A Not-Motorized Implantable Device for Partial Circulatory Support: A Proof of Concept Experiment

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A fully implantable circulatory assistance device without external connection and lifetime energy supply can eliminate a significant source of morbidity and mortality for patients. Here, we present and discuss concept and preliminary results of an original project for a not-motorized, fully implantable circulatory assistance device. The not-motorized implantable circulatory assistance device (NICA) has been tested into a cardiac simulator that was conceived according to the FDA and ISO standards. The instrumentation incorporated to the cardiac simulator includes probes for the aortic pressure (AoP) proximally to the device, a temperature control system, and one electromagnetic flowmeter to acquire the flow rate (AoF) proximally to the device. A control software allows to modulate the drive parameters such as velocity, acceleration, number of revolutions, the stroke volume, and the heart rate. Experiments have been performed with three different circuit resistances: 2100 dyn s/cm^5, 1400, and 700. The AoF increased in the assisted cycles: 71% at 2100 dyn s/cm^5, 67% at 1400 dyn s/cm^5, and 25% at 700 dyn s/cm^5. NICA performs a partial but significant support of AoF without energy supply. The improvement of AoF increases with the increasing of vascular resistances. The feedback received by this preliminary bench experiment acted as a preliminary proof of concept of this new device.
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Introduction

Implantable circulatory assistance devices have revolutionized patient care and outcomes of heart end stage failure and are approved as a bridge for transplantation, recovery, and also as a destination therapy. The number of left ventricle assistance devices implanted worldwide has increased dramatically and now exceeds the number of cardiac transplants. Many authors suggest nowadays that left ventricle assistance device implantation, not cardiac transplantation, is the main therapy for end-stage heart failure [1–8]. Despite advances in device technology, a sustained internal power source remains elusive. A fully implantable circulatory assistance device without external connection and lifetime energy supply can eliminate a significant source of morbidity and mortality for patients (cable infections and redo) and improve the independence and quality of life of patients [4,5]. While the complex problems with energy sources are the subject of considerable research and investment, very few alternative options for improving cardiac output without energy source have also been taken into account and results were not so significant to be diffuse in clinical practice, such as: dynamic aortic-myoplasty or cardiac-myoplasty [9,10]. Here, we present and discuss concept and preliminary results of an original project for a not-motorized, implantable circulatory assistance device (EPO Patent No. FR3042416 A1) [11].

Methods and Materials

Description of Device. The not-motorized implantable circulatory assistance device (NICA) is described hereinafter in detail. This device is connected in parallel to the aorta (Fig. 1(*a*)). This consists of a bypass duct formed from an upstream segment (1) and a downstream segment (2) with in the middle of the pump chamber (PC) (3). The upstream segment is connected from the upstream (Aam) aorta to the PC (3). PC is connected at the output to the downstream segment whose is connected to the aorta in downstream branch point (Aav). Segments are equipped with a one-way valve (4). PC is formed by an elastically expansible bag (EEB) (31), housed in a (32) rigid casing who protects the bag so that the volume of the bag may vary for receiving or discharging a certain volume of blood analog (BA). According to this first embodiment of the experimental prototype, the material of the bag is a low modulus experimental silicon elastomer (0.4 N/mm^2) so as to not oppose the arrival of the BA flow by the upstream segment (Fig. 2). The nowadays degree of development of the project does not allow to produce the definitive EEB with a high performance elastomer that is essentially a field of interest to share with factories that have a better background in this matter. In order to have a bag with at the same time a low module and good compliance, authors developed a composite bag for experimental use only (a second embodiment of prototype, Fig. 1(*b*)) that has been used in this series of experiments and that is compound by a low module silicon elastomer EEB and an additional elastic component (white arrow, Fig. 1(*b*)) that has been added externally to both side of the EEB. So, Authors improved performances of the EEB without changing this low module experimental silicon elastomer that is cheap and easy to produce in lab. The experiments in this paper described and discussed only the device without energy supply. Because surgical implant of a partial support device is not acceptable without the opportunity to shift to a total support in case of acute severe heart failure, authors also developed a third embodiment of the prototype (with external energy supply) only as a potential development of the device for severe acute heart failure. Figure 3 shows the third embodiment of the prototype with the double bag (red arrow) connected to an external pneumatic pump by a line (white arrow) that can be used together with the device when a total circulatory support is required, as in the case of a severe acute heart failure. It represents "de facto" as a bridge to partial recovery; thus, this additional support can be weaned. But it has not been used at all in these experiments.

Cardiac Simulator. The cardiac simulator was conceived according to the Food and Drug Administration (FDA) guidance [12] and the ISO 5840:2010 standard [13,14]. The instrumentation incorporated to the cardiac simulator (Fig. 4) includes one invasive fluid pressure transducers for the aortic pressure (AoP) proximally to the device, a temperature control system, and one electromagnetic flow-meter to acquire the flow rate (AoF) proximally to the device. A control software (SIMSCAPE DRIVELINE™) allows to modulate the drive parameters such as

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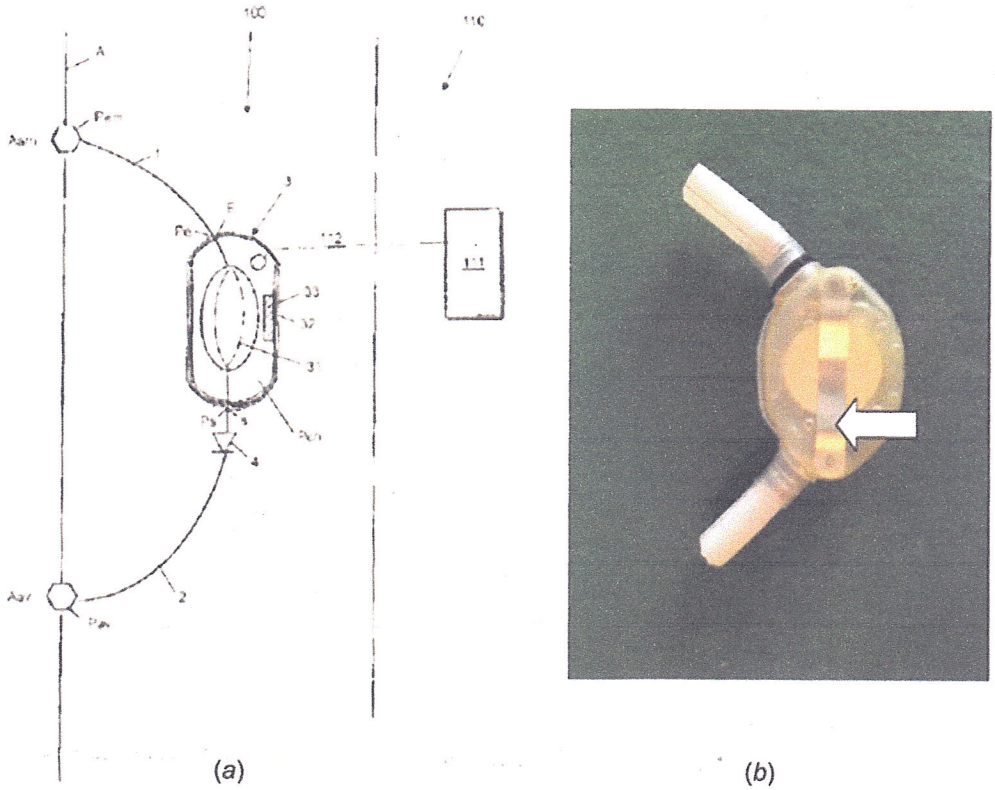


Fig. 1 Not-motorized implantable circulatory assistance device structure: (*a*) drawing from patent: an upstream segment (1) with an inlet for connection to an upstream bypass point (Aam) of the aorta (*a*), —a downstream segment (2) with an outlet for connection to a downstream branching point (Aav) of the aorta, —an elastically expandable chamber (3), connected between the upstream segment (1) and downstream segment (2) for receiving a volume of blood with each systole and discharging during the following diastole, —valves (4)—external drive for total circulatory support (111)—line connecting the device with the external (112)—all the elements (1, 2, 3, 4) being biocompatible. (*b*) Second embodiment of prototype: external elastic component (white arrow).

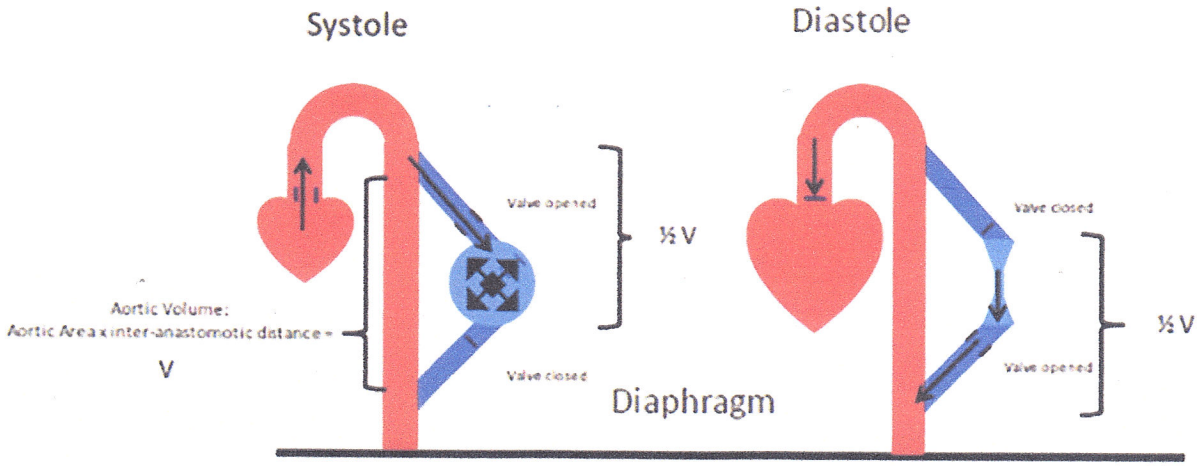


Fig. 2 Scheme of structure and functioning of the device

velocity, acceleration, number of revolutions, the stroke volume, the heart rate, and proper duration of systole (SysD) and diastole (DiaD). The circuit of cardiac simulator has been filled with a glycerol–water mixture with 47.6% by volume of glycerin solution in normal saline solution at 36 °C to have a dynamic viscosity of approximately 4 mPa s as BA fluid. The circuit of cardiac simulator has a baseline resistance of 2100 dyn s/cm^5 and two expansion balloons (EB1 and EB2 see Fig. 4) to decrease resistances, respectively, to 1400 dyn s/cm^5 and 700 dyn s/cm^5 so that to have three different pattern of circuit resistances according to three different degrees of heart failure: severe (baseline), moderate (EB1), and mild (EB1 + EB2). Authors have chosen this approach for its simplicity and effectiveness. It is a well-known inverse relationship between arterial resistances and arterial compliance in both health and disease states including left heart dysfunction [15]. The inverse relationship between arterial resistances and arterial

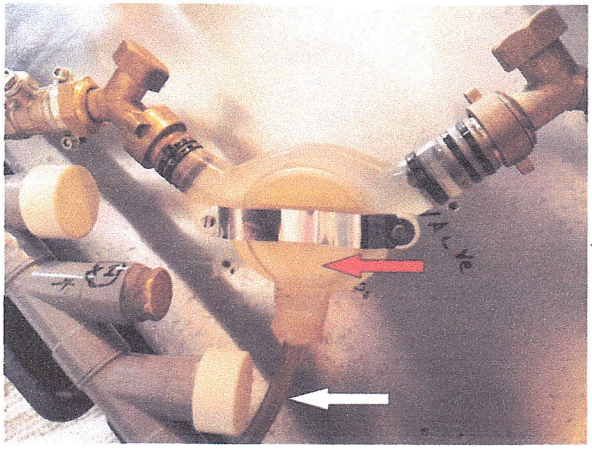


Fig. 3 The third embodiment of the prototype with the double bag (red arrow) connected to external pneumatic pump by a line (white arrow)

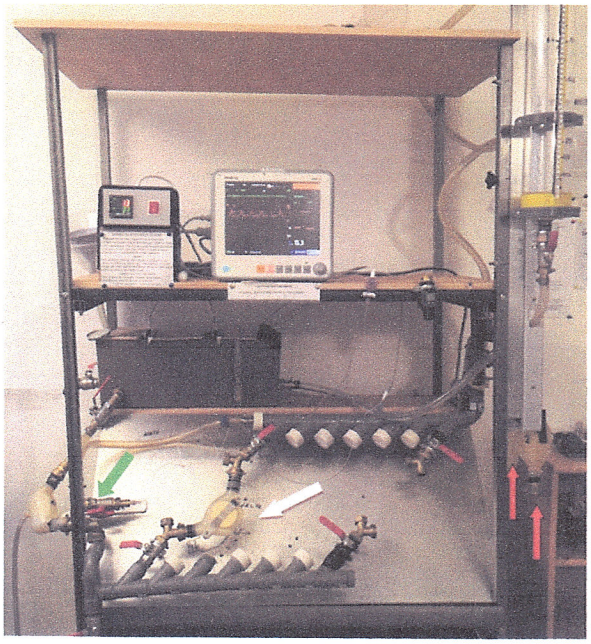


Fig. 4 Not-motorized implantable circulatory assistance device inserted into the cardiac simulator (white arrow); the expansion balloons 1 and 2 (red arrows); proximal position of electromagnetic flow meter and fluid pressure transducer (green arrow). The cardiac simulator was conceived according to the Food and Drug Administration (FDA) guidance and the ISO 5840:2010 standard [12–14].

compliance is usually described by a hyperbolic fit, meaning that a rise in resistances is followed by an inverse reduction in compliance and "vice versa."

Experiments. Experiments have been conducted during an event-free period of 12 consecutive hours divided in three following phases: (1) 3 h with not assisted cycles, (2) 6 h with assisted cycles, and (3) 3 h with not assisted cycles. Three experiments have been performed, one for each pattern of circuit resistances simulating severe, moderate, and mild heart failure: 2100 dyn s/cm^5, 1400, and 700, respectively. All experiments have been performed to stable heart rhythm of 75 bpm and to stable temperature of 36 °C.

Data Recording. An electromagnetic flowmeter Biotronex BL-610 (Biotronex Lab, Silver Spring, MD) and a fluid pressure transducer Baxter Edwards (Irvine, CA) Truwave are placed just after the correspondent aortic valve in the proximal portion of experimental aorta, in other words upstream from the bypass loop (green arrow in Fig. 4). Because of the continuity equation, this position is more significant than into the bypass loop; it represents all the real flow in the main circuit, without bias of the bypass loop (turbulences and/or accelerations).

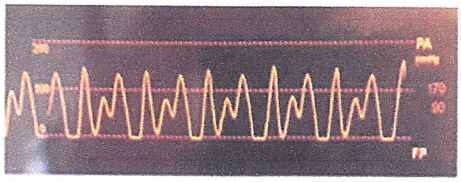
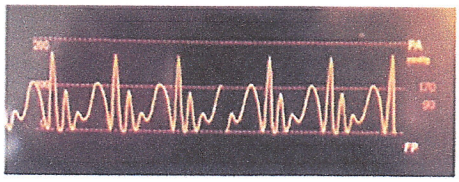
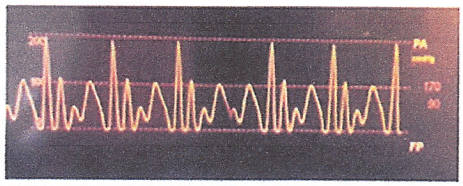
Results

All three experiments have been completely performed. Not statistically significant changes in hemodynamic parameters have been observed within each phase and between phases 1 and 3 of three experiments (as a proof of experimental stability and reproducibility). Comparisons has been performed between phases 1 and 2 (Tables 1 and 2). In the unassisted phases (phase 1), there is an increase in output of +150 ml/min when resistances decrease from 2100 dyn s/cm^5 to 1400 dyn·s/cm^5 (opening of EB1) and +900 ml/min at 700 dyn s/cm^5 (opening EB1 + EB2). The improvement of AoF in the assisted phases (phase 2) has been still more important than in phase 1 (+1250, 1400, 1600 ml/min, respectively, Tables 1 and 2) but the real AoF support that the device outputs have to be calculated by subtracting from flow during assistance of the flow improvement recorded in the unassisted phases: effective support +1250 ml/min (71%) at 2100 dyn s/cm^5, +1250 ml/min (67%) at 1400 dyn s/cm^5, and +700 ml/min (25%) at the 700 dyn s/cm^5. Hence, when the resistances (severe heart failure) are high, the % of increasing of circuit flow during the assistance is much more bigger than it is with low resistances (mild heart failure).

Comments

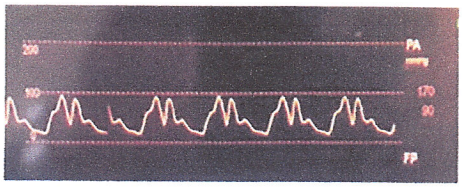
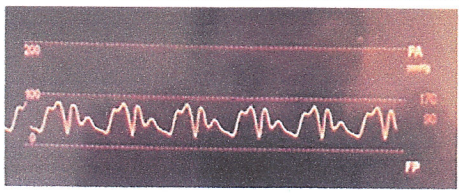
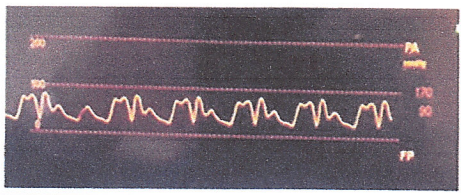
The present invention aims to develop a circulatory assist device that is very compact, simple, fully implantable, autonomous, and therefore nonmotorized. The device performs only partial cardiac support but has a significant interest because to the best of our knowledge a not-motorized fully implantable circulatory assistance did not exist at the time. NICA by mean of its EEB that is connected in parallel to the thoracic descendent aorta acts as a significant augmentation of compliance and consequently reduction of resistances in the proximal thoracic aorta according to the Poiseuille's law. When the pressure in the distal thoracic aorta is lower than the pressure in the filled EEB, the distal valve opens and the pressure in the distal aorta increases again. The proximal valve helps to use the device also in case of mild to moderate aortic regurgitation, because it prevents the equalization of pressure in the proximal aorta during the empeting of the EEB (Fig. 2). Proximal systolic pressure decreases for the increased aortic compliance by distention of the EEB and proximal diastolic pressure increases for lowering of drop of diastolic pressure (Tables 1 and 2). Tables show the pressure curve and the circuit flow for all three experiments at different circuit resistances settings with and without support device: so all data that described the hemodynamic behavior of device are presented. Authors observed a direct relationship between resistances and performances of device; in other words when the resistances are high the % of increase of circuit flow during the assistance is much more bigger than it is with low resistances. Such observations seem to fit with the concept of the device. These preliminary experiments give a proof of concept for this new device that has many potential advantages. The device is not subject to infective contamination of the connection cable to the external power source. The implantation of the device is done without cardiopulmonary bypass (CPB). The embolic risk of the device should be reduced by the shape of the EEB that has the inflow and the outflow directly in line with the main axis. The possible decision to use polypropylene or biologic semilunar valves will reduce anti-embolism

Table 1 Results not assisted

Resistances	Bpm	T	Not assisted	Sp	Dp	ml/min	Support ml/min	Support %
Baseline	75	36		150	0	1750	0	—
+EB1	75	36		190	0	1900	+150	8.5
+EB1+EB2	75	36		200	0	2800	+900	47

Note: baseline: without EB =2100 dyn s/cm^5, +EB1: with expansion balloon 1= 1400 dyn s/cm^5, +EB1+EB2: with expansion balloon 1+ 2= 700 dyn s/cm^5, bpm: beats per minute, *T*: temperature, Sp: systolic pressure, Dp: diastolic pressure.

Table 2 Results assisted

Resistances	Bpm	T	Assisted	Sp	Dp	ml/min	Support ml/min	Support %
Baseline	75	36		98	23	3000	+1250	71
+EB1	75	36		95	25	3300	+1250	67
+EB1+EB2	75	36		90	20	4400	+700	25

Note: baseline: without EB =2100 dyn s/cm^5, +EB1: with expansion balloon 1= 1400 dyn s/cm^5, +EB1+EB2: with expansion balloon 1+ 2= 700 dyn s/cm^5, bpm: beats per minute, *T*: temperature, Sp: systolic pressure, Dp: diastolic pressure.

prophylaxis to antiplatelet therapy alone. Authors argued about polypropylene or biologic valve, because the prototype that has been used presents mechanical valves. This choice is fixed by durability and stability needs required to the prototype. When the device will be totally developed, all component will be completely hematic compatible and at the same the valves also. In addition, since the conduit of outflow is anastomosed in the thoracic juxta-diaphragmatic aorta, the risk of stroke is minimized to the only possibility of peripheral embolism, usually more easily treatable. Because of its extra-cardiac position, the device can be combined with other procedures for heart failure as cardiac resynchronization therapy devices, Mitraclip and transcatheter aortic valve implantation. In the case of adequate recovery of cardiac function, the device is easily removable without the use of CPB. In particular, unlike devices with apical ventricular connection, the removal is devoid of embolic risk and does not involve losing the function of the apical myocardium. The removing of the device should be further facilitated by the interposition between the device and the lung of a sheet of Gorotex that prevents the formation of adhesions between the lung and the device.

In view of the advantages described above, the potential indications of this device are represented by partial circulatory assistance in subjects suffering from chronic left ventricular failure. Furthermore, the concept of the device opens a new point of view in favor of pulsatile devices that are placed in parallel to the descendent thoracic aorta. In conclusion, the absence of external power source cable and thus the reduction of the risk of infection, the minimally invasive implantation (the absence of CPB, the absence of surgical impact on the ventricle), the low risk of cerebral embolism, the low cost of the device, its implementation and its management, make this device attractive for medium-term partial circulatory assistance in elderly patients who do not tolerate more aggressive approaches and who represent the most representative age group. The feedback received by this preliminary bench experimentation acted as a preliminary proof of concept of this new device that after further improvement in materials and setting will be ready for in vivo animal model experimentations.

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