Noninvasive estimation of central venous pressure after Fontan procedure using biochemical markers and abdominal echography

Tatsujiro Oka, MD, PhD,^a Ryuichi Kato, MD,^a Shigehisa Fumino, MD, PhD,^b Kentaro Toiyama, MD,^a Masaaki Yamagishi, MD, PhD,^c Toshiyuki Itoi, MD, PhD,^a and Kenji Hamaoka, MD, PhD^a

Objectives: Patients may develop liver dysfunction, including liver fibrosis, over the long term following Fontan procedure. Therefore, early detection of liver dysfunction is essential to identify those patients who are at risk. We evaluated various laboratory parameters, including liver biochemical markers, hepatic echography findings, and cardiac catheterization outcomes, at an early stage after undergoing Fontan procedure.

Methods: A total of 56 patients who underwent Fontan procedure were included in the study. All patients underwent cardiac catheterization and biochemical markers were evaluated from the samples. Abdominal echography was performed on a subgroup of patients (n = 20) to observe the structure of liver tissues and to measure blood flow in the hepatic vein, portal vein, and hepatic artery.

Results: The mean period of time since Fontan procedure was 2.8 ± 2.1 years. There was a significant correlation between venous pressure and serum levels of γ -glutamyltranspeptidase and type IV collagen 7s domain, which indicated a high probability of liver consolidation. The other biochemical markers were normal. Stepwise regression analyses suggested that by using the ratio of hepatic venous flow and type IV collagen 7s collagen domain concentration, inferior vena cava pressure can be predicted.

Conclusions: Our study showed that we can predict inferior vena cava pressure using noninvasive abdominal echography and biochemical markers at an early stage after Fontan procedure. (*J Thorac Cardiovasc Surg* 2013;146:153-7)

Since 1971, the Fontan operation and its modifications have been used for definitive palliation of patients with various forms of functionally univentricular hearts.¹ However, the Fontan operation can result in various complications, including central venous hypertension,²⁻⁴ depressed dynamic cardiac output,^{3,5} and venous thrombosis.^{5,6} Liver dysfunction over the long term following Fontan operation has been suggested in several studies based on the findings of liver function tests.²⁻⁷ Hepatic abnormalities, including cholestasis, liver fibrosis, hepatomegaly, and liver cirrhosis, may develop after the Fontan operation is performed. A long-term increase in systemic venous pressure after the Fontan procedure may cause abnormalities in liver function. However, it is not known if progression of liver dysfunction involves liver consolidation and changes in central venous pressure in the short term after Fontan surgery, although it is known that venous pressure increases immediately after the Fontan operation is performed. Recently, type IV 7s

collagen domain (7s collagen), which is involved in connective tissue metabolism, has been identified as a biochemical marker for assessing liver consolidation.⁸ Further, several other putative serum markers, such as hyaluronic acid, aspartate aminotransferase/platelet ratio index (APRI),⁹ and FIB-4 score,¹⁰ either alone or in combination, have been evaluated as liver fibrosis markers. The aims of our study were to evaluate the relationship between the various noninvasive liver function findings in the short term after Fontan procedure and hemodynamic parameters from invasive catheterization examination, and to identify the noninvasive parameters from echocardiography and/or laboratory data that were significantly related to these invasive catheterization variables.

METHODS

Between March 2007 and August 2011, the markers for hepatic fibrosis were examined simultaneously in 58 consecutive patients undergoing catheterization after Fontan procedure. Two cases were excluded because they were emergency cases: in 1 case, partial occlusion in the conduit was suspected, and the other case was performed to detect lung bleeding; therefore, 56 patients were enrolled in this study.

This protocol was performed according to the guidelines of the Committee on Research of Kyoto Prefectural University of Medicine, and informed consent was obtained from all patients before their participation in the study.

Laboratory Investigations

We included for analysis those variables that are assumed to be appropriate for assessing liver function based on synthesis, excretion, and hepatocellular damage. Serum concentrations of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline

From the Departments of Pediatric Cardiology and Nephrology,^a Pediatric Surgery,^b and Pediatric Cardiac and Thoracic Surgery,^c Kyoto Prefectural University of Medicine, Kyoto, Japan.

Disclosures: Authors have nothing to disclose with regard to commercial support. T.O. and R.K. contributed equally to this work.

Received for publication Nov 28, 2011; revisions received Sept 3, 2012; accepted for publication Sept 13, 2012; available ahead of print Oct 11, 2012.

Address for reprints: Toshiyuki Itoi, MD, PhD, Department of Pediatric Cardiology and Nephrology, Kyoto Prefectural University of Medicine, 465 Kajicho Kamigyo-ku, Kyoto 602-8566, Japan (E-mail: titoi@koto.kpu-m.ac.jp).
0022-5223/\$36.00

Copyright © 2013 by The American Association for Thoracic Surgery
<http://dx.doi.org/10.1016/j.jtcvs.2012.09.021>

Abbreviations and Acronyms

7s collagen	= type IV collagen 7s domain
APRI	= aspartate aminotransferase/platelet ratio index
ALT	= alanine aminotransferase
AST	= aspartate aminotransferase
GGT	= γ -glutamyltranspeptidase
IVCP	= inferior vena cava pressure
V ₁	= peak velocity toward the conduit
V ₂	= reverse flow toward the liver

phosphatase, and γ -glutamyltranspeptidase (GGT) were routinely obtained at the start of intravenous drip for the anesthetization before catheterization. Levels of 7s collagen and hyaluronic acid were measured as liver fibrosis markers. Measurement of 7s collagen domain was conducted by SRL Inc (Tokyo, Japan), which offers clinical laboratory testing, and the reference range (< 6.0 ng/mL) was defined by SRL Inc using data from healthy control subjects. The APRI and Fibrosis-4 scores are simplified scores of liver fibrosis and are calculated as follows: APRI = (AST/upper limit of normal) $\times$ 100/platelet count⁹; FIB-4 = age (years) $\times$ AST (IU/L)/[platelets (10^9 /L) $\times$ ALT(IU/L)]^{1/2}.¹⁰

Hemodynamic Assessment

At cardiac catheterization, conventional angiography and pressure measurements were performed. We obtained pulmonary artery index scores according to the method described by Nakata and colleagues.¹¹

Hepatic Echography and Doppler Studies

We performed abdominal echography for 20 patients using a Siemens ultrasound system (Sequoia; Siemens, Munich, Germany) equipped with a 4.0 MHz transducer, and with patients in the supine position 1 day before catheterization. Standard echographic imaging was performed from the parasternal, apical, and subcostal windows for the evaluation of liver tissues. Pulsed Doppler recordings of the right hepatic vein, right and left hepatic arteries, and right portal vein were obtained with each patient breathing quietly and in the supine position. We recorded 3 cycles from each window at a sweep speed of 100 mm/second. Further, we calculated the pulsatility ratio (minimal flow velocity: maximal flow velocity [normal value > 0.54]), of the portal vein as a marker of hepatic vein congestion, and the resistance index (peak systolic velocity – end diastolic velocity/peak systolic velocity [normal value < 0.7]).¹² The following parameters were calculated using the hepatic vein flow velocity: peak velocity toward the conduit (V₁) and reverse flow toward the liver (V₂) (Figure 1). From these values, we calculated the ratio of hepatic vein flow (V₂/V₁).

Statistical Analysis

Statistical analysis was performed using JMP9 software (SAS Institute Inc, Cary, NC). Nonparametric data were summarized the as mean, median, standard deviation, and range. The Mann-Whitney U test was performed to compare the groups. Correlations between variables were assessed using Spearman's r correlation coefficient. Subsequently, stepwise multiple linear regression was performed for multivariate analysis.

RESULTS**Baseline Clinical Characteristics**

We enrolled 30 boys and 26 girls with a mean age of 4.8 ± 2.4 years (range, 2.6–13.2 years) (Table 1). The mean age

at the initial Fontan procedure was 2.0 ± 1.3 years (range, 0.8–9.8 years). All patients had undergone an extracardiac conduit Fontan procedure without fenestration. The mean period of time since Fontan procedure was 2.8 ± 2.1 years (range, 0.6–11.0 years). No patient had active protein-losing enteropathy at the time of assessment. Pacemaker implantation was documented in 1 patient.

Biochemical Profiles

The biochemical findings of liver function tests are summarized in Table 1. Among the laboratory findings, only GGT was mildly elevated. Liver cirrhosis and extensive fibrosis could be ruled out if the serum concentration of hyaluronic acid was < 60 μ g/L,¹³ and liver fibrosis could be excluded if 7s collagen was < 6.0 μ g/L.¹⁴ Serum hyaluronic acid levels were above normal in only 4 patients (7%), but 7s collagen was elevated in 35 patients (63%). An APRI score > 1.5 indicates fibrosis⁹; however, no patients had an APRI score > 1.5 . The highest FIB-4 score in our patients was 0.44 (cutoff value > 6.2),¹⁰ suggesting that no patients had extensive fibrosis. These results indicate that 7s collagen and GGT are candidate markers of liver dysfunction.

Hemodynamic Characteristics

The mean left and right ejection fractions were $64\% \pm 7\%$ and $55\% \pm 8\%$, respectively. Inferior vena cava pressure (IVCP) ranged between 9 and 29 mm Hg (mean, 16 ± 4 mm Hg). Serum brain natriuretic peptide was < 40 pg/mL in 52 patients (93%).

Univariate and Multivariate Analyses

Univariate analyses revealed a significant correlation between hemodynamic data and catheterization data (ie, between 7s collagen and IVCP, and between GGT and IVCP [$P < .05$ for both]). There was no correlation between the other liver biochemical markers (hyaluronic acid, APRI, and Fibrosis-4 score) and any of the hemodynamic parameters. Multivariate analyses revealed a weak but significant correlation only between IVCP and 7s collagen and GGT (R^2 , 0.18; $P = .016$). Patients with a 7s collagen > 6.0 ng/mL showed a high incidence of systemic venous pressure ($P < .01$) (Figure 2). Hence, increased GGT and 7s collagen could potentially indicate increased IVCP.

Hepatic Echography Results

With the exception of IVCP, there was no strong indicator of liver dysfunction, such as brain natriuretic peptide or other hemodynamic variables, including end-diastolic volume and ejection fraction, both of which were evaluated by noninvasive examinations (ie, magnetic resonance imaging or echocardiography). Therefore, we examined several hepatic vessel flow patterns from the group of patients undergoing echography ($n = 20$) (Table 2). Compared with

FIGURE 1. A, Schematic of the pulsed Doppler recordings of hepatic vein flow. B, Measurement of the pulsed Doppler recording of hepatic vein flow in a patient who had undergone Fontan procedure (inferior vena cava pressure = 12 mm Hg). C, Measurement of the pulsed Doppler recording of hepatic vein flow in a patient who had undergone Fontan procedure (inferior vena cava pressure = 25 mm Hg). V_1 , Peak velocity toward the conduit; V_2 , peak velocity of reversal wave toward the liver.

V_1 (Figure 1), the value of V_2 was greater in patients with higher IVCP. We thus expressed the ratio of hepatic venous flow as V_2/V_1 . In univariate analysis using hepatic echography findings, we observed a significant correlation between IVCP and the ratio of hepatic venous flow ($P = .028$) (Table 2). With the inclusion of sex and age at enrollment for adjustment in the final models for echography and laboratory investigations, stepwise regression analyses showed that the ratio of hepatic venous flow and the 7s collagen concentration were strong predictors of IVCP ($IVCP = 6.5 \times V_2/V_1 + 0.95 \times 7s \text{ collagen} + 4.9$ [R^2 , 0.47; $P < .01$]).

DISCUSSION

Our results revealed liver function abnormalities in a majority of enrolled patients, even in those with a short interval (mean, 2.8 years) since Fontan operation. In our study, 63% of patients had abnormalities of 7s collagen. Univariate analysis revealed that 7s collagen and GGT were weakly but significantly correlated with central venous pressure. Several investigators have reported that GGT increases significantly after Fontan procedure.^{3,6} Moreover, total bilirubin levels have been found to increase in the long term in patients who undergo the Fontan operation.⁵ In our study, total bilirubin did not increase in the short term after Fontan surgery. Therefore, the serum levels of 7s collagen and GGT can be considered the main abnormal findings despite the difficulty in predicting IVCP using only laboratory data (R^2 , 0.18). Thus, we added the other parameters using noninvasive methods.

TABLE 1. Baseline characteristics of patients

	Units	Mean or n	SD	Median	Range
Age (y)		4.8	2.4	3.7	2.6-13.2
Time since Fontan (y)		2.8	2.1	2.1	0.6-11.0
Sex (male/female)		30/26			
Ventricle type (right/left/both*)		28/24/4			
Biochemistry					
AST	IU/L	40	11	40	12-65
ALT	IU/L	21	8	20	6-40
GGT	IU/L	65	48	56	18-328
T-bil	mg/dL	0.76	0.3	0.69	0.3-1.76
Platelet	$10^9/L$	251	67	243	153-454
7s collagen	ng/mL	6.8	1.7	7	3.6-14
Hyaluronic acid	g/mL	25.1	20	18.5	8-85
APRI		0.48	0.16	0.45	0.16-0.90
FIB-4†		0.17	0.08	0.14	0.05-0.44
BNP	pg/mL	27	50	13	4-276
Catheterization parameter					
%EF					
LV	%	64	7	63	53-79
RV	%	55	8	55	36-70
%Volume					
LV	%	100	31	93	48-186
RV	%	89	30	82	41-148
IVCP	mm Hg	16	4	16	9-29
PA index	mm^2/m^2	296	122	275	53-629

SD, Standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ -glutamyltranspeptidase, 7s collagen, type IV collagen 7s domain; APRI, aspartate aminotransferase platelet ratio index; BNP, brain natriuretic peptide; EF, ejection fraction; LV, left ventricle; RV, right ventricle; IVCP, inferior vena cava pressure; PA, pulmonary artery. *2 criss-cross heart, 2 remote type double outlet RV. †Calculated as age (y) $\times$ AST / [platelet $\times$ (ALT)]^{1/2}.

Hepatocellular tissue damage caused by hepatitis viral infection and drugs, as well as other congenital anomalies, can lead to liver function abnormalities. In Fontan circulation, similar to chronic congestive heart failure,¹⁵ high pressure in the central vein may lead to alterations of the hepatic microvasculature, resulting in chronic centrilobular ischemia and chronic hypoxia. Simple scores (eg, APRI and FIB-4), obtained from patients with hepatitis C virus and alcoholic-induced cirrhosis, were normal because ALT levels and platelets numbers were included in the formulae. Histologic activity and fibrosis do not always correlate with serum transaminase activity. Further, univariate or multivariate analysis revealed that neither AST nor ALT activity was a risk factor, which is consistent with previous findings.³ It is difficult to quantitatively assess hepatic functional reserve or completely determine the severity of chronic hepatic injury or fibrosis based on standard liver blood tests.

The estimation of venous pressure is important; however, central venous pressure is weakly correlated with 7s collagen and GGT. We found that volume size and ejection fraction, which can be measured by noninvasive magnetic resonance imaging and echocardiography, could not be

FIGURE 2. Individual values of inferior vena cava pressure (IVCP) in patients who had undergone Fontan procedure, according to type IV collagen 7s. * $P < .01$.

used to predict the value of central venous pressure. Therefore, we applied a series of hepatic blood flow measurements using liver echography to identify a possible relationship with central venous pressure. We evaluated the relationship between 3 different flow ratios (those for the portal vein, hepatic artery, and hepatic vein). Sherif and colleagues¹⁶ reported that hepatic venous flow dynamics are strongly related to the mean atrial pressure, and that they can be used to estimate mean right atrial pressure. In normal circulation, hepatic venous flow includes the systolic, diastolic, and atrial reversal wave velocities; that is, it is triphasic. Determinants of systolic forward flow include atrial relaxation, descent of the tricuspid annular plane toward the ventricular apex, and right atrial pressure in the normal circulation.¹⁶ In patients with chronic liver cirrhosis, hepatic vein waveforms are classified as monophasic, biphasic, and triphasic (reversed flow in at least 1 phase).^{17,18} We evaluated the flow pattern of hepatic venous flow and defined it as V_1 or V_2 (Figure 1). In patients with liver dysfunction the values of these flow patterns differ from those of normal subjects. In comparison with V_1 (Figure 1), the value of V_2 was greater in patients with higher IVCP. We accordingly defined the ratio of hepatic

venous flow as V_2/V_1 . In both univariate and multivariate analyses, we found a significant correlation between IVCP and the ratio of hepatic venous flow, but found no correlations between IVCP and the flow ratios for the hepatic artery and portal vein flows, even though these are reported to be useful for detecting hepatic venous congestion (Table 2). The change in the inferior vena cava diameter between maximum on expiration and minimum on inspiration, which is used frequently to estimate right atrial pressure in normal circulation,^{17,19} was little in Fontan circulation. Finally, we conclude that the IVCP in patients undergoing Fontan procedure can be accurately predicted according to the hepatic venous flow pattern and 7s collagen, compared with using laboratory data only.

Ghaferi and colleagues²⁰ reported that autopsy examination of liver specimens revealed marked changes in chronic passive congestion in the liver histology more than 1 year after the Fontan procedure was performed in 9 patients with Fontan circulation. Although several serious complications such as hepatic adenoma and hepatocellular carcinoma have been reported over the long term after the Fontan procedure, using abdominal echography we could not detect any pathologic evidence of liver fibrosis, such as distention of sinusoids, dilatation of the portal area, or nodular regeneration, in our study. This suggests that the degree of liver congestion at an early stage after Fontan operation was not sufficiently severe to cause liver fibrosis.

It is important to evaluate the changes of coagulability in patients who have undergone Fontan surgery. The progress of abnormal coagulability and advanced thrombus formation in patients with Fontan circulation have been reported.⁶ On the basis of this evidence, we performed anticoagulation therapy at our institution. For this reason, we excluded some of the simple indices of liver fibrosis, including coagulation indices such as the cirrhosis discriminate score.²¹

Therapy that decreases pulmonary artery pressure and central venous pressure may prevent the progression of liver congestion in patients after the Fontan procedure is performed. Further, antipulmonary hypertensive therapy may affect the progress of liver dysfunction by decreasing the end-diastolic pressure of the ventricle, thus avoiding extensive hepatic investigations in patients with liver dysfunction who are in heart failure. However, this approach has not been used in the case of the Fontan procedure, and its effect on Fontan circulation should be investigated.

TABLE 2. Hepatic echography results

	Mean or n	SD	Range	P*
Evaluation of liver change	0	—	—	—
HV ratio	0.73	0.3	0.2-1.5	.028
PV ratio	0.64	0.12	0.38-0.78	.27
HA ratio	0.76	0.07	0.66-0.92	.13

SD, Standard deviation; HV, hepatic vein; PV, portal vein; HA, hepatic artery. *Significant variables in univariate test for association with inferior vena cava pressure.

CONCLUSIONS

Our study showed that serum levels of GGT and 7s collagen are increased in those patients who have undergone Fontan operation, and that these 2 indicators are significantly correlated with systemic venous pressure. The hepatic venous flow pattern was correlated only with systemic venous pressure at an early stage after the Fontan

procedure was performed. Therefore, the monitoring of hepatic venous flow and 7s collagen may be simple and effective methods for estimating systemic venous pressure and the progress of liver dysfunction.

References

- Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240-8.
- Baek JS, Bae EJ, Ko JS, Kim GB, Kwon BS, Lee SY, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. *Heart*. 2010;96:1750-5.
- Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorf G. Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. *Heart*. 1997;78:154-9.
- Kiesewetter CH, Sheron N, Vettukattill JJ, Hacking N, Stedman B, Millward-Sadler H, et al. Hepatic changes in the failing Fontan circulation. *Heart*. 2007;93:579-84.
- Camposilvan S, Milanesi O, Stellin G, Pettenazzo A, Zancan L, D'Antiga L. Liver and cardiac function in the long term after Fontan operation. *Ann Thorac Surg*. 2008;86:177-82.
- Narkewicz MR, Sondheimer HM, Ziegler JW, Otanni Y, Lorts A, Shaffer EM, et al. Hepatic dysfunction following the Fontan procedure. *J Pediatr Gastroenterol Nutr*. 2003;36:352-7.
- Friedrich-Rust M, Koch C, Rentzsch A, Sarrazin C, Schwarz P, Herrmann E, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. *J Thorac Cardiovasc Surg*. 2008;135:560-7.
- Shimahara Y, Yamamoto N, Uyama N, Okuyama H, Momoi H, Kamikawa T, et al. Significance of serum type IV collagen level of hepatectomized patients with chronic liver damage. *World J Surg*. 2002;26:451-6.
- Wai CT, Greenon JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38:518-26.
- Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43:1317-25.
- Nakata S, Imai Y, Takanashi Y, Kurosawa H, Tezuka K, Nakazawa M, et al. A new method for the quantitative standardization of cross-sectional areas of the pulmonary arteries in congenital heart disease with decreased pulmonary blood flow. *J Thorac Cardiovasc Surg*. 1984;88:610-9.
- Sacerdoti D, Merkel C, Bolognesi M, Amodio P, Angeli P, Gatta A. Hepatic arterial resistance in cirrhosis with and without portal vein thrombosis: relationships with portal hemodynamics. *Gastroenterology*. 1995;108:1152-8.
- McHutchison JG, Blatt LM, de Medina M, Craig JR, Conrad A, Schiff ER, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. *J Gastroenterol Hepatol*. 2000;15:945-51.
- Kubo S, Tsukamoto T, Hirohashi K, Tanaka H, Shuto T, Takemura S, et al. Correlation between preoperative serum concentration of type IV collagen 7s domain and hepatic failure following resection of hepatocellular carcinoma. *Ann Surg*. 2004;239:186-93.
- Shiffman ML. The liver in circulatory failure. In: Shiff ER, Sorrell MF, Maddrey WC, eds. *Shiff's diseases of the liver*. Philadelphia: Lippincott Williams & Wilkins; 2007. 1185-97.
- Nagueh SF, Kopelen HA, Zoghbi WA. Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. *Circulation*. 1996;93:1160-9.
- Moreno FL, Hagan AD, Holmen JR, Pryor TA, Strickland RD, Castle CH. Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. *Am J Cardiol*. 1984;53:579-85.
- Dietrich CF, Lee JH, Gottschalk R, Herrmann G, Sarrazin C, Caspary WF, et al. Hepatic and portal vein flow pattern in correlation with intrahepatic fat deposition and liver histology in patients with chronic hepatitis C. *Am J Roentgenol*. 1998;171:437-43.
- Sefidbakht S, Assadsangabi R, Abbasi HR, Nabavizadeh A. Sonographic measurement of the inferior vena cava as a predictor of shock in trauma patients. *Emerg Radiol*. 2007;14:181-5.
- Ghaferi AA, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. *J Thorac Cardiovasc Surg*. 2005;129:1348-52.
- Bonacini M, Hadi G, Govindarajan S, Lindsay KL. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol*. 1997;92:1302-4.