult for the clinician but has significant therapeutic consequences. The purpose of this study was to evaluate whether such a dichotomy could be obtained with volume challenge during catheterization.

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METHODS AND STUDY SUBJECTS

Patients

Patients presenting for a catheterization after Fontan surgery between September 2005 and February 2011 were subjected to a volume challenge. Catheterizations were indicated as routine follow-up when fully grown (especially in girls with pregnancy wish), with closure of fenestration or if clinically indicated (cyanosis, exercise-intolerance, protein-losing enteropathy). All Fontan patients had undergone extra cardiac total cavopulmonary connection (TCPC) surgery to create an extracardiac conduit. There were no right-to-left shunts at the time of volume challenge. The volume challenge, during catheterization for closure of fenestrations, was done after closure of the fenestrations. Exclusion criteria were a non-sinusoidal rhythm or missing data. The patients or their parents (if underage) provided written informed consent. Our institution's ethics committee on clinical investigations approved the procedure.

Procedures

Most catheterizations were done under general anaesthesia without oxygen supplements, one adult had a catheterization done under local anaesthesia. Normocapnia (pCO₂ 35-45 mmHg) and low positive pressures (maximal PEEP: +5 cm H₂O) were maintained during the procedure. This was done in order to reduce the influence on the haemodynamic measurements^{14,15}. Gradients within the circulation were excluded. Volume challenge was done by administering an intravascular volume bolus within 10 minutes (NaCl 0.9%; 15 cc/Kg). Full diagnostic catheterizations (with fluid-filled catheters) were performed before and after volume challenge. We measured mixed venous pressure (MVP), pulmonary wedge pressure (PcW), ventricular end-diastolic pressure (VEDP) and ventricular end-systolic pressure (VESP) before and after fluid challenge. All measurements were performed during a short period of apnoea. Two to five consecutive steady-state beats were signal-averaged and used for analysis. Mixed venous oxygen saturation (MV-sat) and aortic oxygen saturation (Ao-sat) were also measured before and after fluid challenge. MVP and MV-sat were measured at the coronal end of the conduit. Ventricular dimensions were measured during dimensional ventriculography and/or echocardiography.

Data analysis

Data was inserted in an Excel® spreadsheet (Microsoft Office 2013®). The following data was extracted from the patient's file: age at catheterization, age at completion of Fontan-operation, gender, indication for

catheterization, cardiac pathology, cardiovascular medication and NYHA-classification. The next data was collected during catheterization before and after volume load: amount of volume load, VEDP, VESP, PcW, MVP, Ao-sat, MV-sat, pulmonary vascular resistance (PVR) and ventricular dimension (VEDD, VESD).

Contractility was assessed by determining the fractional shortening: $(VEDD-VEDP)/VEDD \times 100$. The difference between aortic oxygen saturation and mixed venous oxygen saturation was calculated and used as a parameter of change in cardiac output. The difference in pressures and cardiac output before and after volume challenge was calculated.

Statistical analysis

All values were expressed as mean \pm standard deviation. A *P*-value < 0.05 was considered to denote statistical significance.

RESULTS

Age and gender

Thirty-nine catheterizations with volume challenge were done in 35 patients. Most catheterizations were done under general anaesthesia ($n = 38$). Seven catheterizations were excluded due to missing data. Thirty-two catheterizations in 28 patients formed the basis of our analysis (17 males and 11 females). The mean age of the patients at the time of the catheterization was 10.5 ± 5.9 years (range: 3.1-26.0). The mean interval between completion of Fontan surgery and catheterizations was 5.6 ± 4.8 years (range 0.2-18.3).

Diagnosis, indication and current therapy

Anatomic diagnoses were: tricuspid atresia ($n = 9$), pulmonary atresia with intact ventricular septum ($n = 6$), single ventricle: dominant left ($n = 10$), single ventricle: dominant right ($n = 2$), functional single ventricle ($n = 1$). Indications for catheterization were: routine follow-up ($n = 17$), closure of fenestrations ($n = 7$) and clinical deterioration ($n = 8$). All patients received medication at the time of catheterization: acetylsalicylic acid ($n = 23$), clopidogrel ($n = 10$), vitamin K antagonist ($n = 5$), low-molecular-weight heparin ($n = 2$), diuretics ($n = 6$), beta blockers ($n = 2$), angiotensin-converting enzyme inhibitors ($n = 8$), and/or digoxin ($n = 3$). Only 1 patient received pulmonary vasodilators (bosentan).

Saturation

The aortic saturation and mixed venous oxygen saturation before and after volume challenge are shown

in table 1. The mean MV-sat increased from $65.9 \pm 8.7\%$ O₂ (range: 47.5-77.0) after volume challenge to a mean oxygen saturation of $73.4 \pm 7.4\%$ O₂ (range: 54.0-86.0) (P -value: 0.002). The mean arterial-venous oxygen gradient (AVOG) was reduced from $28.3 \pm 7.5\%$ (range: 18.0-48.5) to $22.8 \pm 7.5\%$ (range: 9.0- 44.0) after volume load (P -value < 0.05).

Haemodynamics

Data of individual haemodynamic changes after volume load are summarized in table 2. All but two had fractional shortenings above 25%. MVP increased from 14.6 ± 2.8 mmHg (range: 10.0-21.0) to 18.3 ± 3.3 mmHg (range: 10.0-21.0; P < 0.05) after volume challenge. VEDP increased from 10.0 ± 4.4 mmHg (range: 2.0-19.0) to 13.7 ± 6.3 mmHg (range: 3.0-29.0; P < 0.01) after volume challenge.

Heterogeneous reactions

Different patterns in pressure changes were observed after volume load. To analyse these patterns catheterizations were divided into three artificial subgroups. Most ($n = 17$) showed a similar pressure increase at the pre-cardiac and pre-pulmonary sites (increase MVP = VEDP (with a range of ± 2 mmHg)). Some

($n = 8$) had a bigger increase in MVP than in VEDP. Others ($n = 7$) reacted to volume load with a bigger pressure increase in VEDP than in MVP. No clear significant differences or correlations within the clinical criteria (underlying cardiopathy, complications, NYHA-classification, indication, AVOG, transpulmonary gradient, fraction of shortening) were observed between these small artificial subgroups.

Subgroup with subsequent catheterizations

Four patients were included twice at different phases after the completion of the TCPC. In three of the four patients the first catheterization with volume challenge was done in regular follow-up, and their second catheterization was indicated after developing clinical signs (protein-losing enteropathy, exercise intolerance, cyanosis). The difference in pressure change in these subsequent catheterizations showed no common trend.

One subsequent catheterization was done to evaluate the haemodynamic situation after initiating treatment with bosentan. This patient showed a different response to volume load after almost 4 years of treatment. During the first volume challenge the mixed venous pressure rose with 10 mmHg (VEDP rose with 1 mmHg). The volume challenge after four years of treatment showed a smaller

Table 1 Mean haemodynamics and oxygen saturations of total study population and subgroups

	Total population		Group 1		Group 2		Group 3	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
MVP (mmHg)	14.6 ± 2.8 [10-21]	18.3 ± 3.3 [11-24]	14.7 ± 2.3 [10-19]	17.4 ± 3.1 [11-24]	12.6 ± 2.1 [10.5-16]	19.4 ± 3.4 [14.5-23]	16.7 ± 3.2 [13.5-21]	19.1 ± 3.4 [13-32]
PcW (mmHg)	11.9 ± 3.7 [4-19]	15.7 ± 3.6 [7-23]	12.3 ± 3.5 [7-19]	14.6 ± 1.6 [13-18]	9.9 ± 4.5 [4-16]	16.0 ± 6.2 [7-23]	13.6 ± 1.5 [12-16]	17.5 ± 2.5 [15-21]
VEDP (mmHg)	10.0 ± 4.4 [2-19]	13.7 ± 6.3 [3-29]	9.7 ± 4.6 [2-19]	12.1 ± 5.1 [5-24]	8.5 ± 4.9 [2-15]	10.8 ± 5.8 [3-17]	12.4 ± 2.0 [10-16]	21.0 ± 3.7 [18-29]
VESP (mmHg)	88.9 ± 20.4 [61-150]	97.1 ± 20.4 [64-140]	84.5 ± 17.4 [62-130]	91.3 ± 17.7 [71-128]	90.9 ± 27.9 [61-150]	101.6 ± 25.5 [64-140]	97.6 ± 16.8 [77-122]	106.1 ± 18.2 [74-126]
Sat MVP (% O ₂)	65.9 ± 8.7 [47.5-77]	73.4 ± 7.4 [54-86]	66.7 ± 7.6 [50-77]	72.7 ± 5.5 [57-78]	60.5 ± 10.0 [47.5-72]	73.5 ± 13.8 [54-86]	68.6 ± 9.1 [56-77]	74.6 ± 7.1 [63-83]
Sat Ao (% O ₂)	94.7 ± 3.8 [81-98]	95.5 ± 3.8 [84-99]	93.7 ± 4.7 [81-98]	95.2 ± 3.5 [88-99]	96.0 ± 1.2 [95-98]	98 ± 0.8 [97-99]	96.1 ± 0.7 [95-97]	94.3 ± 5.1 [84-97]
AVOG (% O ₂)	28.3 ± 7.5 [21-48.5]	22.8 ± 7.5 [9-44]	27.0 ± 5.9 [18-37]	23.1 ± 4.0 [19-35]	33.4 ± 9.1 [26-48.5]	24.5 ± 13.6 [13-44]	27.6 ± 9.1 [19-40]	21 ± 9.4 [9-34]
Transpulmonary gradient (mmHg)	3.1 ± 2.1 [-1-8]	3.8 ± 2.5 [0-8]	2.9 ± 2.0 [-1-6]	4.1 ± 2.1 [1-7.5]	3.7 ± 2.9 [0-8]	4.9 ± 3.1 [0-8]	2.9 ± 1.5 [1.5-5]	1.5 ± 1.0 [0-2]

The mean \pm standard deviation and range in measured pressure and oxygen saturation before (pre) and after (post) volume challenge are shown for the different locations. The mean of calculated arterio-venous oxygen gradient and transpulmonary gradient are noted. AVOG:arterio-venous oxygen gradient, MVP: mixed venous pressure, PcW: pulmonary wedge pressure, Sat MVP: mixed venous oxygen saturation. Sat Ao: aortic oxygen saturation, VEDP: ventricular end-diastolic pressure, VESP: ventricular end-systolic pressure. Sat MVP: mixed venous oxygen saturation. Sat Ao: aortic oxygen saturation. Data is shown for the total study population and each subgroup: group 1 (pressure increase MVP = VEDP), group 2 (pressure increase MVP > VEDP) and group 3 (pressure increase MVP < VEDP).

Table 2 Individual haemodynamics and oxygen saturations

Cath.	Age Fontan (years)	Age cath. (years)	Diagnosis	NYHA	FS rest (%)	MVP rest (mmHg)	VEDP rest (mmHg)	AVOG rest (%O ₂)	MVP VL (mmHg)	VEDP VL (mmHg)	AVOG VL (%O ₂)
1**	13.8	26	Tri-A	1	–	10	2	–	11	5	–
2	2.9	5.4	DILV	3	35.00	11	6	35	21	7	–
3*	2.9	9.1	DILV	2	37.50	13	11	37	15	15	22
4	3.25	4.2	DILV	2	37.78	12	4	–	14.5	4	–
5*	3.25	6.1	DILV	1	30.00	14.5	12	24	19	20	–
6	3.3	5.8	DORV	1	30.61	13	6	37	15	7	35
7*	3.3	7.1	DORV	1	33.33	11.5	2	48.5	15	3	–
8	3.7	14.7	Tri-A	1	30.77	15	14	26	21	17	44
9*	3.7	15.3	Tri-A	3	30.00	16	10	–	23	9	–
10	5.6	9.9	Pu-A	1	30.00	16.5	2	34	21	7	24
11	3.6	4.1	Tri-A	3	28.89	11	9	20.5	13	9	22
12	13.4	16.3	DILV	2	24.32	15	8	20	16	9	19
13	5.7	14.7	DILV	2	30.19	11	5	27.5	23	13	13
14	3.2	3.9	Pu-A	3	27.03	16	8	35	17	9	–
15	5.2	6.9	DORV	2	32.14	13.5	7	25	16	8	–
16	3.2	4.1	DILV	1	40.54	13.5	12	31	13	20	29
17	3.4	9.6	DILV	2	38.10	14.5	9	28	17	11	23
18	4.8	14.1	Pu-A	2	39.66	14	15	30	21	17	18
19	2.9	3.3	Tri-A	1	35.90	10.5	12	–	17	16	23
20	6	11.4	TvF	1	30.00	21	12	20	22	18	21
21	2.2	6.8	Tri-A	2	30.91	17	15	18	17	14	–
22	2.5	3.1	Tri-A	2	40.28	21	16	40	23	29	34
23	3.25	12.9	Pu-A	2	30.00	14	15	26	21	20	20
24	5.2	14.2	Tri-A	1	45.12	19	19	24	24	24	23
25	4.4	15.9	Tri-A	1	23.81	17	11	25	18	14	21
26	2	14.6	DILV	1	40.30	16	14	20	19	21	13
27	4.4	22.7	DILV	2	41.33	13	6	24	18	10	26
28	6.6	16.8	DILV	2	27.00	14	11	19	17	21	20
29	5.4	13.5	Pu-A	–	46.15	17	10	39	21	18	9
30	4.6	5.1	DILV	1	30.00	16	10	28	18	11	21
31	3.1	3.6	Tri-A	2	16.18	15	11	27	19	14	22
32	3.7	13.8	Pu-A	2	40.63	17	15	23	20	18	23

Data of all catheterizations included in the study are shown in this table. Age at completion Fontan, age at catheterization are noted. The pressures before and after volume challenge are shown for the different locations. Arterio-venous oxygen gradient and fractional shortening are shown. AVOG: arterio-venous oxygen gradient, FS: fractional shortening, MVP: mixed venous pressure, VEDP: ventricular end-diastolic pressure. Subsequent catheterizations are indicated with an asterisk (*). Catheterization done under local anaesthesia is indicated with a double asterisk (**).

increase of MVP (2 mmHg) and a higher increase in VEDP (4 mmHg). The trans-pulmonary gradient and the PVR at rest was reduced from 5.5 mmHg and 0.16 Woods units to 3.0 mmHg and 0.08 Wood units, respectively, after treatment.

Complications

No complications occurred following fluid application or general anaesthesia.

DISCUSSION

Prevention and treatment of late circulatory failure in a Fontan circulation becomes important in the post-operative management. Therapeutic strategies will only be successful when aimed at the limiting factor^{16–18}. The search for the limiting factor, causing late circulatory failure in a Fontan circulation, has led to a dichotomy in therapeutic strategies. Several studies attributed the failure of the circulation to a primary cardiac

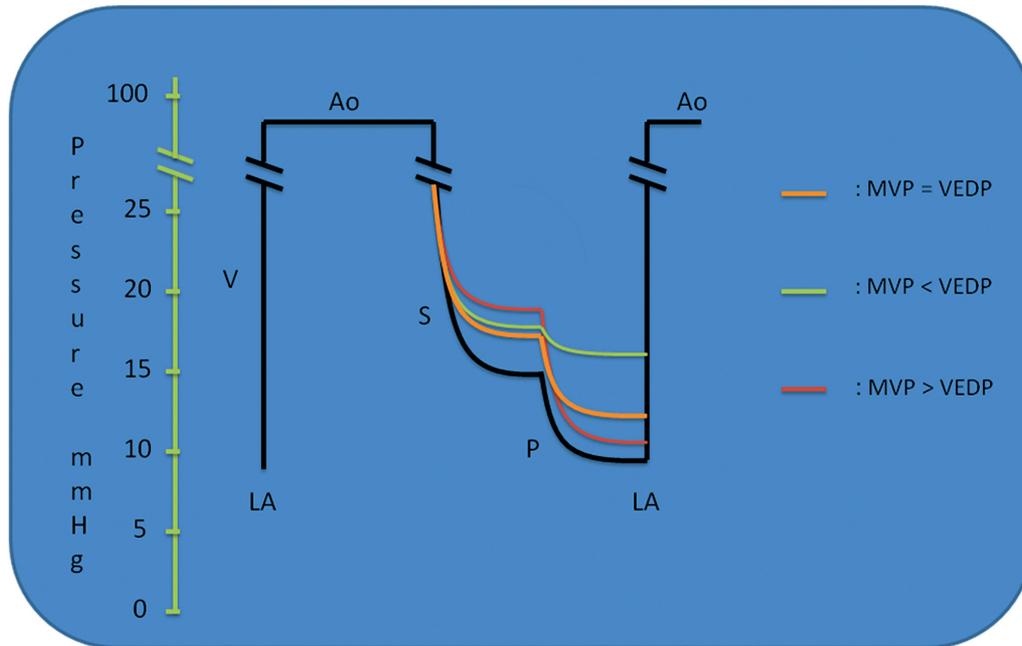


Fig. 1. Schematic representation of the Fontan circulation and the pressure changes. The Fontan circuit at rest (black line): the systemic veins are connected to the pulmonary artery, without a subpulmonary ventricle or systemic atrium. The pulmonary circulation (P) is connected in series with the systemic circulation (S). The systemic venous pressures are markedly elevated. The different patterns in pressure change following volume load are represented for each theoretical subgroup: non-differentiating pattern (orange line: pressure increase $MVP = VEDP$), group with pulmonary limiting factor (red line: pressure increase $MVP > VEDP$) and the group with pulmonary recruitment (green line: pressure increase $MVP < VEDP$). Ao: aorta, LA: left atrium, LA: left atrium, MVP: mixed venous pressure, V: ventricle, VEDP: ventricular end-diastolic pressure, S: systemic circulation, P: pulmonary circulation.

problem while other studies postulated a pulmonary factor^{12,19}.

Volume challenge (a surrogate for physiological stress) acts as a stressor on the circulation. Healthy individuals will have enough reserve capacity to cope with the additional stress (increase in cardiac output and minor pressure increase)^{20,21}. A patient whose circulation functions at its limits will respond to the volume challenge with pressure increase prior to the limiting factor. Nowadays the connection itself, such as the current cavo-pulmonary connection, is no longer a limiting factor; stenosis and energy loss by flow disturbance have become rare complications^{22,23}. The patients included in this study had good ventricular functions, so the limiting factor will most likely be found within the pulmonary vasculature.

The pressures measured at rest in the Fontan circulation showed a pattern consistent to previous findings in Fontan patients¹⁰(figure 1). As expected in a heterogeneous population of Fontan patients (clinically stable vs clinical deterioration) we observed a heterogeneous response in pressure changes after volume challenge. The heterogeneous patterns in pressure changes suggest

inter-individual differences in mechanisms to cope with volume load. The capacity to recruit pulmonary vessels might be a major player in the volume load response of total cavopulmonary connections.

Most patients showed a concordant increase in MVP and VEDP, suggestive of a Fontan circulation with reserve capacity. Fontan patients with a lower MVP increase (compared to VEDP increase) are assumed to have a pulmonary vasculature with reserve. This adaptive capacity of the lungs is probably due to recruitment. Patients showing a larger increase in MVP are assumed to have a pulmonary limiting factor: elevated PVR.

Catheterization performed to evaluate the haemodynamic situation after initiating treatment for pulmonary hypertension (bosentan; 4 years of treatment) showed a lower transpulmonary gradient and PVR after treatment. The pattern of pressure change (after volume challenge) evolved from a pattern with pronounced MVP increase to a pattern with equal increase in MVP and VEDP. These findings support our hypothesis and show that the pattern of pressure change after volume challenge can indicate patients who might benefit from a treatment with pulmonary vasodilators.

The identification of different patterns following volume load yields a better understanding of the complex physiology of the Fontan circulation, but additional investigations are needed. The ability to identify the limiting factor in each Fontan patient is of great value. Therapeutic interventions influencing the pulmonary vascular resistance failed to cause an overall improvement in a non-selected population of patients with a failing Fontan circulation. Nonetheless, several individuals showed some improvement²⁴. It is important to develop a reliable test identifying patients who might benefit from the expensive treatments focusing on pulmonary vascular resistance.

LIMITATIONS

This study investigates a small non-selective group of patients after Fontan operation. As a consequence, interpretation of comparison between these subgroups should be cautious. The division into three subgroups according to their pattern in pressure change is artificial. Therefore further statistical analysis on these subgroups is of little value. This study was designed to illustrate the presence of different patterns in pressure change after

volume load and not to identify any criteria to divide this population into clinical subgroups. Most patients underwent catheterization under general anaesthesia which might introduce bias.

CONCLUSIONS

The mechanisms involved in controlling the cardiac output in a Fontan circulation are complex and not yet fully understood. We analysed the pressure changes after volume load to obtain information regarding the location of the limiting factor of cardiac output. We distinguished different patterns in pressure changes with the potential to indicate the location of the major limiting factor in each Fontan circulation. A pattern with a larger increase in MVP is assumed to have a more important pulmonary limiting factor. Further investigation with inclusion of clinical and haemodynamic parameters and therapeutic response is necessary. Our findings open perspectives to understand the complex physiology of the Fontan circulation and to tailor treatment.

CONFLICT OF INTEREST: none.

REFERENCES

- Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971; **26**: 240-8.
- Gentles TL, Mayer JE, Gauvreau K, Newburger JW, Lock JE, Kupferschmid JP, Burnett J, Jonas RA, Castañeda AR, Wernovsky G. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. *J Thorac Cardiovasc Surg* 1997; **114**: 76-91.
- Amodeo A, Galletti L, Marianeschi S, Picardo S, Giannico S, Di Renzi P, Marcelletti C. Extracardiac Fontan operation for complex cardiac anomalies: seven years' experience. *J Thorac Cardiovasc Surg* 1997; **114**: 1020-31.
- Veldtman GR, Nishimoto A, Siu S, Freeman M, Fredriksen PM, Gatzoulis MA, Williams WG, Webb GD. The Fontan procedure in adults. *Heart* 2001; **81**: 330-5.
- Jonas RA, Castaneda AR. Modified Fontan procedure: atrial baffle and systemic venous to pulmonary artery to anastomotic techniques. *J Thorac Cardiovasc Surg* 1988; **3**: 91-6.
- Conte S, Gewillig M, Eyskens B, Dumoulin M, Daenen W. Management of late complications after classic Fontan procedure by conversion to total cavopulmonary connection. *Cardiovasc Surg* 1999; **7**: 651-5.
- Cilliers A, Gewillig M. Fontan procedure for univentricular hearts: have changes in design improved outcome? *Cardiovasc J S Africa* 2002; **13**: 111-6.
- Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25-year experience with 216 patients. *J Am Coll Cardiol* 2001; **37**: 933-9.
- Mitchell ME, Ittenbach RF, Gaynor JW, Wernovsky G, Nicolson S, Spray TL. Intermediate outcomes after the Fontan procedure in the current era. *J Thorac Cardiovasc Surg* 2006; **131**: 172-80.
- Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M. The Fontan circulation: who controls cardiac output. *Interact Cardiovasc Thorac Surg* 2010; **10**: 428-33.
- Bridges ND, Lock JE, Castaneda AR. Baffle fenestration with subsequent transcatheter closure. Modification of the Fontan operation for patients at increased risk. *Circulation* 1990; **82**: 1681-9.
- Senzaki H, Masutani S, Ishido H, Kobayashi T, Sasaki N, Asano H, Kyo S, Yokote Y, Ishizawa A. Ventricular afterload and ventricular work in Fontan circulation. Comparison with normal two-ventricle circulation and single ventricle circulation with Blalock-Taussig shunts. *Circulation* 2002; **105**: 2885-92.
- Sorensen GK, Ramamoorthy C, Lynn AM, French J, Stevenson JG. Hemodynamic effects of amrinone in children after Fontan surgery. *Anesth Analg* 1996; **82**: 241-6.
- Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourgh O, Jardin F. Cyclic changes in right ventricular output impedance during mechanical ventilation. *J Appl Physiol* 1999; **72**: 966-70.
- Lü F, Lin J, Benditt DG. Conscious sedation and anesthesia in the cardiac electrophysiology laboratory. *J Cardiovasc Electrophysiol* 2013; **24**: 237-45.
- Williams DB, Kiernan PD, Schaff HV, Marsh HM, Danielson GK. The hemodynamic response to dopamine and nitroprusside following right atrium-pulmonary artery bypass (Fontan procedure). *Ann Thorac Surg* 1982; **34**: 51-7.
- Barber G, Di Sessa T, Child JS, Penloff JK, Laks H, George BL, Williams RG. Hemodynamic responses to isolated increments in heart rate by atrial pacing after a Fontan procedure. *Am Heart J* 1988; **115**: 837-41.
- Cohen MI, Rhodes LA, Wernovsky G, Gaynor JW, Spray TL, Rychik J. Atrial pacing: an alternative treatment for protein-losing enteropathy after the Fontan operation. *J Thorac Cardiovasc Surg* 2001; **121**: 582-3.
- Shachar GB, Fuhrman BP, Wang Y, Lucas RV Jr, Lock JE. Rest and exercise hemodynamics after the Fontan procedure. *Circulation* 1982; **65**: 1043-8.

20. Mandarino WA, Pinsky MR, Gorcsan J 3rd. Assessment of left ventricular contractile state by preload-adjusted maximal power using echocardiographic automated border detection. *J Am Coll Cardiol* 1998; **31**: 861-8.
21. Pinsky MR. Using ventilation-induced aortic pressure and flow variation to diagnose preload responsiveness. *Intensive Care Med* 2004; **30**: 1008-10.
22. Pizarro C, De Leval MR. Surgical variations and flow dynamics in cavopulmonary connections: A historical review. *Semin Thorac Cardiovasc Surg* 1998; **1**: 53-60.
23. Sundareswaran KS, Pekkan K, Dasi LP, Whitehead K, Sharma S, Kanter KR, Fogel MA, Yoganathan AP. The total cavopulmonary connection resistance: a significant impact on single ventricle hemodynamics at rest and exercise. *Am J Physiol Heart Circ Physiol* 2008; **295**: 2427-35.
24. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing Fontan circulation. *Cardiol Young* 2009; **11**: 1-9.