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ORIGINAL RESEARCH ARTICLE

Hepatocyte growth factor predicts failure of Fontan circulation

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Abstract

Aims This study aimed to assess the value of the hepatocyte growth factor (HGF) as an independent predictor of a Fontan circulation failure.

Methods and results This retrospective case–control study included 34 consecutive patients (19 men and 15 women) who underwent a post-operative cardiac catheterization after a Fontan operation at the Saitama Medical University International Medical Center between April 2017 and December 2019. We divided the patients into two groups according to the HGF level: HGF $<$ 0.4 ng/mL (n = 20, normal HGF group) and HGF $\geq$ 0.4 ng/mL (n = 14, elevated HGF group). The age at the time of the cardiac catheterization was 59.3 ± 7.9 months. The range of the duration between the Fontan operation and the cardiac catheterization was 37.5 ± 7.9 months. The age (P = 0.417), gender (P = 0.08), morphology of the functional ventricle (P = 0.99), presence or closure of the Fontan fenestration (P = 0.704), and rate of medication use (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) (P = 0.99) were equivalent between the two groups. Laboratory parameters including the brain natriuretic peptide level (P = 0.085), serum creatinine level (P = 0.27), and aspartate aminotransferase level (P = 0.235) were similar between the two groups. The elevated HGF group had a higher C-reactive protein level than the normal HGF group (0.42 ± 0.14 and 0.05 ± 0.01 mg/dL, P = 0.005). The elevated HGF group had a higher central venous pressure (CVP) level than the normal HGF group (13.4 ± 0.7 and 9.7 ± 0.4 mmHg, $P < 0.0001$), and the HGF was positively correlated with the CVP (P = 0.0004, r^2 = 0.33). The SvO_2 level was significantly lower in the elevated HGF group than in the normal HGF group (61.9 ± 2.3% and 75.0 ± 1.2%, $P < 0.0001$), and the HGF was negatively correlated with the SvO_2 ($P < 0.0001$, r^2 = 0.65). Of the 34 patients, six underwent catheter interventions. Patients who underwent catheter interventions had a higher HGF level than those who did not (0.44 ± 0.03 and 0.37 ± 0.01 ng/mL, P = 0.032). The receiver operating characteristic curve created for the discrimination of a catheter intervention revealed that an HGF value of $>$0.405 ng/mL could detect the need for a catheter intervention with 75.0% sensitivity and 83.3% specificity. A multivariable regression analysis showed that an elevated HGF was an independent predictor of an elevated CVP (β-coefficient 21.2, SE 5.5, P = 0.0005) and decreased SvO_2 (β-coefficient −92.9, SE 12.4, $P < 0.0001$).

Conclusions The HGF is an independent predictor of a failure of a Fontan circulation. The HGF is an indicator for an additional catheter intervention after a Fontan operation.

Keywords Hepatocyte growth factor; Fontan circulation; Heart failure

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Introduction

A normal cardiovascular system consists of pulmonary and systemic circulation, with synchronized right and left ventricular pumps. In these circumstances, systemic venous return is pumped out from the right ventricle to the pulmonary arteries and the oxygenated pulmonary venous return is pumped out from the left ventricle to the systemic circulation.

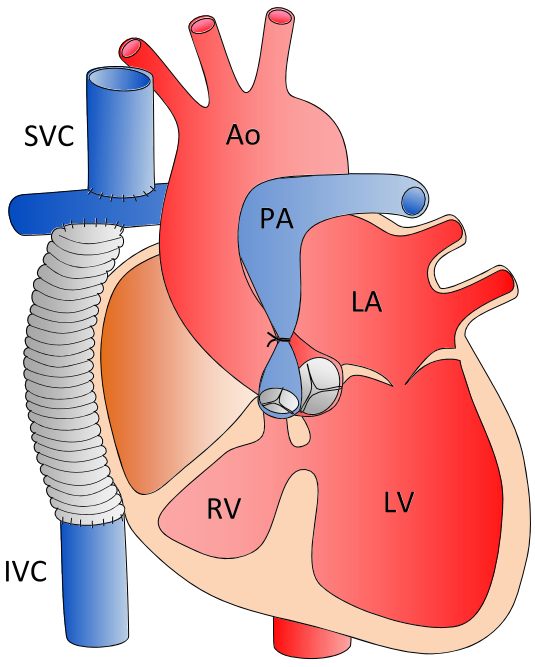
Some complex congenital heart diseases are characterized by a single functional ventricle, and the single functional

ventricle needs to maintain both the pulmonary and systemic circulation. The single functional circulation results in mixing of arterial and venous blood, arterial desaturation, and a chronic volume overload of the single cardiac ventricle.

In 1971, Francis Fontan and Eugene Baudet reported on a new approach to the operative treatment of these malformations, separating the systemic and pulmonary circulation systems.[1] In the Fontan circulation, the systemic veins are directly connected to the pulmonary arteries and the single functional ventricle acts as the only chamber of the systemic circulation. Since their first description, many modifications have been introduced. Nowadays, the inferior vena cava is routed to the pulmonary artery typically using either an intra-atrial lateral tunnel pathway, or an extracardiac conduit (*Figure 1*). In a Fontan circulation, the cardiac output is determined by the transpulmonary flow rather than the cardiac contraction itself.

Hepatocyte growth factor (HGF) is a mesenchyme-derived growth factor originally identified in the plasma of partially hepatectomized rats and later isolated from rat platelets and human plasma.[2–4] It has marked and varied effects on epithelial cells, endothelial cells, and other cell types, including on the angiogenic, mitogenic, anti-apoptotic, and anti-fibrotic activities.[5,6] Plasma HGF concentrations are reported to be increased in cardiovascular diseases, such as congestive heart failure, acute myocardial infarction, hypertension, and atherosclerosis.[7–10] Previous experimental studies have implicated HGF in the process of ventricular remodelling and have suggested cardioprotective effects.[11] Although there is a growing body of clinical and experimental evidence, studies on the value of the HGF in patients with congenital heart disease are limited. Also, there have been no reports regarding the value of the HGF in the assessment of a Fontan circulation. On the other hand, a non-invasive haemodynamic assessment of failure of Fontan circulation is a difficult issue in the outpatient clinic. We focused on the HGF because of its clinical evidence in patients with heart failure and its convenience compared with the other biomarkers. We hypothesized that the HGF may be an informative marker to assess the haemodynamics in patients with a Fontan circulation. Therefore, this study aimed to assess the usefulness of the HGF in patients with a Fontan circulation by analysing the relationship between the HGF level and the various cardiac parameters in these patients.

Figure 1 Fontan circulation. An extracardiac conduit re-routes the blood flow from the inferior vena cava (IVC) to the pulmonary artery (PA). The superior vena cava (SVC) is directly connected to the PA. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.



Methods

Patients and sample collection

This study is a single-centre, retrospective study. This study was approved by the Institutional Review Board of Saitama Medical University (No. 18-051). This study included patients with single ventricular circulation who were admitted to the Saitama Medical University International Medical Center to undergo a post-operative cardiac catheterization after a Fontan operation between April 2017 and December 2019. In our institution, we create a Fontan fenestration in all patients at the time of the Fontan operation. Also, we routinely perform cardiac catheterization after a Fontan operation to assess the post-operative haemodynamics. Patients were excluded if there was lack of laboratory or catheterization data or if their guardians declined to participate in the study. We reviewed the demographic data including the age, gender, underlying diagnosis, morphology of the systemic ventricle, presence or closure of a Fontan fenestration, medication use including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and cardiac catheterization data such as the central venous pressure (CVP), arterial oxygen saturation (SaO_2), mixed venous oxygen saturation (SvO_2), cardiac index (CI), and pulmonary vascular resistance (Rp) from the medical records. Also, we reviewed the laboratory data including the HGF, brain natriuretic peptide (BNP), serum creatinine, aspartate aminotransferase (AST), C-reactive protein, and cardiothoracic ratio on the chest X-rays on those days.

Routine blood tests were performed in all patients at the time of admission. It is known that the intravenous administration of heparin markedly increases the HGF level.[12] Therefore, we needed to avoid measuring the HGF at the time of

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the cardiac catheterization. The HGF was measured by a SpectraMax® ABS/ABS Plus (Molecular Devices Japan Inc., Tokyo, Japan). The normal range of the HGF was 0–0.4 ng/mL. To assess the usefulness of the HGF, we divided the patients into two groups according to the HGF level: HGF $<$ 0.4 ng/mL (n = 20, normal HGF group) and HGF $\geq$ 0.4 ng/mL (n = 14, elevated HGF group). All cardiac catheterizations were performed under intravenous anaesthesia with room air in the catheterization laboratory.

Statistical analysis

All continuous data are expressed as the mean ± standard deviation. Categorical data were performed with Pearson's χ^2 test or Fisher's exact test. Comparisons between the two groups were performed using Mann–Whitney U test. Comparisons within groups were made using an analysis of variance. Pearson's correlation analysis was used to assess the relationships between the HGF and the catheterization parameters. An analysis of the multivariate regression was also performed to determine the independent effect of the HGF. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP Version 11.2.0 (SAS, Cary, NC) and GraphPad Prism Version 5.01 (GraphPad Software, Inc., La Jolla, CA) software.

Results

Baseline characteristics

A total of 38 consecutive patients underwent cardiac catheterization during the study period. Of the 38 patients, four patients were excluded from the study because of lack of required data during hospital stay. Therefore, a total of 34 patients met inclusion criteria for the study. The patients included single right ventricles (n = 10), tricuspid atresia (n = 8), single left ventricles (n = 6), hypoplastic left heart syndrome (n = 5), pulmonary atresia with an intact ventricular septum (n = 3), and Ebstein's anomaly (n = 2). The age at the time of the cardiac catheterization was 59.3 ± 7.9 months. The range of the duration between the Fontan operation and the cardiac catheterization was 37.5 ± 7.9 months. Of the 34 patients, 18 patients were prescribed with ACE inhibitors or ARBs.

Table 1 demonstrates the baseline characteristics of the normal HGF group and elevated HGF group. The age, gender, morphology of the functional ventricle, and presence or closure of the Fontan fenestration were equivalent between the two groups. Also, the rate of medication use (ACE inhibitors or ARBs), laboratory data including the BNP, serum creatinine, and AST, and cardiothoracic ratio on chest X-ray were similar between the two groups. On the other hand, the elevated HGF group had a higher C-reactive protein level than the normal HGF group (0.42 ± 0.14 and 0.05 ± 0.01 mg/dL, respectively, P = 0.005).

Hepatocyte growth factor level and cardiac catheterization data

Table 2 demonstrates the comparison of the catheterization data between the normal HGF group and the elevated HGF

Table 2 Comparison of the catheterization data between the normal HGF group and the elevated HGF group

N = 34	HGF $<$ 0.4	HGF $\geq$ 0.4	P value
CVP (mmHg)	9.7 ± 0.4	13.4 ± 0.7	$<$0.0001
SaO_2 (%)	93.5 ± 0.6	93.9 ± 0.7	0.691
SvO_2 (%)	75.0 ± 1.2	61.9 ± 2.3	$<$0.0001
CI	3.9 ± 0.4	3.2 ± 0.2	0.104
Rp (units/m^2)	1.10 ± 0.23	1.46 ± 0.18	0.127

CI, cardiac index; CVP, central venous pressure; HGF, hepatocyte growth factor; Rp, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.

Table 1 Baseline characteristics

	HGF $<$ 0.4 (n = 20)	HGF $\geq$ 0.4 (n = 14)	P value
Age (months)	53.9 ± 9.7	67.1 ± 13.4	0.417
Male (n)	14	5	0.08
Morphology of the ventricle (n)			
Right/left	9/11	6/8	0.99
Fenestration (n)	15	9	0.704
ACEIs and/or ARBs (n)	11	7	0.99
BNP (pg/mL)	20.9 ± 5.3	36.1 ± 6.8	0.085
Serum creatinine (mg/dL)	0.30 ± 0.02	0.33 ± 0.02	0.27
AST (U/L)	37.5 ± 1.9	41.6 ± 3.1	0.235
C-reactive protein (mg/dL)	0.05 ± 0.01	0.42 ± 0.14	0.005
Cardiothoracic ratio (%)	48.6 ± 1.1	51.0 ± 1.5	0.205

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; HGF, hepatocyte growth factor.

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group. The CVP level was significantly higher in the elevated HGF group than in the normal HGF group (13.4 ± 0.7 and 9.7 ± 0.4 mmHg, respectively, $P < 0.0001$). Also, the SvO_2 level was significantly lower in the elevated HGF group than in the normal HGF group (61.9 ± 2.3% and 75.0 ± 1.2%, respectively, $P < 0.0001$). There was a positive correlation between the HGF and the CVP ($P = 0.0004$, $r^2 = 0.33$) (*Figure 2*). Similarly, there was a negative correlation between the HGF level and the SvO_2 ($P < 0.0001$, $r^2 = 0.65$) (*Figure 3*). On the other hand, SaO_2, CI, and Rp were equivalent between the two groups.

Hepatocyte growth factor level and catheter intervention

Of the 34 patients, six patients underwent catheter intervention. The procedures included balloon dilation for a Fontan anastomosis ($n = 3$) and stent implantation for a left pulmonary artery ($n = 3$). Of the six patients who underwent catheter interventions, five were in the elevated HGF group. Patients who underwent catheter intervention had a higher HGF level than those who did not underwent a catheter intervention (0.44 ± 0.03 and 0.37 ± 0.01 ng/mL, respectively,

Figure 2 Relationship between the hepatocyte growth factor (HGF) and the central venous pressure (CVP). The HGF was positively correlated with the CVP.

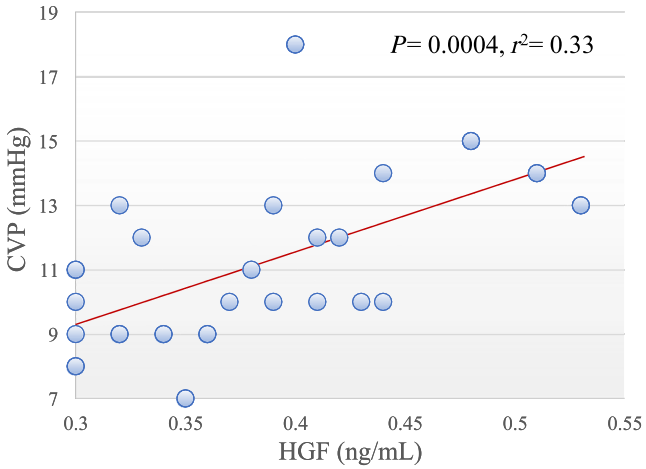
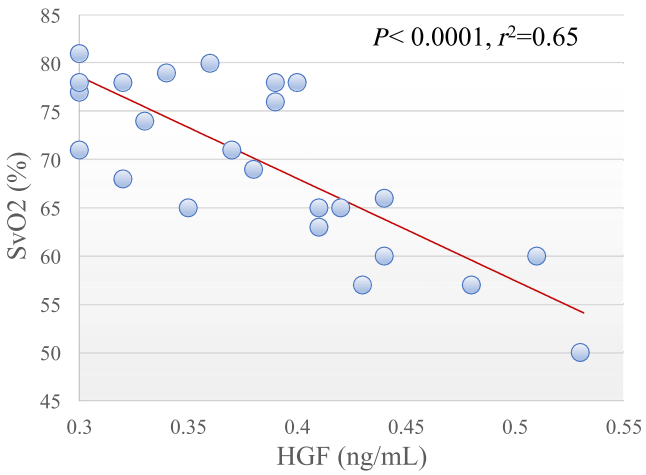


Figure 3 Relationship between the hepatocyte growth factor (HGF) and the mixed venous oxygen saturation (SvO_2). The HGF was negatively correlated with the SvO_2.



P = 0.032). The receiver operating characteristic curve created for the discrimination of catheter intervention revealed that an HGF value of >0.405 ng/mL could detect the need for additional catheter intervention with 75.0% sensitivity and 83.3% specificity (*Figure 4*).

Cardiac catheterization data and other parameters

The relationship between the cardiac catheterization data and the other parameters including the laboratory data and cardiothoracic ratio on the chest X-rays was assessed in the same manner. The BNP had a mild negative correlation with the SvO_2 (P = 0.0007, r^2 = 0.2) and Rp (P = 0.04, r^2 = 0.12). On the other hand, the BNP was not associated with the CVP, SaO_2, or CI. The C-reactive protein level correlated with a higher CVP (P = 0.005, r^2 = 0.22) and lower SvO_2 (P = 0.007, r^2 = 0.21). However, there was no relationship between the C-reactive protein level and the SaO_2, CI, and Rp. The cardiothoracic ratio on the chest X-ray was negatively correlated with the SvO_2 (P = 0.001, r^2 = 0.29) and SaO_2 (P = 0.013, r^2 = 0.18). The serum creatinine level was positively correlated with the CVP (P = 0.0002, r^2 = 0.11). The AST was not associated with these parameters.

Multivariable regression analysis

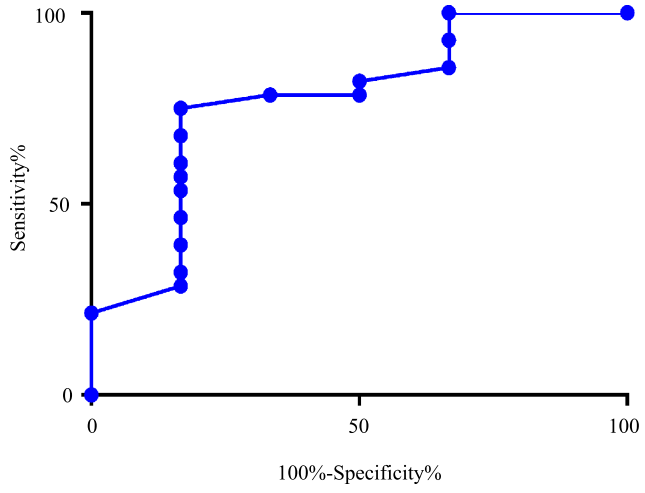
Finally, a multivariable regression analysis was performed to assess whether the HGF was an independent and the strongest factor to predict a higher CVP and lower SvO_2 after a Fontan operation. In the multivariate regression analysis, including that for the HGF, BNP, C-reactive protein, serum creatinine, and cardiothoracic ratio, which might have affected the higher CVP and lower SvO_2, the HGF was an independent predictor of an elevated CVP (β-coefficient 21.2, SE 5.5, P = 0.0005) and decreased SvO_2 (β-coefficient −92.9, SE 12.4, $P < 0.0001$).

Discussion

In the present study, we found that an elevated HGF was independently correlated with a higher CVP and lower SvO_2 in a Fontan circulation. To the best of our knowledge, this is the first study to assess the relationship between the HGF and a Fontan circulation.

In a Fontan circulation, the lack of pulsatility of the pulmonary circulation is thought to induce endothelial dysfunction, which leads to an increased CVP. Such an increment would lead to a decreased cardiac output and lower SvO_2, increased risk of Fontan failure, and decreased survival.[13] Therefore, regarding the relationship between an elevated HGF and the higher CVP, a lower SvO_2 may suggest that the HGF is a prognostic marker for failure of a Fontan circulation. Because a non-invasive haemodynamic assessment of failure of a Fontan circulation is a difficult issue in the outpatient clinic, the HGF becomes a good index to assess the cardiac status in this situation. At present, the BNP is regarded as a prognostic marker in paediatric heart failure patients. However, in patients with a Fontan circulation, it is noted that they have lower than expected BNP levels relative to their ventricular function and functional status because of their reduced preload and limited preload reserve. In fact, the BNP level

Figure 4 Receiver operating characteristic curve for the discrimination of catheter intervention. A hepatocyte growth factor value of >0.405 ng/mL could detect the best sensitivity and specificity for a catheter intervention.



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was not an independent predictor of a higher CVP and lower SvO_2 in the present study.

Also, we found that a higher HGF level was associated with a higher rate of catheter intervention. We speculated that residual lesions such as stenosis of the Fontan route yield excessive pressure and a volume overload to a Fontan circulation. This leads to an elevated CVP and decreased SvO_2, which was reflected by the HGF elevation.

It is reported that angiotensin II suppresses the HGF production in vascular cells. A previous study reported that an impaired HGF production was restored with ACE inhibitors through angiotensin II inhibition in patients with congestive heart failure.[14] However, this hypothesis is controversial. Ueno *et al*.[10] reported that the administration of ACEIs did not affect the HGF level in patients with congestive heart failure. In the present study, we could not find a relationship between the administration of ACE inhibitors and the HGF level. HGF is regarded as one of the most potent mitogens specific to endothelial cells and is suggested to contribute to vascular protection or repair.[15] Also, HGF exerts multipotent actions through its receptor c-*Met* in various target organs including the heart and vessels.[16] Therefore, we speculated that the renin–angiotensin II system or use of ACE inhibitors, at least, was not the main source of the HGF elevation in patients with a Fontan circulation. Also, we found that the elevated HGF group had a higher C-reactive protein level than the normal HGF group. It is known that patients with heart failure have increased levels of circulating pro-inflammatory cytokines such as interleukin 6. A previous report showed that the HGF level was positively correlated with the serum interleukin-6 levels.[10] These reports and our results suggest that inflammatory factors may be involved in the HGF production in congestive heart failure, including a Fontan circulation.

In the present study, the AST level was equivalent between the normal HGF group and the elevated HGF group. It is known that liver congestion may be one of the main sources of an increased HGF level in heart failure.[10] We consider that an elevated CVP and decreased SvO_2 may be reflected by an HGF elevation in the earlier phase before the sign of liver congestion becomes apparent.

There is growing body of clinical evidence of HGF in patients with heart failure. Rychli *et al*.[17] reported that HGF is a strong and independent predictor of mortality in advanced heart failure and, in particular, in ischaemic heart failure. Also, Pérez-Calvo *et al*.[18] reported that HGF identifies mortality in patients with acute heart failure regardless of left ventricular ejection fraction, ischaemic origin, or renal function. These reports suggest that the usefulness of HGF can apply to various clinical conditions in patients with heart failure. In the present study, we expanded its range of applications to patients with a Fontan circulation for the first time. An HGF elevation suggests congestive heart failure with an elevated CVP regardless of the inflammatory status, renal function, and hepatic function in a Fontan circulation.

This study had some limitations to be noted. First, because the size of our study was small, the findings need to be confirmed in a larger study. Second, there were no data regarding the normal range of the HGF in paediatric patients. Therefore, we applied the normal range of the HGF in adults.

In conclusion, we report for the first time that HGF is an independent marker to predict heart failure in a Fontan circulation regardless of the inflammatory status, renal function, or hepatic function. Also, HGF is an indicator for an additional catheter intervention after a Fontan operation.

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Conflict of interest

None declared.

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