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Review

CARDIOSIM©: The First Italian Software Platform for Simulation of the Cardiovascular System and Mechanical Circulatory and Ventilatory Support

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Abstract: This review is devoted to present the history of CARDIOSIM© software simulator platform, which was developed in Italy to simulate the human cardiovascular and respiratory system. The first version of CARDIOSIM© was developed at the Institute of Biomedical Technologies of the National Research Council in Rome. The first platform version published in 1991 ran on PC with disk operating system (MS-DOS) and was developed using the Turbo Basic language. The last version runs on PC with Microsoft Windows 10 operating system; it is implemented in Visual Basic and C++ languages. The platform has a modular structure consisting of seven different general sections, which can be assembled to reproduce different pathophysiological conditions. The software simulator can reproduce the most important circulatory phenomena in terms of pressure and volume relationships. It represents the whole circulation using a lumped-parameter model and enables the simulation of different cardiovascular conditions according to Starling's law of the heart and a modified time-varying elastance model. Different mechanical ventilatory and circulatory devices have been implemented in the platform including thoracic artificial lung, ECMO, IABP, pulsatile and continuous right and left ventricular assist devices, biventricular pacemaker and biventricular assist devices. CARDIOSIM© is used in clinical and educational environment.

Keywords: CARDIOSIM©; numerical simulator; lumped parameter model; e-learning; mechanical circulatory support; ventilatory; cardiovascular system; heart failure; clinician

Materials and Methods

A narrative review was performed focusing on CARDIOSIM© applications in cardiovascular simulation. A systematic approach was used for the study identification and selection. The article search was performed in Medline (through PubMed), Cochrane Library, Embase, Web of Science and Clinical Trials databases. A substantial literature search was conducted to review the literature from 1991 to May 2022. Only articles published in English were considered. The MeSH keywords used were: "CAR-

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DIOSIM©", "cardiovascular system", "numerical simulation", "mechanical assist device", "mechanical ventilation", "heart failure", "ventricular assist device", "time-varying elastance "and "software simulator". The MeSH keywords were combined using the boolean operators AND and NOT. The search was extended through the reference lists of the recruited texts. Relevant secondary references were also captured.

Studies were considered eligible when investigating cardiovascular simulations using CARDIOSIM© software. Exclusion criteria were: studies written in other than English language; studies evaluating cardiovascular simulators different than CARDIOSIM© software; reviews, metanalyses and commentary were automatically excluded. Two reviewers (BDL and MC) independently selected the articles by reading the titles and abstracts. Disagreements were resolved by discussion between the two reviewers or through third party adjudication (CDL). After the selection, each title/abstract/full text was independently evaluated by each of the authors. A standardized approach was used to collect the data, which included the article's first author, publication year, simulated condition, implemented simulator module, results.

1. Historical Overview

The first Italian software platform for simulation of the cardiovascular system and mechanical circulatory and ventilatory support was developed at the Institute of Biomedical Technology (ITBM of Rome) of the National Research Council (CNR) in 1991. In the previous two years, researchers of this institute and those of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) laid the foundations to create a software platform that implemented the numerical models of the cardiovascular system based on a modular approach to allow continuous updates and further development. The researchers from ITBM implemented the first version of the platform named CARDIOSIM© using the language Turbo Basic (released by Borland Software Corporation in 1987). The cardiovascular software simulator ran on PC IBM compatible with disk operating system (MS-DOS) and with one Megabyte RAM.

The first version of the simulator was copyrighted in 1991 (copyright n. 320896, application date July, 22, 1991) [1]. Figure 1 shows a screenshot from the first version of CARDIOSIM© (left side) and an image of the Turbo Basic language development environment (right side).

Subsequently, a collaboration between researchers from the Polish Academy of Sciences and researchers from the Sapienza University of Rome led to the design and development of the second version of CARDIOSIM©. Visual Basic and C ++ languages were implemented in the new version, which ran on PCs with Windows operating system. This version was protected by a second copyright in 1999 (copyright n. 001252, application date May, 15, 1999) [2]. Over the years, new modules designed in collaboration with researchers from national and international institutions have been included within the platform. For example, one of the latest modules introduced within the platform can simulate the behavior of ECMO (Extra-Corporeal Membrane Oxygenation) support and the interaction with the cardiovascular network. This module was developed at the Cardiovascular Numerical/Hybrid Modelling Lab (Rome) of the Institute of Clinical Physiology (IFC-CNR) in collaboration with researchers from the Institute of Physiology of RWTH Aachen University (Germany); Department of Human Movement and Sport Sciences, "Foro Italico" 4th University of Rome; Department of Biomedical Engineering, University of Strathclyde (Glasgow) and Department of Clinical, Internal Anesthesiology and Cardiovascular Sciences, "Sapienza" University of Rome. The version 7.3.2 of the software platform is currently available.

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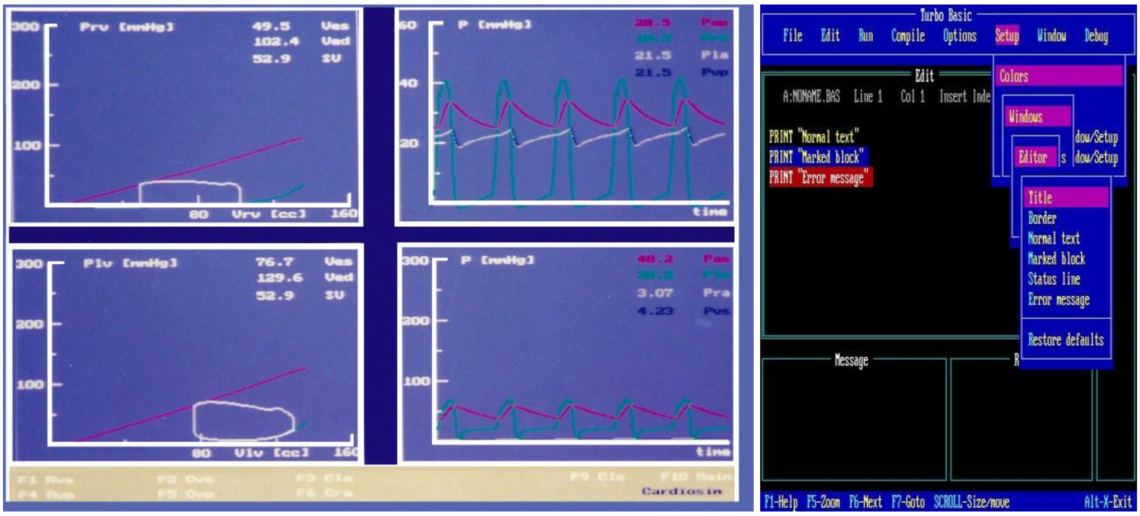

Figure 1 Output screen (left) produced using the first version of CARDIOSIM© implemented using the Turbo Basic language. Left lower (upper) window: left (right) ventricular pressure-volume loop with stroke volume (SV) end-systolic (Ves) and end-diastolic (Ved) volume values. Right lower side of the output screen: instantaneous waveforms and mean values (calculated during a cardiac cicle) of systemic arterial (Pas) and right (Pra) atrial pressures. Right upper side of the output screen: instantaneous waveforms and mean values (calculated during a cardiac cicle) of pulmonary arterial (Pap) and left (Pla) atrial pressures. Right side: screenshot of the Turbo Basic language development environment.

Over the years, the platform has been used as a research tool both in the bioengineering environment and in the clinical environment and has made it possible to carry out studies that have been published in high impact international journals.

In addition, CARDIOSIM© has been used for practice and learning needs of experienced professionals and those in training programs from different disciplines [3]. Simulation-based learning has become the way forward to develop the knowledge, skills and attitude of healthcare professionals whilst protecting patients from unnecessary risks. In medicine, simulation offers good scope for training of interdisciplinary medical teams. An increasing number of national and international healthcare institutions and medical schools has benefited from the use of CARDIOSIM© platform. Many more are considering its use. In Italy, for example, the software simulator has been used to supplement the syllabus of a high level master course for continuing medical and/or nursing education named "The virtual patient for cardiology training" [4] organized by "Sapienza" University. The course is run by a team of researchers from the IFC-CNR, the Institute of Physiology of RWTH Aachen University and the Department of Clinical, Internal Anesthesiology and Cardiovascular Sciences, "Sapienza" University. The software has also been used to complement the "Models of Biological Systems" course for bioengineering students. To date, CARDIOSIM© has been hired by six international institutions.

Starting from 2011, a web page providing information about the platform and its potential applications; the various modules featuring the software and the bibliography derived from the use of CARDIOSIM© software simulator was created by the Biomedical Sciences Department of the CNR (DSB-CNR) [5].

2. Numerical models of ventricle, atria and septum

CARDIOSIM© software simulator platform has a modular structure consisting of seven different general sections (Figure 2), which can be assembled to reproduce different pathophysiological conditions. The complexity of the assembled model depends on the context in which it must be used.

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The left and right ventricular filling and ejection phases are described separately in the first version of the numerical simulator [6, 7]. The contraction and ejection phases are implemented using a modified time-varying elastance model [8-10]. The left (right) ventricular loop, the End-Systolic Pressure-Volume Relationship (ESPVR) and the End-Diastolic Pressure-Volume Relationship (EDPVR) can be plotted on the pressure-

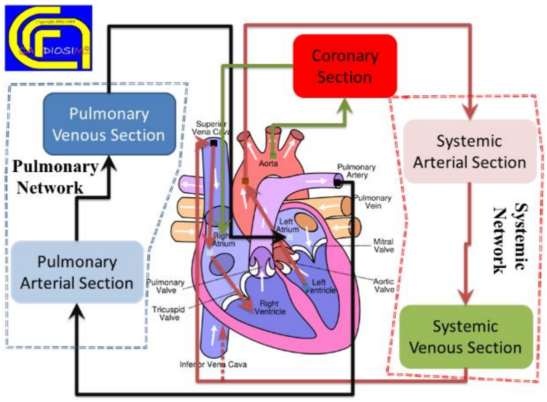

Figure 2 Seven sections implemented in CARDIOSIM©: left and right heart (atrium and ventricle) sections, systemic and pulmonary arterial compartments, systemic and pulmonary venous sections and finally the coronary circulation. (Reprinted with permission from Ref. [5],Copywright© 1991–2019 C. De Lazzari).

volume plane. This model allows the replication of Starling's law of the heart. The behavior of left (right) atrium is described as a linear capacity with a constant value of compliance and unstressed volume neglecting the contractile atrial activity (Table 1).

Table 1. Evolution over time of the Ventricle, Atria and Septum Models.

First Version	Second Version	Version 7.3.2
Left and right ventricular filling and ejection phases are described separately. The contraction and ejection phases are implemented using a modified time-varying elastance model [6, 7].	Left and right ventricular filling and ejection phases are described separately. The contraction and ejection phases are implemented using a modified time-varying elastance model.	Left and right ventricular filling and ejection phases are described separately. The contraction and ejection phases are implemented using a modified time-varying elastance model.
The behavior of left (right) atrium is described as a linear capacity with a constant value of compliance [6, 7].	The behavior of left (right) atrium is described as a linear capacity with a constant value of compliance.	The behavior of left (right) atrium is described as a linear capacity with a constant value of compliance.
--------	--------	Both ventricles are modelled according to the time-varying elastance model [8-12].
--------	--------	Both atria are modelled according to the time-varying elastance model [8-12].
--------	--------	The septum is modelled according to the time-varying elastance model [8-12].
		The time-varying interventricular and interatrial septum is modelled [12].

In version 7.3.2 of the platform, a time-varying elastance model describes the behaviour of both native ventricles and atria. The time- varying elastance theory is based on the instantaneous relationship between ventricular (atrial) pressure and volume.

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The mechanical properties of the ventricle are related to the ECG signal. The time-varying elastance (for each ventricle) is based on the electro-mechanical interaction by synchronizing the different phases of the left ventricle with the ECG signal. The left/right time-varying elastance is a function of the left/right ventricular systolic elastance, left/right ventricular diastolic elastance and finally, left/right ventricular activation function modelled according to ECG timing.

The left/right atrial time-varying elastance is modelled on the electro-mechanical interaction by synchronizing phases of the atrial cycle with ECG signal. The left/right atrial time-varying elastance is a function of left/right atrial systolic elastance, left/right atrial diastolic elastance and left/right atrial activation function.

The concept of atrial/ventricular interdependence considers the properties of one atrium/ventricle to be a function of the properties of the contra-lateral one. The time-varying interatrial/interventricular septum is described as a function of interatrial/interventricular septum diastolic elastance, interatrial/interventricular septum systolic elastance and interatrial/interventricular septum systolic elastance [8-12].

3. Numerical model of systemic and pulmonary circulation

Systemic and pulmonary circulations are modelled with zero-dimensional (0-D) or lumped-parameter models. 0-D models eliminate the variation in space and allow the description of pressure and flow as a function of time in a specific compartment of the circulatory system [13]. Zero-dimensional modelling is widely used particularly for the analysis of average values and the interaction between an assist device and the cardiovascular system [15-17]. Although 0-D modelling gives less detailed predictions of pressure and flow waveforms, it has shown great potential and flexibility for clinical application with particular reference to the pathophysiology of heart failure, guidance for patient selection and the hemodynamic impact of device intervention [16, 18]. A combined approach of lumped-parameter modelling, pressure-volume analysis and modified time-varying elastance has a significant potential for daily use within the constraints of a clinical setting.

Table 2 shows the evolution over time of numerical models of the systemic section using RLC elements.

4. Numerical model of coronary circulation

Coronary circulation models are implemented in CARDIOSIM© assuming that local blood flow in the myocardium is determined by the waterfall mechanism. In the first version of the numerical software simulator, the behavior of the coronary bed was modelled with resistor in series with a diode and a battery [6, 7]. The diode-battery combination represents the intramyocardial pressure. The battery voltage is assumed proportional to left ventricular pressure (LVP), with a proportionality constant that decreases from lumen to epicardium where values are considered negligible. This electrical circuit cannot describe all the oscillatory pressure-flow relations observed experimentally. For instance, systolic arterial back-flow that occurs for low inflow pressures cannot be represented using the waterfall model.

Table 3 shows the evolution over time of numerical models of the coronary circulation.

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Table 2. Evolution over time of Numerical Models of the Systemic Section.

First Version	Second Version	Version 7.3.2
Systemic arterial section modelled with modified windkessel (RLC) or Three Cell Model [6, 7].	Systemic arterial section modelled with modified windkessel (RLC) or Three Cell Model. (R is a resistance, L is an inertance and C is a compliance)	Systemic arterial section modelled with modified windkessel (RLC) or Three Cell Model.
Systemic venous section modelled with RC elements.	Systemic venous section modelled with RC elements.	Systemic venous section modelled with RC elements.
--------	Systemic arterial section modelled with: splanchnic and extra-splanchnic peripheral and venous circulation (both modelled with 2-WM elements) and the peripheral and venous circulation in active muscle compartment (modelled with 2-WM elements).	Systemic arterial section modelled with: splanchnic and extra-splanchnic peripheral and venous circulation (both modelled with 2-WM elements) and the peripheral and venous circulation in active muscle compartment (modelled with 2-WM elements).
---------	---------	Systemic circulation modelled with: ascending aorta, carotid arteries, descending aorta, peripheral arteries, systemic veins circulation and vena cava section. The compartments are modelled with RC and RLC elements.
---------	---------	Systemic network modelled with: ascending aorta, thoracic and abdominal aorta, superior (inferior) vena cava SVC (IVC) and lower and upper body [22]. The compartments are modelled with RC and RLC elements.

Table 3. Evolution over time of Numerical Models of the Coronary Section.

First Version	Second Version	Version 7.3.2
Waterfall model [6,7].	Waterfall model	Waterfall model
--------	RC model. The two resistances in series mimic the arteriolar, the capillary and venous resistance. The capacitance mimics the large intramyocardial compliance.	RC model. Two resistances in series mimic the arteriolar, the capillary and venous resistance. The capacitance mimics the large intramyocardial compliance.
--------	--------	The coronary bed is composed of two main arteries (modelled with RC elements) perfusing the left and right ventricles.
--------	--------	RC model with subendocardial, middle and subepicardial layers of the left ventricular wall [23].

5. Mechanical ventilatory assistance

Starting from the first version, CARDIOSIM© has allowed the simulation of assisted mechanical ventilation by varying the mean value of intrathoracic pressure.

Any mode of artificial ventilation of the lungs (except Continuous Airway Pressure) generates cycling changes of intrathoracic pressure. Different clinical studies have shown that the influence of mechanical ventilation support on hemodynamics in

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steady state can be reproduced by changing the mean value of intrathoracic pressure [19-21]. The mean thoracic pressure (Pt) can be defined using the equation:

$$P(t) = \frac{1}{T}\int_0^T p_t(t)dt$$

where $p_t(t)$ is the instantaneous thoracic pressure and T represents the ventilatory cycle time. Thus, incorporating the thoracic pressure in all the numerical models of the different cardiovascular sections (i.e. ventricles, atria, thoracic aorta, pulmonary arterial section etc.), it is possible to simulate the effects induced by mechanical ventilation simply by changing the level of Pt.

In addition, the software platform is suitable to carry out various studies focused on the interaction between the cardiovascular system, mechanical ventilatory support and mechanical circulatory assist devices (MCADs) [22-35].

6. Mechanical circulatory assist devices

Pulsatile and continuous flow mechanical circulatory assist devices can be modelled in the software platform. Left/right ventricular assist device (LVAD/RVAD) can be connected either "in series" or in parallel mode. When the LVAD (RVAD) is connected "in series" mode, the pump draws blood from the atria and ejects it into the aorta (pulmonary artery). When the LVAD (RVAD) is connected in parallel mode, the pump draws blood from the ventricle and ejects it into the aorta (pulmonary artery). If necessary, both LVAD and RVAD can be activated simultaneously to obtain a BVAD configuration.

A thoracic artificial lung (TAL) has also been implemented in CARDIOSIM© using RLC elements. The numerical model was developed in cooperation with researchers from Innsbruck Medical University [33]. The connection to the pulmonary circulation can be either in series, in parallel or in a hybrid mode. TAL input is connected to the right ventricular outflow tract in the hybrid mode. Outlet flow from the hybrid TAL splits between two grafts: the first outlet graft is connected to the pulmonary circulation through a resistance (R); the second one is linked to the left atrium through the RL element. These resistances allow blood flow splitting between the TAL and the pulmonary circulation. The hybrid mode enables sufficient levels of blood flow to both native lungs and TAL, while maintaining an intermediate load to the right ventricle [33].

The following Extra-Corporeal Membrane Oxygenation configurations were implemented in the software platform [22]:

Central Veno-Arterial ECMO ($VA_{RA\text{-}DA}$-ECMO): ECMO draws blood from the right atrium (RA) and ejects it into the descending aorta (DA).

Veno-Venous ECMO ($VV_{IVC\text{-}SVC}$-ECMO): ECMO draws blood from the inferior vena cava (IVC) and ejects it into the superior vena cava (SVC).

Veno-Arterial ECMO ($VA_{FV\text{-}TA}$-ECMO): ECMO draws blood from the femoral vein (FV) and ejects it into the thoracic aorta (TA).

Table 4 shows the different numerical models of MCADs implemented within the software platform during the various versions.

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Table 4. Evolution over time of Numerical Models of Mechanical Circulatory Assist Devices.

First Version	Second Version	Version 7.3.2
Numerical model of pneumatic left ventricular assist device (LVAD) [7].	Numerical model of pneumatic left ventricular assist device (LVAD).	Numerical model of pneumatic left ventricular assist device (LVAD).
--------	Numerical model of pneumatic right ventricular assist device (RVAD).	Numerical model of pneumatic right ventricular assist device (RVAD).
--------	Numerical model of pneumatic biventricular assist device (BVAD) [27].	Numerical model of pneumatic biventricular assist device (BVAD).
---------	Numerical model of pneumatic total artificial heart (TAH).	Numerical model of pneumatic total artificial heart (TAH).
---------	First numerical model of Intra-Aortic Balloon Pump (IABP) [28, 29].	First numerical model of Intra-Aortic Balloon Pump (IABP).
---------	---------	Numerical model of intraarterial axial flow blood pump (Hemopump® HP31) connected to the cardiovascular network as LVAD and/or RVAD [30, 31].
---------	---------	Numerical model of pulsatile LVAD blood flow (PUCA Pump) [32].
---------	---------	Numerical model of biventricular pacemaker (BiV) [11].
---------	---------	Numerical model of Thoracic Artificial Lung (TAL) [33].
---------	---------	Numerical model of centrifugal blood pump connected to the cardiovascular network as LVAD and/or RVAD [34].
---------	---------	Second numerical model of Intra-Aortic Balloon Pump (IABP) [35].
---------	---------	Numerical model of Impella (LVAD)*.
---------	---------	Numerical model of Extra-Corporeal Membrane Oxygenation [22].
---------	---------	Numerical model of ECMO joint with the first numerical model of Intra-Aortic Balloon Pump (IABP)*.
---------	---------	Numerical model of ECMO joint with Impella (LVAD)*.

*Presented at international conference but not published in peer-reviewed journal.

A graphical representation of the different modules implemented in the software platform can be observed in Figure 3.

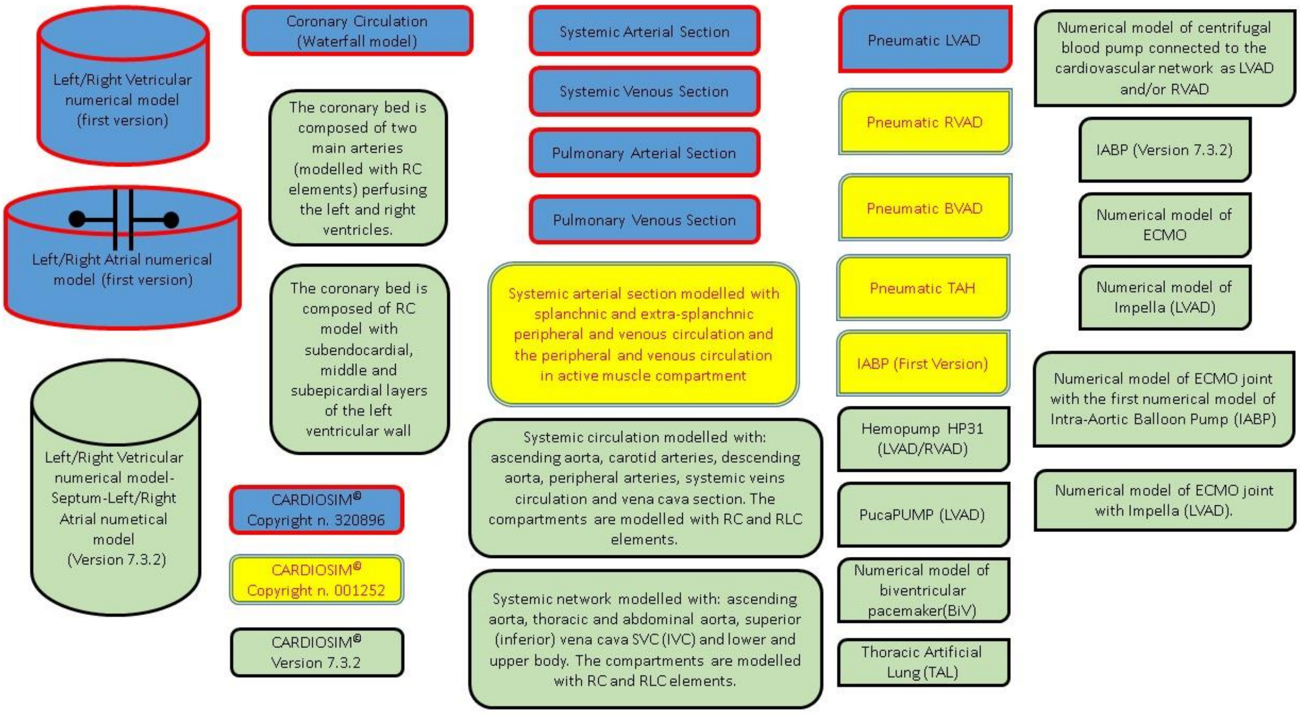

Figure 3 Graphical representation of all the modules implemented in CARDIOSIM© software simulator. Blue modules were implemented in the first version (copyright n. 320896). Blue and yellow modules were implemented in the second version (copyright n. 001252). All modules (blue, yellow and green) are implemented in the last version 7.3.2.

7. Clinical application of CARDIOSIM©

Since the first version of CARDIOSIM©, the numerical simulator has been used to carry out studies both on animal models [36] and in a clinical setting [11, 16, 21, 23, 37, 38]. Figure 4 shows a screen output from one of the latest version of the software platform obtained during the analysis of hemodynamic parameters measured in a clinical setting. Seven patients underwent electrocardiographic and echocardiographic evaluation before and after biventricular pacemaker (Biv) implantation, more specifically 24 hours, seven days and six months following CRT. The effects of Biv were evaluated in a clinical setting. The cardiovascular condition of a patient before (A) and six months after (B) biventricular pacemaker implantation is derived [11].

Figure 5 shows two tables with clinical and simulated hemodynamic parameters before cardiac resynchronization therapy (CRT), after seven days and six months thereafter [11].

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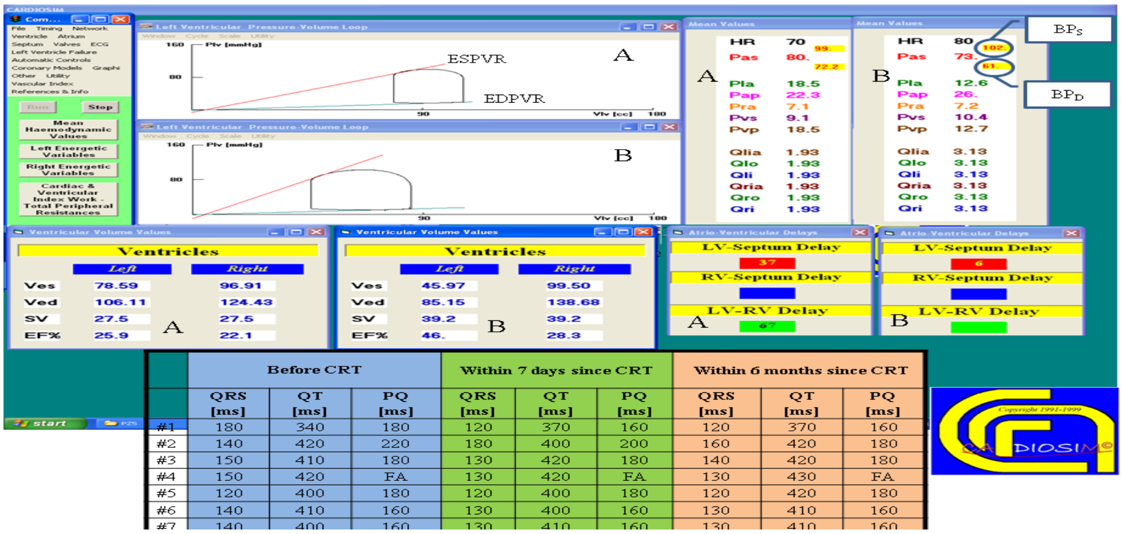

Figure 4 Screen output from CARDIOSIM©. For patient #5, the hemodynamic conditions before (A) and six months after (B) BiV implantation are available. The cardiac cycle of the left ventricle is defined in the pressure-volume plane. ESPVR (EDPVR) is the end systolic (end diastolic) pressure volume relationship. Pas is the mean (evaluated during the cardiac cycle) systolic arterial pressure, Pap is the mean pulmonary arterial pressure, Qlia (Qria) is the input flow of the left (right) atrium. Ves (Ved) represents the end systolic (diastolic) ventricular volume, SV is the stroke volume. "LV-Septum Delay" represents the intra-ventricular delay time and "LV-RV Delay" represents the inter-ventricular delay time. Vlv is the left ventricular volume. The Table shows the measured ECG parameters in seven patients before cardiac resynchronization therapy (CRT), after seven days and six months following CRT. The electrocardiographic parameters are: PQ, QRS and QT duration. (Reprinted with permission from Ref. [39],Copywright© 1991–2019 C. De Lazzari).

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Clinical Parameters

			Before CRT				Within 7 days since CRT				Within 6 months since CRT			
	sex	age	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]
#1	M	75	76	90	60	70	75	94	62	73	75	95	60	72
#2	M	82	75	110	60	77	75	100	60	73	75	110	70	83
#3	F	78	68	110	70	83	66	100	60	73	64	100	60	73
#4	F	70	80	130	85	100	75	120	80	93	70	110	70	83
#5	M	86	70	100	70	80	70	100	60	73	80	100	60	73
#6	M	67	64	110	80	90	68	123	75	91	70	120	75	90
#7	M	63	65	100	60	73	70	105	60	75	70	110	70	83

Simulated Parameters

	Before CRT				Within 7 days since CRT				Within 6 months since CRT			
	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]	HR [beats/min]	BP_S [mmHg]	BP_D [mmHg]	AoP [mmHg]
#1	76	90,7	58,3	70	75	92,8	62	73	75	91,4	60,9	72
#2	75	112	59	77	75	101,5	61,5	73	75	109,6	69,7	83
#3	68	110	71,7	83	66	101	61,8	73	64	101,4	61.6	73
#4	80	130,5	88	100	75	119,2	81,9	93	70	110	71,8	83
#5	70	99	72,2	80	70	101,9	61,7	73	80	102	61	73
#6	64	109,7	79,3	90	68	121,2	76,4	91	70	125,8	72,8	90
#7	65	100.4	62,8	73	70	102,2	64,4	75	70	111,3	72,3	83

Figure 5 Comparison beetwen clinical and simulated hemodynamic parameters (for seven different patients) before cardiac resynchronization therapy (CRT), after seven days and six months following CRT. (Reprinted with permission from Ref. [39],Copywright© 1991–2019 C. De Lazzari).

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Conflicts of Interest: The authors declare no conflict of interest.

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