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Mathematical modelling of the maternal cardiovascular system in the three stages of pregnancy

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ABSTRACT

In this study, a mathematical model of the female circulation during pregnancy is presented in order to investigate the hemodynamic response to the cardiovascular changes associated with each trimester of pregnancy. First, a preliminary lumped parameter model of the circulation of a non-pregnant female was developed, including the heart, the systemic circulation with a specific block for the uterine district and the pulmonary circulation. The model was first tested at rest; then heart rate and vascular resistances were individually varied to verify the correct response to parameter alterations characterising pregnancy. In order to simulate hemodynamics during pregnancy at each trimester, the main changes applied to the model consisted in reducing vascular resistances, and simultaneously increasing heart rate and ventricular wall volumes. Overall, reasonable agreement was found between model outputs and in vivo data, with the trends of the cardiac hemodynamic quantities suggesting correct response of the heart model throughout pregnancy. Results were reported for uterine hemodynamics, with flow tracings resembling typical Doppler velocity waveforms at each stage, including pulsatility indexes. Such a model may be used to explore the changes that happen during pregnancy in female with cardiovascular diseases.

1. Introduction

Pregnancy is associated with physiologically significant but reversible changes in maternal hemodynamics and cardiac function in response to both foetal and maternal demands. Namely, maternal circulation needs to accommodate for an increase in blood volume to provide the nutrients and oxygen supply necessary for an optimal growth of the foetus through the placental circulatory system. In most female these demands are met without compromising the mother but they may prove to be a threat in mother with cardiovascular diseases. Conversely, if maternal hemodynamics do not change, adverse effects on the uteroplacental circulation can lead to foetal compromise. Therefore the maternal cardiovascular system must achieve a balance between foetal needs and maternal tolerance. Changes happen throughout the pregnancy: they begin as early as 4–5 weeks of gestation to facilitate the development of an optimal environment for the foetus to thrive, and tend to plateau during the second and early third trimesters [1]. Maternal adaptations differ according to the involved tissue or organ, and, due to the dynamic nature of pregnancy, the timing and degree of adaptation may vary between subjects. However, it is possible to distinguish common hemodynamic phenomena characterising each trimester of physiological pregnancies. Major changes include increase in blood volume, cardiac output, heart rate and oxygen consumption, decrease in systemic vascular resistance and alteration in distribution of blood flow favouring pregnant uterus, breasts and kidneys.

Systemic vascular resistance (SVR) decreases in early pregnancy, reaching the minimum in the second trimester (−30% to −35% compared to values observed 3–6 months after delivery), and subsequently rising up to −20÷−27% [2,3]. This is due to systemic vasodilatation mediated by hormonal changes and the opening of the low resistance uteroplacental circulation. Plasma volume and red blood cell mass progressively increase until the beginning of the third trimester, when they start stabilising until delivery [4]. Nevertheless, the larger increase in plasma volume with respect to the haematocrit is responsible for an approximately 10% decrease in total blood viscosity, facilitating diffusion across the placenta and

Abbreviations: CO, cardiac output; CVP, central venous pressure; EDV, end-diastolic volume; ESV, end-systolic volume; HR, heart rate; LB, lower body; LPM, lumped parameter model; LV, left ventricle; MAP, mean aortic pressure; PI, pulsatility index; PVR, pulmonary vascular resistance; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; UB, upper body.

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avoiding thromboembolic risks for the mother. Besides haemodilution, peripheral arterial vasodilation is the main responsible for SVR reduction, which, in turn, activates compensatory homeostatic mechanisms allowing for the maintenance of arterial blood pressure. Namely, the heart rate (HR) increases from the first trimester, gradually reaching +20% in the third one. Similarly, the stroke volume (SV) rises in the first trimester to a maximum of around +30% in the second trimester without significant changes in the remaining weeks [5]. Consequently, the cardiac output (CO) begins to increase at few weeks of gestation, continuing steadily and plateauing (around +40%) at 32 weeks [5]. While the rise in CO is mainly caused by the increase in SV during the early stages, HR contributes the most in late pregnancy when SV is nearly constant.

The vascular district showing the most significant flow increase is the uterine circulation, peaking at 10–20% of CO in the third trimester compared to about 1% in non-pregnant female [1,6]. Renal perfusion rises by more than 30% by mid-pregnancy, remaining constant until delivery. In addition, pulmonary blood flow rises throughout pregnancy, as a consequence of considerable reduction (about −30% at the end of the first stage and plateauing in the rest of gestation) in pulmonary vascular resistance (PVR) [7,8].

The physiological changes in preload and afterload of the heart, related to blood volume increase and peripheral vasodilation, respectively, are accompanied by remodelling of all four cardiac chambers. Ventricles progressively increase in their diastolic dimension, while atria augment their average size, from the first trimester to the end of pregnancy. To sustain the increased workload, data suggest the two ventricles experience a rise in their wall thickness and mass with some debate on the entity [9–11]. Emerging MRI data indicate an increase reaching about +48% and +39% for the left ventricle (LV) and right ventricle (RV), respectively, at late pregnancy [12].

Thus far, plenty of clinical data has been collected for the analysis of such an intricate network of phenomena characterising pregnancy [2–5] and hypotheses on the physiological pathways have been advanced with no definitive answers. Most of the engineering studies has focused on the foetal circulation, especially on the placental gas exchange [13–17]. However, no mathematical models have been developed to examine the effects of pregnancy on the maternal cardiovascular system. The present study aims to develop a mathematical model of the pregnant female circulation, in order to investigate the hemodynamic response of the model to the cardiovascular changes associated with each trimester of pregnancy, and compare it with literature data. A deeper understanding of the hemodynamic changes in healthy pregnancies is mandatory to get to a better understanding, and therefore better management strategies, of pregnancies in mothers with pre-existing cardiovascular diseases or arisen complications.

2. Materials and methods

Mathematical modelling of the circulatory system during pregnancy was achieved through several consecutive steps. First, a lumped parameter model (LPM) of the circulation of a healthy non-pregnant female was developed, based on literature models of adult male circulations [18,19]. This was accomplished by adding a block representing the uterine circulation, and scaling the lumped parameters according to proper powers of the body weights ratio [20], assuming 75 kg body weight for the male model and 58 kg as representative of a 30-year-old female body weight. The LPM included the heart, the upper body (UB) and lower body (LB) systemic circulations, and the pulmonary circulation (Fig. 1, top). Systemic and pulmonary districts included great vessels and peripheral vasculatures, which were divided into arterial-arteriolar, capillary and venous portions. Three-element models comprising a compliance, a linear resistance and an inertance represented the

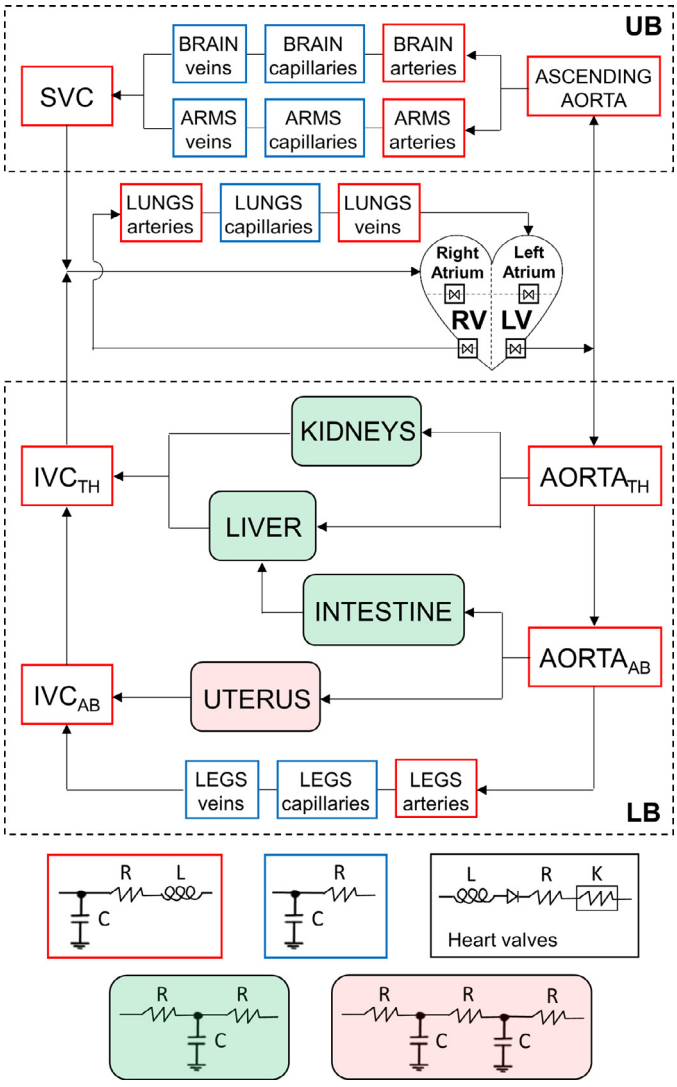

Fig. 1. Schematic of the model. Colour-coded lumped parameter blocks are reported at the bottom. IVC: inferior vena cava; TH: thoracic; AB: abdominal. For the other acronyms, please refer to the list of abbreviations.

great vessels and the arterial-arteriolar portions of peripheral vasculatures, whereas blocks including one or more compliances and resistances were used for the capillary and venous portions of peripheral vasculatures and for the abdominal organs circulations. Heart valves were described by three-element models comprising an inertance, a linear resistance and a non-linear resistance, combined with a diode assuring unidirectional flow (Fig. 1, bottom). The resting state was simulated at a HR of 75 beats per minute (bpm). Then, the model was tested at increasing HR and varying vascular resistances in order to verify the response to parameter changes involved in pregnancy. After these procedures, model parameters were modified according to the circulatory scenarios characterising the physiology of each gestational phase, and the resulting hemodynamic quantities were evaluated. The LPM was implemented in Matlab® R2014b (The MathWorks, Inc.) using, as integration algorithm, the Runge–Kutta–Fehlberg of the 4th/5th order with variable time step ranging from 1e−6 s to 1e−3 s. For each model configuration, 30 cardiac cycles were simulated to assure periodicity of the solution, but only the last 3 cycles were used for calculation of time averaged values. The entire simulations required less than 2 min on an Intel® Core™ i7 (2.93 GHz) personal computer.

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