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ORIGINAL ARTICLE

Significance of right atrial tension for the development of complications in patients after atriopulmonary connection Fontan procedure: potential indicator for Fontan conversion

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Abstract Elevated right atrial (RA) pressure and progressive RA dilation are thought to play pivotal roles in the development of late complications after atriopulmonary connection (APC) Fontan surgery. However, no clear cut-off value for RA pressure or RA volume has been determined for stratifying the risk of developing Fontan complications. We hypothesized that RA tension, which incorporates information about both RA pressure and volume, might help predict the risk of developing complications. We retrospectively studied 51 consecutive APC Fontan patients (median postoperative period 14 years). RA tension was computed from the RA pressure and RA radius, which was calculated from RA volume measured by RA angiography. The correlation between the cardiac catheterization hemodynamic data and the complications of APC Fontan was investigated. Of the 51 patients, 28 had complications, including liver fibrosis ($n=28$), arrhythmia ($n=8$), protein-losing enteropathy ($n=1$), and RA thrombosis ($n=1$). Among the hemodynamic data, RA volume and RA tension, but not RA pressure, were significantly higher in patients with complications than in those without ($P=0.004$ and $P=0.001$, respectively). The cut-off level for RA tension to predict Fontan complications was 26,131 dyne/cm by receiver operating characteristic curve (area under the curve 0.79, sensitivity 71.4%, and specificity 73.9%). The present study demonstrated the significance of RA tension rather than high venous pressure for the development of Fontan complications. Amid the uncertainty about clinical outcomes, the present results, subject to further validation, may contribute to the indications for Fontan conversion.

Keywords Right atrial tension · Atriopulmonary connection Fontan · Fontan complications

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Introduction

Since the first introduction of Fontan surgery, atriopulmonary connection (APC) has been the main procedure used to create a Fontan circuit. Although the procedure certainly contributes to an initial improvement in oxygen saturation, exercise capacity, and quality of life in patients with a single ventricular circulation, it has become well acknowledged, as patients live longer, that many of them develop characteristic late complications, including liver fibrosis/dysfunction, atrial tachyarrhythmias, protein-losing enteropathy (PLE), and thromboembolism [1–7]. Elevated central venous pressure (CVP), which is inevitable in the Fontan circulation, is thought to play a pivotal role in the development of these complications. In addition, progressive right atrial (RA) dilation is considered to be another important factor that triggers and induces such complications, by causing slow and turbulent venous blood flow [8, 9]. However, it is also true that clinical outcomes often differ considerably among patients with similar levels of CVP or similar degrees of RA dilation (RA volume), and there is no clear cut-off value of CVP or RA volume for stratifying the risk of developing Fontan complications. Nevertheless, it is possible that a combination of these two key factors, rather than CVP or RA volume alone, may better predict the risk of developing complications. The present study was conducted to test this hypothesis by examining the association between APC Fontan complications and RA tension, which incorporates information about both RA pressure (CVP) and volume.

Materials and methods

All patients gave written informed consent, and local ethics committee approved the study protocol. We retrospectively studied 51 consecutive APC Fontan patients (median age 22 years, postoperative period 14 years) who underwent cardiac catheterization between October 2005 and July 2013. All the patients had the simple APC Fontan procedure just closing interatrial communication with anastomosis between right atrial appendage and pulmonary artery. The indications for catheterization in these patients were based on our institutional protocol for routine checkup more than 10 years after Fontan completion ($n=43$), or hemodynamic evaluation for complication of arrhythmias ($n=8$). Hemodynamic data obtained by catheterization, including arterial oxygen saturation, systemic blood flow (Qs), pulmonary vascular resistance (Rp), and ejection fraction (EF), as well as the end-diastolic pressure (EDP) and volume (EDV) of the single ventricle were extracted from our catheter database. No patients had a significant amount of shunt flow arterio-pulmonary collateral arteries that necessitated coil embolization or surgical ligation. We also calculated RA volume based on Simpson's method for biplane RA angiography. RA tension was then computed from mean RA pressure and RA radius according to Laplace's law as follows [10]:

$$\begin{aligned} \text{RA tension (dyne/cm)} &= \text{transmural pressure} \times \text{radius}/2 \\ &= \text{RA pressure} \times 1333 \times \sqrt[3]{(3 \times \text{RA volume} / 4\pi)} / 2 \end{aligned}$$

RA radius was calculated from RA volume assuming a spherical RA.

We also assessed the prevalence of complications, including liver fibrosis, PLE, atrial tachyarrhythmia, or thrombosis. Liver fibrosis was diagnosed by ultrasound performed by two independent experienced sonographers. The diagnosis of liver fibrosis was made when there were any of the following findings: irregularity of liver surface and edge, uniformity of liver substance and liver swelling, and irregularity of liver vessels. Because it is difficult to evaluate early stage liver fibrosis by ultrasound, liver fibrosis diagnosed in this study corresponds to a stage F3 or above in the new Inuyama classification [11].

Correlations between hemodynamic data (RA tension, RA pressure, RA volume, Qs, EF, Rp, arterial oxygen saturation, EDP, and EDV) and the prevalence of Fontan complications were determined.

Statistical analysis

Data were analyzed using SPSS II (SPSS Inc., Troy, NY). Numeric variables were expressed as medians, with ranges in parentheses. An unpaired t test was used to detect factors influencing the prevalence of Fontan complications, after the patients had been divided into two groups according to the presence or absence of complications. Receiver-operating characteristic (ROC) curves were then designed to identify cut-off values for RA pressure, volume, and tension for predicting Fontan complications. The best possible cut-off point was defined as the highest Youden Index (specificity + sensitivity − 1). Values of $P<0.05$ were considered statistically significant.

Results

Of the 51 patients studied, 28 had complications; all of these had liver fibrosis, one had both liver fibrosis and PLE, seven had both liver fibrosis and atrial tachyarrhythmia, and one had liver fibrosis, RA thrombosis, and atrial tachyarrhythmia. In patients who underwent further hepatic evaluation by computed tomography ($n=3$) or liver biopsy ($n=1$), the findings supported the ultrasound diagnosis (i.e., liver fibrosis).

Table 1 summarizes the patients' demographic and hemodynamic data according to the presence or absence of complications. There were no significant differences between the two groups in the underlying cardiac disease, including morphology of ventricle or demographic data. While cardiac output and RA pressure did not differ significantly between the two groups, RA volume and RA tension were significantly higher in patients with complications than in those without. The ROC curve analysis revealed that the cut-off values for RA volume and RA tension for predicting Fontan complications were 77.9 mL/m^2 (area under the curve [AUC] 0.73, sensitivity 0.68, and specificity 0.61) and 26,131 dyne/

Table 1 Demographic and hemodynamic data of 51 patients and the results of the unpaired *t* test after patients had been divided into two groups according to the occurrence of complications

	$n=51$	Complication $n=28$	No complication $n=23$	*P*
Age (y)	22	21.7 (8–35)	24.5 (13.0–40.1)	ns
Males (%)	58	61	56	ns
Postoperative period (y)	14.0	16.6 (6.2–28.9)	17.8 (11.2–26.0)	ns
Cardiac anatomy				
Tricuspid atresia	16	8	8	ns
Double inlet ventricle	13	7	6	ns
Pulmonary atresia/intact septum	11	6	5	ns
Hypoplastic left heart syndrome	1	1	0	ns
Heterotaxy	6	4	2	ns
Other	4	2	2	ns
Morphology of ventricle		Right 7, left 19, other 2	Right 4, left 17, other 2	ns
Cardiac catheterization data				
Qs ($L/min/m^2_{BSA}$)	2.2	2.2 (1.3–3.5)	2.1 (1.5–3.0)	ns
EF of main ventricle (%)	54	54 (43–69)	53 (28–74)	ns
EDV of main ventricle (% of normal)	88	91 (35–282)	87 (47–139)	ns
EDP of main ventricle (mmHg)	8	8 (4–14)	8 (3–13)	ns
Rp (woods)	2.2	2.3 (0.5–7.4)	1.9 (0.9–3.6)	ns
Arterial oxygen saturation (%)	96	95 (79–99)	96 (83–99)	ns
RAp (mmHg)	12	13 (8–22)	12 (8–19)	ns
RAv (mL)	120	195 (44–578)	111 (35–184)	0.004
RA tension (dyne/cm)	26,595	29,611 (14,640–51,653)	22,922 (14,275–39,247)	0.001
Plasma BNP (pg/mL)	87.6	130.0 (6.0–570.1)	110.2 (9.1–538.2)	ns

Qs cardiac index, *EF* ejection fraction, *EDV* end-diastolic volume, *EDP* end-diastolic pressure, *Rp* pulmonary resistance, *RAp* right atrial pressure, *RAv* right atrial volume, *RAtension* right atrial tension

cm (AUC 0.79, sensitivity 0.71, and specificity 0.74, respectively) (Fig. 1). Figure 2 demonstrates a scatter-plot of RA pressure and volume for each patient, with a relationship indicating the RA tension cut-off value of 26,131 dyne/cm. It is notable that, when the RA becomes dilated, even a low level of venous pressure

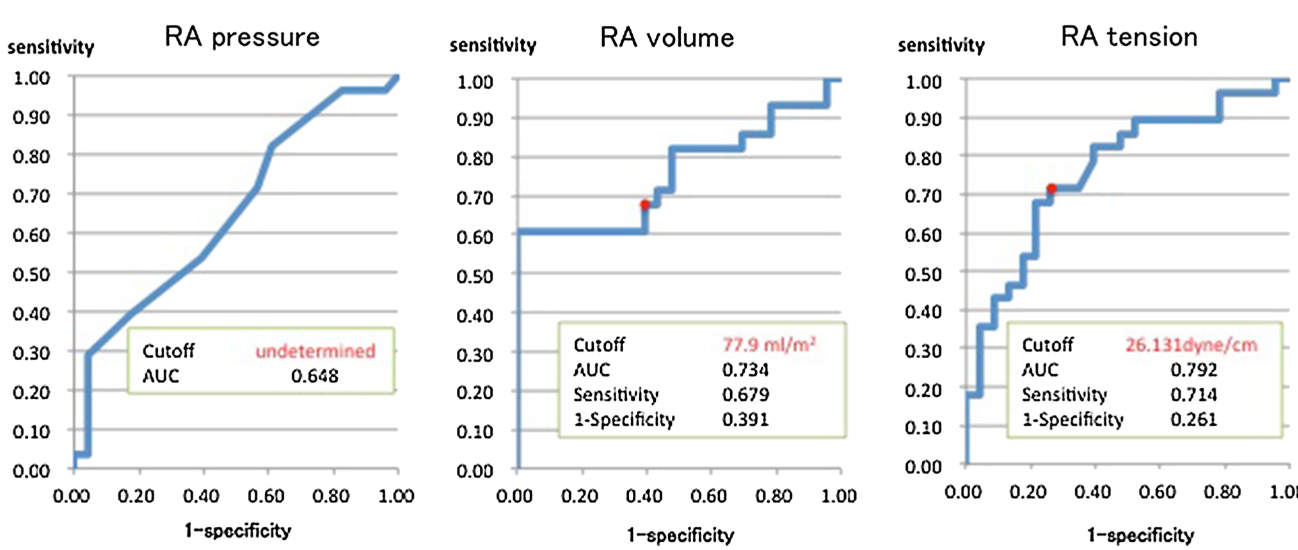

Fig. 1 Receiver operating characteristic curves for prediction of Fontan complications by right atrial pressure, volume, and tension. *RA* right atrium, *AUC* area under the curve

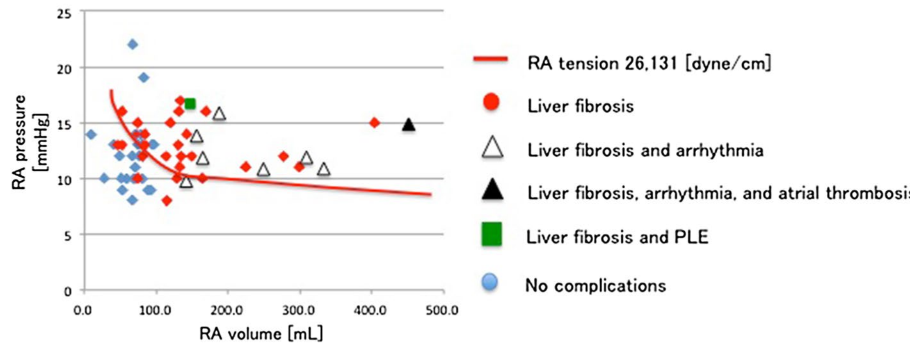

Fig. 2 Cut-off line of right atrial tension for predicting Fontan complications on the scatterplots depicting the right atrial volume and pressure of 51 patients. *RA* right atrium

(RA pressure) yields a large RA tension that is associated with complications.

Discussion

The present study demonstrated for the first time that RA tension is a critical factor rather than age, morphology of ventricle, and hemodynamic data, including arterial oxygen saturation in patients developing complications after APC Fontan surgery. Increased RA tension is the result of two major aspects of the pathophysiology of APC Fontan: the direct effects on the RA wall and the changes in blood flow dynamics due to the dilated RA.

Effects of RA tension on RA wall

Increased RA tension implies increased mechanical stress imposed on the RA wall. Mechanical stress is known to be an important stimulus for myocardial structural remodeling that leads to myocardial fibrosis and hypertrophy [12], and recent studies suggested an important association between atrial fibrosis and atrial fibrillation (AF) [13, 14]. Interestingly, an electrophysiological study [15] of APC Fontan patients demonstrated a significant correlation between the prevalence of fractionated potentials and low-voltage zones, which are the electroanatomic correlate for atrial fibrosis [16, 17]. Therefore, atrial fibrosis induced by increased RA tension may lead to atrial electrical remodeling and resultant tachyarrhythmia. Recently, particular interest has been generated in the role of angiotensin system blockade in reversing the electrical and structural remodeling of diseased atria, and the preventive effect of angiotensin blockade in AF has been demonstrated [18]. Whether blockade of the angiotensin cascade may also help to delay or prevent—or even to reverse—the electrical and structural remodeling of the RA in APC Fontan patients is a question that deserves future investigation.

In addition to its impact on electrical remodeling and arrhythmogenicity, atrial structural remodeling induced by increased mechanical stress may also play a role in atrial thrombosis, because endothelial dysfunction of the atrial wall can enhance platelet activation and thus coagulability [19].

RA tension and blood flow dynamics

The other important pathophysiology implicated in the increased RA tension is an alteration in venous flow dynamics. Increased tension caused by RA dilation causes stagnation and turbulence of blood flow, regardless of the levels of CVP. This would obviously be associated with a susceptibility to thrombosis. In addition, a dilated RA should increase the capacitance of the venous system, and increased venous capacitance requires more blood volume to maintain preload. Increased blood volume coupled with slow venous flow can cause systemic organ congestion. Increased CVP (RA pressure) is generally considered a hallmark of congestion in the Fontan circulation. However, an important implication of the present study, as Fig. 1 demonstrates, is that venous flow stagnation, rather than high venous pressure per se, is important for hepatic congestion, and perhaps for the development of PLE, in which lymphatic congestion is an important underlying pathophysiology.

Clinical implications

As shown in Fig. 2, when the RA volume is as small as 50 mL, RA pressure can increase up to 18 mmHg without reaching the cut-off value for RA tension of 26,131 dyne/cm. However, RA pressure needs to be less than 10 mmHg under conditions, where RA volume exceeds ~300 mL. According to Laplace's law, even a small elevation in RA pressure causes an increase in RA tension, and to a greater extent in a dilated RA than in a small RA. This means that, even in patients with low levels of CVP at rest, greater mechanical stress can be imposed on the RA wall during daily life activity when CVP inevitably increases. Therefore, modification of the daily lifestyle may become more important in APC Fontan patients with higher RA volume and tension.

Fontan conversion, a conversion of APC Fontan to a total cavopulmonary connection with an extracardiac conduit has been demonstrated as effective in improving the Fontan status [20–22]. However, there has been no clear indication as to the appropriate timing of Fontan conversion to prevent or delay the development of late complications. The results of the present study suggest that RA tension, which incorporates both RA mechanical load and flow dynamics, may provide useful information in this regard. APC Fontan patients with levels of RA tension below 26,131 dyne/cm may have a lower incidence of hepatic fibrosis and other complications following Fontan conversion. By unit conversion, 26,131 dyne/cm is equal to 19.6 mmHg/cm. Based on the definition of RA tension (RA pressure in mmHg × radius/2), we can derive the easier expression, RA pressure × radius ≥ ~40, as a conversion criterion for clinical use.

Limitations

There are several potential limitations that deserve further discussion. First, we assumed the RA to be a sphere, which may not be necessarily true. However, Panayiotou et al. showed the RA tension changes during relief of cardiac tamponade using Laplace's law to calculate the RA radius [10]. Moreover, in our study, the mean value of three-directional RA radii (vertical, horizontal, and sagittal) calculated from the anteroposterior and lateral projections of RA angiography was very close to the RA radius estimated from RA volume assuming a spherical RA (3.09 vs. 3.20, $P = 0.90$ by paired t test). Thus, the assumption of a spherical RA appears valid for the dilated RA in APC Fontan patients. Second, although RA tension, among other variables, best predicted Fontan complications, there was some overlapping of data. In particular, some developed liver fibrosis even with RA tension below the proposed cut-off value (Fig. 2). Other factors, such as pre-Fontan status, genetic background, or a daily lifestyle that may affect dynamic changes in RA pressure and tension, might also contribute to the development of complications, and this issue needs further clarification.

In summary, the results of the present study indicate the significance of RA tension, rather than high CVP, for the development of Fontan complications. Amid the uncertainty about clinical outcomes, the present results, subject to further validation, may contribute to the indications for Fontan conversion.

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Compliance with ethical standards

Conflict of interest None to declare.

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