Establishment and assessment of the hepatic venous pressure gradient using biofluid mechanics (HVPG$_{BFM}$): protocol for a prospective, randomised, non-controlled, multicentre study

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ABSTRACT

Introduction Portal hypertension (PH) is a severe disease with a poor outcome. Hepatic venous pressure gradient (HVPG), the current gold standard to detect PH, is available only in few hospitals due to its invasiveness and technical difficulty. This study aimed to establish and assess a novel model to calculate HVPG based on biofluid mechanics.

Methods and analysis This is a prospective, randomised, non-controlled, multicentre trial. A total of 248 patients will be recruited in this study, and each patient will undergo CT, blood tests, Doppler ultrasound and HVPG measurement. The study consists of two independent and consecutive cohorts: original cohort (124 patients) and validation cohort (124 patients). The researchers will establish and improve the HVPG using biofluid mechanics (HVPG$_{BFM}$)model in the original cohort and assess the model in the validation cohort.

Ethics and dissemination The study was approved by the Scientific Research Projects Approval Determination of Independent Ethics Committee of Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number 2017–430T326). Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT03470389.

Strengths and limitations of this study

► This study will establish a new method to calculate hepatic venous pressure gradient (HVPG) and diagnose portal hypertension (PH) based on biofluid mechanics.
► This study will demonstrate the numerical correlation of measured and simulated HVPGs.
► This study will assess the diagnostic accuracy of simulated HVPG for the diagnostics of PH and clinically significant portal hypertension (CSPH).
► This study will include only cirrhotic patients, and thus, this model might not be suitable for other patients.
► This study requires Doppler ultrasound to measure the portal system and the hepatic venous system, which is difficult to perform.

However, the HVPG measurement is available only in few hospitals due to its invasiveness and technical difficulty.[3] In recent years, there are already several non-invasive PH assessment methods, including clinical examination, ultrasound, elastography, CT and MRI,[4] few of which, however, were proved to be accurate enough to replace the invasive HVPG measurement. Therefore, a less-invasive and accurate assessment method is needed and would be useful in the diagnosis and evaluation of PH.

Biofluid mechanics is the study of mechanisms of biological flows (liquid and gas) and their inter-relationships with physiological and pathological processes by using fundamental principles of fluid mechanics.[5] Fortunately, recent advances in biofluid mechanics and image-based modelling make it possible for cardiologists to calculate fractional flow reserve, which is the gold standard assessment

INTRODUCTION

Portal hypertension (PH), an increased blood pressure of the portal vein and its branches, is one of the most severe syndromes caused by chronic liver diseases. Hepatic venous pressure gradient (HVPG) is currently the gold standard to detect PH.[1] HVPG value greater than 5 mmHg is defined as PH; HVPG value higher than 10 mmHg is considered as clinically significant portal hypertension (CSPH), which is highly associated with hepatocellular carcinoma and severe complications, including gastro-oesophageal variceal haemorrhage, hepatic encephalopathy and ascites.[2]

of the haemodynamic significance of coronary stenoses.[6] Moreover, biofluid mechanics may offer a new method for physicians to make an accurate assessment of HVPG noninvasively. The aim of the present study was to establish and validate the hepatic venous pressure gradient using biofluid mechanics ($HVPG_{BFM}$) model.

METHODS AND ANALYSIS

Study design overview

This study is a prospective, randomised, non-controlled, multicentre trial in patients with cirrhosis.

Study population

Consecutive patients with liver cirrhosis, who meet the inclusion criteria and none of the exclusion criteria, at Shanghai Ninth People's Hospital, Renji Hospital and Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine will be screened daily for study eligibility. Recruitment began on 20 March 2018 and will continue until 248 participants have been recruited.

Inclusion criteria

1. Patients at least 18 years of age.
2. Patients with cirrhosis (diagnosed by ultrasound, CT, MRI, FibroScan or liver biopsy) scheduled for HVPG measurement.

Exclusion criteria

1. Female patients who are pregnant or nursing.
2. Patients who are medically unstable, terminally or seriously ill, or patients whose clinical course is unpredictable.
3. Patients with clinically unstable cardiac disease, for example, congenital heart defect, arrhythmia or uncontrolled heart failure (New York Heart Association class IV).
4. Patients with respiratory distress syndrome or clinically unstable pulmonary disease, for example, pulmonary hypertension, pulmonary emboli, pulmonary vasculitis or emphysema.
5. Patients with severe coagulation disorders.
6. Patients with unstable occlusive disease or thrombosis within the hepatic, portal or mesenteric veins.
7. Patients with ascites, primary biliary cholangitis, hepatocellular carcinoma or hepatic decompensation (Child-Turcotte-Pugh class C or Model for End-Stage Liver Disease score greater than 25).
8. Patients who are allergic to iodinated contrast.

Ethics and informed consent

The trial complies with the latest Declaration of Helsinki. Written informed consent forms will be obtained from patients or patients' legal guardian or patients' next of kin before the study begins. All participants can quit the study at any time without penalty or impact on the treatment. The study protocol, statistical analysis plan, informed consent form and case report form have already been approved by the Scientific Research Projects Approval Determination of Independent Ethics Committee of Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number 2017–430 T326).

Objectives

The primary objective of this study was to determine the numerical correlation between $HVPG_{BFM}$ and HVPG. The secondary objective was to determine the diagnostic accuracy of $HVPG_{BFM}$ for the diagnostics of PH and CSPH. The gold standard for the diagnosis will be the HVPG measurement.

Procedure of the study

Consecutive patients are randomly assigned 1:1 to either the original cohort or the validation cohort. Randomisation is based on the computer-generated random digits table. This study consists of two independent and consecutive stages:

1. Establishment and improvement of the $HVPG_{BFM}$ model. For 124 patients in the original cohort, biofluid mechanics specialists will use each patient's CT, blood tests, Doppler ultrasound and HVPG results to adjust the parameters of the $HVPG_{BFM}$ model in order to make each patient's $HVPG_{BFM}$ and HVPG values match well.
2. Assessment of the $HVPG_{BFM}$ model. For 124 patients in the validation cohort, biofluid mechanics specialists will use each patient's CT, blood tests and Doppler ultrasound results to calculate each patient's $HVPG_{BFM}$ according to the $HVPG_{BFM}$ model established previously. Biofluid mechanics specialists will make no changes to the $HVPG_{BFM}$ model and will have no access to patients' HVPG results in this cohort. Finally, the researchers will compare each patient's $HVPG_{BFM}$ and HVPG values and assess the $HVPG_{BFM}$ model.

Each patient's Doppler ultrasound, CT and HVPG measurement will be done in similar conditions in the afternoons. Each patient will fast for at least 8 hours and lay on the examination table for at least 10 min before the examinations. Each patient's Doppler ultrasound and HVPG measurement will be performed before or at least 1 day after the CT. CT, blood tests, Doppler ultrasound and other clinical data will be inaccessible to professionals for HVPG measurements in order to prevent certain biases. Each patient's CT, blood tests, Doppler ultrasound and HVPG measurement will be performed within 30 days, and treatments that may affect HVPG values will be avoided during this period.

The study design and procedure are shown in figure 1.

Examination

CT

Each patient will undergo an abdominal contrast-enhanced CT by multidetector row CT scanners according to the protocol.[7 8] The following parameters will be used: voltage, 120 kVp; current, automatic; collimation, 1.24–1.25 mm; slice thickness, 0.625–2.5 mm; slice interval,
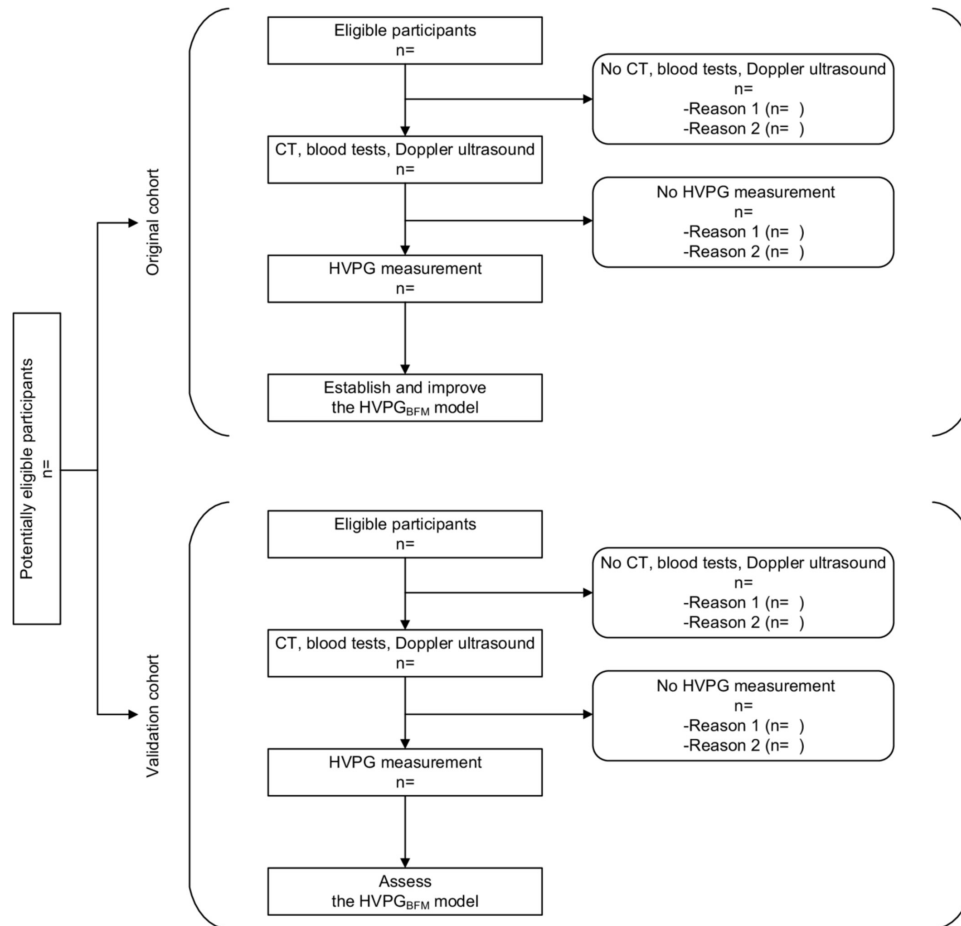
Figure 1 Study design and procedure. HVPG, hepatic venous pressure gradient; $HVPG_{BFM}$, hepatic venous pressure gradient using biofluid mechanics.

1.0–2.0 mm; matrix size, 512×512; and rotation time, 0.5 s. A non-ionic iodinated contrast agent (600 mg of iodine/kg of body weight, 300–370 mg of iodine/mL, 3–5 mL/s) will be injected. Portal venous phase imaging will be performed 60–70 s after the beginning of intravenous contrast injection. The CT scan will be done during deep inspiration breath-hold.

Blood tests

Each patient's blood samples will be collected from the cubital vein for blood viscosity test and density measurement. The blood viscosity test will be done by a ZL9100C blood rheology analyser (Zhongchi, China). The blood density measurement will be done by weighing 1 mL of blood: 1 mL of blood will be pipetted by a Thermo Scientific Finnpipette F1 Pipettor onto a YP-B2002 electronic balance (Guangzheng, China) for weight measurement. The blood density measurements will be repeated at least three times and then be averaged.

Doppler ultrasound

Each patient will undergo an abdominal Doppler ultrasound scan to measure the inner diameters, the blood flow direction and the maximum blood flow velocity of the inferior vena cava, the hepatic veins, the portal vein and its main branches according to published

recommendations.[9–11] A colour Doppler ultrasound system and its matched 3–5 MHz probe will be used. High-quality images will be obtained by using optimised settings. The 12 measurement positions (right branch of the portal vein, left branch of the portal vein, the portal vein, proximal part of the splenic vein, distal part of the splenic vein, the superior mesenteric vein, the inferior mesenteric vein, the right hepatic vein, the middle hepatic vein, the left hepatic vein, the suprahepatic inferior vena cava and the infrahepatic inferior vena cava) are shown in figure 2. Each measurement will be done during deep inspiration breath-hold, and insonation angles of 45°–55° will be used. All measurements will be repeated at least twice and then be averaged. Intraobserver variability and interobserver variability should be less than 10%.

HVPG measurement

HVPG will be measured by professionals according to established standards.[3] The right internal jugular vein will be cannulated under local anaesthesia by using a 6-French introducer (TERUMO Radifocus RS*A60K10SQ, Japan) under ultrasonographic guidance, then a 5.5-French compliant balloon-tipped catheter (Edwards Lifesciences Fogarty 12TLW805F35, USA) connected with a pressure monitoring set (Edwards Lifesciences TruWave PX260,
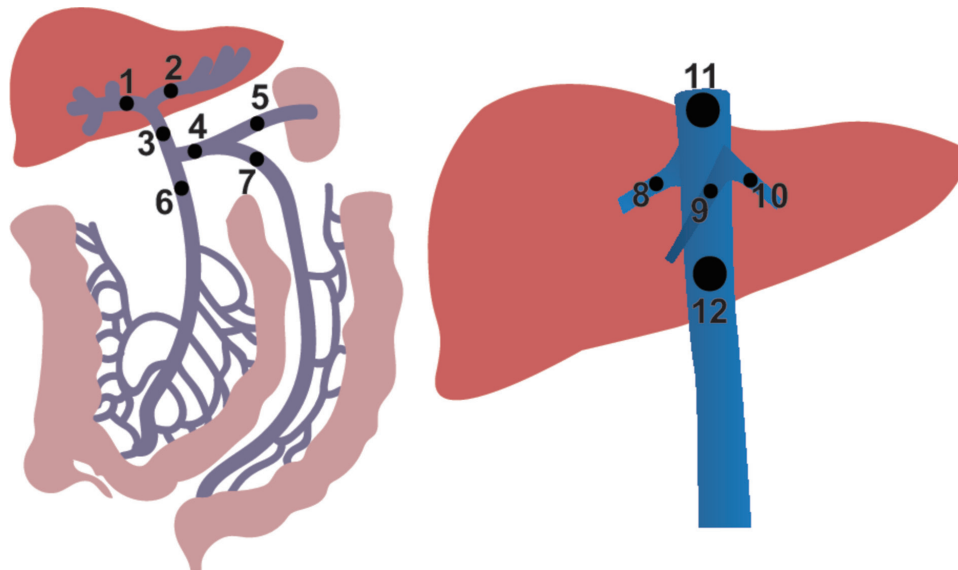
Figure 2 Ultrasound measurement positions. 1, right branch of the portal vein; 2, left branch of the portal vein; 3, the portal vein; 4, proximal part of the splenic vein; 5, distal part of the splenic vein; 6, the superior mesenteric vein; 7, the inferior mesenteric vein; 8, the right hepatic vein; 9, the middle hepatic vein; 10, the left hepatic vein; 11, the suprahepatic inferior vena cava; 12, the infrahepatic inferior vena cava.

USA) will be guided into the right or middle hepatic vein for the measurement of wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP). WHVP will be measured when inflating the balloon to totally occlude the hepatic vein (confirmed by the slow injection of small amounts of contrast dye into the vein by hand without observing its reflux or washout through communications with other hepatic veins); FHVP will be measured when placing the catheter tip freely in the hepatic vein, at approximately 3 cm from its opening into the inferior vena cava. All measurements will be taken until the tracing remains stable (over 60 s for each WHVP and over 20 s for each FHVP). All measurements will be taken while the patient is resting quietly and breathing smoothly to avoid artefacts. WHVP measurements will be taken at least in triplicate, and tracing will be permanently recorded to allow independent review and to exclude artefacts. HVPG will be calculated from the difference between average WHVP and average FHVP, namely, HVPG=WHVP−FHVP. Sedation is not essential, but moderate conscious sedation (0.2 mg/kg intravenous midazolam) is acceptable if the patient feels uncomfortable.

Computation
Geometry
Biofluid mechanics specialists will use IQQA-Liver software V.2.0 (EDDA Technology, USA) to convert the CT images from Digital Imaging and Communications in Medicine format files into stereolithography (STL) format files and create the simulation model of blood flow area in blood vessels accordingly. The model surface will then be meshed into triangle surface grids, each measuring from 0.2 to 1.0 mm, and the body meshes will be created accordingly. One case is shown in figure 3.

Physical property
Biofluid mechanics specialists will use the blood viscosity of different shear forces (high, medium and low) to calculate the overall viscosity (formula 1). Define a, b and c (a+b+c=1) as weighting coefficients.

$$\text{Formula } 1: \quad overall\ viscosity = a \times viscosity_{high} + b \times viscosity_{medium} + c \times viscosity_{low}$$

Boundary conditions
Biofluid mechanics specialists will calculate the blood flow velocity at the boundaries of the main blood vessels according to the blood flow direction and the maximum blood flow velocity (measured by Doppler ultrasound), the inner diameter (obtained from the STL format files) and the principle of mass conservation (formula 2). Define d (0.7<d<1) as the maximum blood flow velocity attenuation coefficient. One case is shown in figure 4.

$$\text{Formula } 2: \quad average\ blood\ flow\ velocity = d \times blood\ flow\ velocity_{maximum}$$

The Navier-Stokes equations
The whole blood can be assumed to be an incompressible Newtonian fluid and blood flow can be modelled by the Navier-Stokes equations as follows:

$$\text{Formula } 3: \quad \frac{\partial \rho}{\partial t} + \nabla \cdot \left(\rho \vec{\nu} \right) = S_m$$

$$\text{Formula } 4: \quad \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}\left(\rho \nu_x \right) + \frac{\partial}{\partial r}\left(\rho \nu_r \right) + \frac{\rho \nu_r}{r} = S_m$$

$$\text{Formula } 5: \quad \frac{\partial}{\partial t}\left(\rho E \right) + \nabla \cdot \left(\vec{\nu}\left(\rho E + p \right) \right) = \nabla \cdot \left(k_{eff}\nabla T - \sum_j h_j \vec{J}_j + \left(\acute{\tau}_{eff} \cdot \vec{\nu} \right) \right) + S_h$$

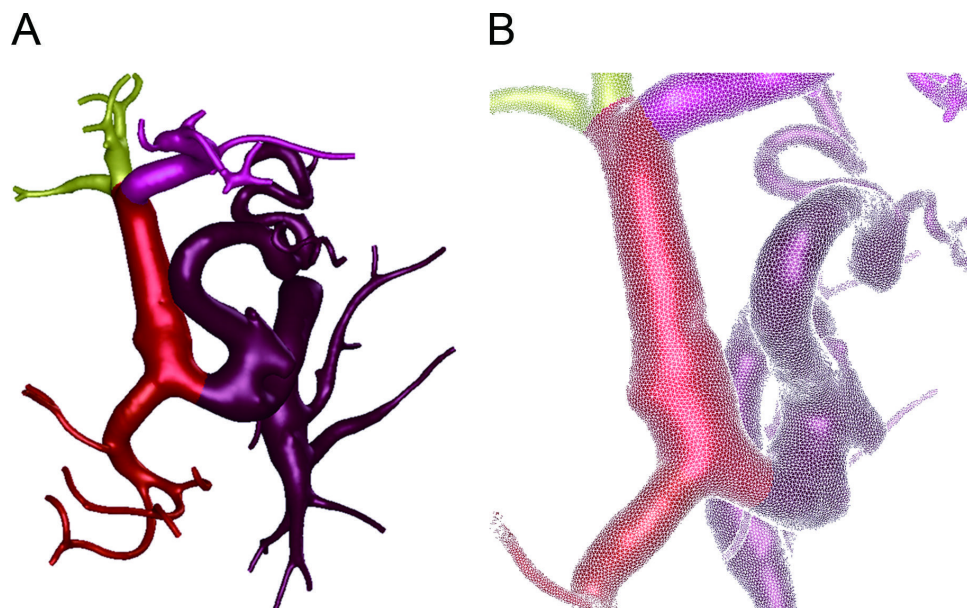$$\text{Formula } 6: \quad E = h - \frac{p}{\rho} + \frac{\nu^2}{2}$$

Figure 3 An example of the simulation model of a portal venous system and its body meshes. (A) The simulation model of a portal venous system. (B) The body meshes of the simulation model.

$$\text{Formula 7}: \quad \frac{\partial}{\partial t}\left(\rho \vec{\nu}\right) + \nabla \cdot \left(\rho \vec{\nu}\vec{\nu}\right) = -\nabla p + \nabla \cdot \left(\acute{\tau}\right) + \rho \vec{g} + \vec{F}$$

$$\text{Formula 8}: \quad \acute{\tau} = \mu\left[\left(\nabla\vec{\nu} + \nabla\vec{\nu}^{T}\right) - \frac{2}{3}\nabla \cdot \vec{\nu}I\right]$$

ρ: density; ν: velocity; S_m: mass added to the continuous phase; x: axial coordinate; r: radial coordinate; v_x: axial velocity; v_r: radial velocity; h: enthalpy value; p: static pressure; $\acute{\tau}$: stress tensor; $\rho\vec{g}$: gravitational body force; $\vec{F}$: external body force; μ: molecular viscosity; I: unit tensor.

Establishment and improvement of the HVPG$_{BFM}$ model in the original cohort

Empirical coefficients in initial: a=0.05, b=0.05, c=0.9 and d=1. Calculate the overall viscosity and average blood flow velocity (formulas 1 and 2) of one patient in the original cohort. Use the FLUENT software V.6.3 (ANSYS, USA) to solve the Navier-Stokes equations (formulas 3–8) and to get the simulated blood pressure on each volume grid. One case is shown in figure 5. The simulated HVPG will be calculated from the difference between simulated portal pressure (PP$_{BFM}$) and simulated hepatic venous pressure (HVP$_{BFM}$), namely, HVPG$_{BFM}$=PP$_{BFM}$−HVP$_{BFM}$. Compare the simulated and measured HVPGs. If they do not match well (their difference greater than 5%), then modify the values of a, b, c and d. If the simulated HVPG is higher, then increase the value of a and reduce the values of b and c; if the measured HVPG is higher, then reduce the value of a and increase the values of b and c. If the simulated and measured HVPGs cannot match well by modifying the values of a, b and c, then modify the value of d. If the simulated HVPG is higher, then reduce the value of d; if the measured HVPG is higher,
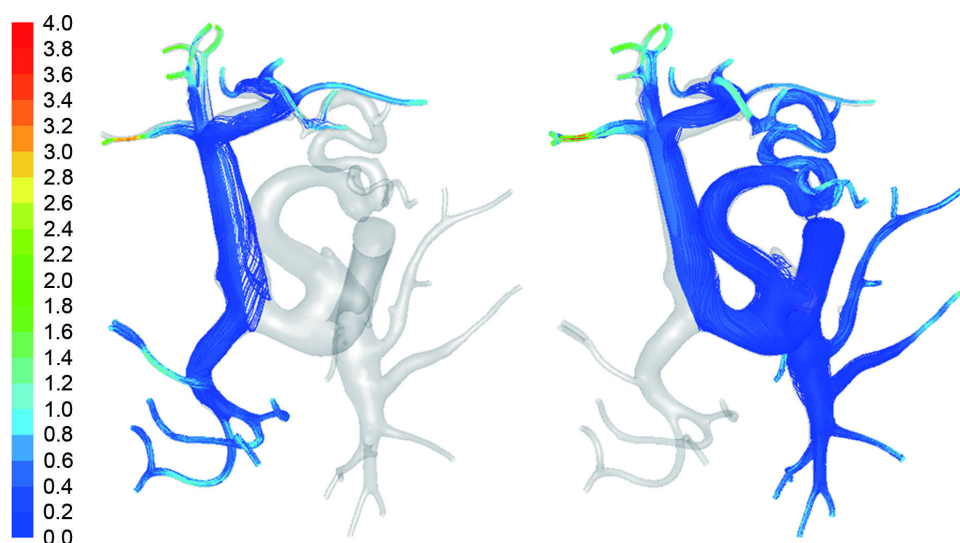

Figure 4 An example of the blood flow velocity (m/s) of the portal vein and its branches.

then increase the value of d. Repeat this process until the simulated and measured HVPGs match well (their difference less than 5%). Record the values of a, b, c and d and the whole process for one patient is completed. Apply this process to each patient in the original cohort and record the values of a, b, c and d of each patient.

Divide all patients into nine groups according to their overall blood viscosity (high, medium and low) and their average blood flow velocity (high, medium and low): HighVis&HighVel, HighVis&MidVel, HighVis&LowVel, MidVis&HighVel, MidVis&MidVel, MidVis&LowVel, LowVis&HighVel, LowVis&MidVel and LowVis&LowVel. Calculate the statistical mean values of a, b, c and d of each group.

Calculation of the HVPG$_{BFM}$ in the validation cohort

First, determine each patient's group according to the blood viscosity and blood flow velocity. Second, use the values of a, b, c and d of the specific group to calculate the geometry, physical property and the boundary conditions of each patient. Third, use the FLUENT software to solve the Navier-Stokes equations and get the simulated blood pressure on each volume grid. Finally, calculate the HVPG$_{BFM}$.

The summarised computation process is shown in figure 6.

Patient and public involvement

Patients and the public were not involved in the design of the study.

Sample size calculation

Sample size was calculated by PASS Software V.19.0.1 (NCSS, LLC, USA). The 'Bland-Altman Method for Assessing Agreement in Method Comparison Studies' procedure was used.[12] The result showed that a sample of 112 subjects would achieve 80% power to detect agreement when the confidence level of the limits of agreement is 0.950, the confidence level of the CIs about the limits of agreement is 0.950, and the maximum allowable difference is 3.000. The mean and SD of the sample differences are anticipated to be 0.184 and 1.163, which were obtained from previous canine experiments. It is anticipated that 10% of the patients recruited are likely to be excluded due to various reasons and therefore the target recruitment for each cohort is 124 patients. The total sample size is 248 patients.

Statistical analysis plan

Discrete variables will be summarised by frequencies and percentages and analysed by the χ^2 test. Continuous variables will be checked for normal distribution and summarised by either mean and SD or median and IQR as appropriate. Comparison of continuous variables will be performed by using Student's t-test or analysis of variance for normally distributed variables and the Mann-Whitney U test or the Kruskal-Wallis test for non-normally distributed variables as appropriate.

The numerical correlation between HVPG$_{BFM}$ and HVPG in the validation cohort will be analysed mainly by using Bland and Altman's limits of agreement analysis.[13] Bias is defined as the mean of the difference between HVPG$_{BFM}$ and HVPG. Upper and lower limits of agreement are defined as the average difference±1.96 SD of the difference. The numerical relationship between HVPG$_{BFM}$ and HVPG in the validation cohort will also be analysed with intraclass correlation coefficient, allowable total error and limits for erroneous result zones for agreement measurement, Lin's concordance correlation coefficient and linear regression analysis.

The diagnostic accuracy of HVPG$_{BFM}$ for the diagnostics of PH (HVPG≥5 mmHg) and CSPH (HVPG≥10 mmHg) in the validation cohort will be assessed by its sensitivity, specificity, false-negative rate, false-positive rate, positive predictive value, negative predictive value, diagnostic accuracy, Youden index, likelihood ratio (LR+ and LR−), Cohen's kappa and receiver operating characteristic (ROC) curve analysis. The diagnostic accuracy of HVPG$_{BFM}$ will also be compared with the diagnostic accuracy of other published non-invasive methods.[4 14]

All tests of significance will be at the 5% significance level. Analyses will be conducted using SPSS Statistics V.24.0, NCSS Statistical Software V.19.0.1 (NCSS, LLC,
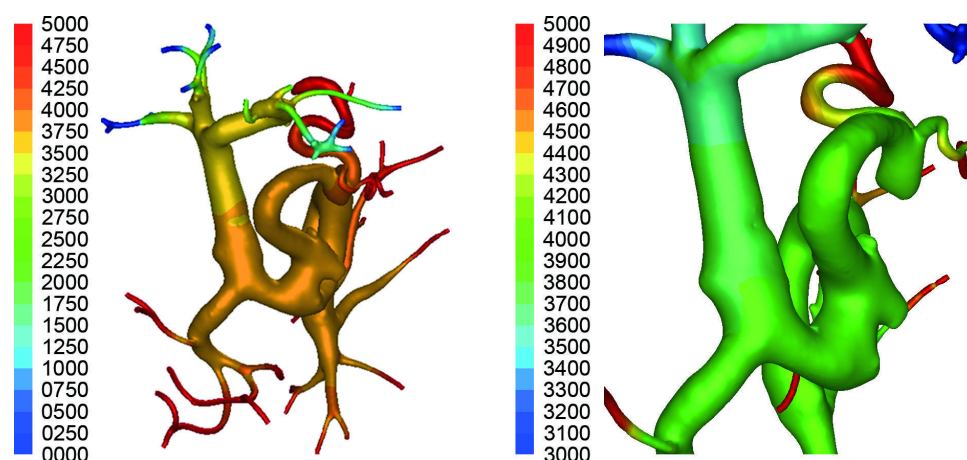

Figure 5 An example of the blood pressure (Pa) of the portal vein and its branches.
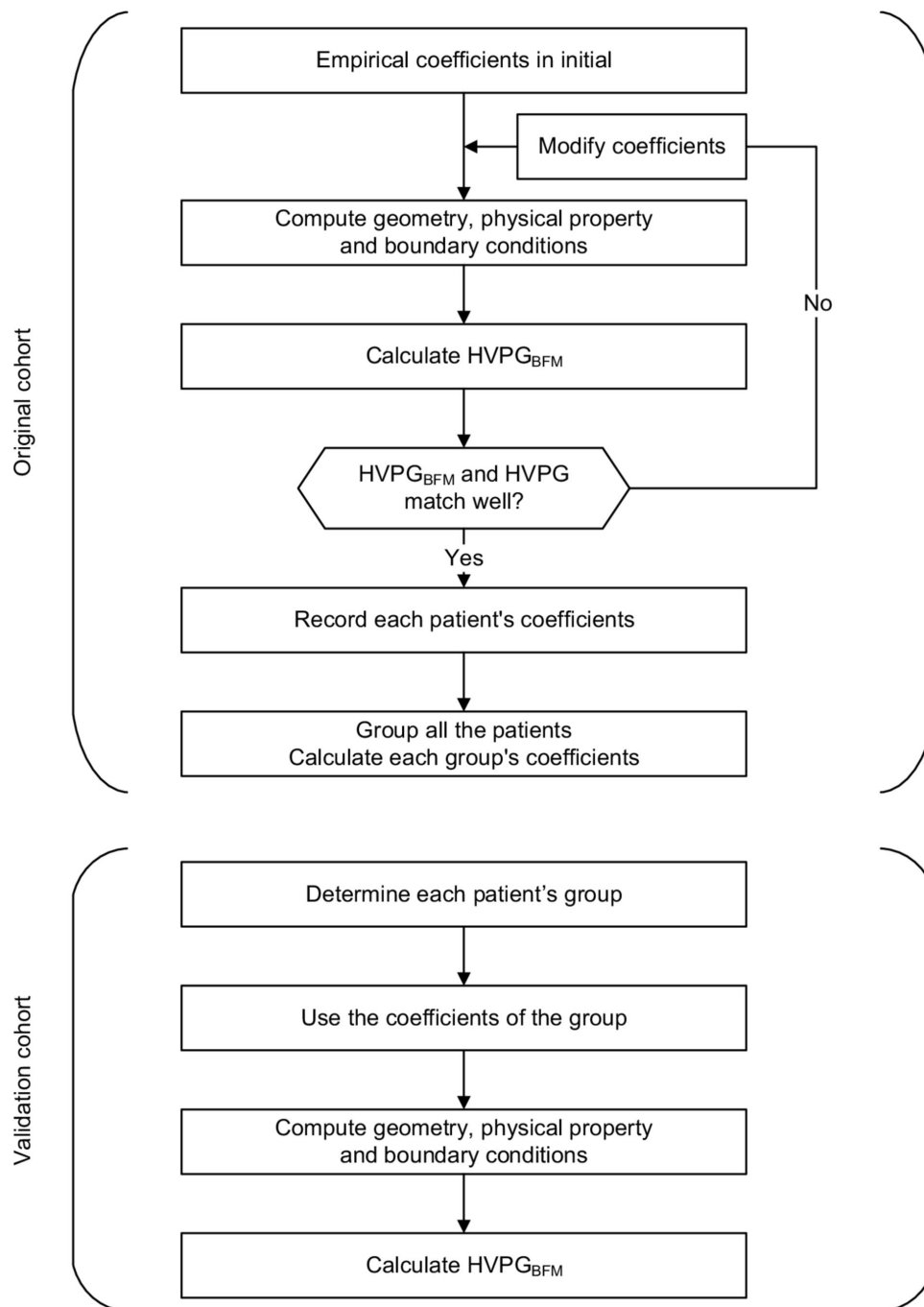
Figure 6 The process of the HVPG$_{BFM}$ computation. HVPG, hepatic venous pressure gradient; HVPG$_{BFM}$, hepatic venous pressure gradient using biofluid mechanics.

USA) and MedCalc Statistical Software V.18.11 (MedCalc Software bvba, Belgium).

DISCUSSION

It is a truth acknowledged that PH is a critical syndrome because it may cause severe complications, including gastro-oesophageal variceal haemorrhage, hepatic encephalopathy and ascites.[15] The HVPG measurement is of great importance because not only is it the gold standard to detect PH but also it is associated with hepatocellular carcinoma and severe complications. HVPG equals the difference between WHVP and FHVP, representing the portal perfusion pressure. Although WHVP is about 1 mmHg lower than portal pressure (PP) in the normal liver, it is equivalent to PP in liver cirrhosis.[16–18] As a result, for patients with liver cirrhosis, HVPG equals the difference between PP and hepatic venous pressure (HVP), namely, HVPG=WHVP–FHVP=PP–HVP. Since HVPG measurement is invasive and available in few hospitals, a new detection method is needed. Although many assessment methods have emerged in recent years, few of them proved to be accurate and dependable. So, we call for a new, less-invasive and accurate assessment method.

Fortunately, recent advances in biofluid mechanics and image-based modelling provide us with a new way to solve this problem. According to previous studies, the IQQA software can be used to reconstruct the spatial structure of the blood vessels precisely, and the FLUENT software can be used to simulate the blood flow in vessels accurately.[19–25] Moreover, it has been reported that Navier-Stokes equations can be used to compute the haemodynamics of the cerebral arterial and venous system.[26 27] Since the inner diameters of the inferior vena cava, the hepatic veins, the portal vein and its main branches are much larger than the diameters of red blood cells, and the blood flow is relatively steady and fast in these big vessels, the whole blood can be assumed to be an incompressible Newtonian fluid, and thus the blood flow can also be modelled by the Navier-Stokes equations.[28 29] So, in theory, we can use IQQA and FLUENT software to process patients' CT, blood tests and Doppler ultrasound data; compute their geometry, physical property and boundary conditions; and then calculate the simulated PP and HVP by the Navier-Stokes equations. Since HVPG equals the difference between PP and HVP in patients with liver cirrhosis, the simulated HVPG will be calculated from the difference between simulated PP and simulated HVP, namely, $HVPG_{BFM}=PP_{BFM}-HVP_{BFM}$.

In previous experiments, we made a model of PP assessment by using biofluid mechanics in canines and found out a strong correlation between simulated PP and measured PP. We then applied this model to several portal hypertensive patients who underwent portosystemic shunts or splenectomy with periesophagogastric devascularisation and came up with similar results. These findings proved our method to be feasible. The aim of this study was to establish and assess a novel model to calculate HVPG based on biofluid mechanics and to further verify the feasibility of this method. In view of the complicated computation process, we will later develop a software, which will enable physicians to acquire simulated HVPG and PP values with only a few clicks, if this model proves to be credible. As a result, it will be easier for physicians to monitor HVPG and PP values of patients in the future, which will be helpful for diagnosing and evaluating the severity of cirrhosis and PH.

This study has two main limitations. The first limitation is about the inclusion criteria. One of the premises of our model is that the PP should be equivalent to WHVP, so only patients with cirrhosis will be recruited. Our model is unsuitable for normal people and patients with noncirrhotic PH or other liver diseases (including nodular regenerative hyperplasia, cholestatic liver disease and primary biliary cholangitis) because their HVPG does not mirror the portal pressure gradient. Patients with hepatocellular carcinoma will be excluded because of the possible arteriovenous fistulae and vascular invasion. Moreover, patients with advanced or decompensated cirrhosis will also be excluded because of their severe PH. Another limitation is the difficulty in performing Doppler ultrasound measurements. Because of the air within the gastrointestinal tract and other interference, it is hard to acquire the blood flow direction and the maximum blood flow velocity at all 12 positions. Since the blood flow in both the portal system and the hepatic venous system follows the principle of mass conservation, we will be able to calculate some of the missing data. The data of the portal vein, the suprahepatic inferior vena cava and the infrahepatic inferior vena cava are important and essential; for the right and left branches of the portal vein, only one of them is essential; for the proximal part of the splenic vein and the superior mesenteric vein, only one of them is essential; for the right, middle and left hepatic veins, only two of them are essential; for the distal part of the splenic vein and the inferior mesenteric vein, neither of them is essential because they do not flow directly into the portal vein. Although the computation will be able to proceed with some data missing, the result will be less accurate. It is reported that MRI can also obtain the blood flow direction and the velocity of the vessels, and this may serve as an alternative.[30]

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