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Predicting the risk of post-hepatectomy portal hypertension using a digital twin: a clinical proof of concept

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- Audebert: software creation, methodology
- Allard: data collection, analysis
- Sa Cunha, Castaing, Cherqui, Adam : data collection, review manuscript
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Abbreviations:

AA: ascending aorta

CO: cardiac output

Ea: amplitude of elastance

Eb: basal elastance

Fflowmet: calibration of the algorithm is based on intraoperative flow measurements obtained using a flowmeter

Flit: calibration of the algorithm is based on liver flow estimates from the intraoperative cardiac output (repartition % from the literature)

Fmri: calibration of the algorithm is based on preoperative flow measurements from MRI

HA: hepatic artery

HR: heart rate

IVC: inferior vena cava

P: pressure

PCG: portocaval gradient

PHLF: post-hepatectomy liver failure

PHT: portal hypertension

PV: portal vein

PVE: portal vein embolization

Q: flow rate

R: resistance

ABSTRACT

Background & Aims: Despite improvements of medical and surgical techniques, post-hepatectomy liver failure (PHLF) remains the leading cause of death in that context. High postoperative portal vein pressure (P_{PV}) and portocaval gradient (PCG) are the most important determinants of PHLF, and are not predictable using current tools. Our aim was therefore to evaluate a digital twin to predict the risk of postoperative portal hypertension (PHT).

Methods: We prospectively included 47 patients resected for major hepatectomy. A mathematical (0D) model of the entire blood circulation was assessed and automatically calibrated from patient characteristics. Hepatic flows were obtained from preoperative flow MRI (n=9), intraoperative flowmetry (n=16), or estimated from cardiac output (n=47). Resection was then simulated in these three groups and the P_{PV} and PCG computed were compared to intraoperative data.

Results: Simulated post-hepatectomy pressures did not differ between the three groups, comparing well with collected data (no significant differences). In the entire cohort, the correlation between measured and simulated P_{PV} values was good (r=0.66, no adjustment to intraoperative events) or excellent (r=0.75) after adjustment, as well as for PCG (respectively r=0.59 and r=0.80). The difference between simulated and measured post-hepatectomy PCG was ≤ 3 mmHg in 96% of cases. Four patients suffered from lethal PHLF for whom the model satisfactorily predicted their postoperative pressures.

Conclusions: We demonstrated that a 0D model could correctly anticipate postoperative PHT, even using estimated hepatic flow rates as input data. If this major conceptual step is confirmed, this algorithm could change our practice toward more tailor-made procedures, while ensuring satisfactory outcomes.

LAY SUMMARY

Post-hepatectomy portal hypertension is a major cause of liver failure and death, but no tool is available to accurately anticipate this potential lethal complication for a given patient. We propose here a mathematical model aiming to predict the portocaval gradient at the end of liver resection, tested on a cohort of 47 patients receiving major hepatectomy. We succeeded to model perioperative hemodynamics and this could modify the current decisional algorithms to resect cirrhotic and non-cirrhotic patients.

Data availability statement: All the data may be available on request to corresponding author

INTRODUCTION

The surgical and perioperative management of patients undergoing liver resection has changed dramatically over the last thirty years. Despite these improvements, postoperative mortality remains a considerable concern with mortality exceeding 10%(1). Post-hepatectomy liver failure (PHLF) is the main cause of mortality(2), largely explained by an excessive rise in portal vein pressure (P_{PV}) and the portocaval gradient (PCG) due to a reduction of the parenchymal vascular bed leading to higher intrahepatic resistance(3).

The BCLC guidelines recently changed from a strict contra-indication to resect in the event of pre-existing portal hypertension (PHT)(4) towards recognizing a progressive risk dependent on the resection extent and the MELD score(5). However, although preoperative PHT is undoubtedly a risk factor for serious complications(6), its predictive value is poor(7,8) and the most accurate predictor has been shown to be the post-resectional PCG value that can predict both PHLF and early mortality(9,10). Hence, the focus is here on post- rather than pre-resection liver pressures. Unfortunately, this variable cannot be anticipated using current tools.

With the development of numerical medicine, recent multi-parametric algorithms have attempted to predict postoperative outcomes(11,12) but these calculators are not designed to reflect the patient specific hemodynamic data. On the other hand, some models of the entire human circulation have been developed and some are emerging in the field of liver hemodynamics. While none has yet been used in routine practice, such modeling, which is mainly based on closed-loop 0D simulations (a lumped parameter model, i.e. a compartmental model of the entire circulation, without any spatial dimension in equations) may efficiently reflect physiological or surgical situations(13,14). Other models have explored the consequences of partial hepatectomy(15,16). Our team recently reported a 0D model tested on

partial hepatectomies in pigs(17), followed by a clinical feasibility study(18). These promising results led us to think that this digital twin might assist our decision-making strategy and patient selection, and potentially avoid a surgery in the event of predictable high risk of postoperative PHT. Another advantage of such physiological models over statistical ones, is that they provide mechanistic interpretation of the causes of postoperative PHT for a specific patient or for inter-patient variability, and they quantify hemodynamics variations due to intraoperative events that play a role on top of the main surgical act(15,16).

Our aim was thus to apply our 0D model into a large-scale human series and to assess its accuracy in the setting of major hepatectomy, focused specifically on anticipating postoperative PCG.

PATIENTS AND METHODS

a) Clinical and Paraclinical Features

Study Population

Forty-seven non-consecutive patients resected in our tertiary center were prospectively included and followed up until postoperative day 90. The patients were informed and gave their consent to participate to this study which had been approved by the local Ethics Committee (ID RCB: 2018-A03316-49). The inclusion criteria were open major hepatectomy with access to intraoperative measurements of vascular pressures and anesthesiologic parameters. No clinical or surgical decisions were based on the results of the numerical simulations, which were performed retrospectively.

Preoperative Imaging and Preparation

- All patients underwent a contrast CT scan during the month prior to surgery. Liver volumetry was performed by a single operator (NG) using Myrian XP-Liver (Intrasense, Montpellier, France). In the event of an indication for portal vein embolization (PVE), the liver volumes used in the algorithm were considered after PVE.
- Some patients (n=9) underwent a flow MRI within the preoperative month to quantify cardiac output (CO), as well as portal vein (PV) and hepatic artery (HA) flows [Q_{PV} , Q_{HA}]. Details about MRI examinations are provided in supplementary data.

Intraoperative Measurements to Run or Validate the Algorithm

For all forty-seven patients (excepted specific indication), all measurements were collected just before and then after hepatectomy (i.e. after hemodynamic stabilization, immediately before parietal closure):

- Heart rate (HR),
- CO estimated from the thermodilution technique or pulse contour analysis,
- Mean arterial pressure (P_{AO}),
- IVC and PV pressures measured by a transducer connected to a needle inserted into the vessels. In all the patients, pressure measurements were taken twice,
- Q_{PV} and Q_{HA} measured in sixteen patients using a transit-time ultrasound flowmeter,
- Volume of blood loss and total volume infused,
- Administration of a vasoconstrictor.

Postoperative outcomes, including PHLF(19,20), were collected up to postoperative day 30.

b) Mathematical Model and Parametrization

Mathematical model of the entire blood circulation

The model has been described elsewhere in detail(17,18,21). The human cardiovascular system can be seen as a hydraulic network (the vessels), driven by a power source (the heart). This analogy identifies fluid flow with an electrical intensity and pressure with voltage, which enables modeling of the entire circulation like an electrical circuit. Viscous dissipation through vessels and valves is modeled by resistances, while electronic capacitances (or elastances) represent vessel and cardiac compliance.

The model developed for partial hepatectomy is able to represent dual liver perfusion (arterial + venous systems) and its interaction with the rest of the cardiovascular system. Our previous scheme was adapted to human anatomy (Fig. 1): the liver was modeled as two parallel components (two hemilivers), whose parameters (namely resistances in the portal network, arterial network and liver tissue: R_{PV} , R_{HA} , and R_l) were indexed on the mass of each

hemiliver. In addition to the cardio-pulmonary system, it included three blocks: the digestive organs, the liver, and a single block representing all other organs. The pulsatile activity of the heart was represented by periodic time-varying elastances $E(t)$ with two parameters for each of the four cardiac contractile chambers, as well as a nonlinear valve function for each cardiac valve. Overall, the model produced a system of 32 differential-algebraic equations.

Procedure for Model Calibration (see Appendix for more details)

In the pre-hepatectomy stage, the model needs to reflect the patient's state. The model parameters were set such that the model variables are close to the measured data (Fig.1 right) for each patient. To compensate for the few patient data available to set all model parameters, assumptions were also taken from the literature(17,21). In a first step, all the systemic and pulmonary parameters were estimated. Then, the heart block parameters were set based on HR and an optimization algorithm (covariance matrix adaptation evolution strategy(22)), so that the model variables matched the best six of a patient's major hemodynamic measures: CO, P_{AO} , P_{PV} , $PCG (=P_{PV}-P_{IVC})$, Q_{PV} and Q_{HA} .

In the event of PVE (n=12), the system was tuned according to the pre-resection data, taking account of any pre-existing absence of right (total or sectorial) portal flow.

This calibration step requires flow and pressure measurements before resection. In this work we propose two possibilities for flow measurements (*Flit* and *Fmri*) that will be compared and verified with intraoperative measurements before resection (*Fflowmet*). These three different types of input data were considered and compared (Fig. 2) in view of further preoperative and non-invasive data use of algorithm:

- *Fflowmet*: Pre-resectional values measured as Q_{PV} and Q_{HA} through flowmeter (n=16),

- *Flit*: Estimated flows = Q_{PV} and Q_{HA} were considered from the literature as being 20% and 5% of the pre-resectional CO values provided by anesthesiologists(23,24) (n=47),
- *Fmri*: Q_{PV} , Q_{HA} and CO provided by preoperative flow MRI (n=9, of which 5 also underwent complete intraoperative flowmetry measures).

Virtual Hepatectomy

After optimizing the parameters according to preoperative patient data, hepatectomy was simulated by decreasing the mass of the resected part to 0 (Fig. 3). A complete simulation lasted about 45 minutes.

Furthermore, during surgery, the hemodynamic status of the patient may change. Thus, an “adjusted” simulation was also performed that considered intraoperative data, i.e. the HR after resection, variations in blood volume and potential drug-induced vasoconstriction or surgery-induced vasodilation. Note that only “unadjusted” virtual hepatectomy simulations could be run, with the current methodology, before resection.

For adjusted simulations, in the case of a fibrotic liver (fibrosis \geq F2 Metavir), we considered that the portal vessels cannot adjust to an increase of pressure (rigid vessels) whereas in all other cases (normal or weakly fibrotic livers, as well as all unadjusted simulations), the PV resistance depended on P_{PV} (17).

c) Statistical Analysis

The primary objective of the study was to predict the postoperative PCG in the whole cohort with a precision of ± 3 mmHg (choice compatible with clinical decision-making and intraoperative precision of instruments), using estimated flow data (*Flit*) as input. The secondary objectives were to analyze the accuracy of pressures simulations, and to compare

the simulation results according to the input data (*Fmri*, *Flit* or *Fflowmet*). The sample size calculation is justified in supplementary data.

RESULTS

Population Characteristics, Perioperative Features

We included 47 patients (gender ratio M/F: 55%/45%), with a mean age of 63 ± 12 years. The indication for resection was malignant disease in 41 cases (87%): cholangiocarcinoma (n=24), hepatocellular carcinoma (n=11) and colorectal metastases (n=6). The mean MELD score was of 7.9 ± 2.1 , and the mean platelets count was of 260 ± 86 giga/L. A fibrotic (\geq F1 fibrosis) and cirrhotic (F4) parenchyma were observed in 10 (21%) and 3 (6%) percent of cases, respectively. The median MELD score of cirrhotic patients was 9. The mean number of resected segments was 4.7 ± 1.2 (median percentage of resected volume: 58.7%, range:16-89%). Five patients (10.6%) died postoperatively, following PHLF (n=4) or extra-hepatic complications (n=1). Concerning the four PHLF-related deaths (three efficiently drained perihilar cholangiocarcinoma + 1 hepatocellular carcinoma/cirrhosis), all underwent preoperative PVE (two complete, two uncomplete [2 segments only]) and all of them presented a future remnant liver volume to body weight ratio higher than 0.5% (median: 0.9%, range: 0.64-1.1) with a median percentage of resected volume = 58.8% (range: 40-69%, right hepatectomy (n=1) or right extended to segments 1+4 (n=3)). Their median pre-resectional P_{PV} and PCG values were 16 [11-22] mmHg and 9 [8-11] mmHg respectively, while their post-hepatectomy P_{PV} was 23.5 [18-30] mmHg and PCG was 17.5 [14-20] mmHg. Among these 4 PHLT patients, 2 presented a pre-resectional PCG ≥ 10 mmHg.

Simulations on the Whole Cohort based on Estimated Flows (*Flit, no invasive flowmeter measurements*).

Thirty-six patients (77%) experienced intraoperative events which meant that adjusted simulations differed from unadjusted simulations. In 14 cases (14/36=39%), this modification only concerned a variation in blood volume.

As shown in Fig. 4A, the predictions of post-resectional P_{PV} and PCG were quite accurate and indeed improved slightly when intraoperative events were considered. There was no significant difference between measured and simulated values for either variable.

The correlation between measured and simulated P_{PV} values was moderate ($r=0.66$, $p<0.0001$, no adjustment to intraoperative events) or strong ($r=0.75$, $p<0.0001$) after adjusting for hemodynamic modifications (Fig. 4B) and for PCG ($r=0.59$ and $r=0.80$, respectively, $p<0.0001$). Concerning the simulated PCG, the performance of the 0D model to predict a post-hepatectomy PCG value ≥ 10 mmHg was:

- Unadjusted simulations: sensitivity=69%, specificity=94%, positive predictive value=82%, negative predictive value=89%,
- Adjusted simulations: sensitivity=100%, specificity=94%, positive predictive value=87%, negative predictive value=100%.

Unadjusted simulations enabled an accuracy of 72% within the primary endpoint and with a calculated bias of -0.72 mmHg. As illustrated in Fig. 4C, two patients presented an adjusted simulated PCG that was outside the primary objective (absolute values of the difference between the simulation and measurement: 3.2 and 5.1mmHg), meaning that 95.7% of adjusted predictions were within the ± 3 mmHg margin. The calculated bias was -0.05 mmHg. These two patients underwent almost bloodless left hepatectomy on non-cirrhotic liver. In the first patient, the measured PCG fell by 3 mmHg between pre- and post-resection whereas the simulation showed a slight increase in the gradient as might be expected in such a situation with no significant intraoperative event, hinting at a measurement error. In the second case, the measured PCG value rose from 1 to 7 mmHg after resection, without any clear explanation, whereas the simulation only predicted a PCG increase of 1 mmHg: this example highlights the uncertainty of pre-resection measurements when the PCG is low.

The four patients who died postoperatively from PHLF had simulated post-hepatectomy PCG values within this margin of error, with a median adjusted predicted PCG of 16.9mmHg [range=13.3-20 mmHg]. Using a ROC (receiver operating characteristic) analysis, we determined that the best cut-off points for post-resectional measured P_{PV} and PCG values to anticipate PHLF were 17.5mmHg (area under the curve=0.94, $p=0.004$, sensitivity=100%, specificity=84%) and 13.5mmHg (area under curve=0.98, $p=0.002$, sensitivity=100%, specificity=93%), respectively. Among these four deceased patients, three presented an unadjusted predicted P_{PV} that was higher than 17.5mmHg.

Comparison of Pre-Resectional Flow Data According to Three Measuring Methods

By comparing the Q_{PV} and Q_{HA} flow values provided by MRI (*Fmri*), intraoperative flowmeter (*Fflowmet*) and estimated measurements (*Flit*), there was no statistically significant difference ($p>0.15$ for each comparison; Wilcoxon matched pairs tests). In the *Fflowmet* group, median Q_{PV} and Q_{HA} represented 15.3% [3-26] and 3.6% [1-7] of total CO, and respectively 82% [40-93] and 18% [7-59] of total hepatic flow.

Calibrations and Simulations from Flows Measured through a Flowmeter vs Values Estimated from the Literature as Input Data: Does it Matter?

Secondary results comparing post-resectional simulations obtained using real flow measured as input for the algorithm, versus literature-based estimated flows. This aimed to understand if patient-specific liver flow data led to most accurate simulations than literature-based flow data.

As shown in Fig. 5, the preoperative calibration did not differ between the two types of input flow data ($p=0.93$). By applying the *Fflowmet* or *Flit* as input for the algorithm calibration, we reached highly significant correlations for P_{PV} and PCG ($r=0.99$, $p<0.0001$)

between the simulated variables and patient measurements, whatever the input chosen (Fig. Supplementary data). This means that in both cases, calibration of the model was successful in reflecting the patient's state prior to resection. When performing virtual hepatectomy, model predictions for the unadjusted simulations (Fig. 6) did not differ between *Fflowmet* and *Flit* with respect to post-resectional PPV ($p=0.82$) or PCG ($p=0.54$).

Simulations with the MRI Flows as Input Data

Secondary results on post-resectional simulations based on flow MRI data as input for the algorithm, with the view of later preoperative clinical use for decisional algorithm.

The CO and HR data from preoperative MRI and intraoperative pre-resectional anesthesiologic measurements were also comparable ($p=1$ and $p=0.69$, respectively).

The calibrations based on *Fmri* or *Flit* ($n=9$) were not statistically different ($p=0.94$), and the same applied to *Fmri* vs *Fflowmet* ($n=5$, $p=0.31$). (Fig. 5). The unadjusted simulations of post-hepatectomy status based on *Fmri* or *Flit*, as well as those based on *Fmri* vs *Fflowmet* were not statistically different with respect to PPV and PCG.

DISCUSSION

Statement of principal findings

This *feasibility* study is the first application in humans of a 0D model of the entire blood circulation, applied in the setting of liver resection. In 47 patients, we succeeded to anticipate post-resectional P_{PV} and PCG values, two well-known predictors of PHLF(9,25), with a reasonable correlation, even irrespective of intraoperative events.

We showed that it was possible to run the algorithm with various input liver flows, and to reach equivalent accuracy for calibration and simulation.

This study also led us to propose post-resectional cut-offs for P_{PV} and PCG predicting PHLF, respectively 17.5mmHg and 13.5mmHg. This finding, by itself, brings some novelties in the field of PHT because no other team reported such information so far. In 2013, we reported a slightly higher P_{PV} cut-off (20mmHg), this different finding may be explained by our current population cohort including cirrhotic patients (unlike Allard M.A. et al. (9)) more prone to develop liver failure at a lower P_{PV} level.

The four PHLF-related patients who died presented with a preoperative future remnant liver volume ratio of over 0.5% body weight, usually considered to be sufficient for resection(26). This confirms that our digital twin might provide other selection criteria as current ones, and enable safe resection since the simulated (adjusted) postoperative PCG values of these patients were alarming and would have contraindicated the procedure.

Justification of the endpoint and of the need for such a model

We aimed to predict post-resectional P_{PV} and PCG because, until now, no tool could allow such predictions while these variables consensually appear as a major risk factor of PHLF. Roayaie et al. clearly demonstrated that recent guidelines were unable to provide any fair algorithm to select ideal candidate to resection, particularly based on preoperative PHT

level(27). Conversely, using our numerical tool based on patient-specific parameters, we were able to precisely model the risk of post-resectional PHT. This finding highlights the need of such physiological complex model, which by design considers several interplaying factors.

Our model accurately predicted P_{PV} and PCG variations, which are obviously linked. However, because of a possible bias of P_{PV} as a function of central pressure(28), we preferred to focus on PCG, a more reliable and reproducible measure. In fact, in the event of an inaccurate absolute calibration of the instruments used, the PCG remains reliable whereas P_{PV} is not.

One could argue that a clinical primary endpoint would have been more useful for clinicians. In fact, to predict a clinical condition related to PHT (ascites, death) or a biological event (liver failure) would be interesting but, from a statistical point of view, it was not possible to assess the accuracy of our model, by comparing it to a such a rare event. By contrast, all patients had postoperative measures available to compare our simulations results with.

Interpretation with reference to other studies

For several decades, *preoperative* PHT ($PCG \geq 10\text{mmHg}$) was considered as the principal criterion to contraindicate liver resection(29). We now know that, even if the degree of pre-resectional PHT is available, it is a poorer predictor of PHLF than the post-resectional P_{PV} value(9) or even a variation in P_{PV} (25). This justifies the need for a more physiologically realistic tool to prevent PHLF and avoid the exclusion from surgery of potentially curable patients(7). As a proof of that, 50% of our patients with preoperative $PCG \geq 10\text{mmHg}$ presented simple outcomes.

Because of these concerns regarding the predictive value of invasive or non-invasive(30) preoperative PCG alone to select patients for surgery, we developed a digital twins model

applicable to medicine. This 0D model appears to be predictive of hemodynamic fluctuations due to hepatectomy since we were able to report here on increases of P_{PV} of 23% and 24% (unadjusted and adjusted simulations, respectively), which was consistent with the findings of Bogner et al. who reported that mean P_{PV} values rose by 27% after major hepatectomy(25).

Some 0D hemodynamic models have already been reported in the field of hepatology, but no work included predictive and patient-specific simulations. It was therefore not possible to compare our model's performance to others.

Strengths and weaknesses of the study

The main strength of this feasibility study was the large sample size tested and the good performance of the predictions from a model that answers to a daily clinical issue. Knowing that the time required for a single simulation is compatible with everyday practice (<1hour), our findings may largely modify the selection criteria used in routine practice and improve patient outcomes.

Regarding the difference of accuracy between adjusted and unadjusted simulations, we should bear in mind that correlations between unadjusted simulations and measured data need to be interpreted cautiously since post-resectional measures are, *by definition*, the consequences of intraoperative events that are not considered in unadjusted simulations. In fact, the unadjusted simulations represent the effect of the surgical act alone. Unadjusted simulations may also reflect the delayed (mid-term) more stable hemodynamics conditions, whereas intraoperative measures reflect the immediate status after anesthesiologic maneuvers to compensate for blood circulating volume change.

Some limitations of the study must be highlighted. The small sample size of subgroups (*Eflowmet* and *Fmri*) must be kept in mind and encourage us to interpret cautiously statistical results. However, most of the results presented no statistical trend and a larger cohort may not

have bring any significant results.

In the *Flit* group, liver flows were not modulated according to the size of hepatocellular carcinoma (the 5% CO rate chosen could be increased in the case of hypervascularized tumors) or the degree of hepatopathy ($Q_{PV}=20\%$ CO could be an overestimate in the event of fibrosis), so that even better results might be expected following a case-by-case adjustment of estimated flows(31). However, the ratio we chose ($Q_{PV}=4 \times Q_{HA}$) was validated by the flow rate observed in the *Fflowmet* group (ratio: 4.5).

Finally, we did not integrate liver stiffness into our 0D model (because of lacking data in non-cirrhotic patients) even though this parameter is correlated to PCG(32) and to postoperative outcomes(33,34). This may offer a new approach for more refined development, particularly because to date we have adjusted PV elasticity to the fibrosis grade shown in the pathological report, but this information is not always available prior to surgery. Integrating liver stiffness could therefore improve the accuracy of simulation in terms of patient selection.

Further development and use of this 0D model

The current work may be considered as a pilot study necessary to confirm the relevance and feasibility of this model applied, for the first time, in Humans. So far, all the simulations were performed postoperatively, and we now need to assess the clinical impact of such tool in a prospective fashion. In fact, any retrospective or external validation could not be easily applicable as many input data could be lacking. To this end, acquisition data are ongoing and we will analyze on a larger scale different inputs to the algorithm: 1/ Flow MRI phases may be directly acquired during standard MRI for every potential surgical candidate to get the flows; 2/ The combination of cardiac output data alone (easily available from a flow MRI or cardiac sonography performed for anesthetic consultation) with PV/HA flows extrapolated

from the literature (20%/5% or another breakdown adapted to tumor size and/or liver stiffness) might facilitate routine use of our model; 3/ Pressures data obtained from transjugular approach (wedged and free hepatic venous pressure (35)) in order to run the model even in laparoscopy without any access to intraoperative pressure measures; 4/ A population including cirrhotic patients requiring limited (minor) resection should be tested as well, as we know that even small volume resected may lead to severe PHT and liver failure(36).

With such input, we will be able to preoperatively use the model as a clinical-decision tool (=tailored and digital-guided strategy) in order to quantify if the standard decisional-tree is modified (i.e. extent of resection, need for portal flow modulation, recused surgery...), in what frequency, and to assess the outcomes of so-called “extended” indications of liver resections.

CONCLUSION

We have demonstrated that a 0D model of the entire blood circulation could be calibrated to reflect preoperative conditions, and accurately predict postoperative hemodynamic status. The unadjusted simulations may reflect the state of the patient when back to baseline hemodynamics conditions. When taking account of intraoperative events, the model was able to correctly predict postoperative PCG values, particularly in the four patients who died from PHLF, although their preoperative future remnant liver volume ratios were considered as sufficient. In fact, the extent of liver resection alone did not correlate with portal pressure or PCG increase, highlighting the need for a physiological numerical model that naturally integrates the interplay of liver quality, hepatectomy extent and the rest of the circulation. If confirmed by broader prospective studies, this algorithm might crucially change our practices towards more tailor-made procedures. In the near future, if this digital twin is run preoperatively, surgeons could reject patients predicted to have an excessive risk of PHT, or confirm resection in otherwise borderline patients, and ensure satisfactory outcomes. The present 0D model is a concrete example of a numerically-assisted clinical tool that could move practices from empirically-based medicine to a new digital era of enhanced surgery. It not only illustrates that individual outcomes can be predicted, but also confirms that complex hemodynamic systems can be simplified and numerically modeled to create useful digital twins. This model could be considered as “augmented intelligence” as it could assist surgeons with their judgments, regarding patient selection, therapeutic indications and, lastly, to reduce postoperative morbi-mortality.

FIGURE LEGENDS

Figure 1: Schematic representation of the 0D closed-loop cardiovascular model for humans (two hemi-livers).

A complete simulation includes two successive steps:

- A patient-specific calibration according to pre-resection measurements (black box showing the required variables) and data from the literature: each electrical component is adjusted to the patient's characteristics
- A simulation of hepatectomy according to the percentage of each hemi-liver resected, eventually adjusting to blood loss/infusion, variations in heart rate and the administration of vasoconstrictors as well as vessel stiffening in the case of fibrotic livers.

Figure 2: Patient specific flow measures used to calibrate the model provided by flow MRI or intraoperative flowmetry.

Input data to run the 0D algorithm were obtained from flow MRI (A and B, same patient at different cardiac times) or intraoperative flowmetry (C) providing portal (D, up) and arterial (D, down) liver flow estimates.

Figure 3: Example of results provided by a 0D simulation.

Example of a complete simulation of left hepatectomy in terms of changes to portal pressure, portal flow and hepatic artery flow. Hepatectomy is simulated numerically at 27 seconds, leading to an increase in portal flow and a decrease in hepatic artery flow. Total portal flow remains constant.

Figure 4: Comparison between simulated and measured post-hepatectomy pressures on the whole cohort.

The *Flit* (Q_{PV} and Q_{HA} considered as being 20% and 5% of cardiac output, respectively) simulations results are presented here. Adjusted simulations took into account intraoperative

hemodynamic events (i.e. modifications to HR, blood loss and vascular vasoconstriction/vasodilation).

A: comparison between measured and simulated P_{PV} ($p=0.61$, Friedman test) and PCG ($p=0.93$, Friedman test). While statistically non-significant, adjusted simulations tended to be more accurate than standard ones. Graphs represent mean \pm standard error of the mean.

B: correlation between measured and simulated P_{PV} ($p<0.0001$, $r=0.75$, Spearman test).

C: Bland-Altman analysis of measured and adjusted simulated PCG. 95.7% of simulations are within the range: measurement \pm 3mmHg.

Figure 5: Calibration results (1st step of simulation)

The calibration, expressed as the L2 norm and representing a composite score for calibration efficiency, was statistically equivalent in all input situations (a low L2 norm represents an accurate calibration with simulated variables almost equal to measurements). Graphs represent medians with interquartile ranges. Results of calibration are drawn as a function of input data:

A: *Fmri* versus *Fflowmet* ($n=5$). Wilcoxon test, $p=0.31$

B: *Fmri* versus *Flit* ($n=9$, Q_{PV} and Q_{HA} considered as being 20% and 5% of measured cardiac output, respectively). Wilcoxon test, $p=0.94$

C: *Fflowmet* versus *Flit* ($n=16$). Paired t test, $p=0.93$

Figure 6: Comparison between simulated and measured post-hepatectomy pressures in subgroups.

Results of simulations as a function of input data: *Fmri* versus *Fflowmet* versus *Flit* (Q_{PV} and Q_{HA} considered as being 20% and 5% of measured cardiac output, respectively). Graphs represent medians with interquartile range. Friedman tests used for all the analyses.

A: *Flit* vs *Fmri* vs *Fflowmet* (n=5): no statistically significant difference for post-resection P_{PV} (p=0.97) and simulated PCG (p=0.77),

B: *Flit* vs *Fmri* (n=9): no statistically significant difference for post-resection P_{PV} (p=0.57) and simulated PCG (p=0.33),

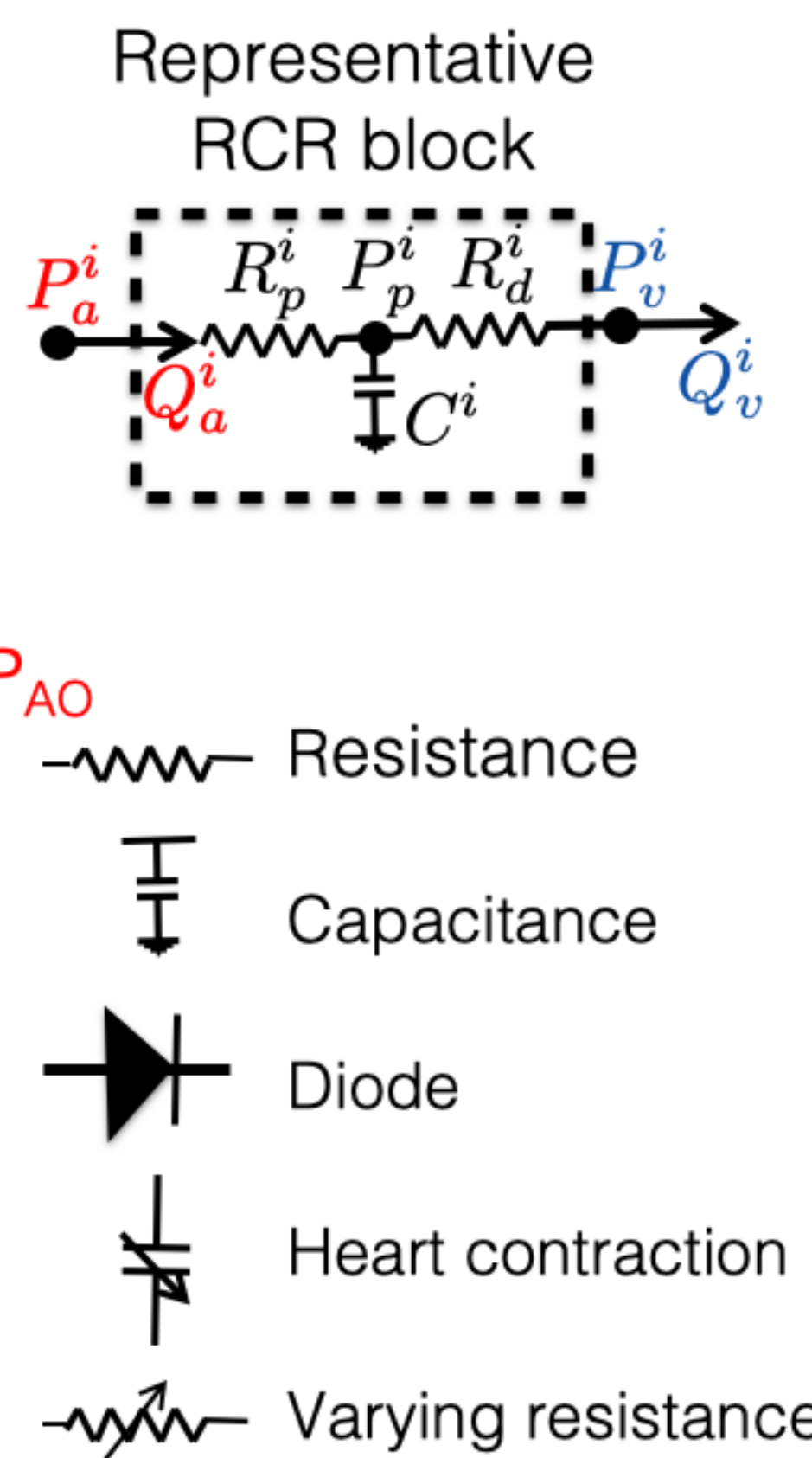
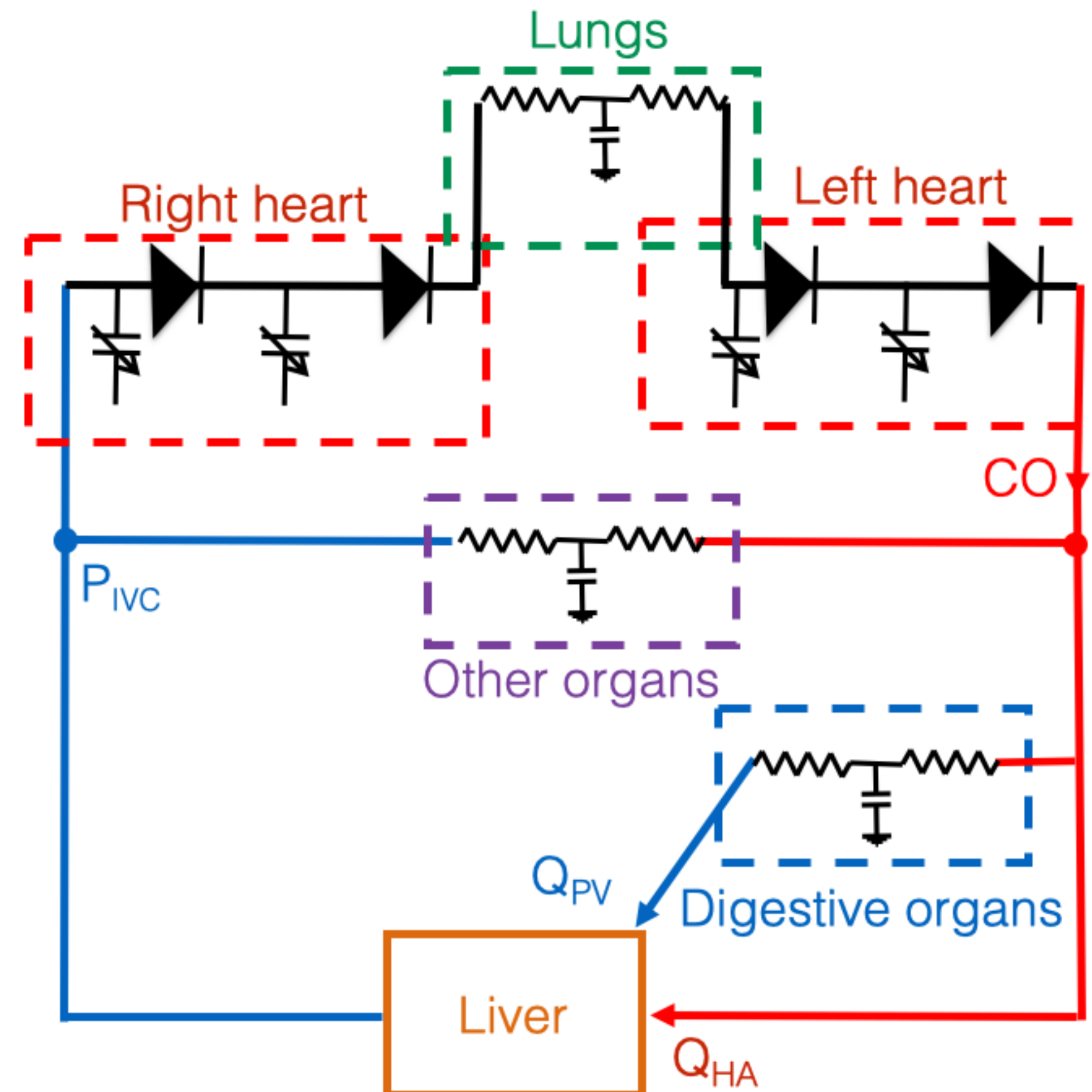
C: *Fflowmet* vs *Flit* (n=16): no statistically significant difference for post-resection P_{PV} (p=0.82) and simulated PCG (p=0.54).

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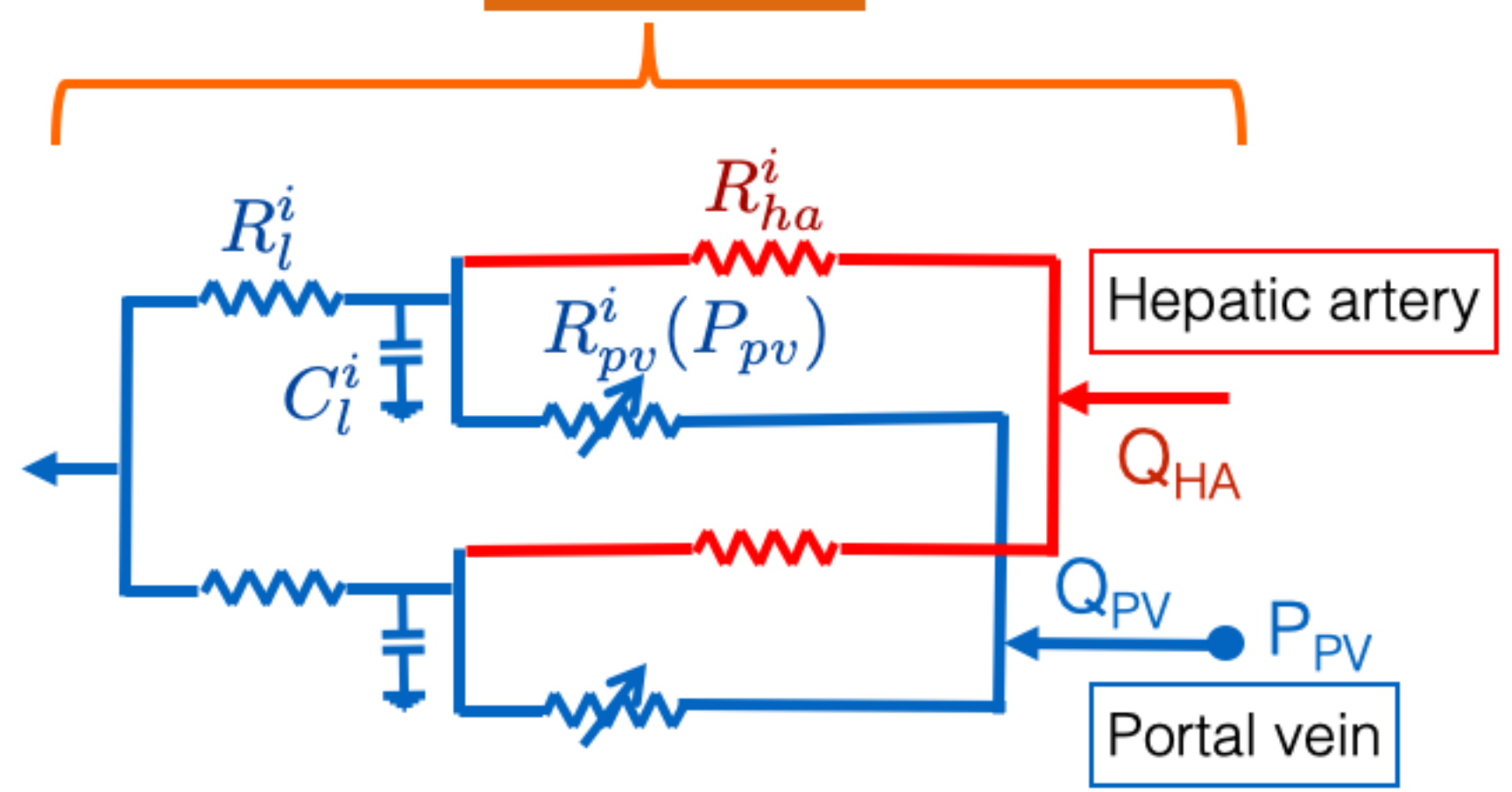
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- Input data required for the model**
- Hear rate (HR)
 - Cardiac output (CO)
 - Mean arterial pressure (P_{AO})
 - Hepatic artery flow (Q_{HA})
 - Portal flow (Q_{PV})
 - Portal vein pressure (P_{PV})
 - Central pressure (P_{IVC})
 - Liver volumes (right and left hemilivers)
 - % resection in right and left hemilivers
 - % of embolized right and left hemilivers

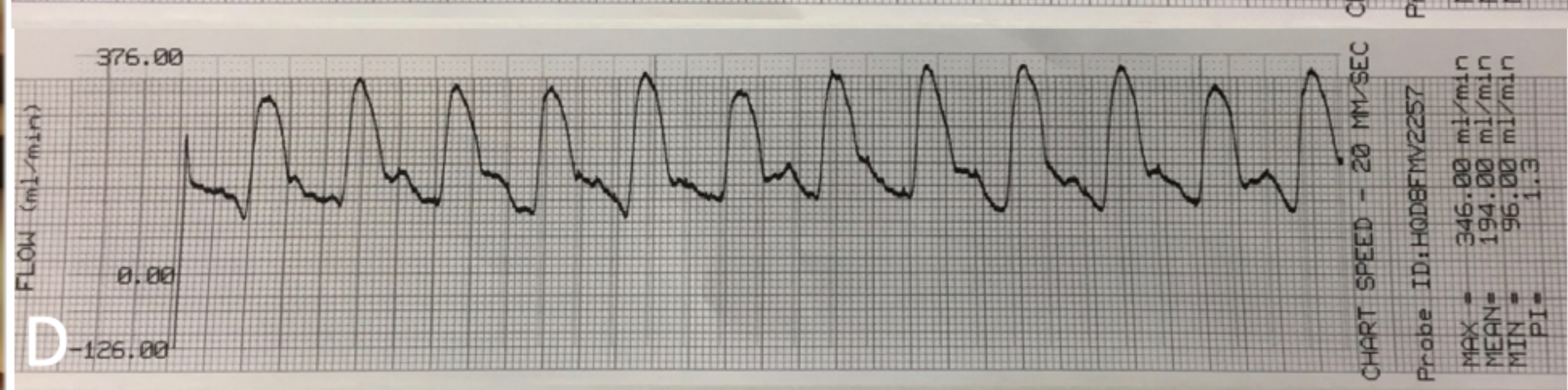
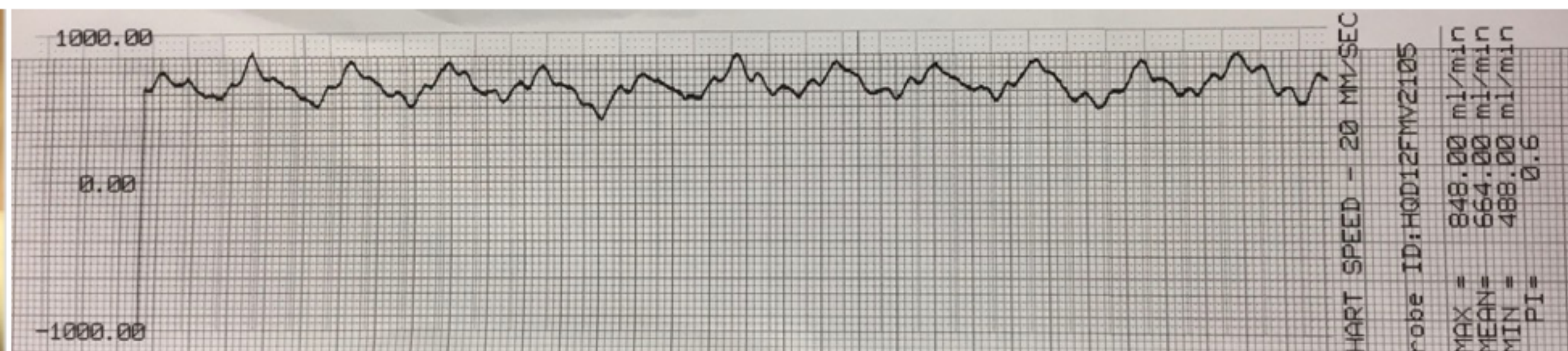
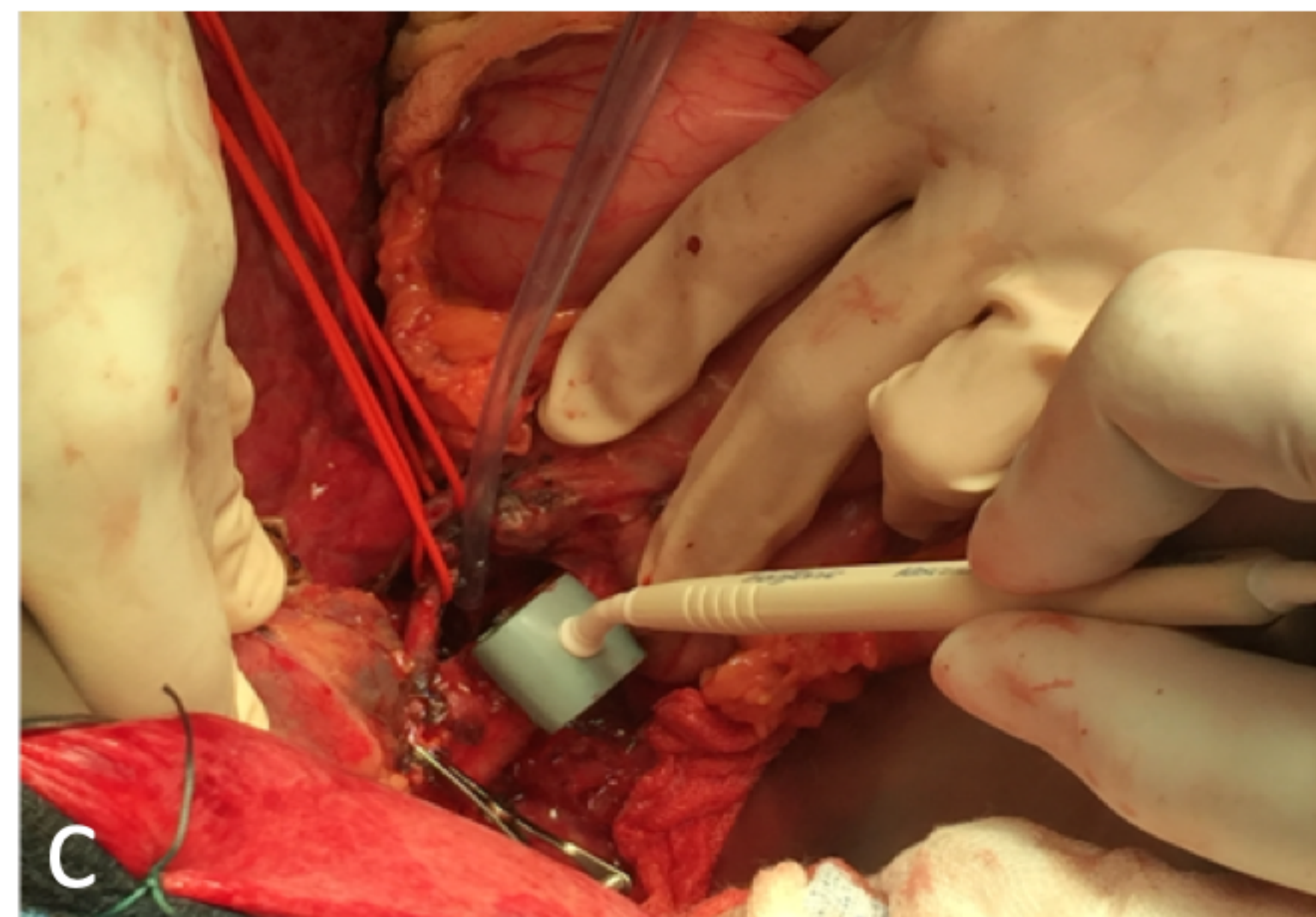
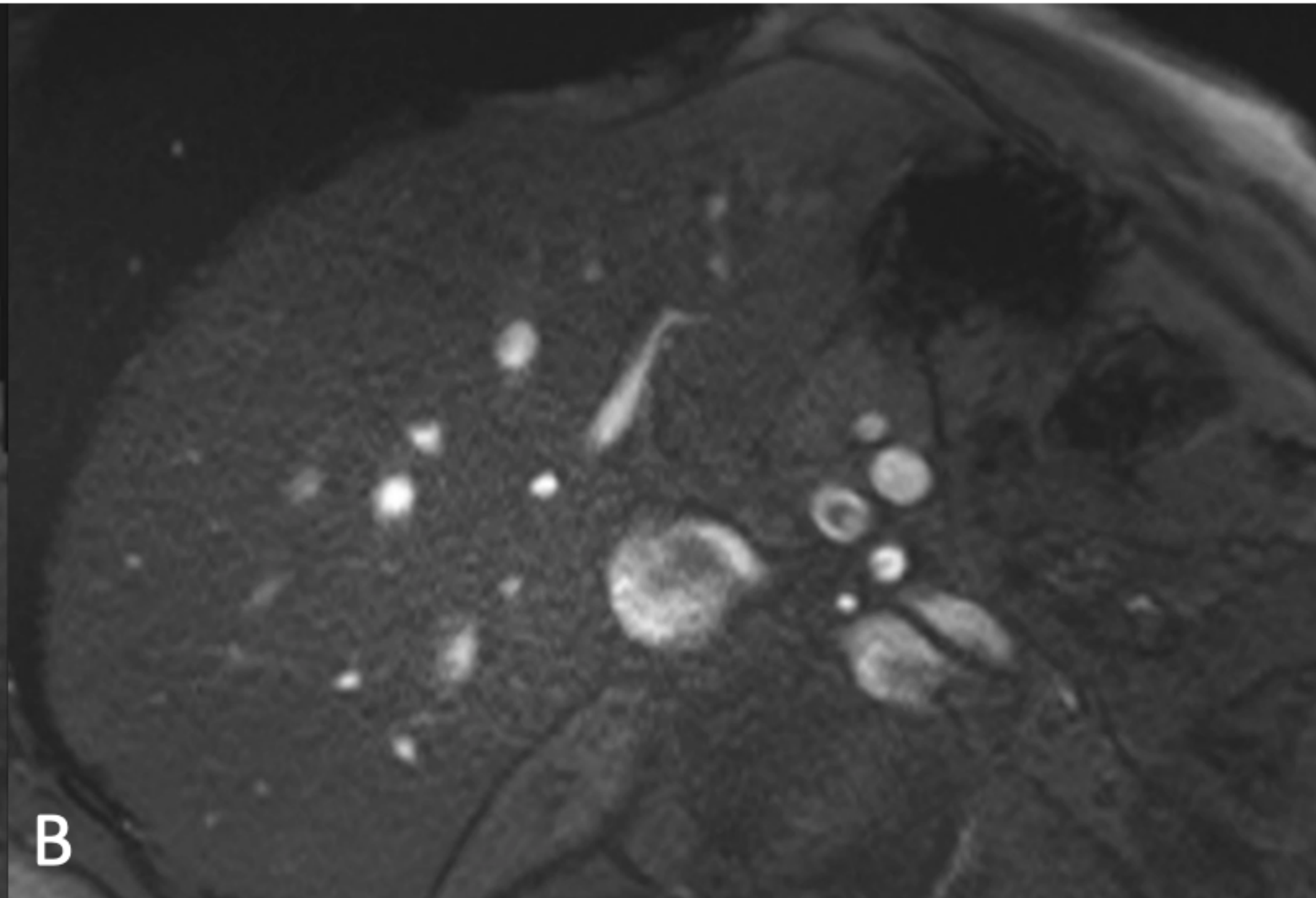
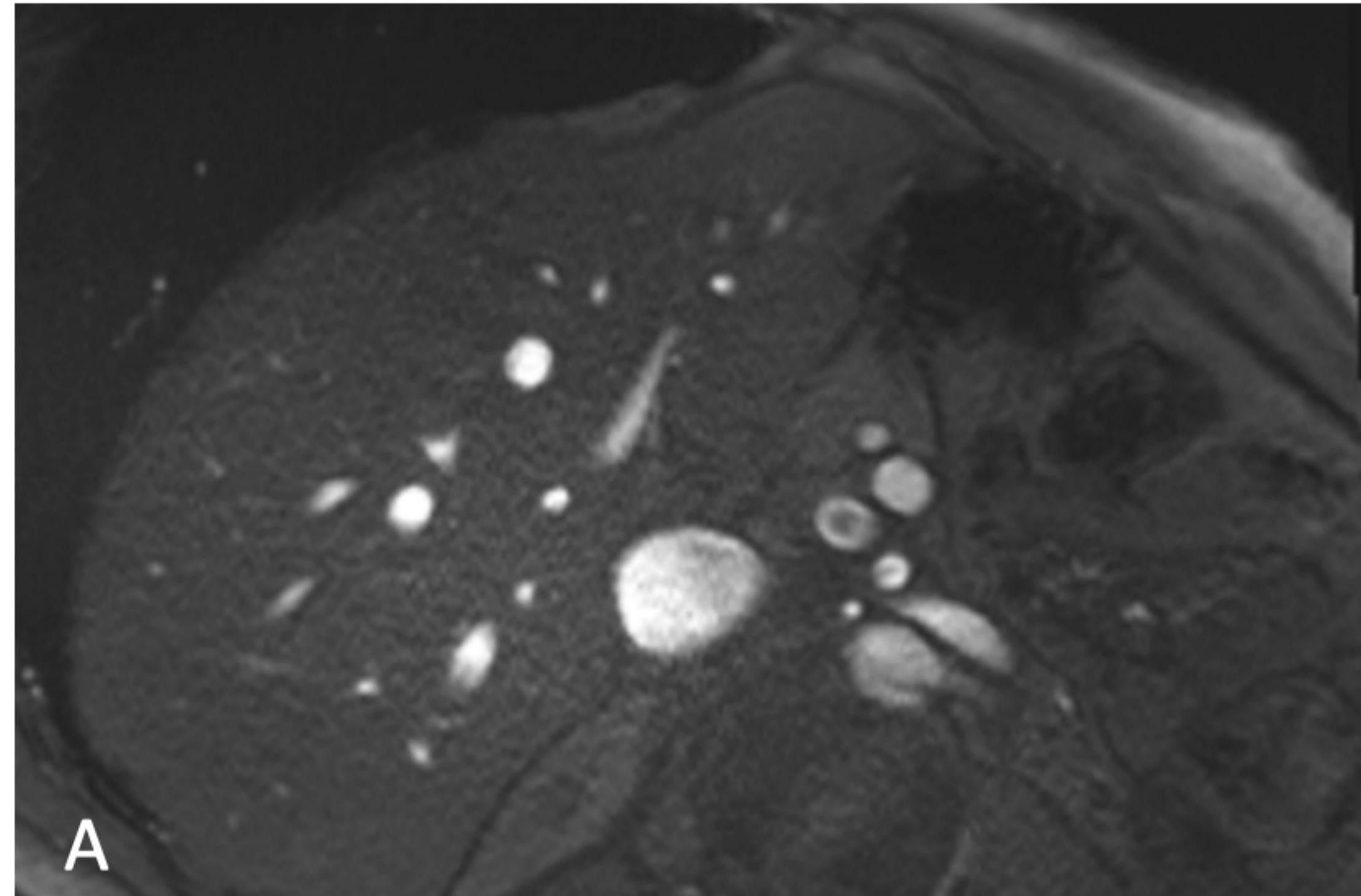


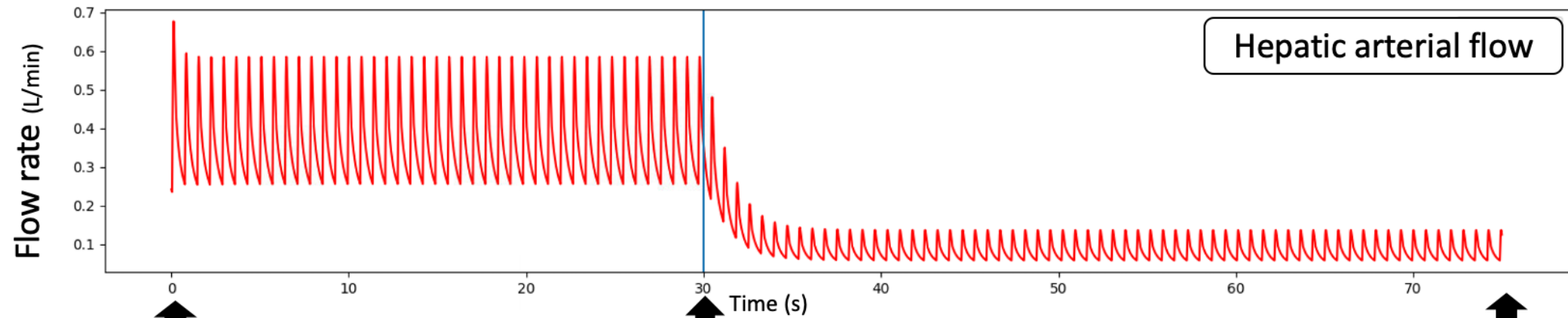
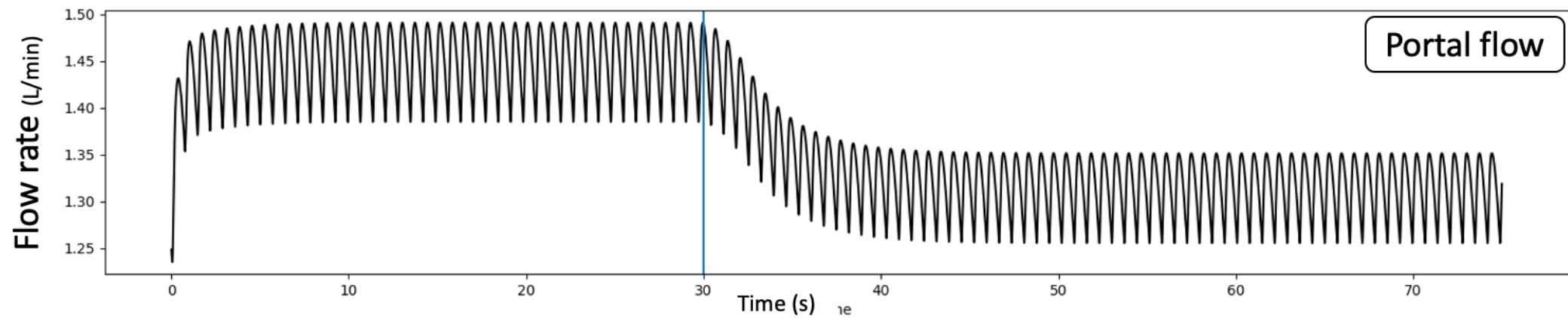
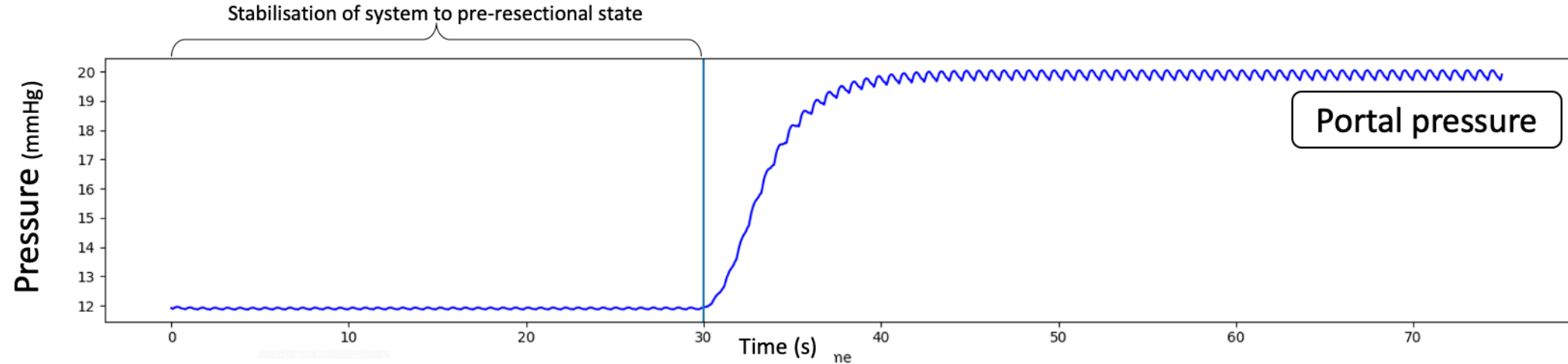
$$R_{pv}^i(P_{pv}) = R_{pv} \frac{M}{M_i}$$

$$R_{ha}^i = R_{ha} \frac{M}{M_i}$$

$$C_l^i = C_l M_i$$

$$R_l^i = R_l \frac{M}{M_i}$$

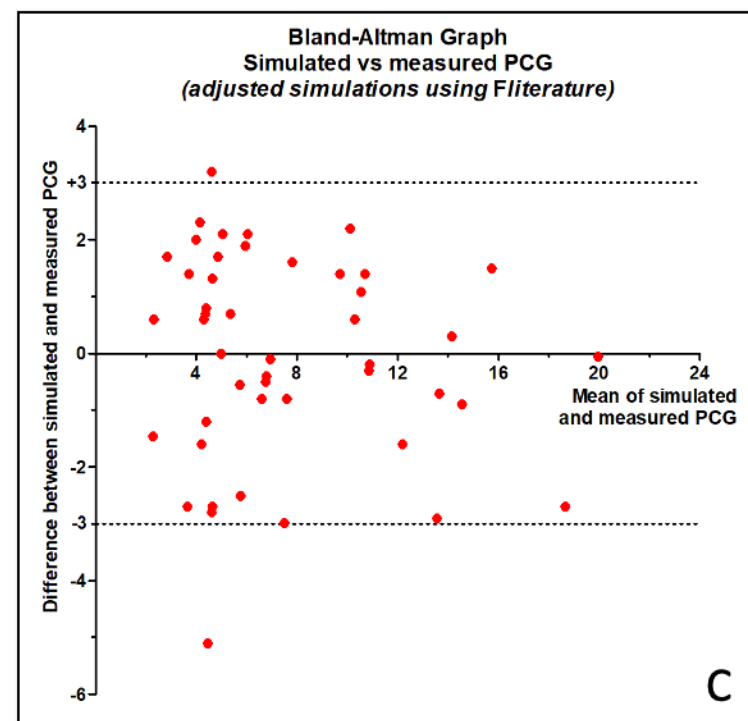
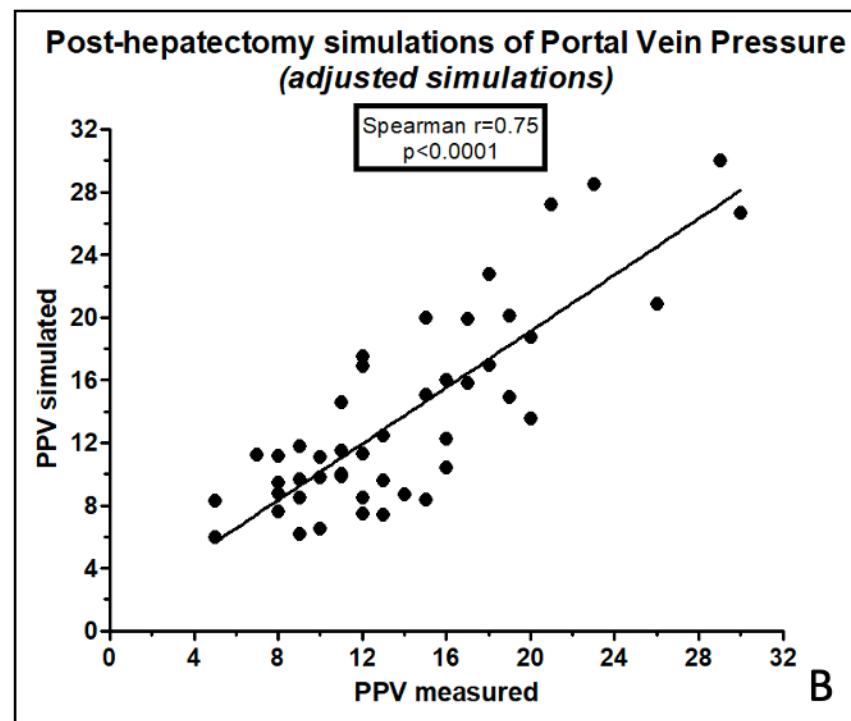
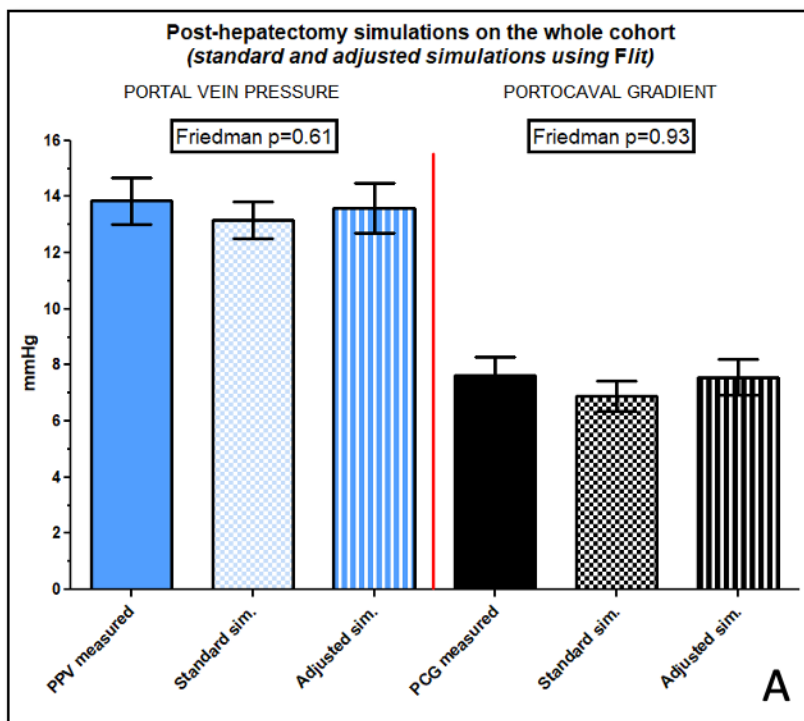




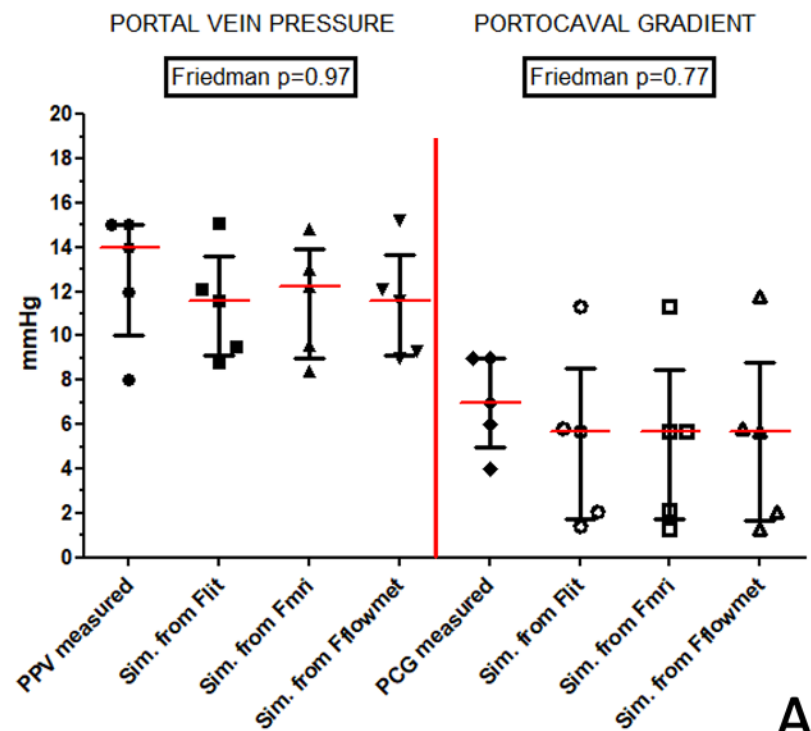
Start sim. with elastance values from calibration

Right extended hepatectomy numerically applied

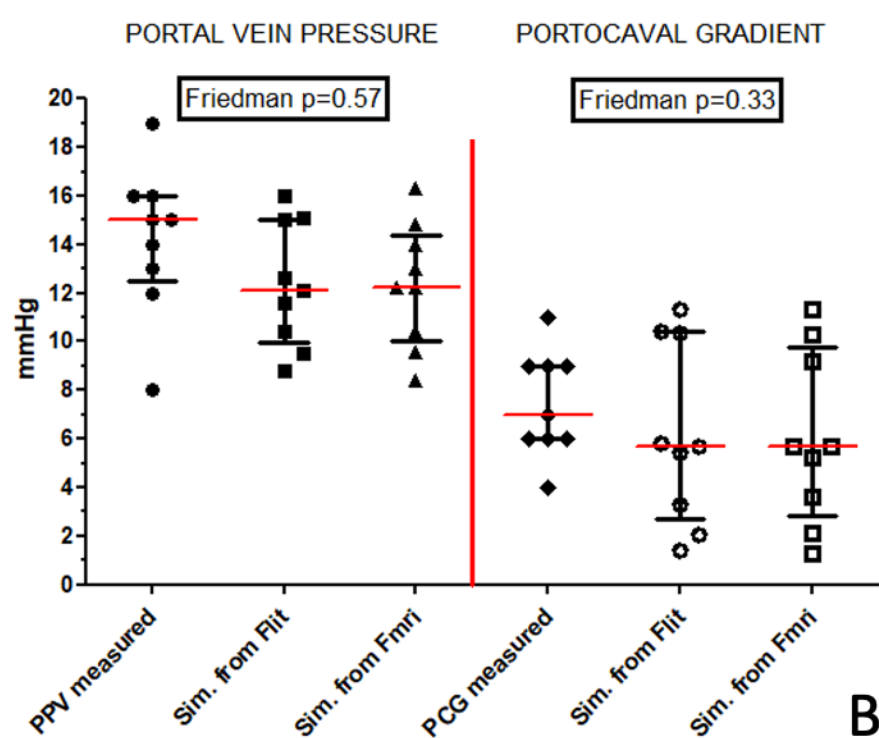
End of simulation = final result



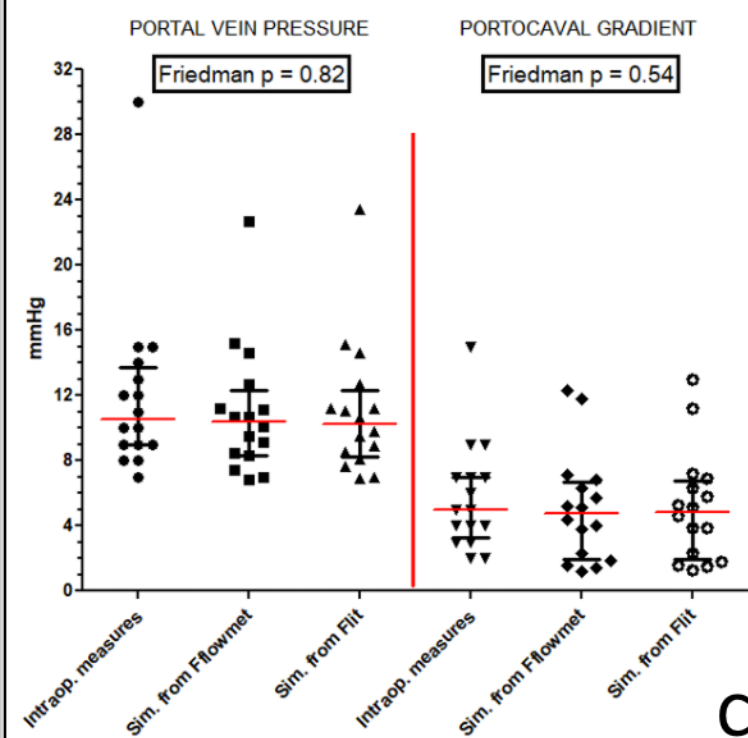
Post-hepatectomy simulations according to input data
Flit vs Fmri vs Fflowmet, n=5



Post-hepatectomy simulations according to input data
Flit vs Fmri, n=9



Post-hepatectomy simulations according to input data
Fflowmet vs Flit, n=16

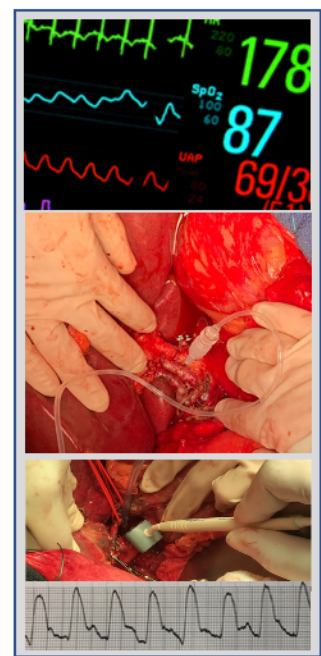
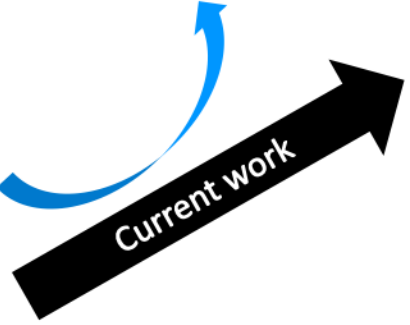


Patient requiring major hepatectomy

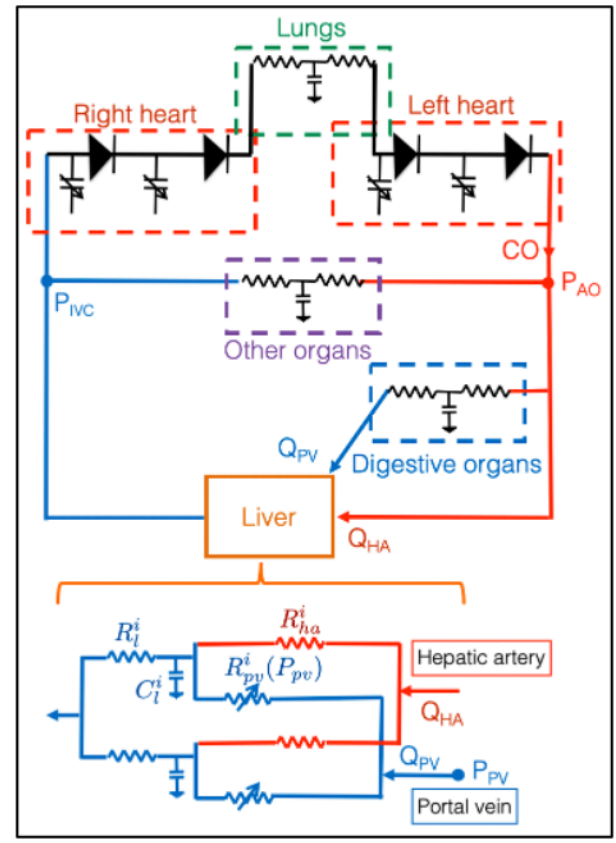
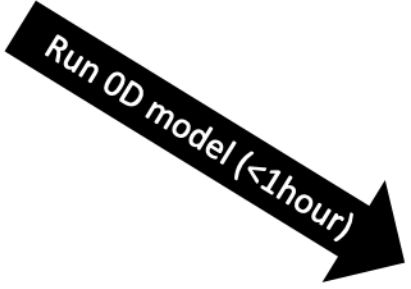


Preoperative concern about postoperative risk of portal hypertension
EASL risk assessment: intermediate or high risk of decompensation
Liver function: discrepancy between current tools available (i.e. normal indocyanine clearance but elevated liver stiffness)
High-risk patient (comorbidities)

Near future simulation performed 100% intraoperatively or even preoperatively

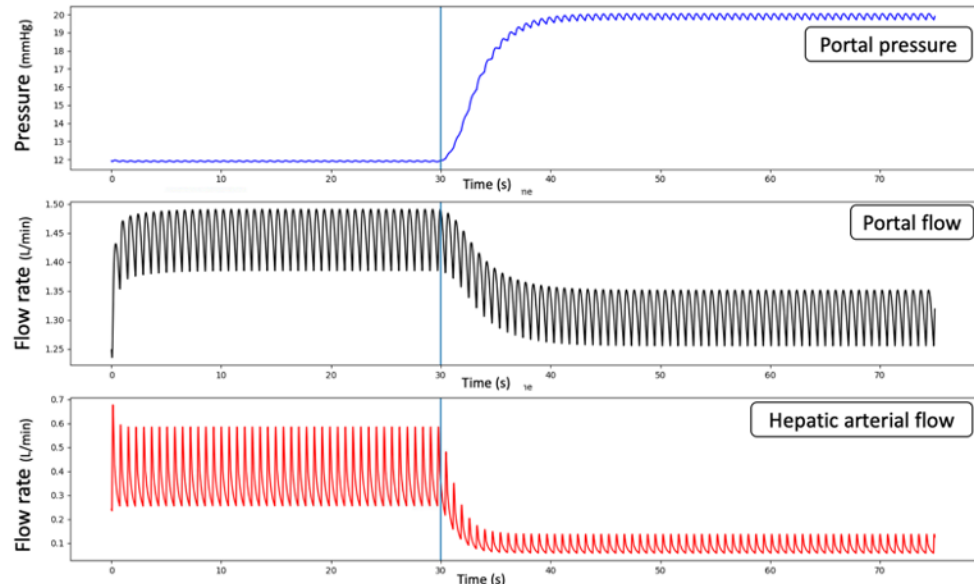


Intraoperative data collection + preoperative volumetric data



Validation of simulations on a cohort of 47 patients

Near future Improvement of the decision-making process
Surgery confirmed / cancelled / modified



Anticipation of postoperative portal/central pressures + flows