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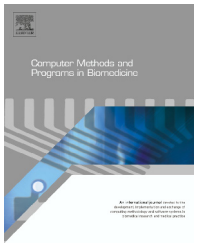

In silico study of the haemodynamic effects induced by mechanical ventilation and biventricular pacemaker

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ABSTRACT

In silico modeling of the cardiovascular system (CVS) can help both in understanding pharmacological or pathophysiological process and in providing information which could not be obtained by means of traditional clinical research methods due to practical or ethical reasons. In this work the numerical CVS was used to study the effect of interaction between mechanical ventilation and biventricular pacemaker by haemodynamic and energetic point of view. Starting from literature data on patients with intra and/or inter-ventricular activation time delay and treated using biventricular pacemaker, we used *in silico* simulator to analyse the effects induced by mechanical ventilatory assistance (MVA). After reproducing baseline and CRT conditions, the MVA was simulated changing the mean intrathoracic pressure value. Results show that simultaneous application of CRT and MVA yields a reduction of cardiac output, left ventricular end-diastolic and end-systolic volume when positive mean intrathoracic pressure is applied. In the same conditions, when MVA is applied, left ventricular ejection fraction, mean left (right) atrial and pulmonary arterial pressure increase.

1. Introduction

In this paper we present a study based on the interaction among the cardiovascular system, the biventricular pacemaker and the mechanical ventilatory assistance. Such a study follows a previous work of ours in which we studied the interaction among the cardiovascular system, the mechanical ventilatory assistance, and various devices for mechanical circulatory assistance [1,2].

Patients affected by symptomatic heart failure (HF) resulting from systolic dysfunction can be helped by cardiac resynchronization therapy (CRT) [3,4]. This therapy is realized using a biventricular pacemaker that produces a simultaneously pacing of both the left and right ventricles. Biventricular pacing resynchronizes the timing of global left ventricular depolarization and improves mechanical contractility and mitral regurgitation. CRT may assist weaning from circulatory and respiratory support in critically ill patients with left ventricular systolic dysfunction [5]. Mechanical ventilation (MV) is a form of artificial respiration which uses a mechanical ventilator in order to assist the breathing of patients. It is used when the lungs are not functioning properly. By means of MV and CRT it is possible to assist some critically ill patients affected by cardiorespiratory failure, induced by complex cardiac surgery or emergency cardiac intervention [6–8]. In literature there is a lack of "*in vivo*" data measured on patients receiving simultaneous CRT and MV. *In silico*

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modeling can help to study the effects produced by concomitant CRT [9] and MV on cardiac output, left/right atrial pressure, aortic/pulmonary pressure, left ventricular external work and pressure volume area. The modular numerical simulator of the cardiovascular system CARDIOSIM©, developed at the Institute of Clinical Physiology [10], has been already used to study the interactions among cardiovascular system, different mechanical assist devices (*e.g.* ventricular assist device, biventricular assist device and intraaortic balloon pump) and MV, analysing the effects induced on haemodynamic and energetic variables [11–14]. In the last years the software package CARDIOSIM© has been updated introducing a new module that allows to simulate the effects of a biventricular pacemaker [14,15]. Starting from literature data [16], the software simulator has allowed to reproduce the conditions of seven patients, affected by dilated cardiomyopathy undergoing CRT with biventricular pacemaker. Later on the effects of mechanical ventilation were simulated for each patient, by changing the mean value of intrathoracic pressure [11–14]. Simulated results show that simultaneous application of CRT and MV yields a reduction of cardiac output, left ventricular end-diastolic and end-systolic volume when positive mean intrathoracic pressure is applied. In the same conditions, left ventricular ejection fraction increases together mean left (right) atrial and pulmonary arterial pressure when artificial mechanical ventilation is applied. Small significant increases were observed in mean aortic, systolic and diastolic pressure when MV was applied. Finally, in patients affected by HF and treated with MV, the application of a biventricular pacemaker results in an increase both in left ventricular work efficiency and in left ventricular ejection fraction.

2. Materials and methods

2.1. The cardiovascular system model

CARDIOSIM©, the numerical simulator of the CVS, was used to study the interaction among the cardiovascular system, the CRT and mechanical ventilation. The "*in silico*" model is characterized by a modular structure (Fig. 1) that consists in seven modular sections: systemic arterial/venous, left/right heart, pulmonary arterial/venous and coronary circulation. Left/right heart is divided in atrium and ventricle: the mitral/tricuspid valve regulates the flow of blood from the left/right atrium to the left/right ventricle and it is modelled by a diode, with finite flow resistance Rli/Rri. Also aortic/pulmonary valve is modelled by a diode, with finite flow resistance Rlo/Rro (Fig. 1). Among the available modules, within CARDIOSIM©, we have chosen the module that allows to reproduce the ventricular interdependence in order to simulate the inter-ventricular and intra-ventricular dyssynchrony [15–17,19]. In this module the behaviour of both atria and ventricles are modelled by variable elastance model [19–22]. The mechanical properties of the four chambers are related to QT and PQ interval, QRS complex duration and inter-ventricular and/or intra-ventricular activation time delay [16,18]. The behaviour of the septum is reproduced into the chosen module by the time-varying elastance model [16,19,21,22]. In this way the cardiac pump function depends on ordered mechanical events that are orchestrated by electrical timing. This electromechanical coupling occurs within atria, between atria and ventricles, between ventricles, and within the left ventricle (LV). The model described allows to change the atrioventricular delay, the asynchrony between the right ventricle (RV) and left ventricle (LV) [inter-ventricular asynchrony (interVA)] and/or asynchrony within the LV [intra-ventricular asynchrony (intraVA)] [21,22]. In the software package, in order to simulate the systemic arterial circulation, we chose the module characterized by a multiple modified windkessel model [16,23]. In this module, each cell is implemented by a modified windkessel with a characteristic resistance Rcs (Rcs_1 and Rcs_2), an inertance Ls (Ls_1 and Ls_2), a compliance Cas (Cas_1 and Cas_2) [24]. The last element of the module is a variable peripheral resistance Ras (Fig. 1). Resistors represent the viscous property of blood flow, whereas inductances embody the inertia property of blood flow. Capacitors model the elastic property, or compliance of the vessels wall. The behaviour of the pulmonary arterial circulation was reproduced using a modified windkessel with a characteristic resistance Rcp, an inertance Lp, a compliance Cap and a variable peripheral resistance Rap [16]. The pulmonary (systemic) venous circulation was implemented using a compliance Cvp (Cvs) and a resistance Rvp (variable resistance Rvs) [23]. To simulate the behaviour of the coronary circulation, it was used the module in which, the endocardial, the middle and the epicardial layers of the left coronary bed, are modelled using RC elements [16]. The numerical simulator is able to reproduce the Starling's law of the heart [11,24–27]

2.2. The mechanical ventilation model

The influence of MV or ventilatory support of any type on CVS simulator may be modelled by changing the mean value of intrathoracic pressure (Fig. 1):

$$Pt = \frac{1}{Ti + Te} \cdot \left(\int_0^{T_i} p_i(t) \cdot dt + \int_{Ti}^{Ti+Te} p_e(t) \cdot dt \right) \quad (1)$$

$p_i(t)$ and $p_e(t)$ are instantaneous intrathoracic pressure changes during respectively inspiratory and expiratory periods. T_i (T_e) is inspiratory (expiratory) time. In this study we focused our attention on the mean intrathoracic pressure (*Pt*) values expressed by Eq. (1). In this way, we take into account both the actual amplitude of intrathoracic pressure and the time period, when this pressure is applied. As for each 5 cm H_2O increment in airway pressure, we may expect 1–2 mmHg increase of intrathoracic pressure [28,29]. By changing *Pt* during simulations in the range of −4 to +5 mmHg, it is possible to cover all the possible ventilatory modes, from spontaneous breathing, to artificial ventilation with high positive end expiratory pressure (PEEP). PEEP may be applied during both spontaneous ventilation and mechanical ventilation in order to improve patient's oxygenation. Fig. 1 shows in which sections and points the mean (constant) value of the intrathoracic pressure is added. In this paper [11], we presented the equations used to solve the network reported in Fig. 1, including the *Pt* parameter.