

# Computational Study on Cardiac-Coronary Interaction in Terms of Coronary Flow-Pressure Waveforms in Presence of Drugs: Comparison Between Simulated and *In Vivo* Data

C. De Lazzari, E. Del Prete, I. Genuini, F. Fedele

**Abstract**—Cardiovascular human simulator can be a useful tool in understanding complex physiopathological process in cardiocirculatory system. It can also be a useful tool in order to investigate the effects of different drugs on hemodynamic parameters. The aim of this work is to test the potentiality of our cardiovascular numerical simulator CARDIOSIM<sup>®</sup> in reproducing flow/pressure coronary waveforms in presence of two different drugs: Amlodipine (AMLO) and Adenosine (ADO). In particular a time-varying intramyocardial compression, assumed to be proportional to the left ventricular pressure, was related to the venous coronary compliances in order to study its effects on the coronary blood flow and the flow/pressure loop. Considering that coronary circulation dynamics is strongly interrelated with the mechanics of the left ventricular contraction, relaxation, and filling, the numerical model allowed to analyze the effects induced by the left ventricular pressure on the coronary flow.

**Keywords**—Cardiovascular system, Coronary blood flow, Hemodynamic, Numerical simulation.

## I. INTRODUCTION

CARDIOVASCULAR simulator (CVS) models can have different useful purposes. For example, the use of cardiovascular simulators allows a more precise assessment of the level of understanding of system behavior [1].

Paper presents an application of the software package CARDIOSIM<sup>®</sup> [2] developed by the Institute of Clinical Physiology (U.O.S. of Rome). This software implements a closed-loop of the cardiovascular circulation and of the coronary network. The tool has been developed to integrate the complete model using a sophisticated GUI (Graphical User Interface).

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In software, the dynamics of the coronary system is complicated by its own dependence on the mechanical properties of the coronary vessels. Several types of coronary system models were proposed in literature, focusing on different aspects of coronary system behavior. The lumped parameter models were based on well-controlled coronary pressure-flow measurements and simplified assumptions. In CARDIOSIM<sup>®</sup> the coronary circulation was modeled in order to reproduce the behaviour of epicardium, subendocardium and middle layer by using a lumped parameter model [3]. Each layer reflects the effects of ventricular pressure [4]. The aim of this work is to reproduce "*in vivo*" flow/pressure coronary waveforms, measured in baseline conditions and in presence of Amlodipine (AMLO) and Adenosine (ADO), using the CVS software package CARDIOSIM<sup>®</sup>. In this work, unlike a previous study [5], the attention was focused on the venous parameters of the coronary numerical model that influence the coronary blood flow. In particular it was previously observed how the ventricular pressure affecting the coronary venous circulation acts on the coronary flow/pressure waveforms (F/P loops) [6],[7]. In previous papers [5],[8] during the computer simulations we did not consider the possible effects induced by the time-varying intramyocardial compression on the coronary venous circulation.

The results show that: the CVS adequately provides appropriate magnitudes and trends that are in agreement with measured data; the venous parameters of the coronary model influenced the coronary blood flow and the F/P loops.

## II. METHODS

### A. Numerical model

CARDIOSIM<sup>®</sup> is a modular CVS that can be assembled in different ways depending on the type of the study to be performed. In the present work the CVS was assembled as in Fig.1. The closed-loop model of the cardiovascular system consists of seven different sections, including coronary circulation. All circulatory sections are implemented using lumped parameter models. Pulmonary arterial section is

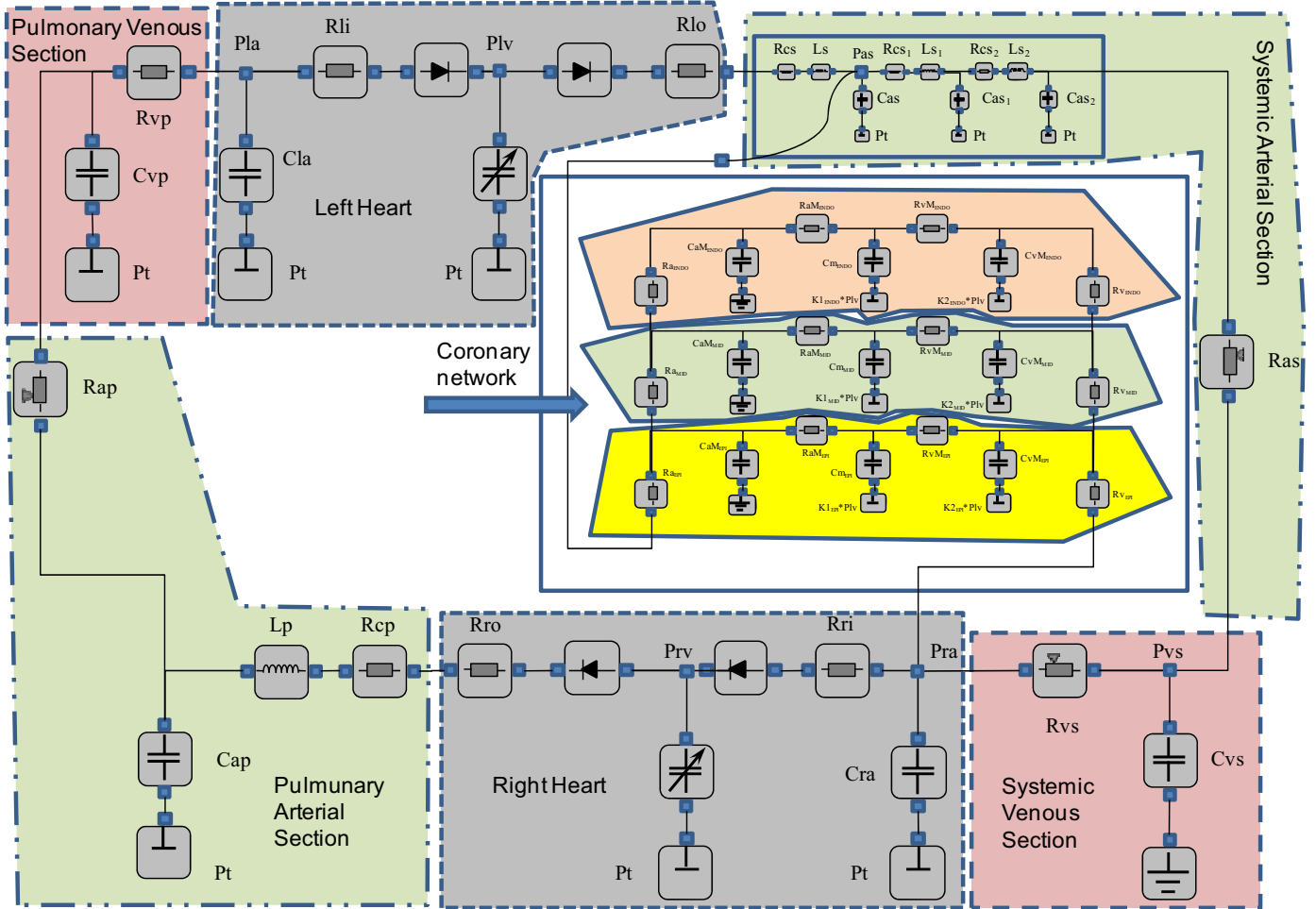


Fig. 1 Electric analogue of the numerical closed-loop cardiovascular system including coronary circulation. Rli (Rri) is the left (right) input valve resistance; Rlo (Rro) is the left (right) output valve resistance; Ras (Rap) is the variable systemic (pulmonary)arterial resistance; Rvs is the variable systemic venous resistance; Rcp is the pulmonary arterial characteristic resistance; Rvp is the pulmonary venous resistance; Cvs (Cvp) is the systemic (pulmonary) venous compliance; Cap (Lp) is the pulmonary arterial compliance (inertance), Cla (Cra) is the left (right) atrial compliance; Pas (Pap) is the systemic (pulmonary) arterial pressure; Plv (Prv) is the left (right) ventricular pressure; Pla (Pra) is the left (right) atrial pressure; Pvs is the systemic venous pressure; Pt is the mean intrathoracic pressure

modeled by windkessel model (Rcp, Cap, and Lp) with adjustable resistor (Rap). Pulmonary (systemic) venous section is modeled by the resistance Rvp (Rvs) and the compliance Cvp (Cvs). The value of Rvs can be automatically adjusted [9],[10]. Inside the CVS, the entire systemic arterial tree is modeled by three modified windkessel cells with a variable systemic arterial resistance (Ras) [2],[9]. Pas and the pressure on the compliance Cas1 (Cas2) represent respectively the root aortic pressure and the pressure in the thoracic tract (abdominal tract). The behavior of both ventricles is modeled using a variable elastance model [3],[11],[12]. In the CVS the behavior of both atria is modeled by a single compliance. Heart valves are modeled as a diode with a series resistance.

The coronary network based on the intramyocardial pump concept [14] is showed in Fig. 2 [3],[5],[8]. The paper [14] presented a simple network in which the venous compliance was connected to the ground. In previous papers [5],[8] we

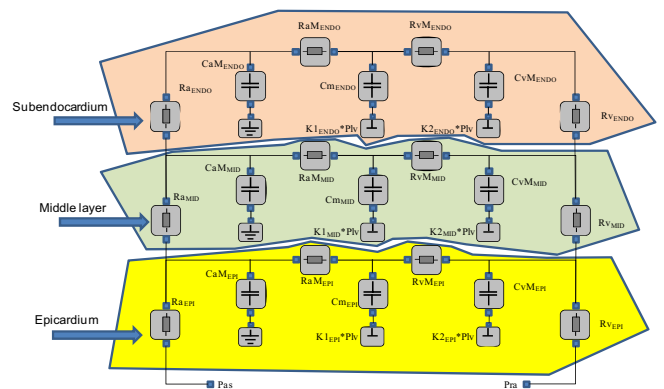


Fig. 2 Electric analogue of the coronary circulation. Three parallel vascular sections reproduce the subendocardial, the middle and the subepicardial layers of the left ventricular wall.  $Ra_i$  is arterial resistance;  $RaM_i$  ( $CaM_i$ ) is the arteriolar resistance (compliance);  $Cm_i$  is the capillary compliance;  $RvM_i$  ( $CvM_i$ ) is the venular resistance (compliance);  $Rv_i$  is the venous resistance. (i= EPI, MID, ENDO.)

presented a complex model of the coronary network derived from the model presented in [14]. In that model [14] venous compliance is connected to ground. In model presented in [3],[5],[8] a time-varying intramyocardial compression is applied through the compliance  $CvM_i$  ( $i=$  EPI, MID, ENDO). Intramyocardial compression is assumed to be proportional to  $Plv$  through the constants  $K2_i$  (Fig. 2). During the simulations carried out in [5],[8], the constants ( $K2_i$ ) have been set to zero. In this way the venous compliances ( $CvM_i$ ) were virtually linked to the ground. From the physiological point of view we have always thought that the venous compliances are affected by time-varying intramyocardial compression (different for each layer). The coronary network is connected (Figs. 1, 2) between the output of the left ventricle and the input of the right atrium. A time-varying intramyocardial pressure (different for each layer) is applied through the compliance  $Cm_i$  ( $i=$  EPI, MID, ENDO). In the coronary model, intramyocardial pressure is assumed to be proportional to  $Plv$  through the constants  $K1_i$ . By changing  $K1_i$  values it is possible to simulate the decrease of arterial inflow and the increase of venous outflow in systole.

### B. "In vivo" data

"In vivo" data presented in previous paper [5] had been used to reproduce "in vivo" and "in silico" F/P loops [15],[8].

Data were measured on different patients during the following conditions:

- baseline conditions;
- intracoronary ADO administration;
- 30 min after the end of AMLO infusion [5].

Electrocardiogram, coronary perfusion pressure, phasic and mean coronary flow velocities were continuously recorded over the entire duration of the study on a dedicated PC by signal acquisition software [5]. Coronary flow velocity ratio was calculated as the ratio of ADO (or AMLO) to baseline mean coronary flow velocity.

### C. "In vivo" vs "in silico" F/P loops

In order to get the measured F/P loops the CVS parameters in both baseline conditions and after AMLO and ADO administration were set as follows:

- the heart rate (HR), systolic time duration and mean AoP were set as "in vivo" values measured in each subject. The systolic (AoPS) and the diastolic (AoPD) systemic aortic pressure were reproduced (starting from "in vivo" values) automatically changing the peripheral resistance values [5],[8].
- The resistances  $Ra_{EPI}$ ,  $Ra_{MID}$ ,  $Ra_{ENDO}$  (representing the resistances of  $>100 \mu m$  vessels) and/or  $RaM_{EPI}$ ,  $RaM_{MID}$  and  $RaM_{ENDO}$  (representing the resistances of  $< 100 \mu m$  vessels), were adjusted in order to reproduce the measured coronary flow values and to obtain the best superimposition of the "in vivo" and "in silico" F/P loops. Extravascular resistance was not modified.
- The  $K1_i$  ( $i=$ EPI, MID, ENDO) constants were adjusted of a similar percentage at the three layers (thus maintaining the baseline transmural gradient).

- The  $K2_i$  constants, influencing the intramyocardial compression effects in the venous coronary vessels, were modified in order to evaluate the effects on the F/P loops.

## III. RESULTS

Fig. 3 shows the software simulator ability to reproduce the coronary blood flow-pressure loops. The figure reports measured and simulated loops, for one patient, in baseline conditions.

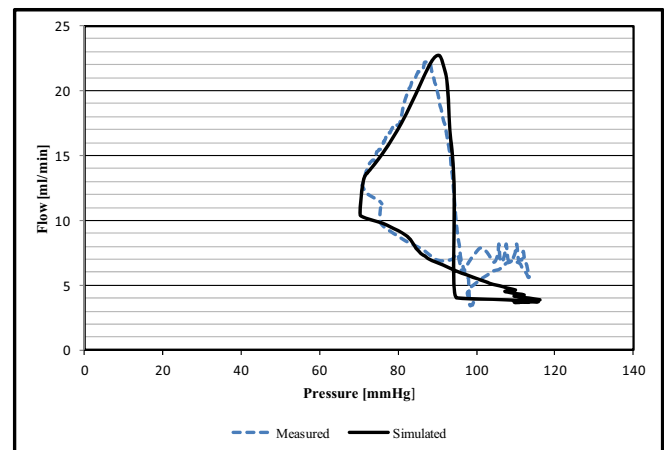


Fig. 3 "In vivo" (Measured – dashed line) and "in silico" (Simulated – continuous line) coronary blood flow/pressure loops. The loops reproduce baseline conditions

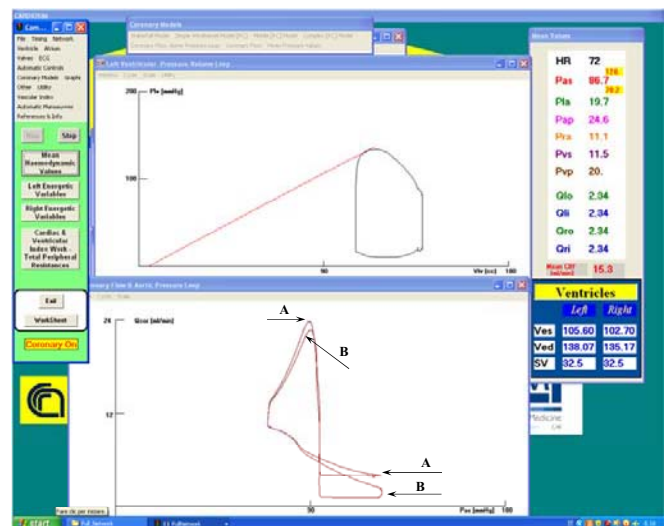


Fig. 4 CARDIOSIM<sup>®</sup> output shows (in the lower window) two different F/P loop obtained starting from baseline condition (loop A) and increasing intramyocardial compression (loop B) in venous coronary circulation. The upper window shows the left ventricular pressure/volume loop

Fig. 4 shows a screenshot of CARDIOSIM<sup>®</sup> software reproducing, for the same patient, the baseline F/P loop (A)

and the effects produced on the F/P loop increasing the  $K2_{EPI}$  and  $K2_{MID}$  values (B).  $K2_{ENDO}$  was not changed.

It is possible to observe the effects produced by intramyocardial compression on the venous coronary vessels: the F/P slope loop shifts down.

The behavior of F/P loops, for two different patients, were simulated, starting from "in vivo" measurements during baseline conditions, since 30 min after the end of AMLO

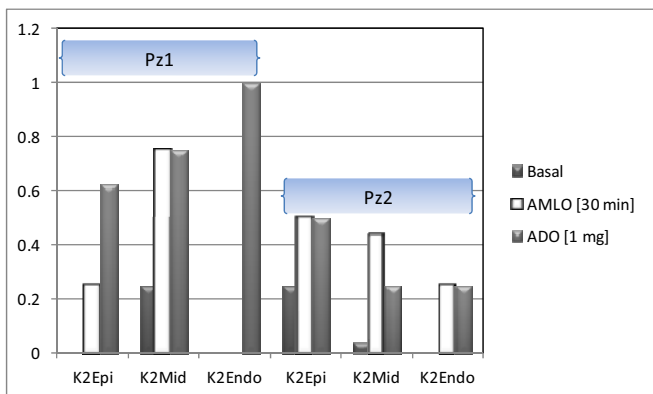


Fig. 5 For two patients are reported the variations of  $K2_i$  constants in basal conditions, since 30 min after the end of Amlodipine infusion and since intracoronary Adenosine

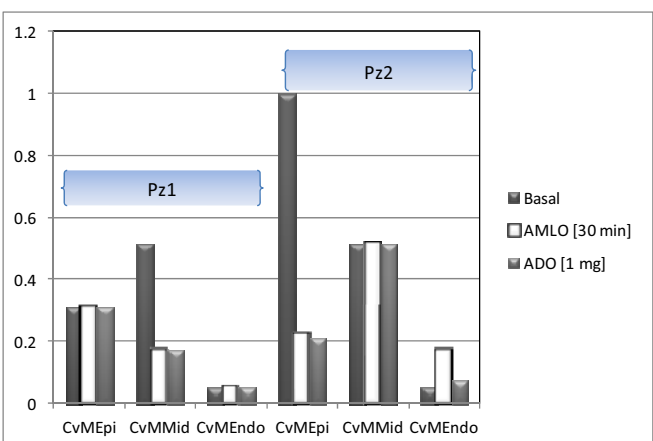


Fig. 6 For two patients are reported the variations of  $CvM_i$  compliances in basal conditions, since 30 min after the end of Amlodipine infusion and since intracoronary Adenosine administration. The data are normalized

infusion and since ADO intracoronary administration. Fig. 5 and 6 show the trend of the constants  $K2_i$  and the compliance  $CvM_i$  during the simulations.

In Pz1 the constant  $K2_{ENDO}$  assumes the same value in basal conditions and since 30 min after the end of AMLO infusion. The value of  $K2_{ENDO}$  was changed to reproduce the F/P loop since Adenosine intracoronary administration.

Fig. 7 and 8 compare the slope [5],[8],[14]-[16] and the  $R^2$  values for measured and simulated F/P loops. The slope of the F/P loop, in correspondence of the late diastolic period, has been considered an index of maximal coronary conductance,

capable of assessing the haemodynamic significance of coronary stenosis [15]. During the late diastolic period the coronary resistance becomes constant and flow linearly declines with the coronary driving pressure.

The simulated loops are obtained changing the  $K2_i$  constants and the  $CvM_i$  coronary venous compliances as described in Fig. 5 and 6.

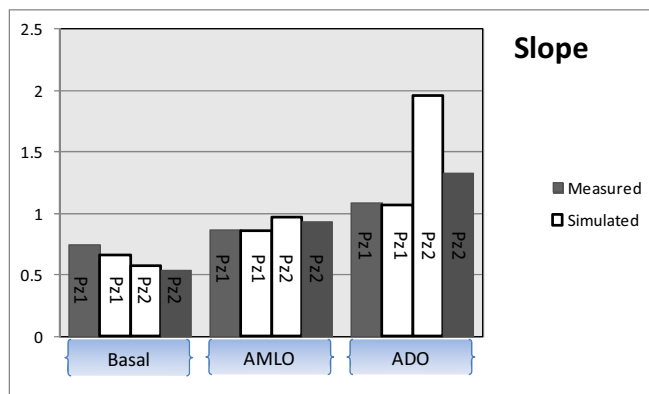


Fig. 7 Compared slope values for F/P loops in measured and simulated conditions. In figure are reported data relatives to two patients in baseline conditions, since Amlodipine infusion and adenosine administration

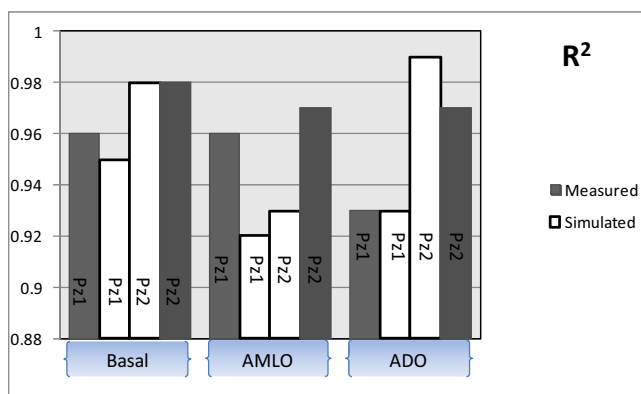


Fig. 8 Compared  $R^2$  values for F/P loops in measured and simulated conditions. In figure are reported data relatives to two patients in baseline conditions, since Amlodipine infusion and adenosine administration

#### IV. CONCLUSIONS

The CVS seem to be a valuable tool to reproduce the effects of some drugs (AMLO and ADO) on the coronary circulation. Despite all the limitations of a cardiovascular network using a lumped parameters model, we evaluated different effects at different levels of the coronary network.

The simulations performed, compared with the "in vivo" data, allow us to predict that there is an intramyocardial compressive effects in the venous coronary vessels that can be represented referring the venous compliances to Plv through the constants  $K2_i$

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