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Partial hepatectomy hemodynamics changes: Experimental data explained by closed-loop lumped modeling

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ABSTRACT

The liver function may be degraded after partial liver ablation surgery. Adverse liver hemodynamics have been shown to be associated to liver failure. The link between these hemodynamics changes and ablation size is however poorly understood. This article proposes to explain with a closed-loop lumped model the hemodynamics changes observed during twelve surgeries in pigs. The portal venous tree is modeled with a pressure-dependent variable resistor. The variables measured, before liver ablation, are used to tune the model parameters. Then, the liver partial ablation is simulated with the model and the simulated pressures and flows are compared with post-operative measurements. Fluid infusion and blood losses occur during the surgery. The closed-loop model presented accounts for these blood volume changes. Moreover, the impact of blood volume changes and the liver lobe mass estimations on the simulated variables is studied. The typical increase of portal pressure, increase of liver pressure loss, slight decrease of portal flow and major decrease in arterial flow are quantitatively captured by the model for a 75% hepatectomy. It appears that the 75% decrease in hepatic arterial flow can be explained by the resistance increase induced by the surgery, and that no hepatic arterial buffer response (HABR) mechanism is needed to account for this change. The different post-operative states, observed in experiments, are reproduced with the proposed model. Thus, an explanation for inter-subjects post-operative variability is proposed. The presented framework can easily be adapted to other species circulations and to different pathologies for clinical hepatic applications.

1. Introduction

Major liver resection (partial hepatectomy) is being performed to treat liver lesions or for adult-to-adult living donor liver transplantation. Due to liver regeneration, during the post-operative period of a few months, the patient re-gains a normal liver mass. However, sometimes liver function is poorly recovered and post-operative liver failure may occur.

Liver hemodynamics is modified by the surgery, which increases the resistance to flow of the organ. To understand it is not easy, partly because the liver is perfused by both arterial and venous blood. Although high portal pressure (Allard et al., 2013), high portal flow (Iida et al., 2007; Vasavada et al., 2014), and high hepatic venous pressure gradient (Sainz-Barriga et al., 2011) are associated with post-surgery liver failure, the link between resected volume and hemodynamics changes remains unclear. Since the liver receives around 25% of the cardiac output, hepatectomy may impact the whole blood circulation. Thus the present work aims to develop a mathematical model to explain the various hemodynamics changes observed in experimental surgeries of twelve pigs. Pig is considered a good animal model for liver.

The proposed model is constructed to satisfy the following requirements. First, the equations must be numerically fast to solve, to explore a diversity of hypotheses with all the pigs data. Second, the number of parameters must remain small enough so that calibration is tractable. Finally, the whole blood circulation must be taken into account, and hepatectomy dynamically modeled. Consequently, a closed-loop lumped model (also called 0D model), taking into account the liver and groups of organs, is presented.

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Different groups have worked on liver hemodynamics modeling, at different liver scales and for various applications. Liver lobule porous models have been proposed, to model glucose transport and metabolism (Ricken et al., 2015), to study the influence of a septum and tissue permeability (Debbaut et al., 2014b), including in cirrhosis (Peeters et al., 2015) or to simulate the impact of deformation on pressure–flow relation (Bonfiglio et al., 2010). At the organ scale, liver π lumped models for multiple vascular generations have been used to study the hypothermic machine perfusion (Van Der Plaats et al., 2004; Debbaut et al., 2014a). A lumped model of the splanchnic and liver circulation has been proposed to illustrate the link between hepatic venous pressure increase, vessel contractility and liver interstitial fluid (Chu and Reddy, 1992). Models have been developed on transport and diffusion of a compound in the liver, including whole-body pharmacokinetics models (Schwen et al., 2015) or to study tumor detection with Magnetic Resonance Images (Bezy-Wendling et al., 2007). Convection is based on resistive models of the different generations of arterial and venous trees. In Lukeš et al. (2014), the flow in liver arterial and venous trees is modeled for the first generations with Bernoulli equation, while a porous media models the flow in the smallest vessels. The trees geometry is based on CT-scans. Hepatic artery flow 3D CFD simulations for rigid and flexible walls have been performed in Childress and Kleinstreuer (2014) to study direct drug-targeting. Liver models have also been developed to study the impact of liver surgery. Flow behavior for different H-Graft diameters has been studied with a resistive model and compared to clinical observations in Rypins et al. (1987). A 3D CFD simulation has been performed in the portal vein before and after right lobe hepatectomy in Ho et al. (2012). The surgery was simulated by changing the geometry. Similarly, for a two-lobe liver lumped model, driving conditions were kept unchanged before and after hepatectomy. Various resection sizes and two different surgical techniques have been simulated using a resistance model, based on cast reconstruction, of rat liver vasculature (Debbaut et al., 2012). Most of these works thus do not consider the dynamics induced by the surgery or the interaction with the rest of the circulation.

The present work proposes to model liver partial ablation dynamically, with a closed-loop 0D model of the cardiovascular system and the liver. In Audebert et al. (2016), we have proposed a numerical scheme for 1D hemodynamics models, and explored in a generic 1D-0D pig model the hepatic artery waveforms, to understand the experimental changes observed during hepatectomy. Here, the impact of the surgery on the liver and on the whole body hemodynamics is identified. Moreover the consequences of blood loss and infusion are studied. The simulations, done for twelve pigs, are quantitatively compared to experimental measurements from 75% pig hepatectomy. Prediction of hemodynamics changes relies partly on liver lobe masses. Thus, several options are tested. The paper is organized in the following manner. Section 2 presents the available experimental measurements, the cardiovascular and liver models and their parametrization. Section 3 shows partial hepatectomy simulation results and comparison with measurements. Section 4 discusses model capabilities.

2. Methods

2.1. Liver surgery – experimental measurements

Hepatectomies are performed on several pigs to study the hemodynamics impacts. Approval of the committee of ethics of animal research, ministry of higher education and scientific research and ministry of agriculture and fishing was obtained. The pig liver is composed of five lobes, usually considered as three main lobes (Court et al., 2003): left lobe, median lobe (subdivided in left medial and right medial lobes) and right lobe (subdivided in right lateral and caudate lobes). The median and left lobes are resected. Since the median lobe is around twice the size of left and right lobes, around 75% hepatectomy is performed.

During surgery, several measurements are continuously recorded. Three pressures and three flows are the basis of parameter tuning and model validation. These measurements are averaged over 20 s during a stable state of the surgery. Pre-resection and post-resection (immediately after surgical clamping) states are considered. The carotid artery (CA), portal vein (PV) and central venous (CV) pressures are measured. The latter is a surrogate for the hepatic vein (v) pressure. The flows are recorded in the aorta above the celiac trunk (celiac aorta), the hepatic artery (HA) and the portal vein. Cardiac output (CO) is estimated assuming celiac aorta flow is around 60% of CO (Lantz et al., 1981) (assuming humans and pigs flow distributions are similar (Swindle et al., 2012)). Heart rate is computed from the CA pressure measurement.

Before and after the surgery a CT-scan is performed with a Siemens Somatom AS definition 128 machine. Image acquisitions are done before, 15, 35, 55 and 75 s after injection of 75 ml of iohexol 350 mg/ml (Omnipaque, GE Healthcare) with a rate of 5 ml per second. From the CT-scans liver volumes are estimated. After ablation, the removed liver is weighted; left and median lobe masses are then assessed. To estimate the liver masses, four different assumptions are made as described in Table 1, with varying predictive capabilities.

2.2. 0D closed-loop model

A 0D hemodynamics model of the entire cardiovascular system (Liang and Liu, 2005; Segers et al., 2003) is coupled to a new model of liver that is structured by lobes. The model aims to represent hepatectomy, i.e. the resection but also other related phenomena. Hence, only the involved organs are included, resulting in five blocks (Fig. 1).

Lungs ($i=L$), digestive organs ($i=DO$) and other organs ($i=OO$) are represented by three-element Windkessel models:

$$\begin{cases} C^i \dfrac{dP_p^i}{dt} &= Q_a^i - Q_v^i \\ R_p^i Q_a^i &= P_a^i - P_p^i \\ R_d^i Q_v^i &= P_p^i - P_v^i \end{cases} \tag{1}$$

where for block i Q_a^i and Q_v^i are arterial and venous flows, P_a^i, P_p^i and P_v^i are arterial, proximal and venous pressures, R_p^i, R_d^i and C^i are proximal and distal resistances and capacitance (Fig. 1).

Heart model: The heart model is based on Suga and Sagawa (1974), Pennati et al. (1997), Liang et al. (2009), and Blanco and Feijóo (2013). To obtain smooth, yet

Table 1
The different mass assumptions description of the total liver, left lobe, right lobe and median lobe. Their degree of certainty increases, and conversely their degree of predictability decreases from A1 to A4: preop calculation, peri-op calculation possible, post-op calculation.

Mass assumption	A1	A2	A3	A4
Total liver mass	estimate with pre-op CT-scan	estimate with pre-op CT-scan	sum of lobe masses	sum of lobe masses
Left lobe mass	1/3 planned resected mass (pre-op CT-scan)	weight after resection	weight after resection	weight after resection
Right lobe mass	planned remaining mass (pre-op CT-scan)	total mass minus left and median lobe masses	equal to left lobe mass	estimate with post-op CT-scan
Median lobe mass	2/3 planned resected mass (pre-op CT-scan)	weight after resection	weight after resection	weight after resection