We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

7,000
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

2

"Flow and Rate": Concept and Clinical Applications of a New Hemodynamic Theory

Sayed Nour
Therapeutic Innovations University of Paris XI,
France

". . . From the heart arise the vessels which go to the whole body . . . if the physician lay the hands or his fingers to the head, to the back of the head, to the hands, to the place of the stomach, to the arms or to the feet, then he examines the heart, because all his limbs possess its vessels, that is: the heart speaks out of the vessels of every limb . . . If the heart trembles, has little power and sinks, the disease is advancing."
The Papyrus Ebers, c. 1534 BC (Stern,1875).

1. Introduction

Cardiovascular disease (CVD) is the first cause of mortality in developed countries, responsible for one death every 34 seconds and the estimated global annual cost is $ 403.1 billion according to recent statistics from the United States (Thom et al., 2006).

Furthermore, congestive heart failure (CHF) has been defined by the NIH, as the new epidemic in the USA, affecting more than 5 million new cases per year with a 5-year survival rate of less than 50% (Zickmund, et al. 2006).

Current therapies for CHF patients include medicinal provision of drugs such as cardiac glycosides, diuretics, AC inhibitors, anticoagulant (Couzens, 2009). However, medicinal therapies are usually insufficient necessitating complementary supports e.g., mechanically with cardiac assist devices (CAD) and/ or biologically with surgical procedures up till orthotopic heart transplants as an ultimate procedure.

Meanwhile, orthotopic heart transplant is still restricted due to the shortage of donors, plus operative morbidity and mortality (Schmauss & Weis, 2008).

Mechanical cardiac assist device (CAD) is usually used temporarily until the patient's hemodynamics improve, may offer an intermediate solution for the lake of donors as a bridge to a heart transplant (Park, et al., 2003), but in the heavy price of several disadvantages.

Permanent replacement of the heart with an artificial heart option is still a work in progress (Carpentier, 2011), with current technology having a short life expectancy. Thus, the artificial heart is primarily used as a bridge to transplant for patients wit biventricular failure. Furthermore the large size of an artificial heart limits its applications in specific categories, regarding body surface area (1.9±0.22 m²), sex (95% men) and age (practically 0% children) (Roussel, et al., 2009).

Unfortunately, those aforementioned therapies still represent cost-effectiveness dilemma for health care systems in modern societies due to high cost, morbidity and mortality.

As a potential solution we are proposing a new therapeutic approach based on a fundamental revision of the entire circulatory system in correspondence to the physiopathology and physics laws applications with new generation of CAD.

The aim is directed to support and restore organ function, rather than to be replaced. Thus, it seeks to remedy the drawbacks of the state of present therapies and includes the innovation of new devices for providing cardiopulmonary and circulatory assistance.

This proposed therapy is based on a main concept (Think endothelial) and on a new hemodynamic theory entitled (Flow and Rate) that seeks to improve hemodynamics, organs microcirculations, restore and preserve the endothelial function by maintaining shear stress-mediated endothelial function with circulatory dynamics forces e.g., pressurized flow and shear rate (Nour, 2006).

1.1 Concept

Conceptually, the cardiovascular system is a closed pressurized hydraulic circuit (Figure 1), which is lined internally with endothelial cells (Samet & Lelkes, 1999; Furchgott, 1981).

Endothelium is constantly exposed to blood components and pulse pressure known as the tangential forces of shear stress (Hoeks et al., 1995).
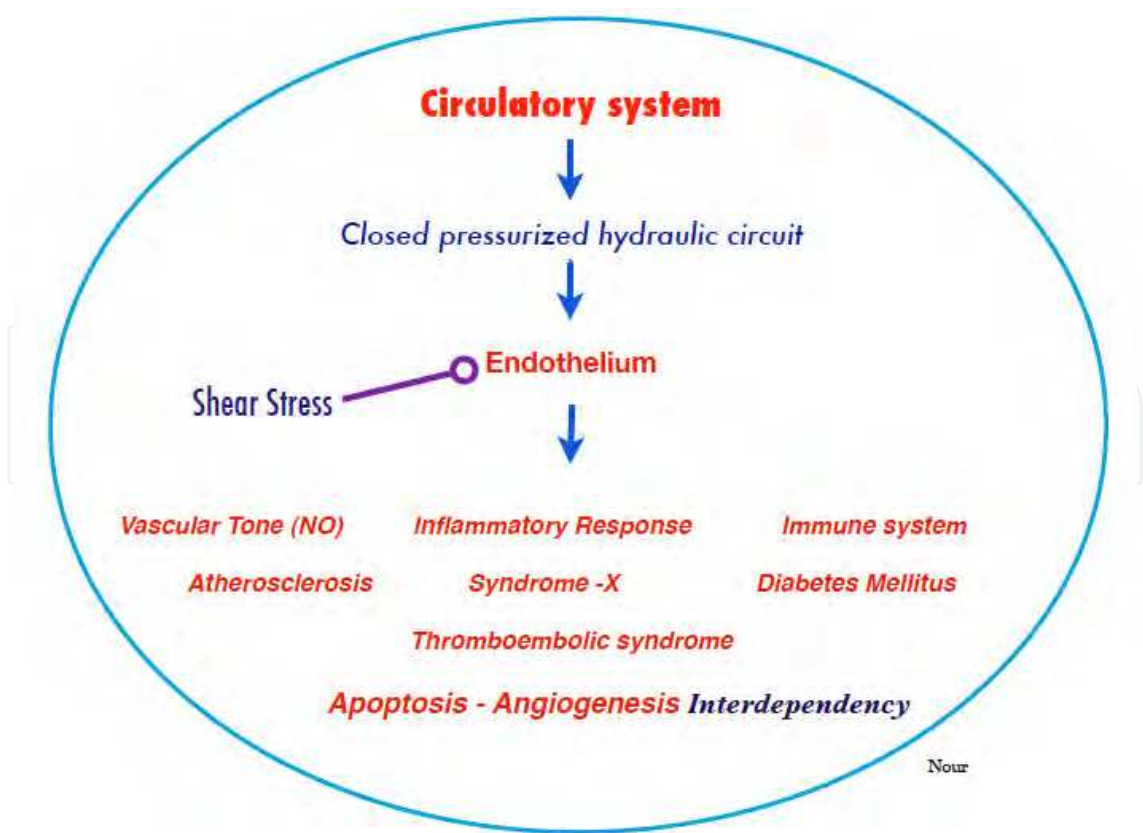

Fig. 1. Circulatory system's shear stress-mediated endothelial function

Shear stress controls and maintains endothelial function, which comprises the vascular tone by the synthesis of nitric oxide (NOS), blood coagulation, the inflammatory response, atherosclerosis, angiogenesis and apoptosis (Petrovic, et al., 2000; Limaye & Vadas, 2007; Lam et al., 2006).

In other terms, shear stress-mediated endothelial function controls embryogenesis, morphogenesis, organogenesis and maintenance of a healthy organism (Adamo, 2009).

In general, fluid movement in hydraulic circuits, which means momentum transfers with frictional losses, depends on driving forces, resistances, viscosity and conduits geometries (Kessler & Greenkorn, 1999).

The heart and peristaltic arteries represent the main circulatory driving forces that usually affect the left heart side.

Otherwise, accessory forces such as the respiratory pump, muscle pump, gravity, atmospheric pressure, oncotic pressure, skin baroreceptors, venous valves, pericardium, etc., are necessary to move up the steady blood flow at the right heart side (Nour, et al., 2009).

Endothelium controls vasoconstriction (e.g. catecholamine), vasodilatation with mediators like nitric oxide (NO) and vascular conditions with several processes like atherosclerosis and angiogenesis-apoptosis interdependency. This simply means that vascular resistances depend on vascular tone and vessels elasticity that are controlled mainly by shear stress-mediated endothelial function.

2. Fluid mechanics and cardiovascular pathophysiology

The clinical application of endothelial shear stress (ESS) should be realized in correspondence to cardiovascular biophysics, pathophysiological conditions as well as laws of fluid mechanics. This means a CAD should adapt the different criteria of each circuit of the right and left heart side (Figure 2), as follows:

1. The left heart circuit: it is characterized anatomically, by two high remodeling zones that represent the main circulatory pumps: the left ventricle (LV) and the aorta with the Valsalva as been shown on (Table1) and (Figure 2). Flow dynamics inside the Valsalva sinuses determines coronary ostia morphogenesis (Hutchins, 1988) and may contribute to a severe hemodynamic deterioration (Palmieri, 2001). So a shear stress-mediated endothelial function must be induced at the left heart side according to the Newton's principles by maintaining a physiological arterial pulse pressure (Feynman, et al., 2005). The LV almost, triples its myocardial mass during the first postnatal month with an important arterial angiogenesis. (Kozák-Bárány, 2001). According to Laplace's law, this LV remodeling could be enhanced by the posterior location of the LV (behind the RV), less limited by the pericardium and sternum, which increases the gravity effect, particularly in the neonatal supine position. The LV remodeling will be continued and maintained later on, influenced by ESS, the spherical shape of the LV (Yacoub, 1995), the elevated vascular resistances and the gravity effect at the aortic root. Disturbed flow dynamics at the left heart side induce atherosclerotic lesion (Samady, et al. 2011)), which is uncommon at the right heart side pulmonary arterial walls, most probably due to the constant delivery of ESS by the respiratory pump.
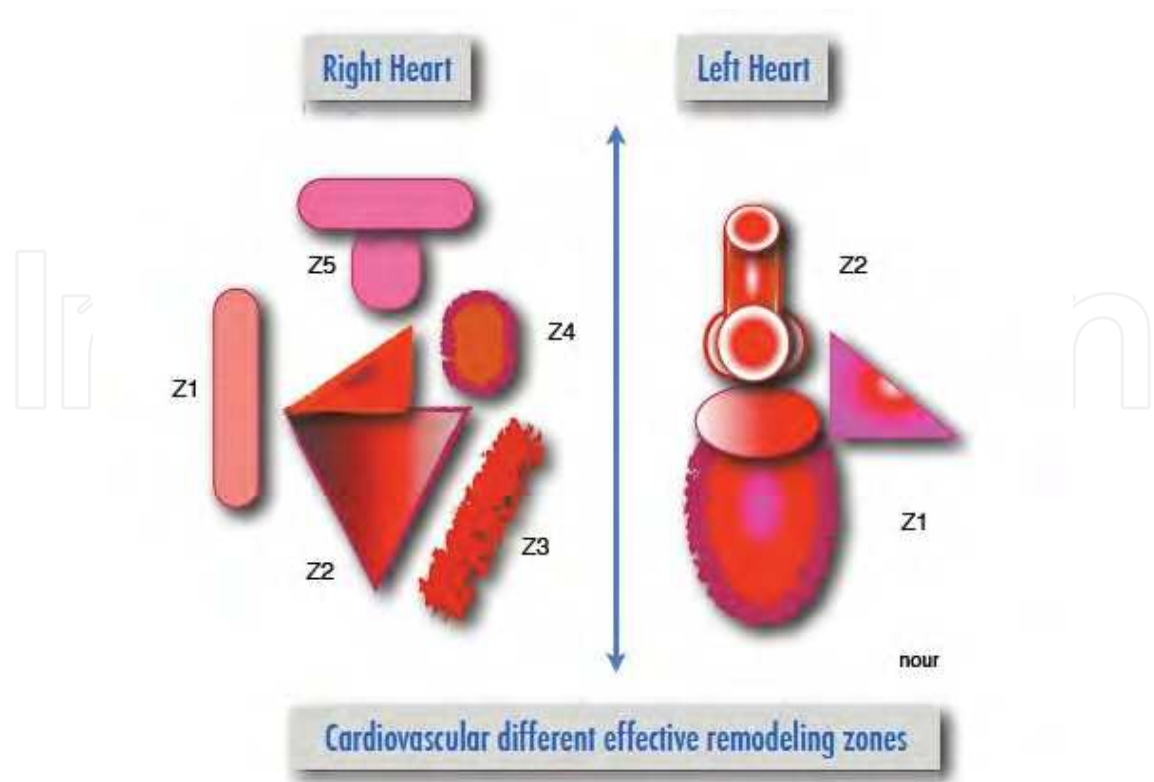
Fig. 2. Left and right heart circuits different remodeling zones

Zones	Sites	Remodeling	Main Factors
Z1	LV	High	$\uparrow$ Laplace $\rightarrow$ posterior to RV less restricted by the pericardium; $\uparrow$ Newton $\rightarrow$ spherical shape (Tumkosit M 2007); $\uparrow$ resistances.
Z2	Aorta + Valsalva	High	$\uparrow$ Shear stress (Newton): peristaltic pump + $\uparrow$gravity effect at the Valsalva; $\uparrow$ Laplace (less restricted external sheath at the arch), $\uparrow$ resistances.

Table 1. Left heart postnatal remodeling zones LV= left ventricle.

2. The right heart circuit: contrarily to the left, the right heart could adjust blood volume and shear rates at 5 different anatomical zones according to its physiological demands. In antenatal period, the right heart receives and pumps in equal rates more volume than the left, but keeps low remodeling due to pressure release through physiological shunts (Clark, 1987). After birth and shunts closure, both right and left ventricles share equal volume and rate inducing equal pulmonary and systemic cardiac output (CO), but remodeling remains inferior at the right heart side most probably due to venous steady flow and ventricular wall trabeculae. As shown in (Table 2) and (Figure 2), it could be identified by five different remodeling zones (Nour, 2009). Normally, the respiratory pump increases shear rates at the pulmonary endothelium externally creating an indirect or reversed pulse pressure shear stress (Newton). But with zones of steady flow and others with low pulse pressure the situation becomes more complex with physics

laws applications. In fact, both Bernoulli (Calvert, 2000), and Newton in addition to the gravity effect of Pascal's law as well (Humbert, 1947), must be considered to deliver a shear stress-mediated endothelial function.

Most importantly, the delivery of ESS with a CAD should be induced without disturbing the physiological remodeling of the right heart circuit (Buckberg, 2006). Direct induction of shear stress according to Newton's law like with an intravenous or intrapulmonary pulsatile perfusion must be avoided as it could induce serious hemodynamic conditions such as an irreversible pulmonary remodeling such us the Eisenmenger syndrome (D'Alto M, et al., 2007) or coronary bypass venous grafts disease. Also, the RV is preload dependant, that could not tolerate to be unloaded (Nour, 2009). This may explain failure of current pulsatile CAD in case of RV failure.

Zones	Anatomical site	Remodeling	Main Factors
Z1	SVC, IVC	Low	Absence of shear rates → Steady flow
Z2	A-V cavity	Mild	Trabeculae
Z3	Septum	Normal	Receiving interseptal left & right coronary supply
Z4	Infundibulum	High	↑ Coronary flow
Z5	PA tributary	Low	↓Pressure, Pulmonary Valve + Infudibulum

Table 2. Right heart postnatal remodeling zones (Nour et al 2009): SVC, IVC: superior & inferior vena cava respectively; A-V: atrioventricular; PA: pulmonary artery.

3. Hemorheological stock: the right heart circuit contains > 64% of blood volume surrounded by an important mass of endothelial cells. This natural stock of blood volume and endothelial mass can be stimulated by a proper pulsatile CAD, adaptable for right heart circuit's biophysics and physiopathology, for inducing shear stress-mediated endothelial function enhancement. Contrarily, to current evidence of high mortality of CHF patients associated with right heart failure (Haddad, 2011), the concept of the present therapeutic approach considers the right heart as a physiological backup for management of almost all types of hemodynamic and circulatory disorders, including CHF patients (Nour S, 2009). As been demonstrated on (Table 3), the right heart afterlaod could improve or deteriorates the global cardiac output (CO) and hemodynamic, for example nitrates therapies that could improve left ventricular MI by lowering the systemic afterload, may worsen and be fatal in case of RV ischemia (Haji, 2000).

Vascular Resistances	Status	Right heart	Left heart
Systemic	Low	Bad hemodynamic[1]	Good hemodynamic
Systemic	Elevated	Good hemodynamic[2]	Bad hemodynamic
Pulmonary	Low	Good hemodynamic	Good hemodynamic
Pulmonary	Elevated	Bad hemodynamic	Bad hemodynamic

Table 3. Dominancy of the right heart over the left heart through pulmonary vascular resistances (Nour, 2008):1= i.e. nitrates therapy in right ventricular ischemia; 2= i.e. epinephrine therapy with cyanotic spells

4. Pulmonary afterload: the influence of the right heart on hemodynamics is observed by the immediate postnatal drop of the pulmonary vascular resistances, triggered by the external shear stress-mediated endothelial function induced by the respiratory pump

(creating an indirect internal pulse pressure closer to Newton's law). Another example is observed in patients in squatting position during cyanotic spells of Tetralogy of Fallot (TOF) that increases the systemic vascular resistances (Senzaki, 2008) and increases the intrapulmonary flow and shear rates in a retrograde manner through the malaigned VSD to lower the pulmonary vascular resistances, followed by global hemodynamic improvement. The increased intrapulmonary shear rate that can be induced by adrenaline injection as well during the cyanotic TOF spells (Table 3), provides shear stress-mediated endothelial function approaching Bernoulli's law. Reduction of pulmonary vascular resistances is an immediate target for hemodynamic improvement that can be achieved by shear stress-mediated endothelial function enhancement directly with an intrapulmonary shear rate enhancement device (e.g. pulsatile catheter); or indirectly with an external pulsatile device (e.g. pulsatile suit).

5. Microcirculation: as is known, human being is a multicellular organism in which cellular biology performs a main role in terms of development, maintenance, proper operation and also failure of vital organs (Vincent, 2008). Maintaining good operation of organs by means of microcirculation in the organ constitutes a characteristic effect of the proposed concept. Microcirculations are controlled by plurality of endothelial mediators of vasodilators, which are dependent on shear stress (Koller, 1993) (Poelmann, 2008). Under normal hemorheological condition, microcirculation behavior approaches that of Newton's law. A symbolic example observed in athletics, high physical performance, which means shear stress-mediated endothelial function, could be achieved with slow heartbeat (shear rate) and increased stroke volume (pulse pressure). In contrast, in any abnormal hemorheological state, microcirculation presents behavior that approaches that of Bernoulli's law, as interpreted by the Fahraeus-Lindqvist effect in which plasma stuck at the inner vascular boundary layers while erythrocytes move faster at the center (Fahraeus & Lindqvist, 1931; Neri Serneri, 1981). This could explain absence of cyanosis in anemic patients with low hematocrite, unlike those patients with high hematocrite, as erythrocytes aggregations at microcirculations induce cyanosis with clinical signs finger clubbing (drumsticks fingers).

2.1 Cardiovascular pathogenesis

Endothelial dysfunction is responsible for almost all types of cardiovascular pathogenesis whatever congenital or acquired (Endemann et al., 2004)

The dependency of the endothelium on shear stress stimuli starts by the placental angiogenesis since the 6th gestational day, once there are normal hemorheolgical maternal factors (Heilmann, et al, 2005). Troubled shear stress forces due to an increased blood pressure (e.g.,preeclampsia) or low hematocrit (anticoagulant drugs), induces congenital anomalies and could interrupt the course of pregnancy (Aron, et al., 2003).

By the 8th gestational day of the intrauterine life, the embryonic vasculogenesis starts due to shear stress enhanced endothelial function, creating the first blood vessels followed by the appearance of the first fetal heartbeat by the 21st day (Meyers, 2007).

Furthermore, disturbed flow dynamics in the prenatal period, could induce congenital anomalies (Al-Ghazali, et al., 1989). Some symbolic examples of cardiac malformations are resumed on (Table 5) of cardiac malformations on (Table 4).

Flow disturbances	Congenital malformations
No flow → no grow	Hypoplastic left heart syndrome (Rao, 1994)
Homogenous flow	Heterotaxy syndrome (Prendiville, 2010).
Excessive flow	Agenesis pulmonary valves (Yeager, 2002).
Modified flow	Conotruncal defects: TGA, TOF, DORV, DOLV, (Rothenberg, 2003).

Table 4. Congenital malformations with troubled flow dynamics: TGA = transposition of great arteries; TOF= tetralogy of Fallot; DORV, DOLV= double outlet right or left ventricle respectively.

In the postnatal period, endothelial dysfunction is a major predisposing factor to hemodynamic troubles, circulatory disorders such as diabetes (Kapur A, De Palma R., 2007), arterial hypertension (Martini, et al., 2006), atherosclerosis (Chatzizisis, et al., 2007) and life-threatening conditions (e.g. cardiogenic shock, multiple organ failure). This could be induced by disturbed flow dynamics due to pump failure and/or elevated vascular resistances. As a symbolic example, right ventricular (RV) failure can occur either due to elevated pulmonary vascular resistances caused by pulmonary oligemia, pulmonary hyperemia; or due to RV pump failure caused by ischemia, congenital anomalies, arrhythmia, valvulopathy, and/or accessory circulatory driving forces failure like with failed Fontan's operation (Pereira & Shirali, 2005).

2.2 Types of endothelial dysfunction

Practically, and in a matter to facilitate the therapeutic approach for cardiovascular pathologies, endothelial dysfunctions could be classified into three categories as follows (Nour, 2009):

- **Type A**: endothelial dysfunction manifested with heart failure.
- **Type B**: includes endothelial dysfunction patients with endothelial dysfunction with normal heart function (e.g. diabetic, systemic arterial hypertension, PAH, erectile dysfunction, etc).
- **Type C**: represented by healthy individuals, liable for endothelial dysfunction pathogenesis under certain circumstances like disturbed atmospheric pressure and gravity (e.g. Astronauts, professional scuba divers, bedridden); fatigue, increased inflammatory responses, increased apopotosis (e.g. athletics, early aging processes).
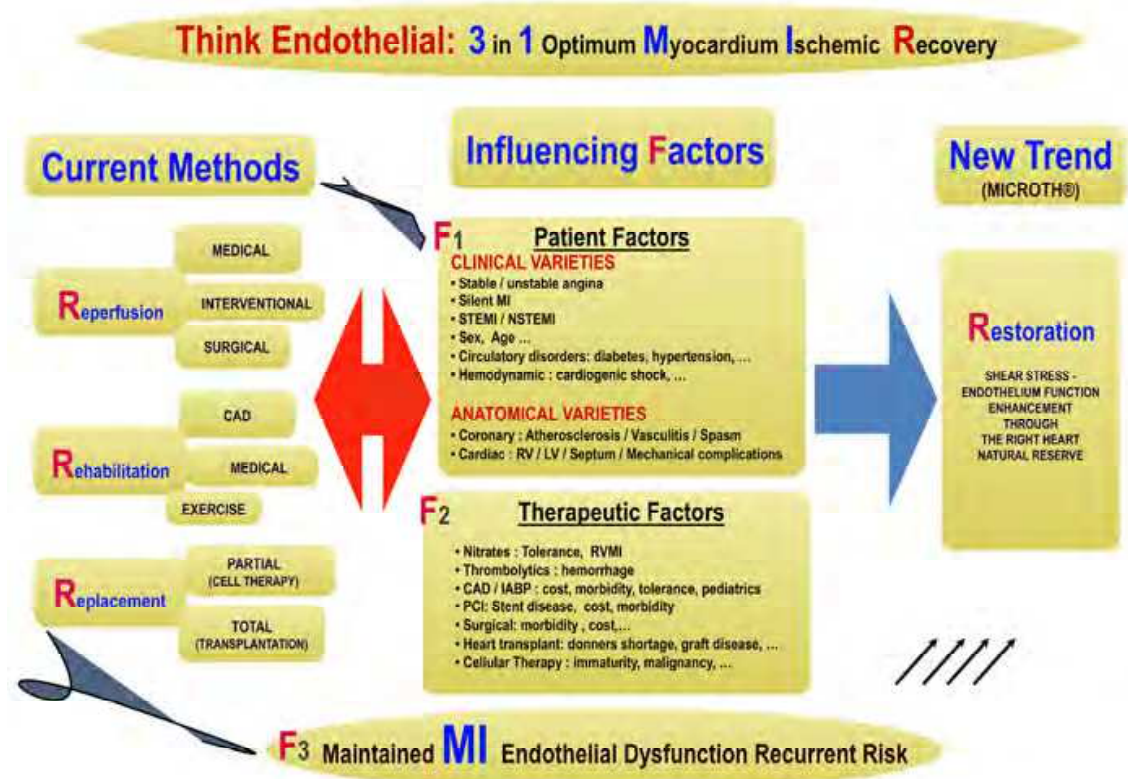
2.3 Endothelial dysfunction vs. current CVD therapies

Usually, endothelial dysfunction occurs as a consequence of pathological and/or interventional cardiovascular conditions, unfortunately with bad prognosis as there is no real curative option. A symbolic example, as been schematized in (Figure 3), regarding the current management of ischemic heart disease (IHD), which is still the leading cause of death so far. Except cracking or bypassing atheroma nothing has been done effectively until present.

As been resumed in (Figure 3): there are three symbolic "R" therapeutic options of myocardial ischemia which means: Reperfusion through an interventional and/or surgical approach; Rehabilitation, with physical exercise or CAD; Replacement with cellular therapy

(WU KH, et al., 2006) or heart transplants. Also there are three conflictual therapeutic factors "F": F1 due to patients clinical varieties like with unstable angina; silent ischemia; ST-elevated myocardial infarction (STEMI) or non-ST elevated myocardial infarction (NSTEMI); mechanical complications of IHD; cardiogenic shock (Berger PB, et al., 1999); age or sex. This is complicated by anatomical variation; variations in myocardial damage that affects the septum, right or left ventricular regions (Haji SA & Movahed, 2000); and variable coronary pathology, including normal, spasmodic, vasculitis, (Newburger, et al., 2004), or classical coronary atherosclerosis. Second factor (F2) is related to therapeutic defects like with nitrates tolerance (Abrams J, 1988); finally the most important factor (F3) is the maintained endothelial dysfunction (e.g. atheroma).

Unfortunately, all those therapeutic options could not resolve the problem, means to restore the main cause of dysfunctional endothelial atherosclerotic plaques (Davignon , et al., 2004). In addition, there are several varieties of MI due to other endothelial dysfunction pathogenesis rather than atherosclerosis such as coronary spasm (Kusama, et al., 2011) or congenital anomalies (McCrindle, et al. 2007), that could not be managed easily with angioplasty or coronary grafts (Gershlick & Thomas, 2007).

Otherwise, restorations of the endothelial function could be provided by the present concept (3R-in-one).

Fig. 3. Current therapeutic options for Myocardial infarction (MI)

3. Current CADs and endothelial dysfunction

In case of disturbed hemodynamic with heart failure, additional circulatory driving forces might be needed such as: a) Bio-assists with surgical procedures like the aortomyoplasty (Bolotin, et al (2001), cardiomyoplasty (Chachques, et al.,2005), and heterotopic heart

transplants (Onuzo, et al., 2000); and/or b) mechanical assists devices: like the cardiopulmonary bypass (CPB), left ventricular assist device (LVAD) (Seyfarth, et al., 2008)or right ventricular assist device (RVAD), and the artificial heart (Unger, et al.,1988).

In general, the present arts of cardiac assists devices can be classified in two categories:

1. Devices that increase coronary blood flow during diastole, in order to improve the oxygenation and thus the performance of the myocardium. This category includes the intra-aortic balloon pump (IABP), (Burkhoff , et al., 2006) and the enhanced external counterpulsation pump (EECP), (Bonetti, et al. 2003). These devices must be synchronized with heartbeat and unsuitable in case of cardiac arrhythmia; and

2. Devices that unload and bypass the heart pump: either partially as achieved by left ventricular assist devices (LVAD), right ventricular assist devices (RVAD), and by extracorporeal membrane oxygenation (ECMO); or completely like with biventricular assist devices, extracorporeal circulation (CBP), hetertopic heart transplant. It should be emphasized that ECMO partially deviates some of the venous blood to an external membrane oxygenator. ECMO does not completely unload the right ventricle (RV) and that may explain its successful applications in pediatrics patients who are more frequently vulnerable to RV failure (Wilmot, et al. 2011).
As a matter of fact, development of CAD remains controversial due to the induced momentum energy losses with the tasks of increased morbidity and mortality.

Most probably, CAD may aggravate hemodynamics, leading to multiple organ failure and death due to several factors that could be directly linked to devices themselves or indirectly due to patients' related factors as follows:

1. Devices related factors:
   a. *Concept and design*: a CAD is typically a lumped model constructed according to laws of physics for driving a Newtonian compressible fluid inside a closed pressurized hydraulic circuits (Roselli RJ & Brophy, 2003), implementing rigid tubes with fixed diameter. Meanwhile in practices a CAD is confronted with a non-Newtonian fluid (blood, running in flexible vessels with different geometries). This confrontation between two opposite pressurized hydraulic circuits (Figure 4) creates a vicious circle of momentum energy losses manifested clinically by increased vascular resistances with endothelial dysfunction (e.g. hemorrhage, thromboembolism, inflammatory response, apoptosis, etc.), up till multiple organ failure.
   b. *Driving forces' drawbacks*: more precisely, roller or centrifugal pumps are usually used to circulate and perfuse blood between the patient and the external circuit most commonly in a steady flow mode of perfusion (Gravlee, 2008). Unfortunately even with biocompatible, materials the effect of sucking and pumping a fragile fluid like blood mechanically with impellers, propellers, or pulsed reservoir, inside narrow rigid conduits create a zone of turbulence and vortices with important energy losses (Geankoplis, 2005). This improper simulation of a ventricular function with current CAD, as it is practically impossible to replace a type III passive pump like the heart, by type II, or I pump (Anderson,1999).
   c. *Installations systems*: usually conduits of tubes, and cannula, made of biocompatible materials (e.g. PVC®, Dacron®, PTFE®, etc.), are used for connection between patient and CAD. In addition, those conduits need to be securely stitched to

cardiovascular tissues, diverted under the skin (tunnelization) to allow proper chest closure, then to be de-aired and checked for leakage or gas emboli before finally connected to their corresponding CAD. Furthermore, the distance between a CAD and the patient' inlet/outlet sites gives rise to dead space, creating an additional momentum energy losses zone(please refer to Figure 8). Finally, the procedures for installing such conduits need to be carried out by experienced surgeons in specialized centers on patients who are fragile, and who have usually already been operated on several times in the past, increasing the risks of morbidity and mortality (e.g. hemorrhages, vascular complications, infections, multiple organ failure).
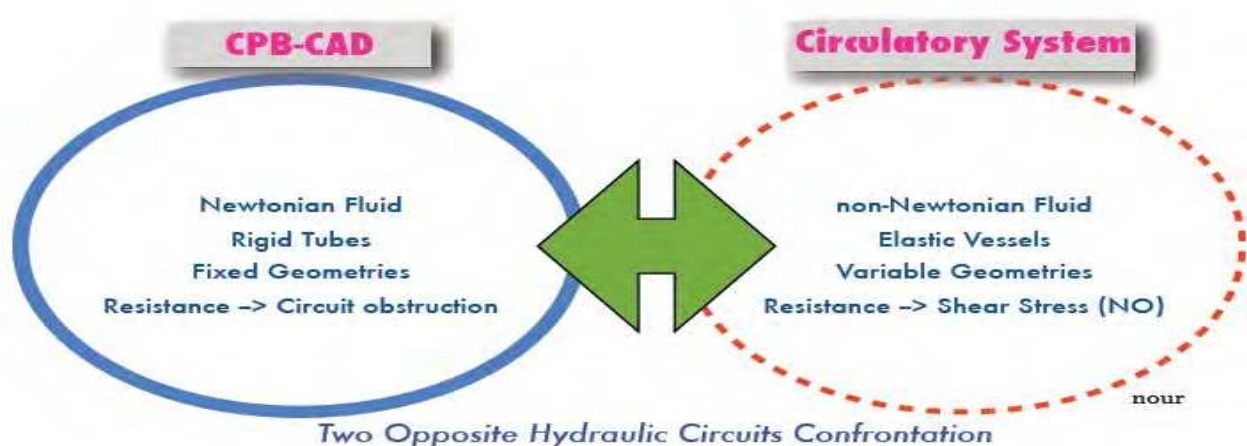
Fig. 4. Circulatory system and CAD create two opposite hydraulic circuits dilemma

2. Patients related factors: The aggravating factors inherent to the patients themselves can be of several kinds such as:
   a. Age, sex: most CAD devices are unsuitable for patients with small body surface area (e.g. children, female) since more than 80% of CAD devices are designed for body areas of more than 1.5 m^2, i.e. corresponding to adult heart patients. In addition CAD are generally first designed for management adult heart diseases and then miniaturized to cope with pediatric populations. However; pediatric patients are more vulnerable to hemodynamic disturbances caused by right heart failure due to congenital anomalies and they are vulnerable to vascular complications caused by small vessels geometries in content (Potapov, et al 2007). Adults usually suffer from ischemic left ventricular heart diseases with atherosclerotic vessels and they are therefore more vulnerable to vascular complications (Nour S, 2008).
   b. Etiology: fate of CHF patients with severe right ventricular (RV) failure (CVP>16mmHg) is worse, compared with those patients with left heart sided pathologies. Current therapies employing CAD to treat CHF patients with severe RV failure (Prutkin et al. 2008), still exhibit a high mortality rate (65%-95%), most probably due to insufficient understanding of the great difference between the right and left heart circuits (Sollano, 1998).
   c. Preclinical studies: in particular, the role of animal models in therapeutic evaluation, which is an extremely essential procedure before proceeding to clinical

applications of new CAD. However, there is still a gape between the chosen animal model and clinical realities as presented in the following examples:

    i.   Current models of myocardial infarction are unfortunately, driven by costs rather than clinical resemblance. For example, rat as a most popular selected model is far from human physiopathology with a heart rate> 400 bpm.

    ii.   Models of acute pulmonary hypertension (PAH), as often done either by hypoxia, monocrotaline, or systemic-pulmonary shunt. However, a lack of robust models of PAH, is still missing due to different spectra of lung tissue between species and humans (Robbins, 2004), (Bauer, et al. 2007).

    iii.   The biventricular heart failure models, often called for testing of cardiac assist devices, which remain difficult to achieve in animals. The most part of these mechanical assists devices are usually tested in computational version (Querzoli, 2011) or WindKessel models, away from the pathophysiological aspect in humans (Olufsen & Nadim A, 2004).

d.   Miscellaneous: finally, the shortage of donors, immunosuppressive drugs drawbacks (e.g. malignancy); coronary atherosclerosis, follow up costs and surgical complications, all contribute to limiting the generalization of such treatments in practice.

4. Proposal

The present concept proposes clinical applications of these tangential forces of shear stress in order to regulate the endothelial function so as to improve the hemodynamic of patients, the overall microcirculation of vital organs, and, when it has failed, to reestablish normal operation of the cardiac pump in a manner that is as physiological as possible, without replacing any organs and without any traumatic intrusion, to provide a method that is as minimally invasive as possible.

Development of a CAD* with an optimum function, which means improving hemodynamics, increasing organ microcirculation, restoring and preserving deficient endothelial function in a diseased human being, should compromise the following steps: maintaining the circulatory flow dynamics in the patient's systemic and pulmonary circulations; and temporarily relieving the heart of its pumping function.

CAD is referred to a "circulatory assist device", instead of the commonly applied term "cardiac assist device".

More precisely there are three manners to stimulate the endothelium with a mechanical assist device as follows (Figure 5):

1.   Direct internal endothelial stimulation that will be induced by an intravascular catheter device.
2.   Indirect internal endothelial stimulations with a pulsatile perfusion flow generated by a pulsatile pipe (tube) device at the left heart side.
3.   External stimulation (pulsatile suit) at the right heart side endothelial with gentle rhythmic squeezing of the venous and lymphatic capacitances reservoirs at the superficial veins and capillaries.
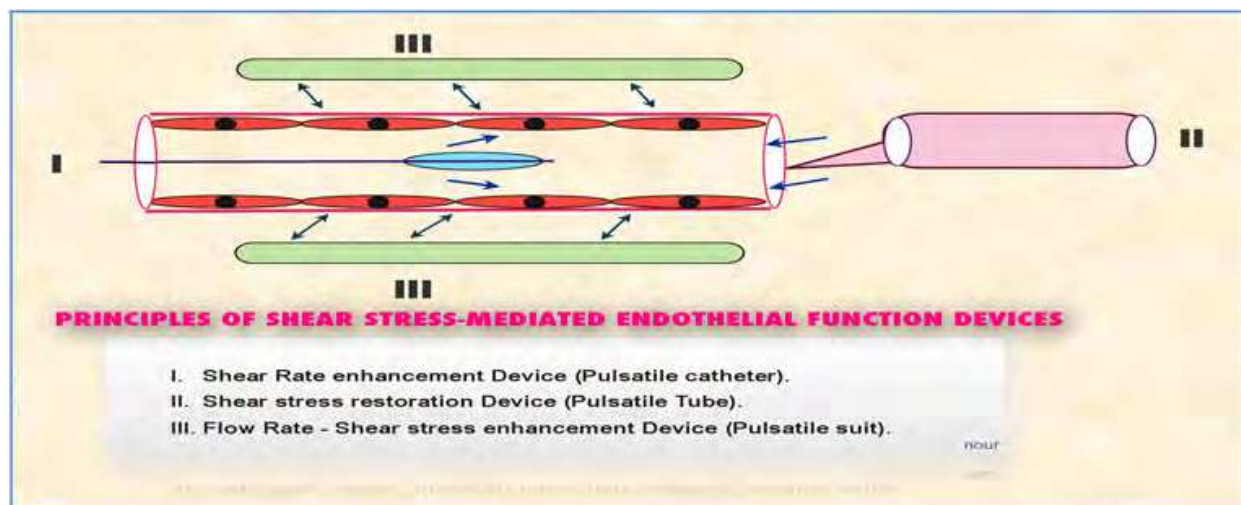
Fig. 5. Methods for shear stress-mediated endothelial function stimulations

According to the present concept, the method consists in using at least one device external to the patient's body and connected by at least a pipe and/or a specific connection element to:

1. Increase the preload of the right ventricle so as to improve myocardial oxygenation and so as to improve its contractility; and/or
2. Unload the left ventricle and diffuse regular pulsatile flow in the proximity of the aortic root so as to improve the hemodynamics of the left ventricle of the heart; and/or
3. Stimulate the endothelium mechanically by shear stress enhancement so as to release several mediators of endothelial vasodilators like nitric oxide (NO), to reduce the systemic and pulmonary vascular resistances (afterload).

5. Synchronization with the diastolic phase

The synchronization of these new pulsatile CAD with the heartbeat is strictly guided by the therapeutic indications according to types of endothelial dysfunction as follows (Nour S, 2009):

*   Type A: this means in case of heart failure, CAD's synchronization is unnecessary and must be unsynchronized with heartbeat.
*   Type B: synchronization of CAD with the heart is necessary to restore the endothelial function.
*   Type C: synchronization of CAD is relative, because according to the Starling's law (Katz, 2002), the cardiac output (CO) adapts to the venous return (RV preload).

6. Devices

In known manner, the prior art constituted in particular by circulatory assistance systems such as LVAD, RVAD, Biventricular AD, etc., simulate the ventricular pump by complex driving forces.

In a manner that is very different, and indeed that is opposite in the physical sense of the word, the devices and methods of the present concept are designed to maintain circulation

in columns of blood within their own physiological containers as constituted by veins and arteries. The idea is to maintain a pulsatile blood stream complying with the biophysical and physiological standards of pulmonary and systemic circulations, by applying mechanical endothelial stimuli of shear stress.

One aspect of the devices and methods of the present concept enables shear stress endothelial stimuli to be increased, thereby enabling a microcirculation opening to be created in various organs of human body by means not only of conventional mediators of vasodilators such as nitric oxide, but also by means of other new vasodilators processing.

6.1 Pulsatile suit

In one aspect of the present method, blood is compressed from the outside of the body by means of a special suit referred to as a 'pulsatile suit", of the kind described in patents applications (WO/2008/000111) and (WO 2010/070018), which suit is used primarily to provide circulatory assistance to the right heart and secondarily as a device that makes it possible to obtain an overall hemodynamic improvement. The pulsatile suit is composed of three layers and must be suitable for the postoperative situations and provided with security features as following:

1. Inner layer made of elastic material (e.g. neoprene) to insure smooth tight massage like pulsed surge at the skin. 2. Middle sandwiched layer filled with gelatinous fluid, to alleviate the vigorous inflation/deflation, power induced by the driving force. 3. External layer made from tougher materials to keep the pulsed wave inwards toward the body. This part is equipped by security air releasing valve to prevent over inflation accident in case of mechanic defect. 4. Holes are previewed in the suit body, in order to facilitate medical administrations and prevent bedsores. 5. Layers thickness and design are modified according to age, body weight and indication of the patient. 6. The back portion of the trunk part of the suit (vest and belt) must not be inflatable in order to avoid any spinal, or back injuries. 7. Blood must be pulsed back from periphery towards the heart in a sloping progressive wave in longitudinal axis. Except at the chest part, pulsations must be started backward - forward towards the front, in a horizontal axis in such a manner to increase venous return within respect of the respiratory movement.

Naturally, this pulsatile suit has detachable parts and may take on various forms such as a hood, a pair of trousers, a jacket, a glove, a boot, or a sock. The parts could be reassembled together in one unit and wrapped tightly around the patient body through straps and zippers, as shown in (Figure 6) and as patents descriptions.

Figures 12 show such suit covering the bottom portion of the human body, which the therapist (doctor, nurse, or even the patient) can put into place without effort. The suit may be connected directly to an external pump, it may be actuated by the therapist himself or herself.

The structure serves advantageously to guide the pulsations it generates, progressively in the venous return direction. It thus constitutes a circulatory assistance device for the right ventricle (RVAD).
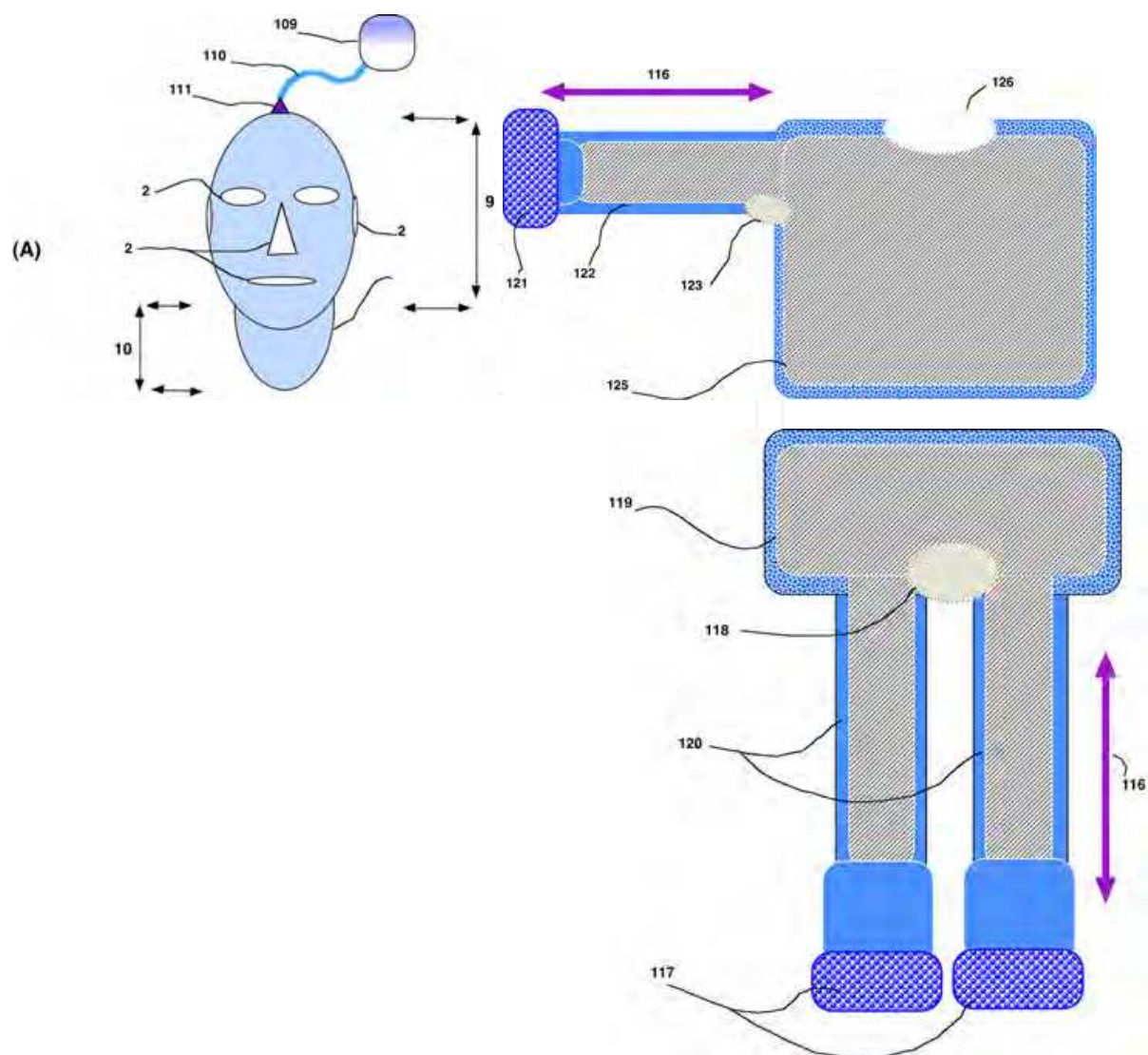
Fig. 6. Pulsatile suit CAD

6.2 Pulsatile tube

In another of its aspects shown in (Figure 7), the method implements at least one specific "pulsatile pipe" that serves to impart pulses to columns of blood, and that is preferably used in the context of providing circulatory assistance to the left ventricle (LVAD). Such a pipe is described in particular in patents applications (WO/2008/000110) and (WO 2010/066899). It may form part of a pulsatile medical kit that also includes a conventional pump (with or without oxygenator) placed at one end of the pipe, and an aortic cannula is placed by surgeon as close as possible to the patient's aorta. It is preferably prefilled in its intermediate space with an inert fluid such as helium, CO_2, etc. This diminishes the risk of embolism since the gas initially present in the pipe is discharged outside the circulation. In addition, the pressure forces required for operating the pulsatile device are reduced. It can readily be understood that this device is invasive to a very small extent. It generates pulsations in most effective manner and it is very easy to implement. It may be put into place surgically via a mini-incision or via a percutaneous approach and then synchronized with the patient's electrocardiogram.
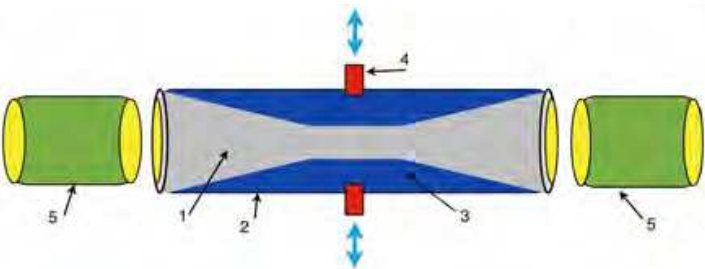
1= Flexible inner tube; 2 = Rigid external tube; 3 = Intermediate chamber; 4 = Ports; 5 = Connectors

Fig. 7. Disposable pulsatile tube (pipe)

A disposable double lumens' tube, which is designed according to the principles of the "Bernoulli" 3rd equation: propagated pulsatile impacts transferred from the intermediate chamber (blue color), would move up the stagnant fluid boundaries' layers at the inner flexible tube (grey color), and push them towards the center in a mater to diminish the traumatic effects of blood and its components. Both tubes (inner & external) are sealed together at their extremities creating a sandwiched space between them with double central orifices connected to a pulsatile console. The tube is adaptable to a conventional CPB arterial line circuit through two standard connectors wedged at each end of the inner tube.

Practically, circulatory perfusing systems create a state of momentum energy losses that could be identified in 6 main zones (Z0-Z5) (Nour S 2008), as follows (Figure 8): (**Z0**) it represents the pre-oxygenator zone, where momentum energy losses depend on types of driving forces (e.g. (e.g. roller or centrifugal pump) to be deleted as well as the oxygenator, which is a major constant site of energy losses; (**Z1**) it is the zone downstream to the oxygenator, where energy losses depend on circuit conduit types (length, width, materials) and fluid viscosity; (**Z2**) it is represented by the pulsatile tube wedged at the arterial perfusion line between the oxygenator and aortic cannula; (**Z3**) it represents the pre-aortic cannula zone, which is the first effective pulsatile zone; (**Z4**) it represents the aortic cannula zone, where the effect of convergent (at the entrance) and divergent (at the tip) energy losses plays an important role (Cutlera D 1999); (**Z5**) it represents the perfused tissues started from the tip of the aortic cannula, causing important divergent momentum energy losses.
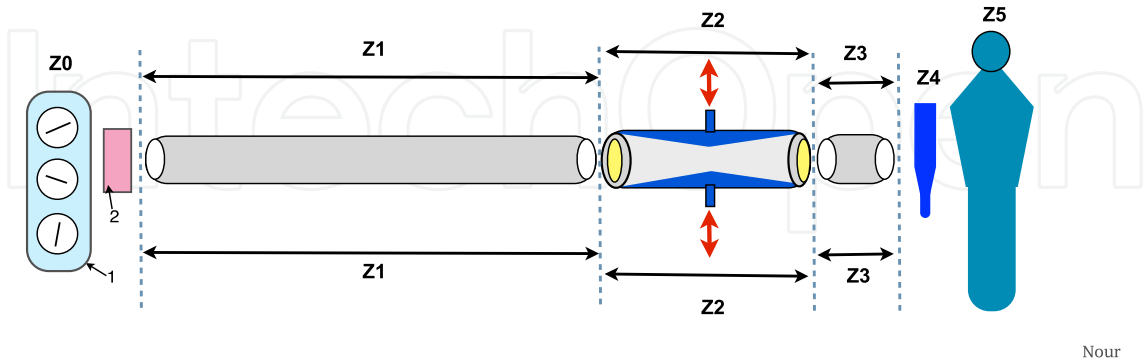

Fig. 8. Main momentum energy losses zone in a circulatory perfusion circuit

Accordingly, the pulsatile tube receives the steady flow from (Z1) downstream to the oxygenator, till (Z2) where the homogenous pulsations from the inner tube's walls move the stagnant laminar boundaries layers towards the center within total respect of Bernoulli's principle, with less vortices and better conservation of blood components.

At (Z3) where the effective pulsatile flow starts, theoretically this pre-aortic cannula zone represents a convergent diffuser with low momentum energy losses at the entrance of the aortic cannula. Meanwhile, a short (Z3)'s distance is requested to reduce turbulence and vortices that might occur due to strong-pulsed flow within a fixed geometries' tube. Furthermore, the pulsatile tube serves to reduce the empty space between monitor system and the tube itself, thereby giving rise to optimized operation with minimum pulsatile pressure; it is thus possible to envisage miniaturizing the device and correspondingly reducing the energy needed for its operation.

As seen in (Figure 12) a pulsatile pipe may be placed between the left subclavian artery and the right subclavian vein.

6.3 Pulsatile catheter

Another aspect of the present method comprises a "pulsatile catheter" comprising a conventional catheter that is surrounded by an inflatable element over a portion of its length (Figure 9). Such a catheter is disclosed in patent applications (US/2011/021987) and (WO 2009/136035).
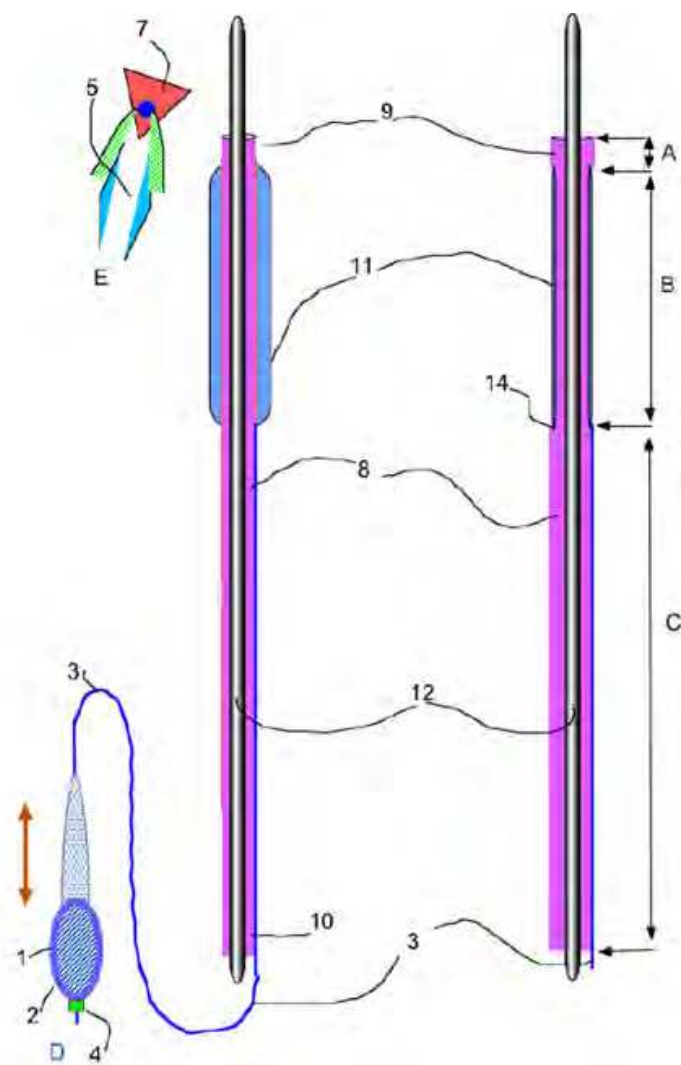

Fig. 9. Intravascular shear rate enhancement device

According to (Figure 9), the invention relates to a device for creating a pulsating inflation of an inflatable component (11) of a catheter (8), comprising: a bag (1) that can be filled with fluid (2); a bag compression means (5) capable of compressing said bag (1) in a pulsed manner; and a connection means (3) connecting said bag (1) to said inflatable component (11) of the catheter (8) and allowing the fluid (2) to move between said inflatable component (11) and said bag (1).

Advantageously, the inflatable element in place around the catheter presents in the deflated state an outside diameter that is less than that of the remainder of the catheter. Naturally, the inflatable element is connected to external inflation means suitable for generating pulsations during inflation. The device advantageously makes it possible to avoid excessively enlarging of the point where the catheter is inserted into a blood vessel.

Such a device is used in particular for PAH with increase in the afterload of the right ventricle (right ventricular failure); the catheter is placed in the trunk of the pulmonary artery by a percutaneous venous approach, preferably in association with a pulsatile suit.

6.4 Pulsatile console

An example of the pulsatile console (Figure 10), is described in patent application (US 2011166515) that console is very simple in design and easy to use. The console enables determined pulsatile pressure to be created and applied to a pipe, a catheter, or ay other equivalent means. A simple source of fluid under pressure such as a bottle of an inert fluid, or of liquid under high pressure constitutes the continuous source that is transformed into a pulsatile source by the pulsatile console as disclosed therein.
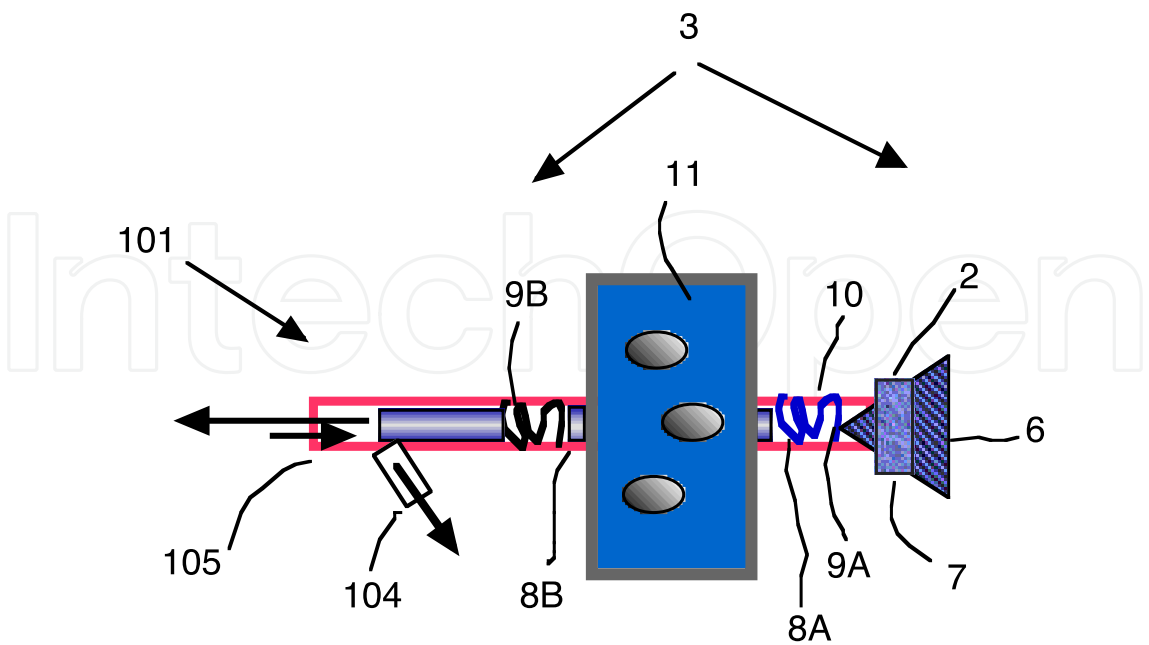

Fig. 10. Portable pulsatile console (Tu-Master).

The invention relates to equipment for applying a determined pulsatile pressure to a medical device, comprising: a withdrawing means (2) designed to withdraw fluid from a source of fluid in continuous flow at high pressure; a conversion means (3) designed to convert said fluid into a fluid in a pulsatile flow at low pressure; at least one application means (105) for applying said fluid, as a low-pressure pulsatile flow, to said medical device; and a means (104) for removing said fluid.

6.5 Smartcan

According to yet another aspect of the present method, a secure and almost non-invasive connection is provided between the patient and external mechanical systems for providing circulatory assistance (Figure 11). This aspect may be achieved by a device of the kind described in patent application (WO 2011/089162).
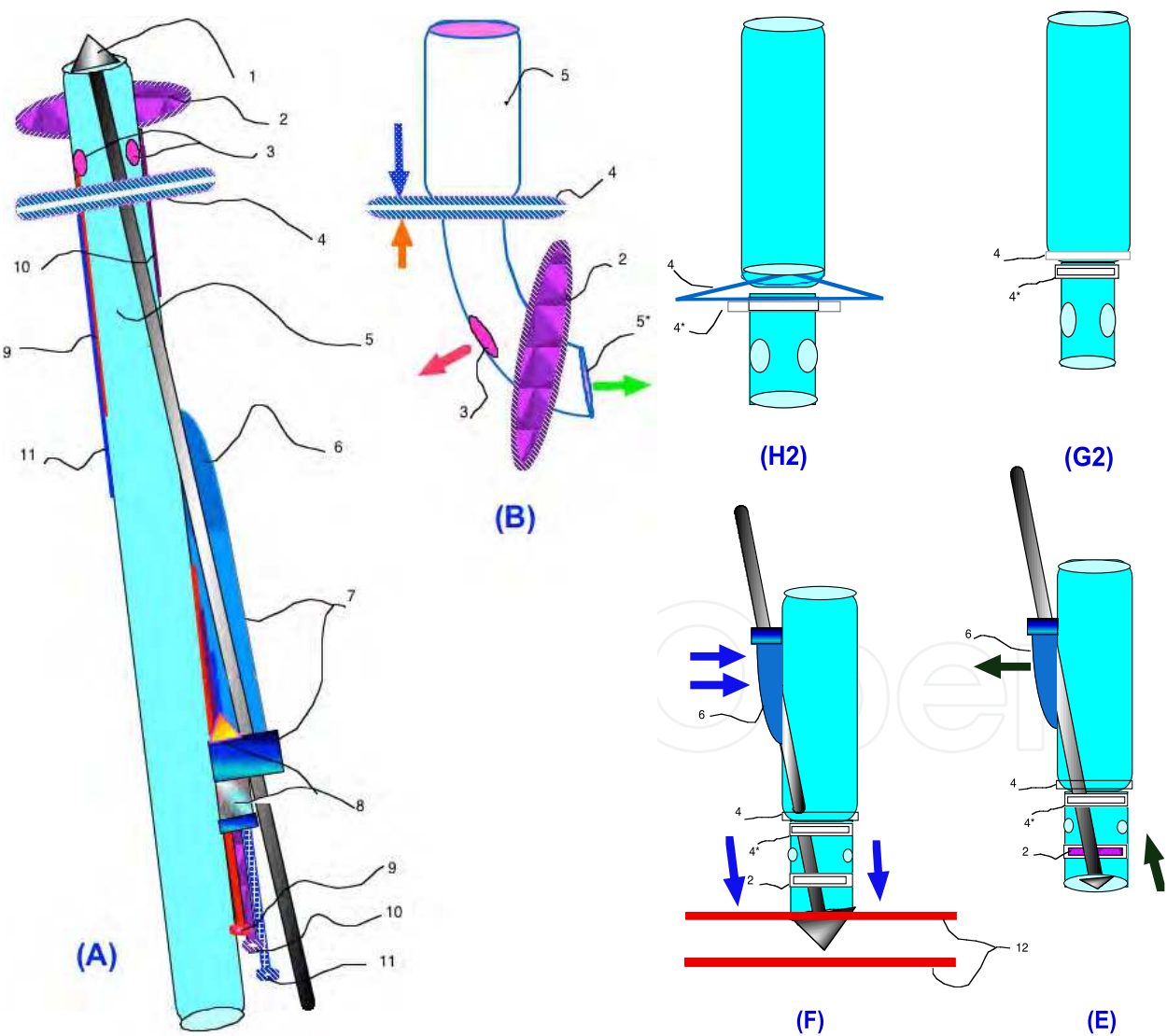
Fig. 11. The Smartcan conduit device

That device entitled the "Samartcan", makes it possible advantageously to group together all of the tools that make it possible to obtain a cardiovascular approach that is effective, fast, safe, and inexpensive. Thus, the tool enables a single operator, makes it possible to avoid all of the traditional steps such as incision, suture stitches, purse strings, etc. That simplifies the operation. Operating costs are thus significantly reduced.

Such a tool may be put into place and moved with assistance and remote guidance, e.g. echocardiography. This avoids blind guidance under the patient's skin for connecting the patient with an external circulatory assistance machine as with prior art methods. Such a connection gives rise to complications for the patient such as infections, hemorrhages, problems of closing the chest, etc.

In an advantageous manner, such a tool can be used as an aortic cannula, a cardiac cannula, a vascular catheter, or indeed as tubing for cavity drainage.

Such a tool, and more precisely the body of the device, is preferably prefilled with a liquid such as heparinized serum in order to reduce the risks of gaseous embolism and in order to shorten operating time.

In a novel and advantageous manner, the distance between such a tool and the patient is very small. In other words, the distance between a circulatory assistance machine (CAD) and the puncture sites (on the patient) is very short; in particular when implantation is performed close to the subclavian artery. This characteristic greatly reduces the energy losses that are inherent to existing devices.

The present invention relates to a single-use device to be used in surgery each time that a vascular approach by means of cannulation or catheterization is deemed indispensable (cardiopulmonary bypass, anesthesia, emergencies, resuscitation), particularly during cardiac surgery or interventional cardiology. Said novel device substantially includes a body (5), a sealing system consisting of two inflatable diskettes (4), a control connector for inflating and deflating the diskettes (4), a tubular unit (6) and a flexible guide (1). Upper right panel: shows a Smartcan with folded (G2) and unfolded (H2) external diskettes. Lower right panel: shows the Smartcan manually controlled guide wire before (E) and after penetrating a blood vessel (F). Left panel global schema of the Smartcan (A) and the proximal end (B) with the intraortic obstructive dikette (2), the cardioplegia delivery holes (3).

6.6 l'Orthèse cardiaque

According to another US patent application in pending, the various devices (pulsatile pipe, suit, and catheter, in particular) implemented in the present disclosure are synchronized together or separately as a function of the patient's hemodynamic parameters.

It relates to a novel therapeutic technique and method of providing mechanical circulatory assistance using a CAD that is minimally invasive. The CAD improves hemodynamics and microcirculation, and restores the endothelial function when it is insufficiently stimulated, particularly for a patient suffering from congestive heart failure (CHF).

The device complies with the patient's hemodynamic parameters as a function of breathing frequency and cardiac rhythm. Heart rhythm is detected by the electrocardiogram or by pacemaker as a function of variation in arterial pressure and/or in systemic and pulmonary resistances.

Synchronizing the pulsatile suit, thereby increasing venous return (preload) and reducing afterload, needs to be performed without hindering the frequency of breathing and without increasing central venous pressure above 16 mmHg. The pulsatile frequency of the suit may be less than the cardiac frequency of the patient (one-third to two thirds of the heartbeat).
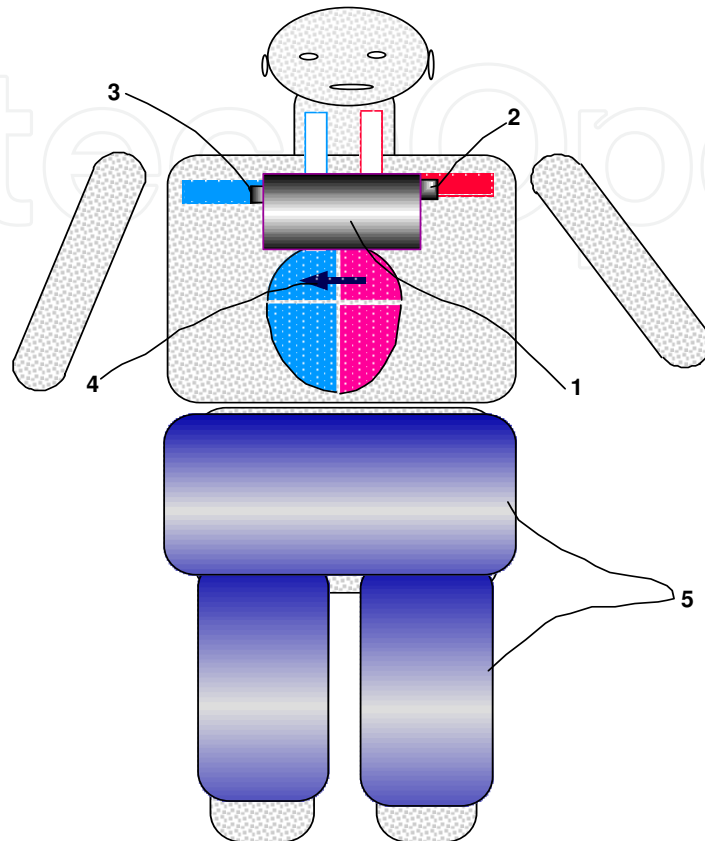
Right panel: l'orthèse with complete suit (full throttle option); left panel: l'orhèse with bottom trouser; 1= pulsatile pipe set; 2 = left subclavian artery tip; 3 = right subclavian vein tip; 4 = arrow defines intraseptal drainage; 5 = pulsatile trouser set; 14 = vest; 15 = sleeves.

Fig. 12. l'Orthèse Cardiaque

In contrast, the pulsatile pipe associated with the patient's electrocardiogram may be synchronized with cardiac rhythm and the pulsatile catheter may be faster than heart rate.

In particular, the devices and methods of the present CAD avoids problem associated with blood circulation through two well-separated circuits (systemic and pulmonary) that are constituted by the vessels and arteries of the patient and by the mechanical circulatory assistance device (s).

All of those pulsatile means enable variations in blood pressure to be created in vessels in application of the physical laws that apply to non-Newtonian fluids. They allow stagnant blood to be moved in compliance with Bernoulli's law, i.e. from the walls towards the insides of the vessels. This therefore gives minimizes the traumatic effects on erythrocytes.

When the heart pump, and in particular the left ventricle, is to be relieved (unload), the practitioner will use a Smartcan device in a version that enables an incision via the tip of the left ventricle or a left intra-atrial transseptal incision.

Similarly, when regular pulsations are to be produced and diffused close to the aortic root, the same device may be inserted as an arterial perfusion cannula in the root of the aorta or in the subclavian artery via a percutaneous approach or by echocardiographic guidance.

Figure 12 shows a patient fitted with a pulsatile suit that covers the bottom portion of the body; in addition, a pulsatile jacket is placed around the patient's thorax and pulsatile sleeves are placed on each of the patient's upper limbs. In this embodiment of the invention a pulsatile pipe is placed between the subclavian artery and the subclavian vein.

Furthermore, the present CAD is suitable for managing various types of heart failure, regardless of the right or left etiology.

On the right heart, by putting pulsatile suit into place, the device makes it possible to reduce the stagnation of venous capacitances; by implementing a pulsatile catheter, it is possible to reduce the pulmonary afterload.

On the left heart putting a pulsatile pipe into place enables physiological pulse pressure to be maintained and directly serves to improve overall hemodynamics by reducing systemic vascular afterload.

Thus, the methods and devices according to the present disclosure may be defined as a circulatory orthosis, as opposed to prosthesis. Unlike orthotopic transplantation, the present disclosure makes it possible to keep the patient's heart in place, thus allowing the patient to wait in relative comfort for a histocompatible donor.

The present method provides bridging treatment prior to transplantation, thereby improving prognosis and morbidity by restoring patient's hemodynamics. As a reminder, present-day mortality is higher for right ventricular failure it lies in the range of 65% to 95%.

The present disclosure makes it possible to restore the endothelial function progressively by maintaining quasi-physiological shear forces on the endothelium; consequently, there is a significant improvement in the function of myocardium, thus making it possible avoid subsequent transplants.

The present disclosure provides and approach that is invasive to a very small extent, since it avoids risky surgical acts, in particular, the invention avoids sternotomy and/or thoracotomy which can be put off until subsequent transplantation.

The devices and method of the present disclosure thus makes it possible to cope with the shortage of donor and with the numerous problems that are associated with antirejection treatments.

In addition, the present CAD is adapted to all age categories, from newborns to patients of great age and/or patients that are most clinically fragile.

7. Experiments

These devices were evaluated in vitro, as well as with clinical volunteers. The in vivo study was approved by the Animal Research Facility at Sun Yat-Sen University and conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No.85-23, Revised in 1996). In original pediatric animal models of acute cardiogenic shock state, created in

piglets. We have avoided any premedication or any prophylactic medical support that may interfere with the endothelial function (e.g. atropine, β-blockers, etc.). Only mechanical cardiac support was provided with the evaluated device compared to traditional therapies in control groups. The clinical volunteers were medical doctors included the author.

7.1 Evaluation of the pulsatile tube device

Perfusions of the circulatory system with devices like the cardiopulmonary bypass (CPB) and CAD disturb endothelial shear stress (ESS), which is responsible for the post-cardiotomy syndrome, increasing liabilities of clot formation, bleeding, disseminated syndrome, etc (Bick et al., 1976)) (Abshire, 2009). This endothelial dysfunction syndrome is most probably occurred due to steady flow, foreign surfaces and the severe momentum energy losses. To overcome these side effects different therapeutic strategies are currently applied (Nour S, 2003), such as: *a) pharmacological supports* using antifibrinolytic (Cooper, 2006), inotropes, vasodilators, platelets, etc. (Nardell, 2009), but with some side effects as well (Ishida, zt al., 2004); b) *normothermia:* that becomes more practiced in CPB with some proven advantages over hypothermia (Pouard, et al., 2006), which may be explained because blood is nearly Newtonian at 37.2°C (Box, et al. 2005). Meanwhile, the benefits of normothermia on myocardial protection and microcirculation improvements remain controversial (Rastan, et al., 2008), as the myocardium is already protected with doses of cardioplegia, while the perfusion of microcirculation is more or less helped by the Fahraeus-Lindqvist effect due to hemodilution; c) *total or partial absenteeism* of CPB: that becomes popular with proven postoperative hemodynamic advantages, *but* it is still a challenging technique reserved for selected groups of patients (Shroyer, et al., 2009); d) *pulsatile perfusion flow devices:* in a matter to keep ESS some pulsatile CPB have proven advantages clinically and experimentally (Ündar, et al.,1999); (Undar, et al. 2006). Despite that, recent studies recommend the unphysiological steady flow (Voss, et al., 2010). This may be explained by pulsatile CPB inadequate curves with the necessity of a double perfusion pumps system to compensate the oxygenators momentum energy losses. Instead associating an intra-aortic balloon pump (IABP) with a conventional CPB, as a cost-effective manner (Onorati, et al., 2007), creates turbulent zones of vortices (Geankoplis, 2005), with vascular complications (Sanfelippo, et al.,1987) and controversial effectiveness (Kadoi Y & Saito, 2000).

Alternatively, the pulsatile tube represents a potential solution for those aforementioned CPB and CAD drawbacks

The pulsatile tube device (Figure 7), was evaluated as a potential solution for these CPB and CAD drawbacks. A device prototype was tested in vitro (a mock circuit) for energy losses studies and in vivo as a LVAD, also the tube prototype was associated in the in vivo study of a Bi-ventricular assist device (l'orthèse).

7.1.1 In vitro study

Materials and methods: a double lumen tube prototype as shown in (Figure 13), composed of: a) external polyvinyl chloride (PVC) (20 cm length, ½ inch diameter). b) Internal Polytetrafluoroethylene (PTFE) (18 cm length, 12mm diameter), reinforced with latex membrane (condom), as a protector against the PTFE micropore. c) 2 connectors (¼ inch) introduced at each end of inner tube and wedged to the PVC tube and securely sealed by

external adhesive straps and rings. A small animal ventilator (HX-300 TaiMeng Technologies Inc®), was applied as a pulsatile generator.

Fig. 13. Pulsatile tube prototype (Dr. Nour)

Mock circulation: with slight modifications from the literatures (Undar et al;, 2006), (Wang, et al., 2009), it was composed of (Figure 14): a roller head pump (Cobe® Cardiovascular Inc.), pediatric oxygenator (Sorin® Lilipput 2 Ecmo) and filter (Sorin® Group hemoconcentrators), primed with fresh piglet's blood mixed with dextrane in concentration of (2/3) and (1/3) respectively. A pediatric arterial line circuit, PVC tube (1.5 m length), 14 FR aortic cannula (DLP® Medtronic, Inc.), venous line (1.5 m length) and simulating vascular resistance partial clamp, positioned downstream to the aortic cannula.
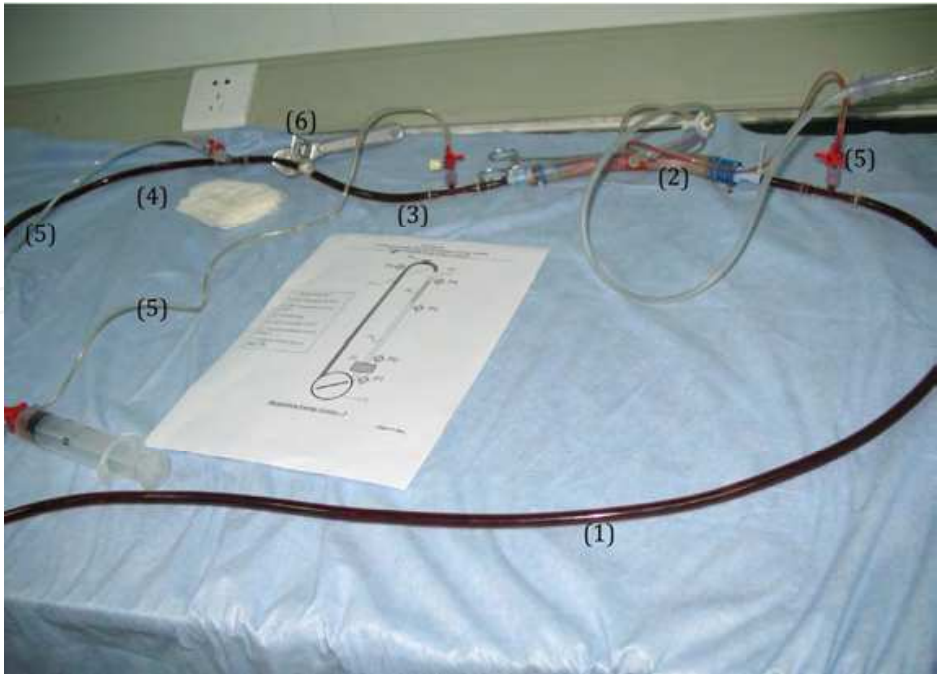
1 = arterial perfusion line; 2 = pulsatile tube; 3 = aortic cannula; 4 = venous line; 5 = pressures lines; 6 = partial tube clamp (simulated resistance).

Fig. 14. Mock-circulation: energy losses circuit (I)

7.1.2 Methods

With variant pump flow rate (400, 600, 800 and1000 ml/min) and fixed pulsation rate (110 bpm), we have compared circuit momentum energy losses during steady and pulsatile flows in 3 different tube positions as following:

- Energy losses I: the tube was positioned downstream to the oxygenator at 6 cm from the aortic cannula (Figure 15-I).
- Energy losses II: the tube was positioned downstream to the oxygenator at 150 cm from the aortic cannula (Figure 15-II).
- Energy losses III: the tube was positioned between pump and oxygenator (Figure 15-III). This position conceptually simulates current devices of pulsatile CPB.

Recorded pressure curves: first in a steady mode, then pulsatile by switching the tube's generator on, were collected at 5 remote distances spots: up and downstream: to oxygenator (P1, P2); to tube (P3, P4) and to resistance (P5) which simulated a systemic arterial perfusion curve in patients.
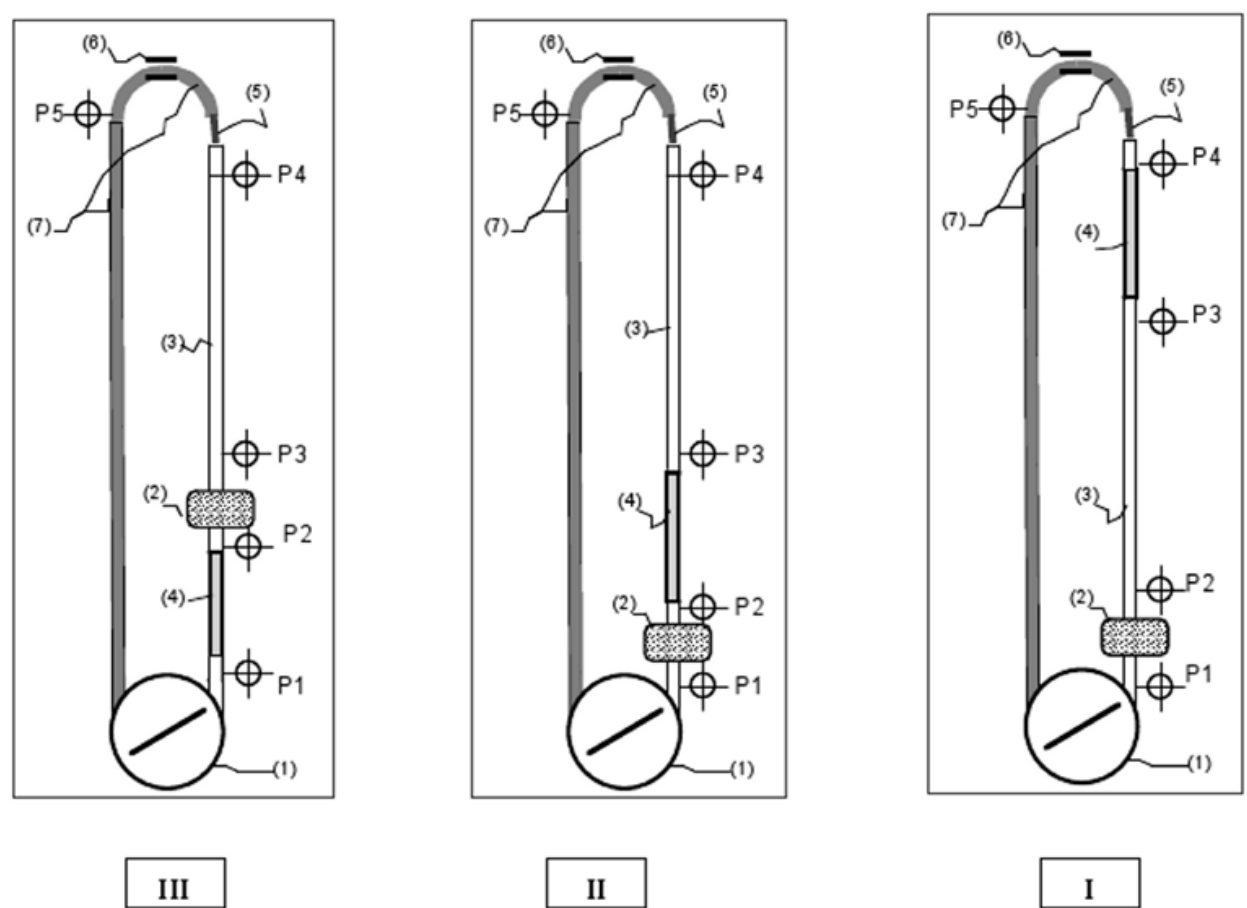
{I} = Pulsatile tube was positioned at *6 cm* distance from aortic cannula; {II} = Pulsatile tube positioned at *150 cm* distance from aortic cannula; {III}. Pulsatile tube wedged between roller pump and oxygenator. 1 = roller pump; 2 = oxygenator; 3 = arterial line; 4 = pulsatile tube; 5 = aortic cannula; 6 = resistance (tube clamp); 7 = venous line. P1, P2, P3, P4, P5 = perfusion pressures recording spots.

Fig. 15. Mock-circulations with 3 different tube positions

7.1.3 Statistics

Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

7.1.4 Results

As been resumed in (Table 5) and (Figures: 16 & 17), momentum energy losses were significantly increased with the pulsatile tube in positions: III and II, compared to position I. Furthermore, there were observations of an increased perfusion pressure at P5 from the initial P1 of those groups (II and III), signifying severe turbulence at the post-cannula zone, which theoretically, corresponds to patient's aorta. There were minimum momentum energy losses with the steady flow in position. I, In contrast to positions II and III, there were important vortices with obstructive zones that created a sort of retrograde flow even before pulsations.

	Groups	P1	P2	P3	P4	P5
	NP (I)	32,5 ±1,3	31,3 ± 1,3	30,3 ± 0,5	30,3 ± 0,5	30,8 ± 0,5
1 -	NP (II)	36,3 ±1,3	37,8 ± 1	39,5 ± 0,6	38,5 ± 0,6	39,3 ± 0,5
	NP (III)	40,3 ±1	42,3 ± 1	43 ± 0,00	42,3 ± 0,6	43 ± 0,00
	Pm. (I)	34,5 ± 1,7	34,5 ± 1,3	33,5 ± 1,7	32,3 ± 1	31,8 ± 1
2 -	Pm. (II)	39,3 ± 0,5	40 ± 0,8	40,8 ± 0,6	40,5 ± 0,6	40,3 ± 0,5
	Pm. (III)	43 ± 1,2	46 ± 2,2	46,3 ± 1,5	44 ± 0,8	44,8 ± 0,5
	Ps. (I)	72 ± 3,5	81 ± 11	92,8 ± 4,9	98 ± 11,5	92,8 ± 5,6
3 -	Ps.(II)	97,3 ± 7	92,3 ± 6	90 ± 11,2	81,3 ± 7,5	82,3 ± 8,4
	Ps. (III)	84,3 ± 6,6	79,8 ± 5,9	79,8 ± 5,5	69 ± 3,9	69 ± 4,2
	Pd. (I)	(-)4,4 ± 3,2	(-)6,5 ± 7,4	(-)13,6±11,7	(-)35,3±8	(-)33,5±13,3
4 -	Pd. (II)	(-)1,1 ± 6,2	(-)7,8 ± 4,4	(-)0,8±9,4	5,6 ±8,4	13 ±3,2
	Pd. (III)	0,5 ± 10	5,3 ± 5,3	7,5 ± 7,5	20,3 ± 3,8	20,3 ± 0,5
	PP (I)	76,4 ± 3,4	87,5 ± 11,8	106,4 ± 15,9	133,3 ± 17,7	126,3±18,6
5 -	PP (II)	98,3 ± 7,9	1OO ± 10,4	100,3 ± 10,3	75,7 ± 15,4	66 ± 6,1
	PP (III)	83,8 ± 9,2	74,5 ± 8,7	72,3 ± 12,6	48,8 ± 7,1	48,8 ± 4,7

P = pressures in (mmHg); I,II,III: correspond to each different 3 circuits; NP: non-pulsatile pressure; Pm: mean pulsatile pressure; Ps: systolic pulsatile pressure, Pd: pulsatile diastolic pressure; PP: pulse pressure; ($p<0.001$).
Pulse pressure was higher at P5 with position I, compared to position II & III. Pm was higher at P5 compared to NP with position I.
N.B. For further details please refer to the following experimental movies site:
http://www.nourmd.com/

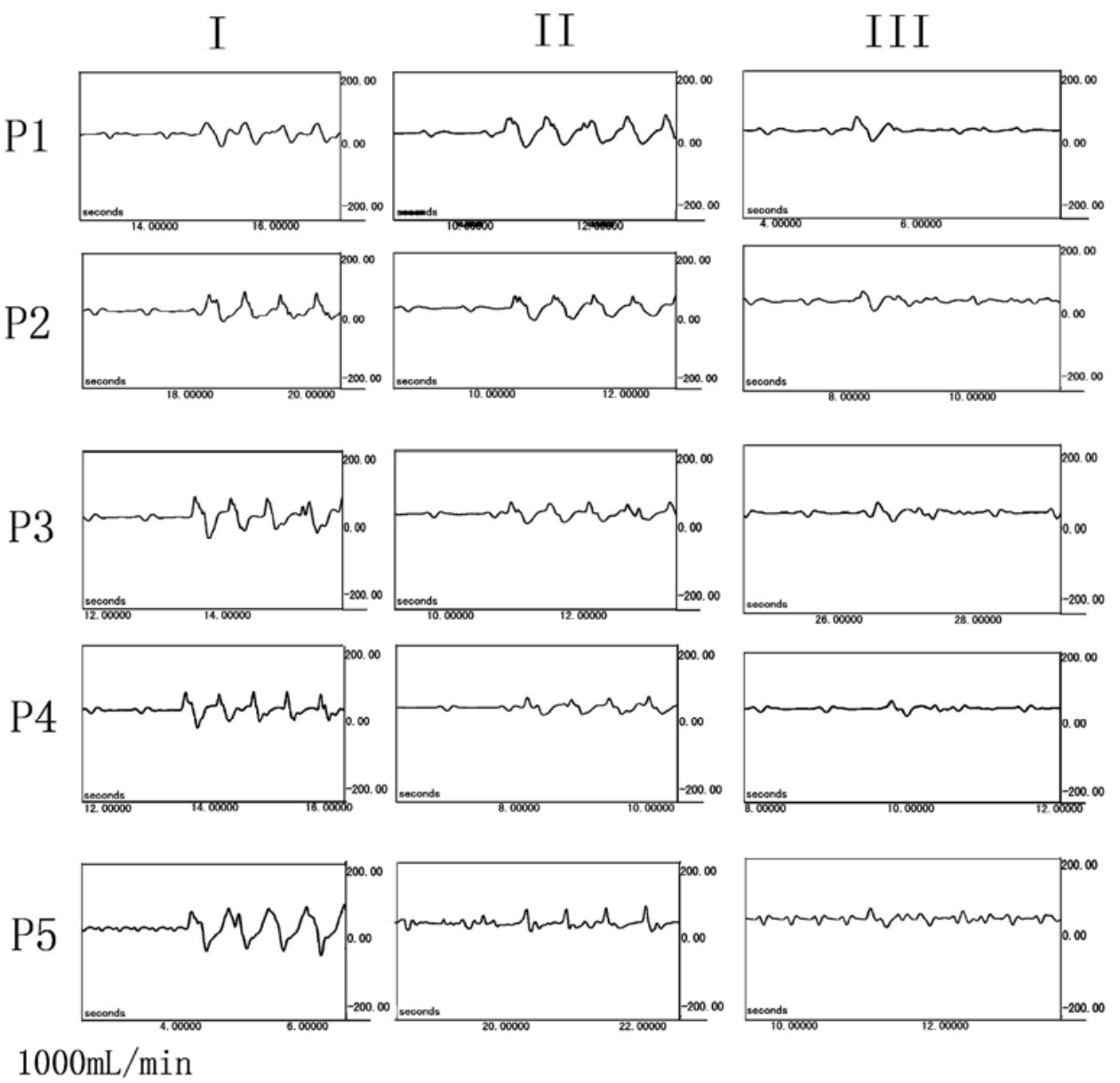Table 5. Results of momentum energy losses, obtained in 3 different mock circuits.

Fig. 16. Perfusions curves obtained in vitro

Perfusion curves (in mmHg) obtained at different circuit sites in 3 different pulsatile Tube positions: I, II, III close & distant from aortic cannula and pre-oxygenator respectively. The perfusion curve amplitude was significantly higher at P5 with position I, compared to positions II & IIII.
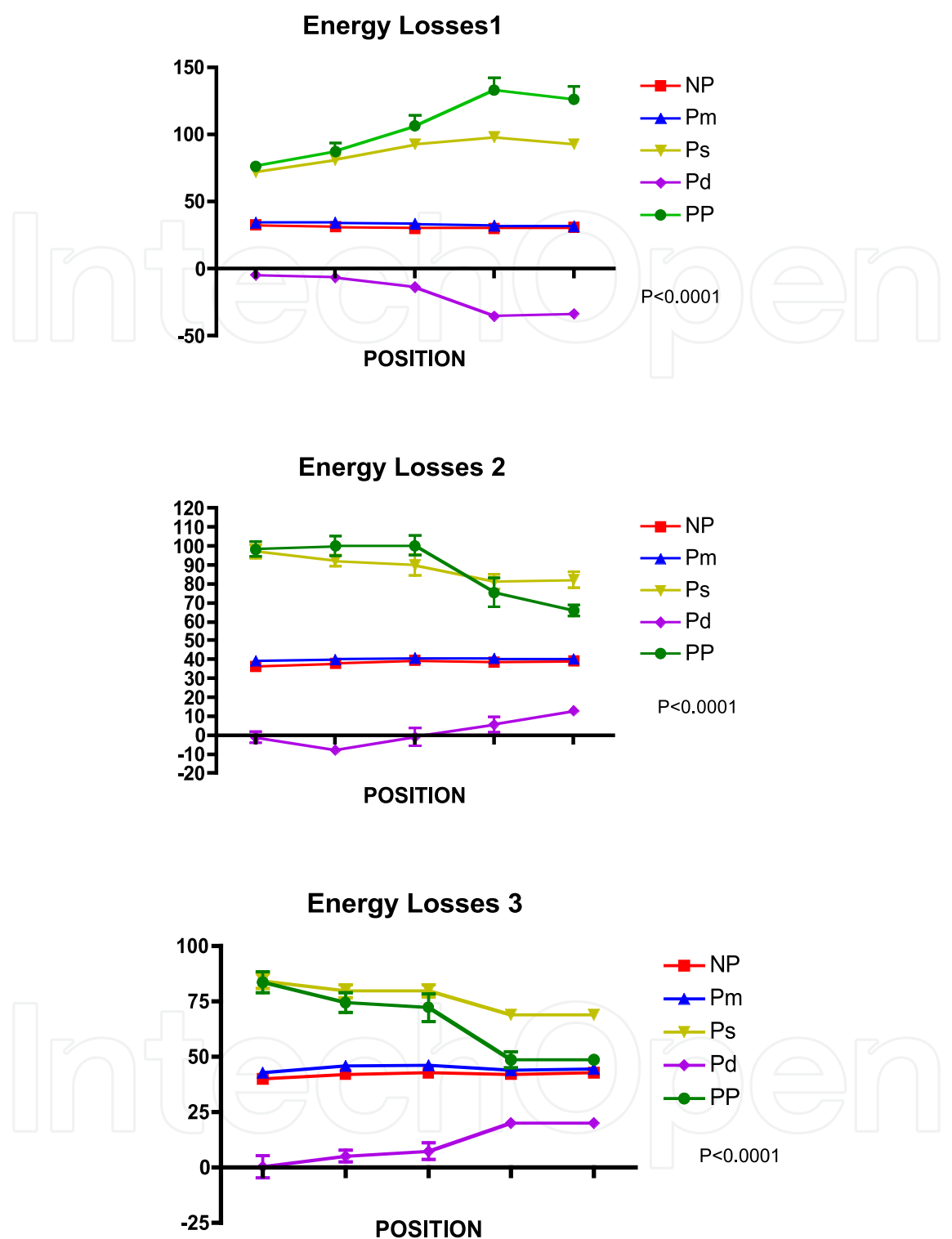
Energy losses 1 (upper panel) = pulsatile tube at 6 cm from aortic cannula; Energy losses 2 = pulsatile tube at 150 cm from aortic cannula; Energy losses 3 = pre-oxygenator pulsatile tube position. P1-P5 = distant circuit spots for perfusion pressure records (mmHg). NP= non-pulsatile; Pm = mean pulsatile pressure, Ps = systolic pressure; Pd = diastolic pressure; PP = pulse pressure. The pulse pressure (green color) was significantly higher with position I compared to positions II & III.

Fig. 17. comparative steady and pulsatile flow perfusion curves obtained from 3 different circuits

PULSE PRESSURE

PULSATILE SYSTOLIC PRESSURE
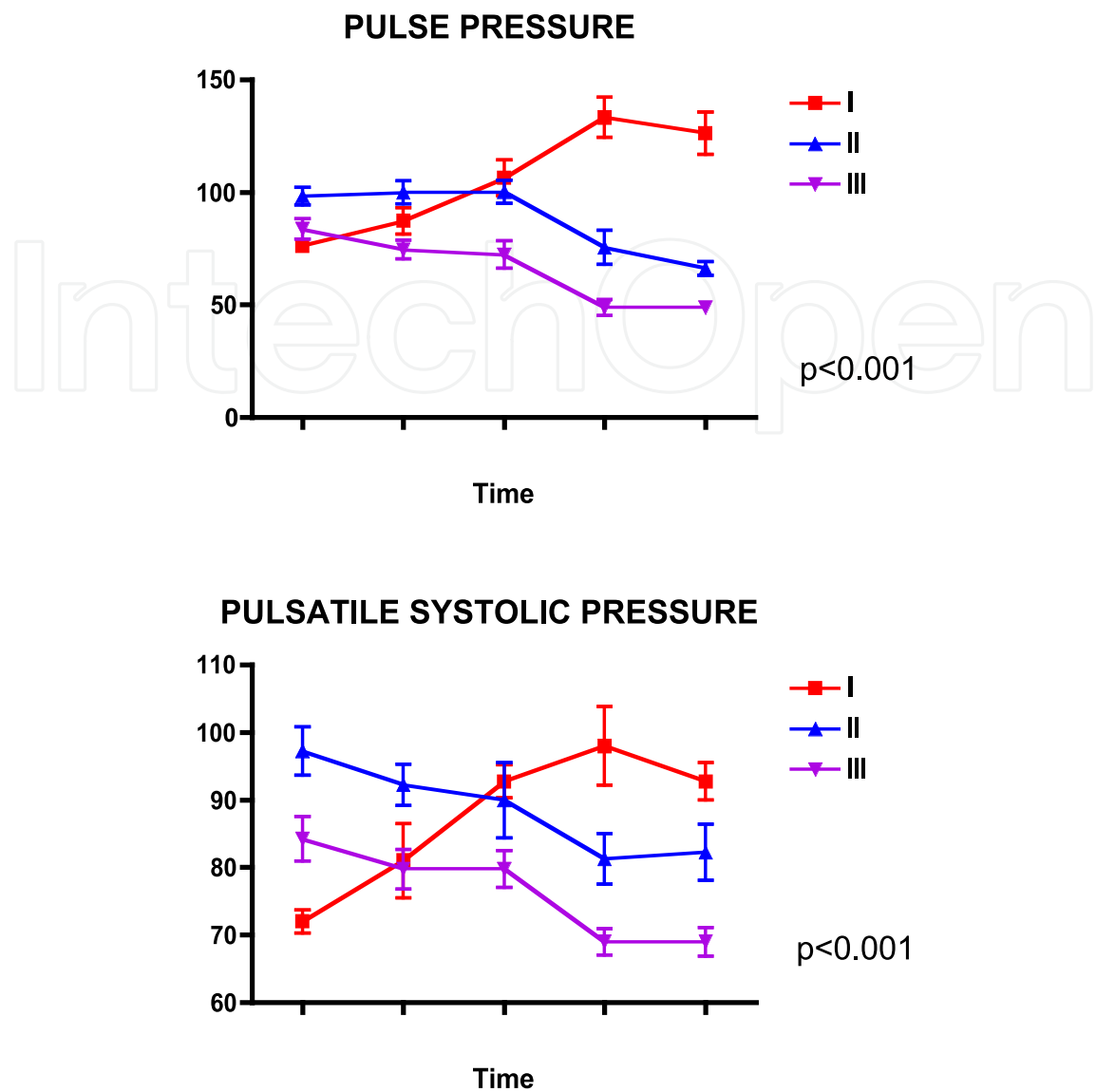
Energy losses with different tube positions: I = pulsatile tube at 6 cm from aortic cannula; II = Pulsatile tube at 150 cm from aortic cannula; III = Pulsatile tube pre-oxygenator. P1-P5 = perfusion pressure records (mmHg) at main circuit energy losses spots. At P5 the pulse pressure (upper panel) as well as the systolic pressure (lower panel) were significantly higher in position I (red color) compared to other positions: II (blue color), and III (violet color).

Fig. 18. Pulsatile flow pulse pressure (upper panel) and systolic pressure (lower panel8)

7.1.5 Comments

In this study, a steady perfusion flow was transformed successfully into pulsatile flow with a simple double lumen tube integrated into the arterial perfusion line of a conventional CPB circuit. According to our previous explanations (Figures 4 and 8), quantification of circulatory perfusion devices (CPB, CAD) depends on their momentum energy losses. The Bernoulli's principles of energy losses could be applied with accuracy in vitro to quantify lumped models like CPB (Undar et al., 2007). In vivo vessels elasticity and vascular tone bring CPB quantification more closer to Newton's law of shear stress as a major stimulant for endothelial NOS / resistances control.

The resulted energy losses have proven the importance of the pre-cannula zone represented in position I by P4, compared to P3 and P2 with positions II and III respectively showing severe turbulent flow with important vortices constitutions at this zone or (Z 3). Finally, the prototype by its position downstream to oxygenator could avoid an important obstructive zone of energy losses, which is almost constant with current CPB necessitating a double perfusion pump system and special low resistance oxygenator.

Conclusion CPB induces momentum energy losses with severe endothelial dysfunction. Current pulsatile devices induce inadequate curves with high costs. Pulsatile tube, adaptable to a conventional driving system could induce homogenous, downstream and nearly physiologic pulsatile perfusion flow with low momentum energy losses. This is a cost-effective method, promising low mortality and morbidity, especially in fragile cardiac patients.

7.2 In vivo study (study in progress)

The pulsatile tube device was tested as a left ventricular assist device (LVAD), in pediatric animal models (piglets) with acute myocardial ischemia.

Materials and methods: in the pulsatile group: a prototype of a pulsatile tube was realized in the same manner as the in vitro study, then a short piece of 14 Fr. PVC tube was modified as a aortic cannula (Figure 19), in a matter to avoid the conastant energy losses caused by current cannulae length with narrow tips. Same a small LV vent was attached to the other end of the tube. The whole system was connected to a pulsatile generator console (HX-300 TaiMeng Technologies Inc®). In the control group: a centrifugal pump (Sorin group Revolution ®), was connected to a standard aortic cannula (12 Fr. DLP®-Medtronic, Inc.) and apical vent (14 Fr. DLP®-Medtronic, Inc.).
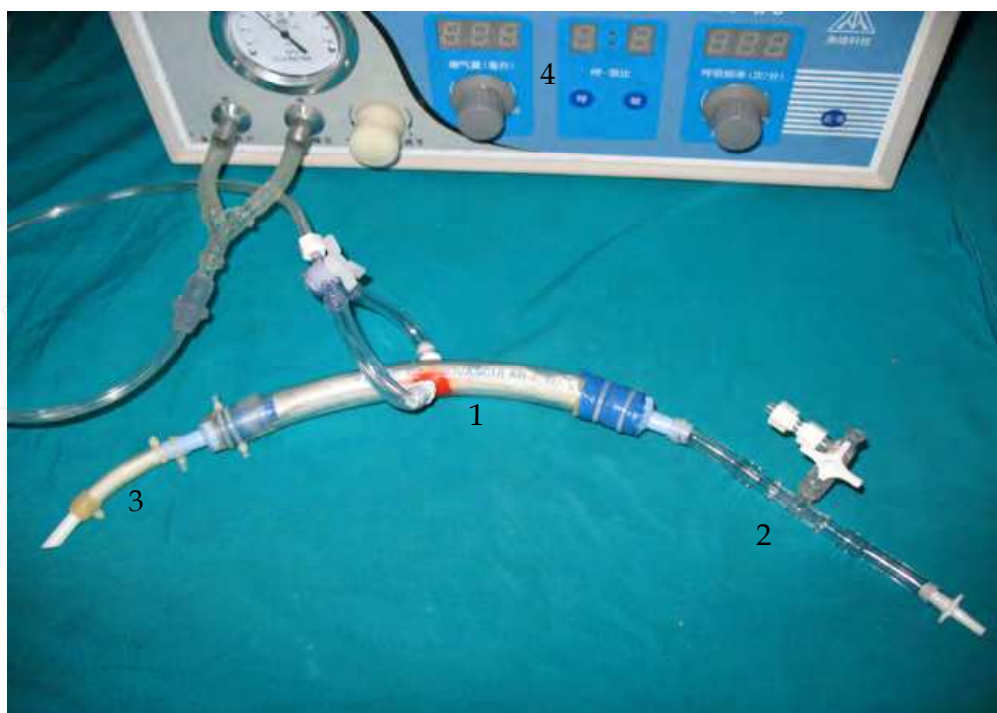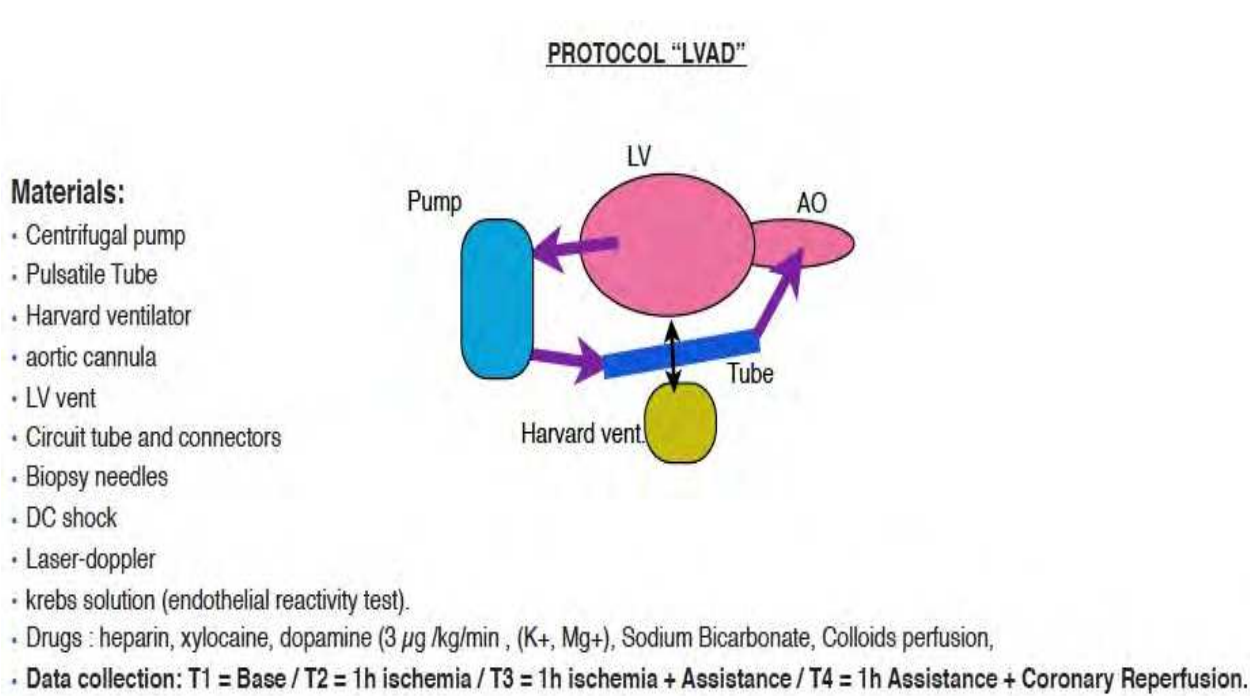

Tube (1) is connected to aortic cannula (2), LV vent (3) and console (4).

Fig. 19. Pulsatile tube prototype used as LVAD

Steps	Maneuvers
1	Anesthesia / sternotomy / pericardectomy / dissection of great vessels.
2	Insertion of an infundibular Swan-Ganz, aortic and apical pursestrings.
3	Hemodynamic measurement / blood test data for Time 1 (T1).
4	Heparin injection (2ml/kg) LAD coronary artery mid-term ligation (snugger).
5	Time 2 (T2) = after 1 hr of ischemia without any medical support
6	LVAD System switched on for 1hr.
7	Time 3 (T3) data collection after 1 hr of assistance with LAD ligation.
8	Removal of LAD snugger (coronary reperfusion + LVAD assistance) for 1hr.
9	Time 4 (T4) data collection before animal sacrifice

Table 6. Summary of the surgical steps

Operative schema and steps of surgical protocol are resumed in (Figure 20) and (Table 6) respectively.


PROTOCOL "LVAD"

Materials:
· Centrifugal pump
· Pulsatile Tube
· Harvard ventilator
· aortic cannula
· LV vent
· Circuit tube and connectors
· Biopsy needles
· DC shock
· Laser-doppler
· krebs solution (endothelial reactivity test).
· Drugs : heparin, xylocaine, dopamine (3 μg /kg/min , (K+, Mg+), Sodium Bicarbonate, Colloids perfusion,
· **Data collection: T1 = Base / T2 = 1h ischemia / T3 = 1h ischemia + Assistance / T4 = 1h Assistance + Coronary Reperfusion.**

(Ao=aorta, LV=left ventricle, vent. = ventilator)

Fig. 20. Schema representing the pulsatile tube as a LVAD

7.3 Results

This ongoing study results showed better hemodynamic with lower cardiac enzymes in the pulsatile group compared to control (Figure 21) and (Table 7).
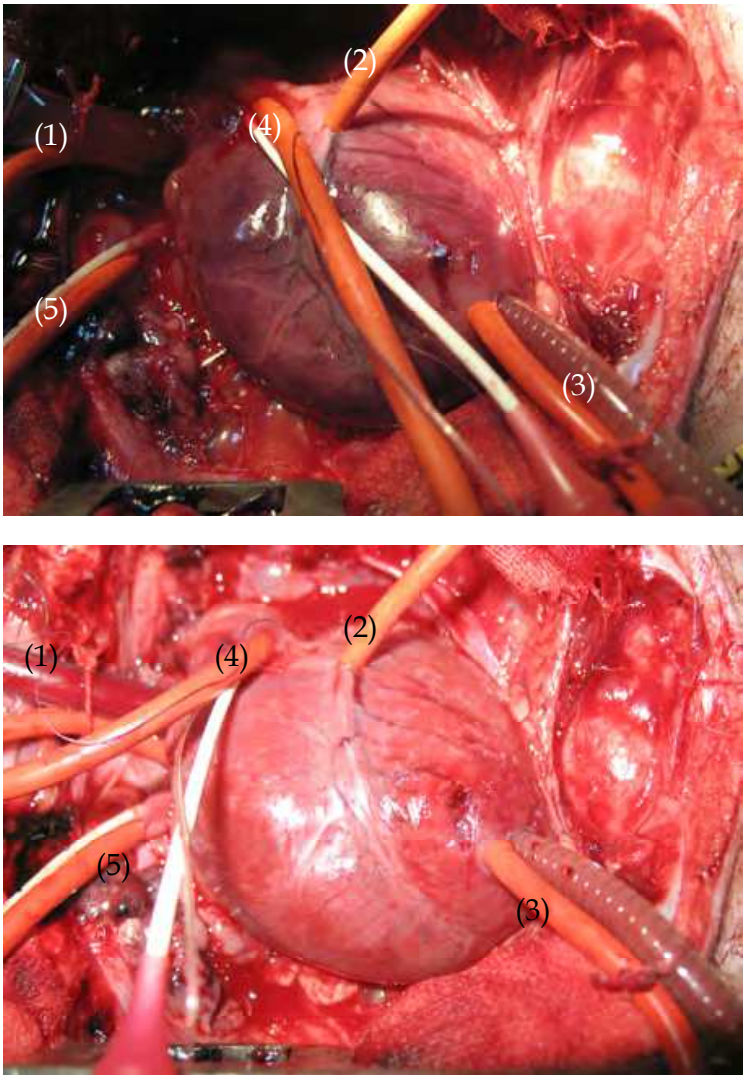
Upper panel: shows a massive myocardial ischemic zone after LAD ligation; Lower panel: ischemic zone after 15 min of pulsatile tube assistance. 1 = Aortic cannula; 2= LAD snugger (permanent coronary occlusion); 3 = left ventricular apical vent; 4 = trans-infudibulum pulmonary artery & Millar right ventricular pressure catheters; 5 = right atrium pressure line.

Fig. 21. Pulsatile tube as LVAD in piglet ischemic model

Test	T1		T2		T3	
	P	**NP**	**P**	**NP**	**P**	**NP**
cTnT*	0.036	0.06±0.07	-	021±0.1	0.029	1.31±0.61
CK-MB*	0.92	0.56±0.41	-	0.89±0.85	0.100	100±4
PLT	351	487±100	-	245±128	47	80±3
Htc	0.27	0.32±0.06	-	0.28±0.08	26	33±7
Lac (v)	1.23	3.3±3.1	-	4.9±4.1	0.6	0.4±0.1

Table 7. Biochemistry results: cardiac enzymes*; P: pulsatile group; NP: non-pulsatile (control group); Plt: platlets: Htc: hematocrit; Lac (v): venous lactate. T1: baseline; T2: 1h of ischemia; T3: after 2h of myocardial assistance.
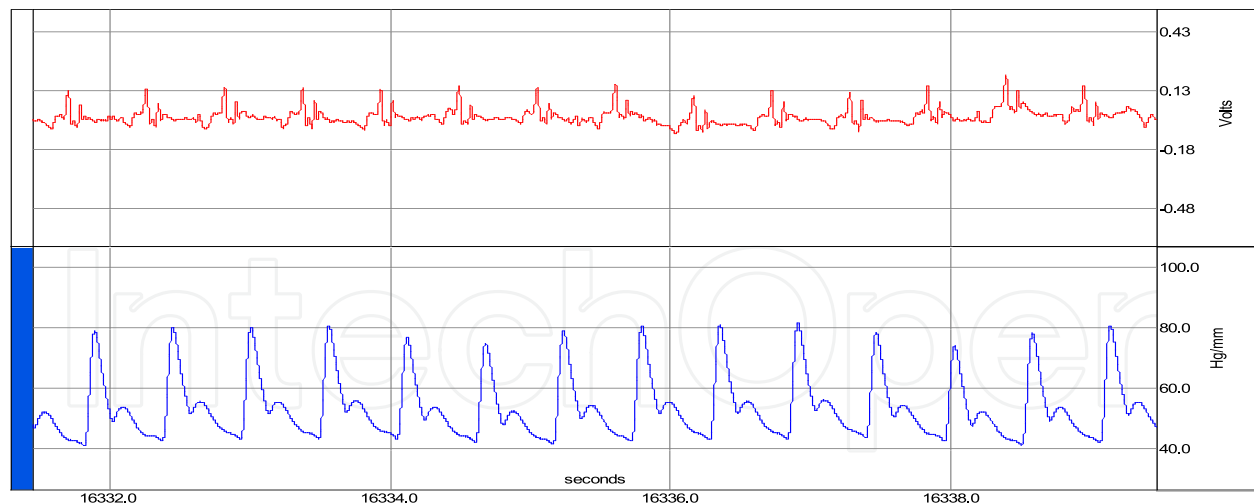
Fig. 22. Pulsatile tube perfusion curve in vivo, as a LVAD in acute MI piglet

The pulsatile tube's perfusion curve was nearly physiologic with complete discharge of the LV and unsynchronized with heartbeatt, as have been demonstrated on the operative movies.

7.4 Operative movies of the pulsatile Tube (LVAD):

-    Pulsatile as a LVAD associated with a conventional roller pump (Cobe® Cardiovascular Inc.): http://www.nourmd.com/
-    Pulsatile tube as a main LVAD, without any other associating driving systems: http://www.nourmd.com/
-    Control group movie, LVAD by (Sorin Group Revolutionary centrifugal pump®): http://www.nourmd.com.

7.5 Comments

The exposed results proved the feasibility as well as the effectiveness of the pulsatile tube as a LVAD. These preliminary results have shown hemodynamic improvement and myocardial recoveries, lower cardiac enzymes in the pulsatile group, compared to control. This hemodynamic improvement was significant in the pulsatile tube group and despite the maintained coronary obstruction in a fragile pediatric model, with very poor coronary collaterals. Interestingly we've tested the tube alone without a perfsuion pump and LV vent, as an endocardial stimulator. Myocardial recovery and macroscopic disappearance of the ischemic zone were obvious after few minutes (< 5min), of unsynchronized pulsations (please refer the attached movie). This was ended by severe vasodilatation and cardiac arrest. Currently, we are trying to overcome these drawbacks, particularly, the inner tube (PTFE) microporosity and vasodilatations, with a new generation of pulsatile tube prototypes.

8. Evaluation of the pulsatile catheter device (in vivo)

Prototype: a standard IABP catheter (8 Fr., 30 cc) was modified. Briefly, its original balloon membrane was peeled off and replaced with a small piece of commercial rubber balloon, secured and tied manually at each end of the catheter. This created an inflatable

compartment of 1×1 cm. The distal part of the prototype was connected to a cardiorespiratory monitor (BIOPAC® physiology monitoring system, ECG channel). For a pneumatic rhythmic driving force, it was attached to a small animal ventilator (HX-300 TaiMeng Technologies Inc®). It was tested for leakage while pulsating in a heparinized saline bath. Once the prototype was inserted into the pulmonary trunk, the circuit inflation volume was adjusted (usually between 50-90 ml) to avoid right ventricular outflow tract obstruction. The ventilator was pulsed at a frequency of 110 cycles/min. The prototype device was tested in two animal model studies for acute MI and acute PAH as follows:

8.1 Acute myocardial ischemia model

(part of the results was presented at the 17th conference of ACTVS, Nour, 2009)

Material and methods: Twelve piglets (8.3 ± 1.5 kg) were given either pulsatile (P: n=6) or non-pulsatile (NP: n=6) nitrates treatment. Both groups underwent permanent left anterior descending coronary artery (LAD) ligation with a median sternotomy (Figure 23). After 1 h of ischemia, heparin was injected (150 IU/kg). In group P, a prototype CAD, driven by a small ventilator, was introduced into the pulmonary trunk and pulsated intermittently over 1 h at 110 bpm, irrespective of heart rate (73 ± 16 bpm). In group NP, nitrates were given (7±2 μg/kg/min) for 1 h. Animals survived ischemia for 2 h in group P vs. 93±30 min in group NP.
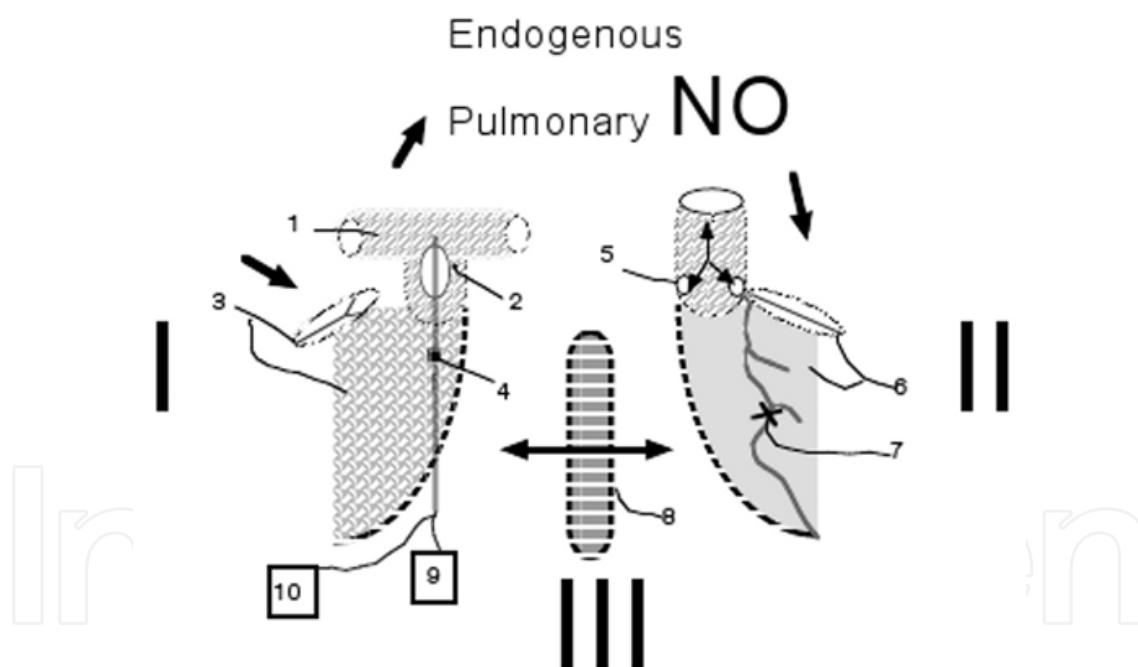
1 = Pulmonary artery (PA); 2 = pulsatile catheter fitting PA trunk; 3 = right ventricle (RV) inlet-outlet compartments; 4= infundibular site of pulmonary catheter insertion; 5 = arrows showing presumed passage of pulmonary eNOS (backward through coronary ostia and/or forward through systemic circulation); 6 = left ventricle (LV) inlet-outlet compartments; 7 = permanent ligation of the left anterior descending coronary artery distal to the second diagonal branch; 8 = interventricular septum; 9 = cardiorespiratory monitor; 10 = pneumatic driving force. I = pulmonary eNOS primarily induced at PA zone with catheter pulsation; II = pulmonary eNOS natural passage through the left heart circuit; III = presumed pulmonary eNOS involvement in myocardial recovery most probably through microcirculation and/or the RV interseptal coronary network.

Fig. 23. Presumed mechanism and passage of induced pulmonary eNOS

With the macroscopic disappearance of infarction (Figure 24), group P exhibited improved hemodynamics (Figure 25) and significantly lower myocardial apoptosis (0.66±0.07) compared to group NP (4.18±0.27), (Figure 26). Vascular resistances (dyne.sec/cm^{-5}.kg^{-1}) were significantly lower (P<0.01) in group P vs. group NP: pulmonary resistance was 119±13 vs. 400±42, and systemic resistance was 319±43 vs. 1857±326, respectively. Myocardial endothelial NO synthase mRNA expression (Figure 27), was higher in group P (0.90±0.09) than in group NP (0.25±0.04; P<0.01), probably due to endogenous pulmonary NO secretion.
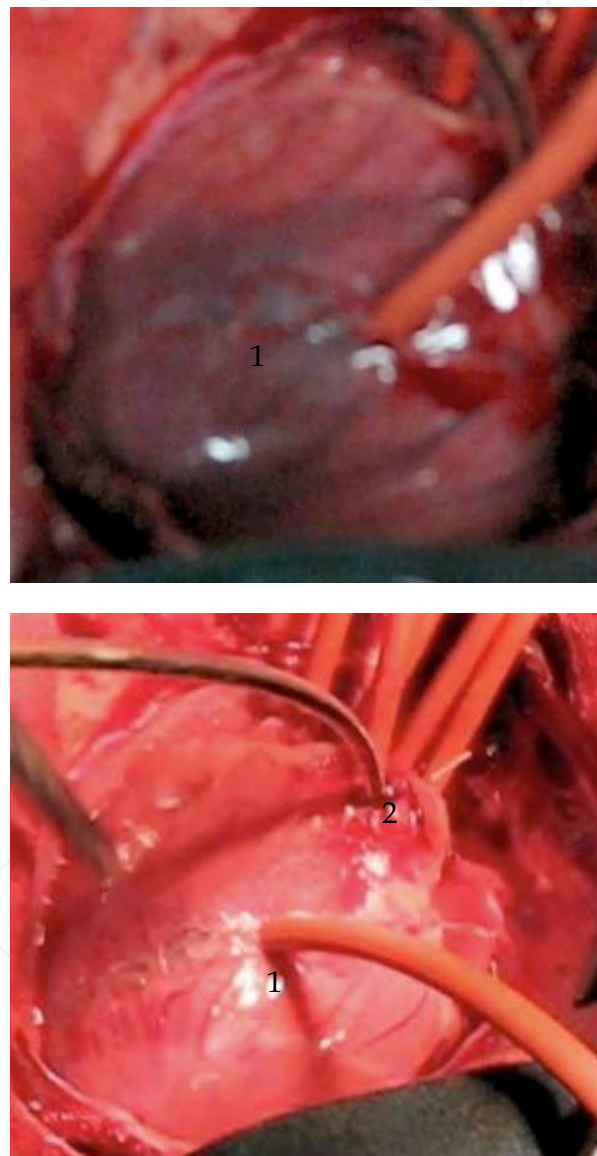
Left panel figure showing dark infarcted myocardial after 50 min of ischemia; right panel figure showing significant reduction of ischemic myocardial zone after 10 min of pulsation; 1 = left anterior descending coronary artery snugger; 2 = infundibular site of the intrapulmonary pulsatile catheter insertion.

Fig. 24. Macroscopic disappearance of the ischmeic zone in group P
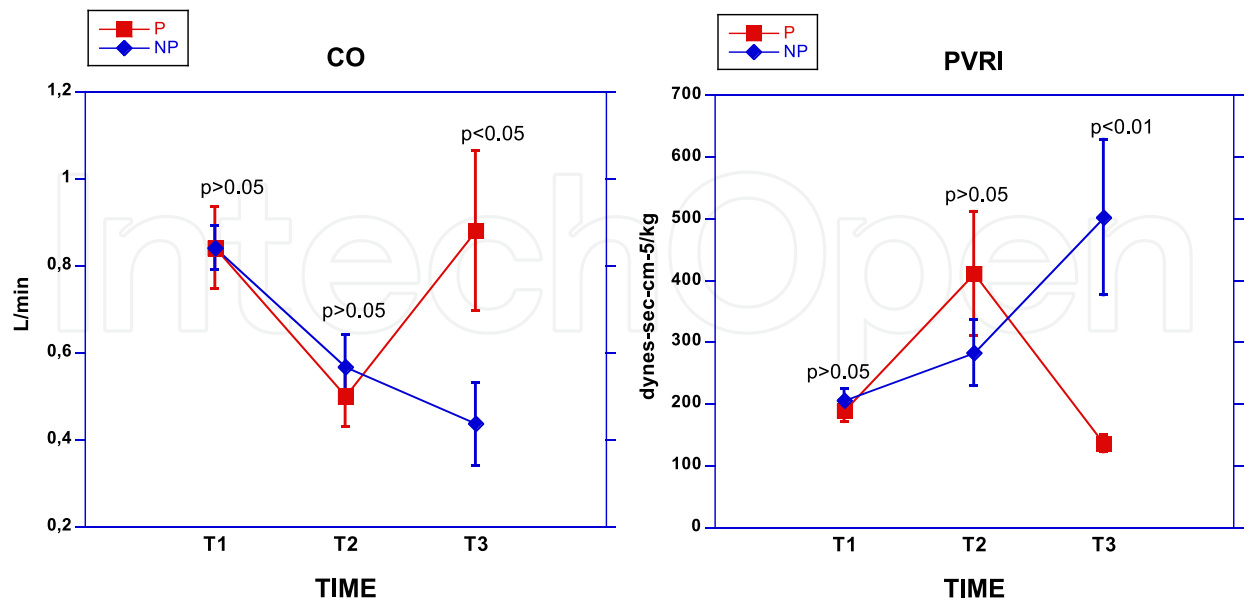
Right panel showing the pulmonary vascular resistances index (PVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). PVRI (dynes.sec.cm^{-5}/kg) were significantly lower (p<0.01) were significantly lower at T3 in group P compared to group NP. Left panel showing the cardiac output (CO) from both groups P and NP. CO (L/min) was with significantly improved at T3 in group P compared to group NP (p<0.01), in group P (red color) compared to group NP (bleu color).

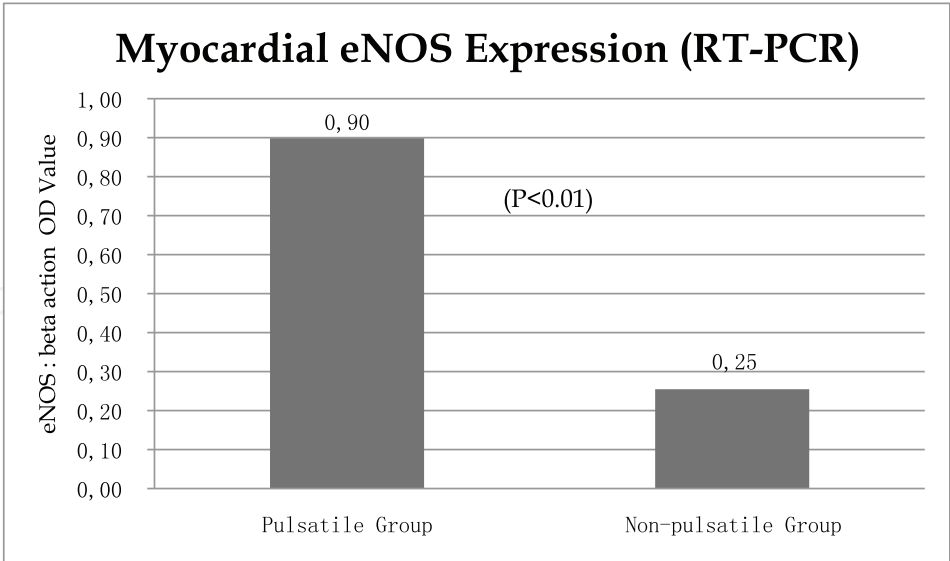Fig. 25. Hemodynamics improvement with the pulsatile treatment in group P
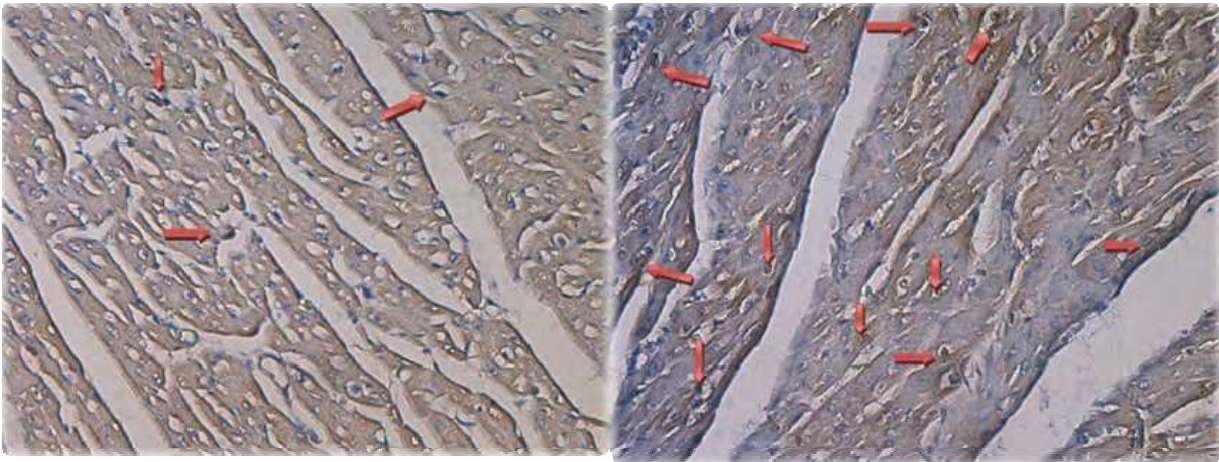
Fig. 26. Myocardial apopotosis (TUNEL test)

Representative figures from both groups showing apoptotic cells manifestations (red arrows), from both groups: group P (left) and group NP (right). The apoptotic index (AI) in group P was significantly lower than that in group NP (P<0.01).

RT-PCR results shown with statistics, in which myocardial eNOS expression was significantly higher in group P (left) compared to group NP (right). (p<00.01).

Fig. 27. Myocardial eNOS mRNA expression
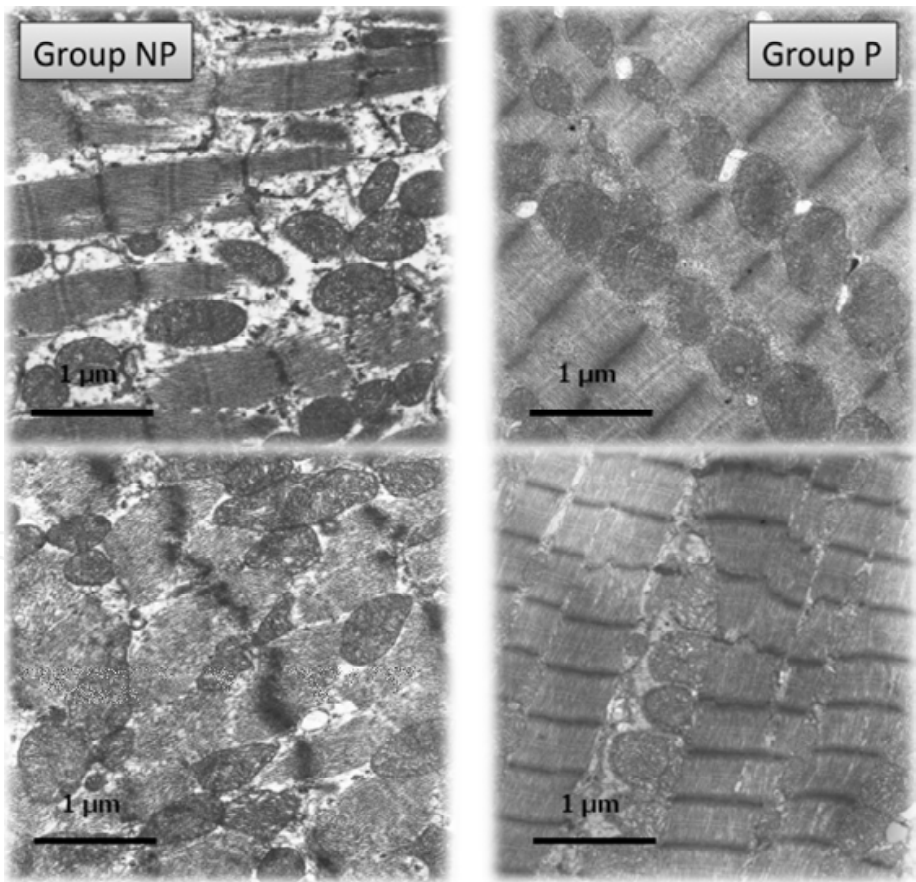
Left panels: samples from the non-pulsatile, nitrate treatment group (NP); right panel: sample from the pulsatile treatment group (P). Notice the relatively well-preserved myocardial microstructure in group P. Bar scale on each graph equals one micrometer.

Fig. 28. Myocardial microstructure visualized with transmission électron microscopy

8.2 Comment

Decalogue of original observations emanated from the present preliminary study as follows:

i.   Hemodynamic improvement, with significant recovery of the myocardial contractility and cardiac output (CO), despite maintained coronary obstruction. This was obvious macroscopically, and confirmed by low myocardial apoptosis manifestation, and relatively well-preserved cardiomyocytes organelles in the pulsatile group P.

ii. Intrapulmonary shear stress enhancement, that was induced successfully and for the first time according to literatures, as that was practiced with uncertain results, using an intra-aortic balloon pump (IABP) (Letsou et al. 1993). The uncertainty is probably due to differences between vessel geometries and catheters diameters, in addition the right heart side has specific morphological particularities that must be considered (Burton, 1954), (Huang W & Yen RT, 1998).

iii. Endogenous vs. exogenous nitric monoxide (NO): generally, NO has an important effects on the cardiovascular system as a potent vasodilator, inhibitor of platelets aggregation and myocardial contarctility (Jones SP & Bolli, 2006). Shear stress induces endogenous NO production by activating endogenous nitric oxide synthase (eNOS). (Chatzizisis et al., 2007), like during physical exercise Walsh et al., 2003). Also exogenously administered NO donors like Nitrates, can to be deleted induce eNOS (Ignarro, et al.,2002). Therefore, the study results showed that physiologically induced NO was superior to exogenous nitrates in acute IHD syndrome.

iv. Microcirculation vs. collaterals, in group P, the increased expression of myocardial eNOS mRNA (Depre, et al. 1997); with fewer apoptotic cells (Mital, et al., 2002) could be explained by endogenous NO due to the intrapulmonary catheter pulsation. Meanwhile the exact mechanisms of action remain to be explored. However several conditions supported the role of microcirculation, as the subendocardial resistance vessels are more sensitive to mediators of vasodilatation and endothelium dependent dilators (Pelc, 1987). In consideration of the short biological lifetime of NO (Doherty et al., 1998), and the maintained coronary ligation, the chosen model is known for poor coronary collaterals, in addition to the immature myocardium in young pig model (Gorge, et al. 1989). This may be explained by an undiscovered endothelial mediator(s) that improved myocardial microcirculation in the group P. in group P.

v.   Reperfusion injury syndrome to be deleted, interestingly the study results showed that immediate myocardial reperfusion might be unnecessary. The procedure, provides stabilization as well as myocardial and hemodynamic recoveries without the urgent need of reperfusion with the well known consequences of the reperfusion injury syndrome (Heinzel, et al., 2008). This was confirmed with our ongoing study, using an intrapulmonary catheter device induced percutaneously through the jugular vein.

vi. Right heart vs. left heart endothelium, this study suggested that the right heart endothelium responded rapidly, to shear stress stimuli, compared to the left heart endothelium, which is most frequently, stimulated with devices like IABP and EECP, known for tolerance and long with long term effectiveness respectively (Pagonas, 2010). We found that the PA endothelium was hypersensitive; a few minutes of intrapulmonary pulsations were more than sufficient to drop systemic and pulmonary pressures. At the beginning of our trials, have observed severe vasodilation with

continuous intrapulmonary catheter pulsation (2 animals were expired). We then shifted from continuous to intermittent pulsation controlled by hemodynamic readings (5-10min pulsation) interrupted by pause intervals (10-15 min).

vii. Venous vs. arterial approach, the systemic arterial approach is most commonly practiced in IHD management, typically with IABP and/or PCI procedures. However, these require specific operative environments with high risks of risk vascular complications (Busch, et al. 1997); (Dangas, et al., 2001). Instead, the study provides a safer and cost-effective venous approach for IHD management that could be done by an ER therapist without the need to specific cardiac centers facilities.

viii. Diastolic CAD synchronizations vs. unsynchronized pulsatile catheter, contrarily to present synchronized cardiac assist devices (CAD), like the IABP, EECP, etc., we believe that unsynchronized catheter pulsation simplifies and broadens its application as an efficient cost-effective method for IHD management. Recorded pressure curves showed that the delivered catheter pulsation was faster than the heart rate; Nevertheless, it did not disturb right ventricular hemodynamic or obstruct the outflow tract.

ix. Suitable for almost all kinds of myocardial ischemia, as been observed, hemodynamic stabilization could be achieved after a few minutes of device pulsation without any pharmacological supports. Positioned inside the PA trunk, the device can reduce pulmonary afterload without jeopardizing preload in case of RV ischemia. Its small dimensions allow applications in pediatrics and other cases of non-atherosclerotic IHD (e.g. congenital, spasm, or vasculitis, induced MI. Moreover, in preconditioned (Bolli R, 2001), hibernating, stunned myocardial or permanent ischemic lesions (Vroom MB & van Wezel, 1996), long term intermittent intrapulmonary or intracoronary sinus catheter pulsation could restore myocardial tissues and dysfunctional endothelial coronary lesions.

x. The pulsatile catheter device vs. CAD, compared to current CAD drawbacks, an autonomous small catheter driven by a portable or implantable pacemaker-like generator, could be safely inserted into the circulatory system of any patient or chosen vessel, including arterial, venous or umbilical. And most probably, it could restore atherosclerotic endothelial lesions and endothelial dysfunction with the pulsatile catheter insertion into the intrapulmonary or intracoronary sinus in coronary atherosclerosis or into the main lumen of a diseased systemic artery (e.g. carotid, renal, femoral, etc.). An enhanced external counter pulsation studies in animal models have shown that regular application of endothelial shear stress stimuli could improve conditions related to atherosclerotic endothelial dysfunction (Zhang, et al., 2007). This could be a supportive argument for the concept.

In summary, An intrapulmonary pulsatile catheter device could improve hemodynamics and recover acute myocardial ischemia efficiently, compared to nitrates. This could be induced with an appropriate intrapulmonary catheter device, adaptable to vessel geometries, regardless of coronary occlusion and irrespective of the heartbeat. The procedure represents an innovative and cost-effective method for IHD management, particularly through an intravenous percutaneous approach (ongoing study).

Operative movie site: http://www.nourmd.com.

## 9. Acute pulmonary arterial hypertension*

Pulmonary arterial hypertension (PAH) is a dysfunctional endothelium disease with increased pulmonary vascular resistances (PVR) and poor prognosis. Current therapies are still insufficient. Alternatively, we propose a the pulsatile catheter device as a more effective for PAH management compared to traditional treatments.

Material and Methods: *Twelve* piglets (10.3 ± 3.8 kg) were given either intrapulmonary pulsatile (P: n=6) or non-pulsatile (NP: n=6) Tadalafil treatment. After median sternotomy and heparin injection (250 IU/kg), both groups underwent aorto-pulmonary surgical shunt during 1 h then removed (Figures 29 and 30). Over a second 1 h period: in group P, a catheter prototype, driven by a small ventilator, was introduced into the pulmonary trunk and pulsated intermittently at 110 bpm, irrespective of heart rate (90.6±10.74 bmp). In group NP, Tadalafil were given orally (1 mg/kg).
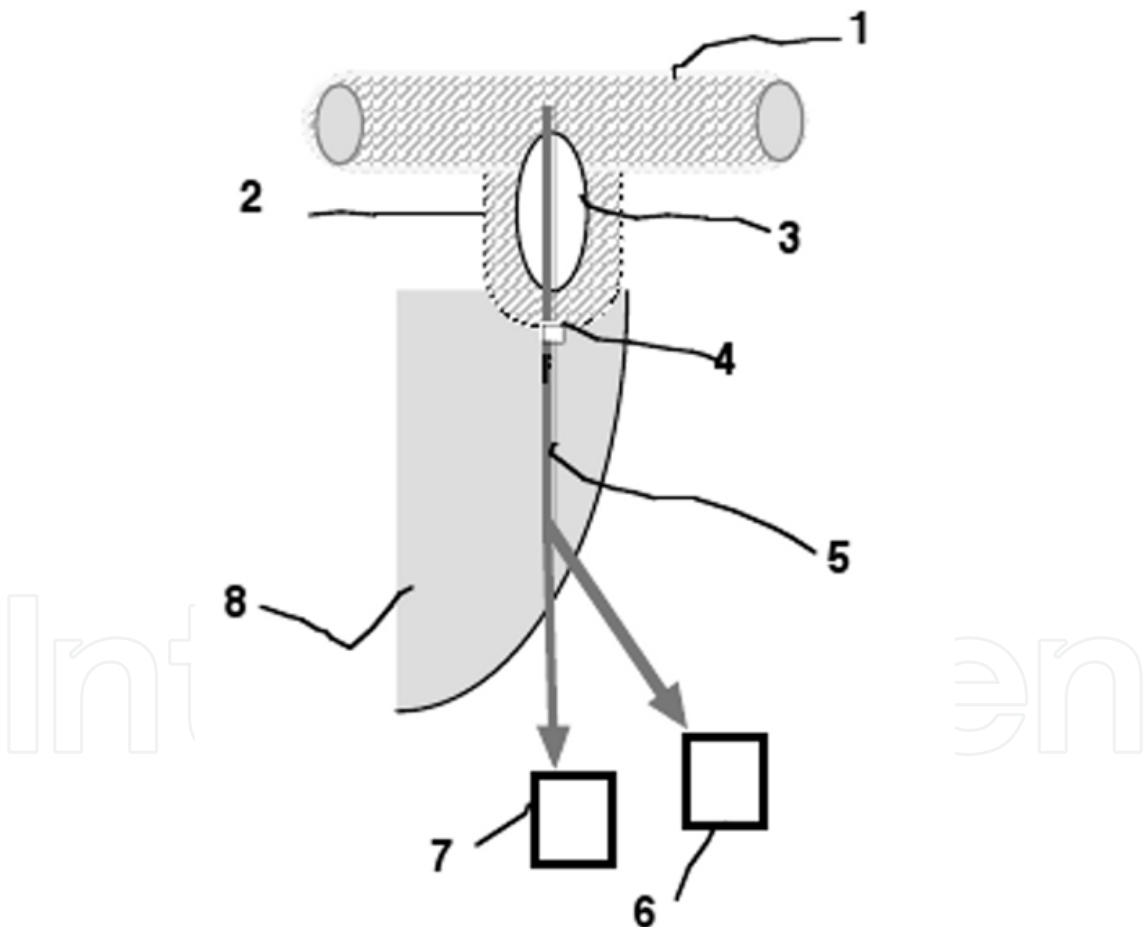
1 = pulmonary artery branch; 2 = pulmonary artery trunk; 3 = inflated balloon in place; 4 = infudibular snugger; 5=catheter shaft; 6= cardiopulmonary monitor; 7 = pulsatile driving system (small animal ventilator); 8 = right ventricular cavity.

Fig. 29. Intrapulmonary pulsatile system
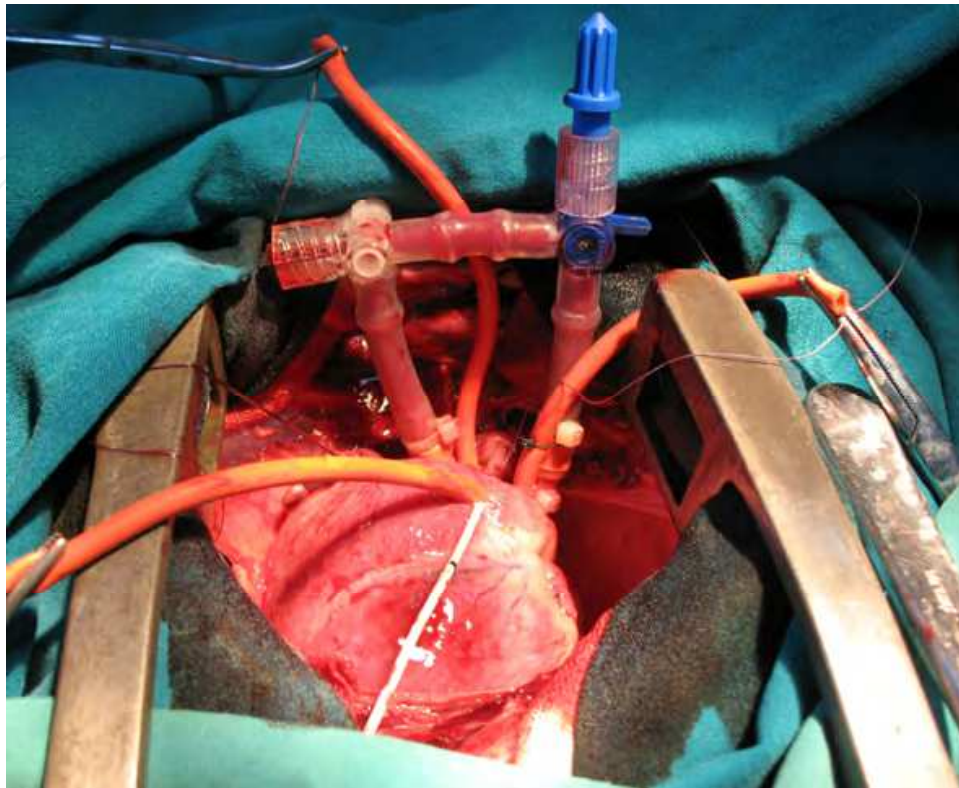
Assembled shunt showing: 2 PVC limbs unequally cut with ½ cm; connected together with silicone tube and equipped with 2 stopcocks and pressure lines connectors, prefilled with heparinized saline and clamped ready before insertion. Aorto-pulmonary shunt in place with infundibular intrapulmonary artery pressure line (white color).

Fig. 30. Aortico-pulmonary "U" shape external shunt system.

*Statstics***:** Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test for eNOS and a 2-way ANOVA for hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

Results: hemodynamic and cardiac output (CO) were significantly (p<0.05) better in group P compared to group NP: CO was 0.56±0.0.26 vs. 0.54±0.11 (L/min) respectively. Mean pulmonary artery pressure (PAP) was significantly dropped in group P compared to group NP: PAP was 9.6±2.97 vs. 32.25.07 respectively. Vascular resistances (dynes.sec/cm^{-5}.kg^{-1}) were significantly lower in group P vs. group NP: pulmonary resistance (Figure 31), was 85±42.12 vs. 478±192.91, and systemic resistance was 298.8±172.85 vs. 1301±615.79, respectively. The endogenous NO synthase expression in PA segments with Western blot analysis was higher from group P (0.81±0.78) vs. (0.62±0.35) in group NP (p>0.05).
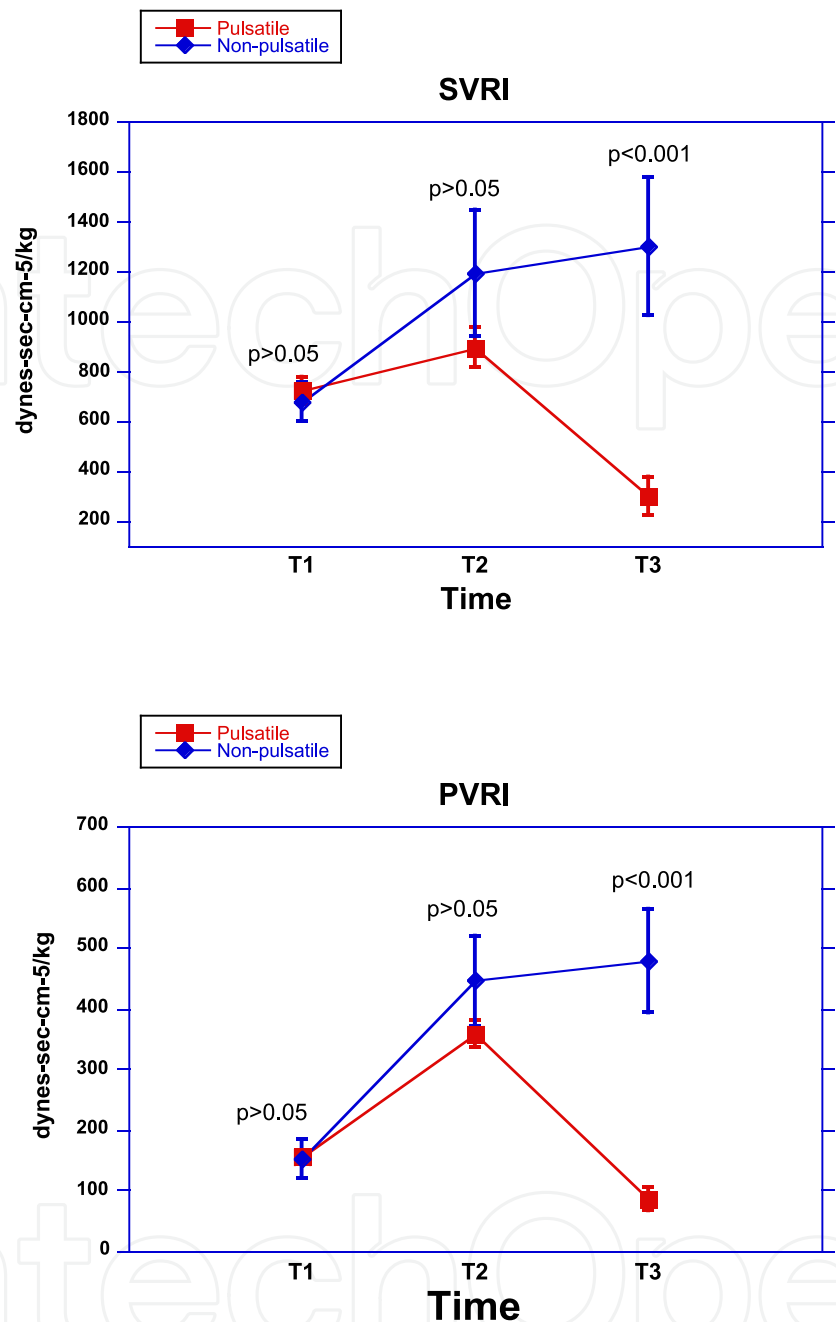
Fig. 31. Systemic and pulmonary vascular resistances indexes

Upper panel: showing data of the systemic vascular resistances index (SVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). Lower panel: showing data of the pulmonary vascular resistances index (PVRI) calculated from pulsatile group (P; red color) and non-pulsatile group (NP; blue color) at three predetermined time: T1= baseline; T2 after 1H of shunt and T3= end of 1h therapy. at T1 (baseline) and the end (T3). Both SVRI and PVRI (dynes.sec.cm^{-5}/kg) were significantly lower (p<0.001) were significantly lower at T3 in group P compared to group NP.

Comment This study confirms the dominancy of the right heart over the left heart and hemodynamic through PVR

The effect of intrapulmonary shear stress enhancement was immediate upon both PVR and SVR in the group P. The significant improvement of hemodynamic with rapid reduction of pulmonary pressure in group P compared to the group NP, confirms the dominancy of shear stress-mediated endothelial function enhancement method over traditional therapies*. Also this confirmed what we have mentioned with the ischemic models regarding the hypersensitivity of the right heart side endothelium of the pulmonary artery compared to systemic arteries.

Conclusions: Induced with an appropriate device, intrapulmonary shear stress-mediated endothelial function enhancement, provides a more effective nearly physiological therapy for PAH.

* Abstract of the study concept was presented at the 16th conference of ACTVS - Singapore, Nour, 2008). Paper in press, submitted to the Pediatric Cardiology Journal (Nour, S 2012).
Operative movies: http://www.nourmd.com.

10. Evaluation of the pulsatile suit device

This concerns the non-invasive devices (pulsatile suit) that were tested in vivo and healthy volunteers (the author and medical doctors colleagues).

10.1 Animal model of acute RV failure*

Cardiac assists devices (CAD) for right ventricular (RV) failure remain controversial with poor results. The purpose of this study was to evaluate a pulsatile suit CAD in an acute RV failure model vs. current therapies.

Material and methods (Figure 32): twelve piglets, divided in two equal groups: pulsatile group P and non-pulsatile group NP. Acute pulmonary incompetence was created surgically through median sternotomy. Management started once severe RV failure observed (48.1±24.5 min): in group P, a pulsatile trouser, driven by pneumatic generator was pulsated intermittently at 40 bpm, irrespective of heart rate (104±27 bmp). Group NP, was treated with oral Tadalafil (1 mg/kg), IV fluids and adrenaline (0.3μg/kg).

Results (Figure 33 & Table 8): after 1 h of therapy, hemodynamic and cardiac output (CO) were significantly ($P<0.05$) better in group P compared to group NP: CO 1±0.2 vs. 0.7±0.2 (L/min) respectively. Mean RV pressure (RVP) and pulmonary arterial (PAP) pressure were dropped in group P compared to group NP: RVP 16±6 vs. 24±2 and PAP 22±1 vs. 31±2 (mmHg) respectively. Vascular resistances indexes (dyne.sec/cm^{-5}.kg^{-1}) were dropped in group P vs. group NP: pulmonary resistance was 174±60 vs. 352±118, and systemic resistance was 611±70 vs. 1215±315, respectively. Western-blot analysis of pulmonary arteries shown higher endogenous NO synthase (eNOS) expression ($p>0.5$) in group P :0.90±0.71 vs. 0.66±0.52 in group NP.

Fig. 32. Pulsatile trouser (intraoperative view)

	Group	PAP	RVP	PVRI	CO
T1	P	24±3 / 15±2	29±4 / 14±5	168±27	0.8±0.3
	NP	23±4 /15±3	34±3 / 7±2	182±42	0.9±0.1
T2	P	41±2 / 27±3	43±2 / 16±5	314±17	0.7±0.2
	NP	42±3 / 25±2	46±2 / 12±3	385±51	0.7±0.2
T3	P	27±2 / 17±2	28±2 / 6±3	174±27	1±0.2
	NP	39±3 / 23±2	42±1 / 7±1	352±52	0.7±0.2

Table 8. Therapeutic response of the right heart hemodynamic parameters (Trouser vs. TadalafilTM): Systolic and diastolic pressures (mmHg) of the right ventricle (RVP) and pulmonary artery (PAP); PVRI: pulmonary vascular resistances index (dynes•sec/cm5/kg); CO: cardiac output (L/min); T1: baseline; T2: nearly 1 h after pulmonary valve disruption; T3: end. P: pulsatile group; NP: non-pulsatile group; (p<0.05).
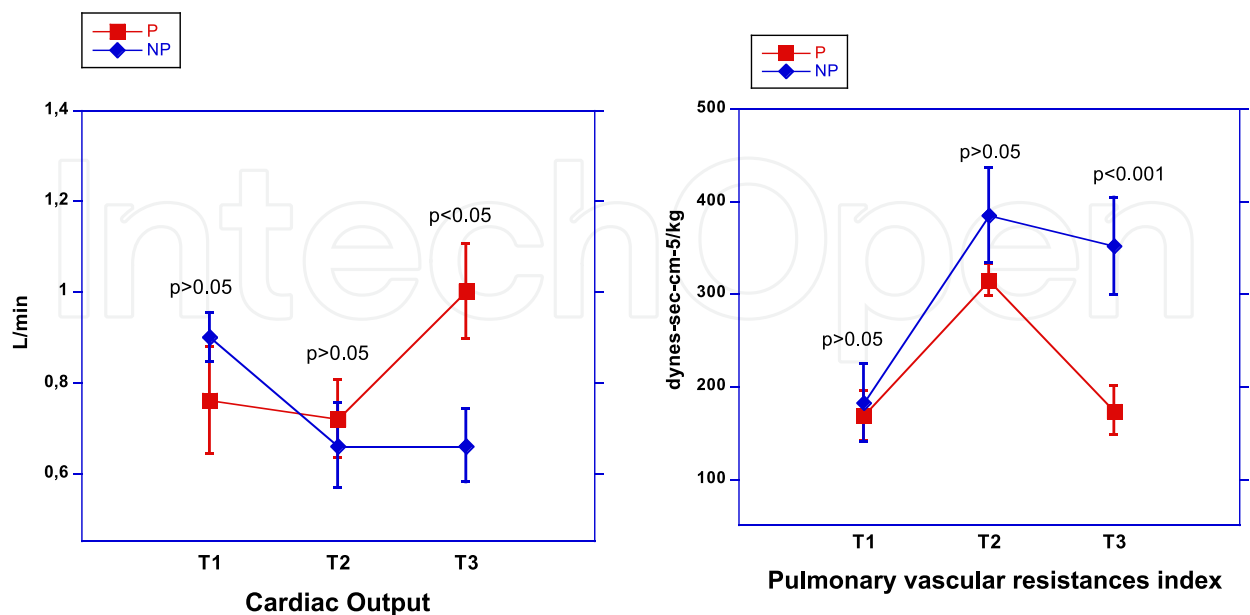
P: pulsatile group (red color), NP: non pulsatile group (blue color); left panel showing cardiac output panel showing pulmonary vascular resistances index (PVRI); right panel showing cardiac output (CO) results obtained from both groups P and NP in three. Data were obtained from both groups (P & NP) at three predetermined time: T1= baseline; T2: nearly 1 h after pulmonary valve disruption and T3= end of 1h therapy. CO (L/min) was significantly improved (p<0.05) at T3 in group P compared to group NP. PVRI (dynes.sec.cm^{-5}/kg) were significantly lower were significantly (p<0.01) lower at T3 in group P compared to group NP. (Two ways ANOVA test)

Fig. 33. Hemodynamic figures

*Paper was submitted to the Asian Cardiovascular & Thoracic Annals Journal (in press Nour, S 2012).
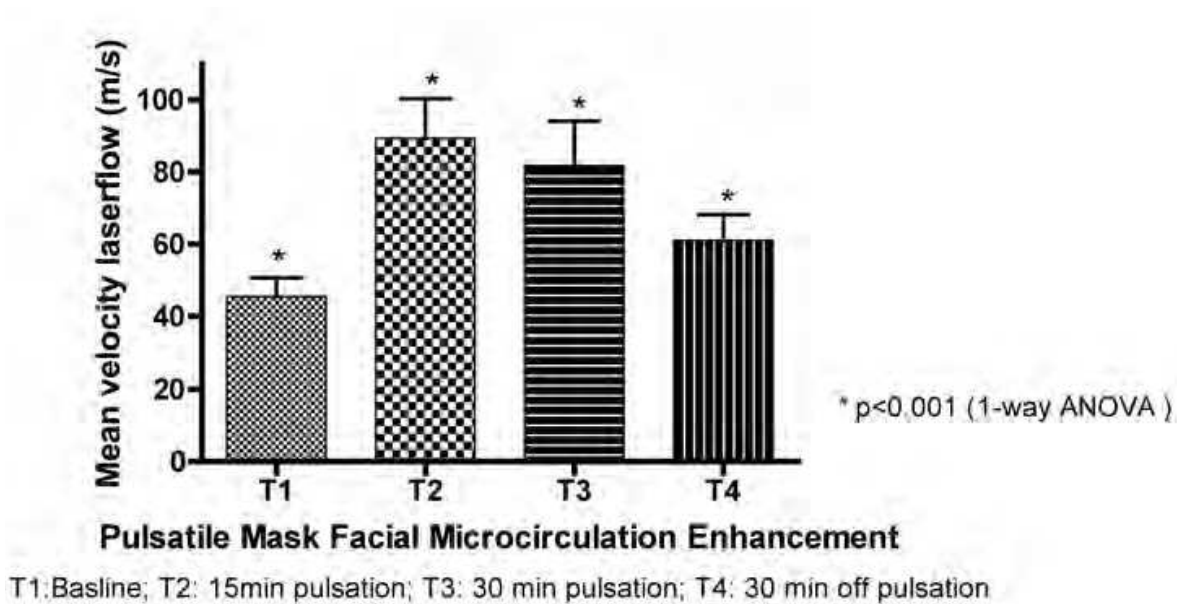
Operative movies: http://www.nourmd.com.

10.2 Clinical volunteers (study in progress)

10.2.1 Mask

Pulsatile mask was tested in healthy volunteers (n=8) from both sex (age:19-68 ys), subjected to 20 minutes of low pressure (0.2-0.6 bars) pulsatile mask, synchronized with diastolic heart rate. *Statistics:* Continuous variables are expressed as the mean±SEM. Comparisons between groups of independent samples were performed with student t-test hemodynamic data. P with a value less than 0.05 was considered statistically significant. GraphPad Prism® software was applied for all the statistical analyses in this study.

Results: hemodynamics and cerebral blood flow was significantly improved (p<0.05), as manifested by Doppler flow measured at the common carotid artery (Figure 35): carotid output: 246±41.73 vs. 294±50.42 (ml/min), and velocity 18±2.4 vs. 21±2.8 (cm/sec). Microcirculation measured from the tip of the nose (Perimed®-PeriScan 3 System), was

45.5±14.6 vs. 89.2±31.1 (p<0.001) with unsynchronized mask pulsations (Figure 34); and from the mandibular angle (measured with Perimed® - PeriFlux System 5000), was 28±12.5 vs. 87±35.2 (p<0.05), with synchronized mask pulsations (Figure 35).

Pulsatile Mask Facial Microcirculation Enhancement

T1:Basline; T2: 15min pulsation; T3: 30 min pulsation; T4: 30 min off pulsation

Upper panel, showing mask device inflated and connected to a generator equipped with a set for hemodynamic measurements (ECG, BP, SaO2); lower panel showing cutaneous microcirculation measured from the tip of the nose at T1: baseline; T2: after 15 min of low pressure pulsation (0.2-0.4 bar) unsynchronized with heart rate; T3: by the end after 30 min of pulsation. T4: 30 min after the end.
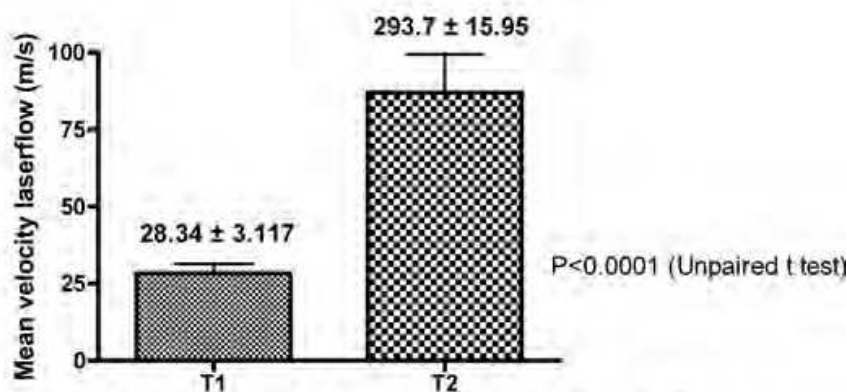
Fig. 34. Pulsatile mask improving facial microcirculation

Synchronized mask pulsations
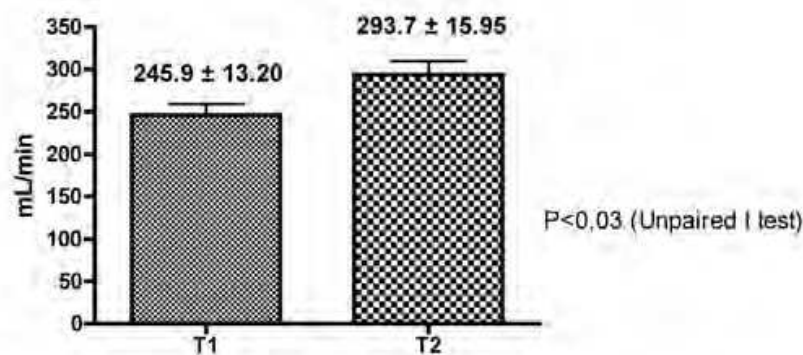
Common carotid doppler flow with synchronized mask pulsations

T1= baseline; T2= after 20 min of synchronized mask pulsations

Facial microcirculation with synchronized mask pulsations

T1= baseline; T2= after 20 min of synchronized mask pulsations

Upper panel carotid flow measured by echo Doppler; lower panel: facial microcirculation (from the mandibular angle)

T1: baseline; T2: after 20 min of pulsations

Fig. 35. Synchronized pualstile mask results

N.B. interestingly the microcirculation's flow shown in (Figure 34), was rapidly increased after 15 min of pulsations, then dropped slightly to pass in plateau over the second 15 min of stimulation. This proves the physiological effect of the device that does not stun endothelial biology, allowing self-cellular regularization in response to induced endothelial vasodilators mediators and unlikely to exogenous NO donors vasodilators (e.g. nitrates).

Movies demonstration of the pulsatile mask:

http://www.nourmd.com.

10.2.2 Trouser

Pulsatile trouser, that covering almost the trunk, was tested in healthy adult volunteers (the author and medical colleagues) (n:6), were subjected to a low pressure (1.2 bars) fixed pulsations (60 bpm) and without synchronization of heartbeat (72± 17 bpm). Results (Figure 36); after 20 min of pulsations, the peripheral microcirculation was measured with laser flowmeter (Perimed®-PeriScan 3 System) at the tip of the finger was significantly improved: 93.5±31.3 vs. 222.4±35.8 (p<0.003).
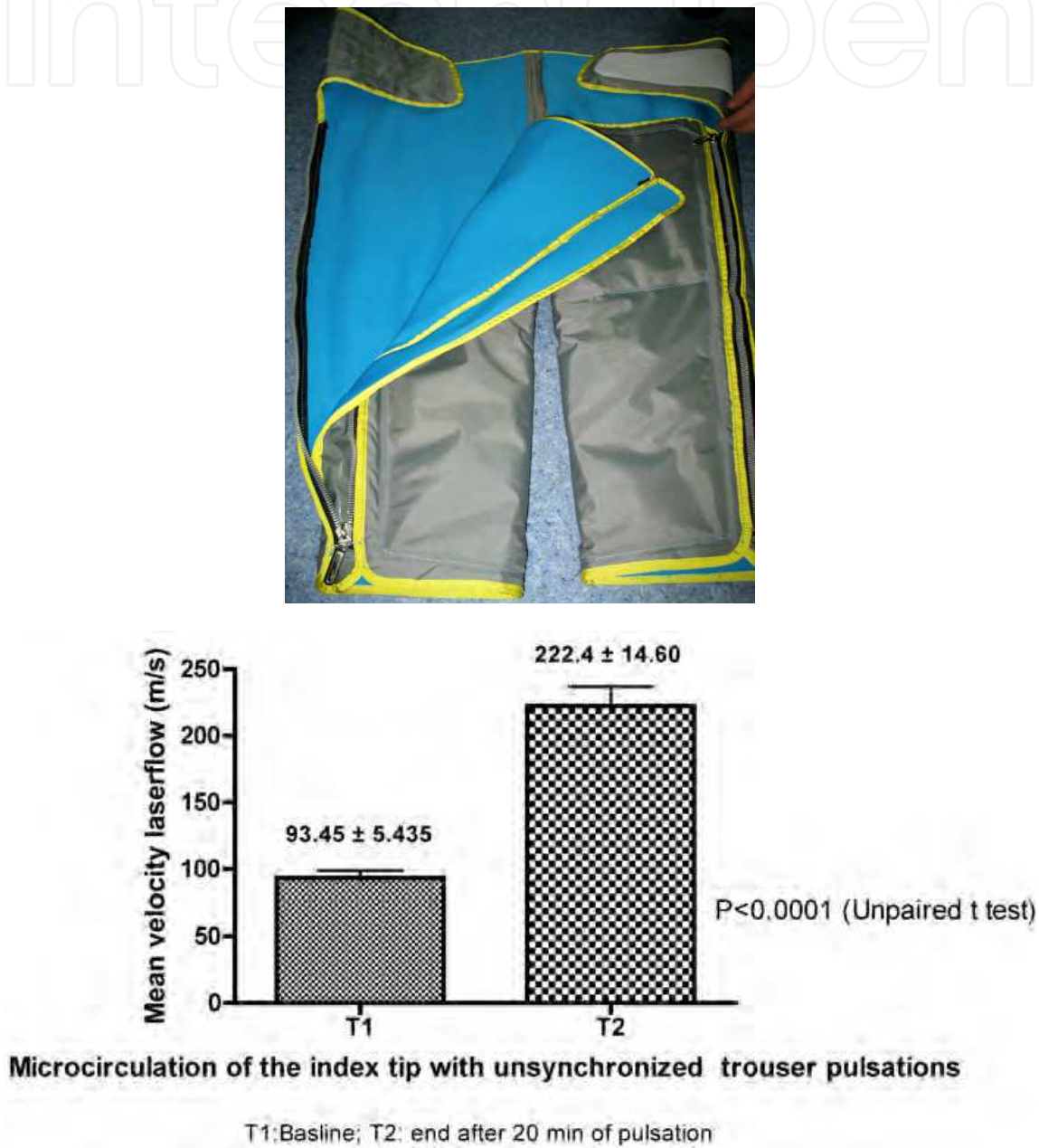
Upper panel: pulsatile trouser's prototype; lower pannel: increased peripheral microcirculation, measured at the tip of the right index (laser flowmeter: Perimed®-PeriScan PIM 3 System)

Fig. 36. Hemodynamic results after 20 min pulsation in 6 volunteers

Movie demonstration http://www.nourmd.com.

11. Evaluation of the Biventricular assist device "L'Orthèse cardiaque" (study in progress)

11.1 In vivo

The device was tested in an acute ischemic biventricular failure (piglet). This was created by mid ligation of the LAD, and elecrocauterization of the RV coronary artery branches, for details refer to the attached operative movies site. The preliminary results shown better hemodynamic responses with the biventricular assist device combing the pulsatile tube as a LVAD and the pulsatile trouser as RVAD (Figure 36).
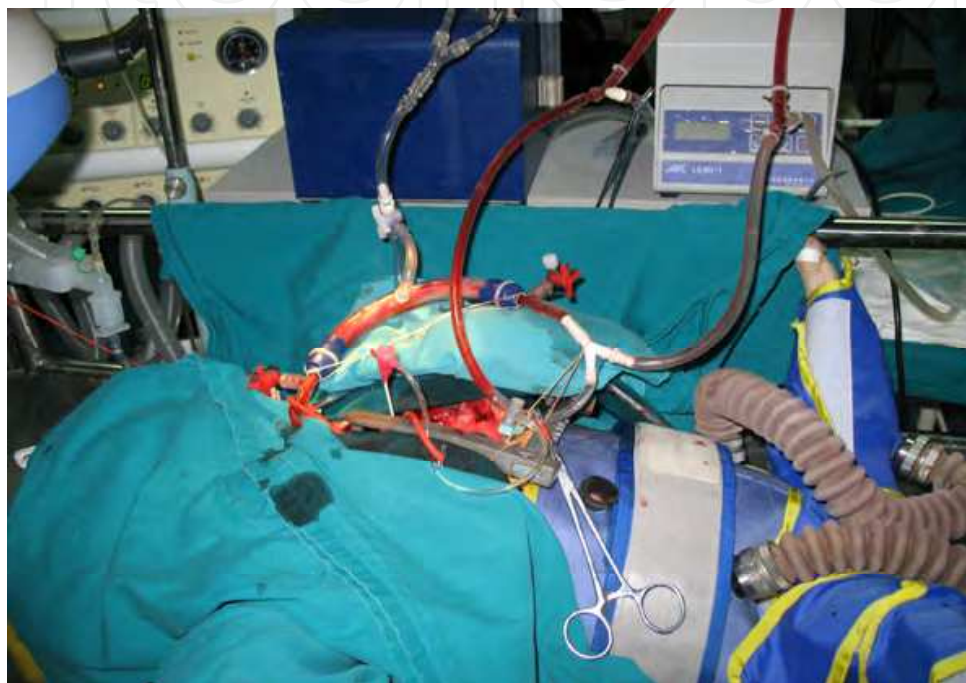

Fig. 37. Biventricular CAD (l'Orthèse cardique) in ischemic model (piglet)

Operative movies: http://www.nourmd.com.

Comment: in this study the device (l'Orthèse cardiaque) was tested as well in total cardiac arrest followed and acute ischemic biventricular failure and cardiogneic shock. The device was successfully capable to circulate the stagnant blood columns within the respect of the biophysical conditions of each heart circuit biophysiological conditions (please refer to the attached movie). The study pending new pulsatile tube constructions. The object is to maintain circulatory flow dynamics and cellular metabolism in case of acute biventricular failure until improvement of hemodynamic or arrangement for heart transplants with compatible donors in nearly physiological condition.

11.2 In clinical volunteer

The pulsatile trouser was indicated in a CHF patient, (a medical consultant from the UK), as an ultimate therapeutic option, according to a consensual patient's request. The patient was short-listed for both heart and kidney transplant, then been removed due to severely deteriorated hemodynamics: EF ≈ 15%, systolic pulmonary arterial pressure >65 mmHg,

and elevated BNP (1100 pg/ml). He was on renal dialysis (6 days/ week), chronic constipations and oxygen sleep dependent.   The pulsatile trouser was applied for 2O minutes daily, in a posture position* with fixed frequency (40 bpm), irrespective of patient's pacemaker (78 bpm) and low inflation / deflation pressure (1.4 bar). The patient recovred regular bowl, and became less dependent on oxygen during the first week of treatment. After two months there was hemodynamic improvement: EF≈ 20%; systolic PAP ≈ 41mmHg and BNP ≈ 500 pg/ml. The patient reintegrated the NHS transplant program. Despite, hemodynamic improvement, the procedure was interrupted because a cholecystectomy was urgently, needed for biliary lithiasis, which may promote to shower pancreatitis with the trouser pulsations.

*N.B. In CHF patients, it is preferred to apply trouser therapy in a posture position, rather than supine position to amplify the gravity effect as an enhancement factor of shear stress with more voluminous columns of venous capacitance.

Movie demo: http://www.nourmd.com.

11.3 Comment

These aforementioned preliminary results have proven the feasibility of the concept as a promising therapeutic approach for CVD. On other word, proven the efficiency of the right heart endothelial reservoir as a physiological therapeutic backup compared to optimum traditional therapies in addressing acute cardiogenic shock state.

The pulmonary endothelium, stimulated with a small size pulsatile catheter that can be introduced intravenously and percutaneously, open a new era in cardiology as almost all types of ischemic heart disease as well as pulmonary arterial hypertension (PAH). Macroscopic disappearance of the ischemic zone confirmed with low myocardial apoptosis and that despite permanent ligation of the coronary artery means improved hemodynamic is more related to open myocardial microcirculation in neonate animal model known with poor coronary collaterals.

A significant drop in the pulmonary vascular resistance was the key of hemodynamic improvement. This can be induced with the proposed pulsatile systems after short period of intermittent shear stress-mediated endothelial function stimulations at the splanchnic and hepatic venous capacitance, or at the pulmonary artery, and irrespective to heart rate.

Pulsatile suit concept results that have been obtained in volunteers also open a new era of therapeutic approach in nearly all types of endothelial dysfunctions pathogenesis as follows: with (Type A), endothelial dysfunction with heart disease patients; in Type B, with endothelial dysfunction and normal heart function (e.g. diabetic, systemic arterial hypertension, PAH, erectile dysfunction, etc); and Type C, as prophylactic in healthy individuals, liable for endothelial dysfunction pathogenesis (Astronauts, bedridden, etc) as well as a circulatory hemodynamic physiological stimulus (e.g. athletics, anti-aging, etc).

The pulsatile mask can improve the cerebral circulation directly through the cavernous venous systems, and systematically through the jugular vein system, current studies show enhancement of the retinal artery flow as well as diameter, which ca be effective in treating early neurodegenerative diseases and stroke patients.

This improvement is observed at points remote from the pulsating zone, i.e. where the suit was being worn.

A clear improvement in microcirculation has also been observed at the fingertips as a result of putting a pulsatile suit (trouser) on the bottom portion of a patient's body as shown in (Figure 36).

Practically, delivery of shear stress stimuli at the compliant pulmonary artery (PA) zone (zone5), can be induced according to the Bernoulli's principles with a small size pulsatile catheter adaptable to the pulmonary trunk geometries for shear rates enhancement at the inner boundaries layers, irrespective of heartbeat without obstructing the right ventricular outflow tract. Meanwhile at the superficial venous capacitance (zone1) shear stress enhancement could be achieved externally with the pulsatile suit.

At the left heart side, an endothelial shear stress will be induced by the pulsatile tube. The pulsatile tube could adapt whether a conventional CPB or CAD, provides a nearly physiological pulse pressure with lowest momentum energy losses, particularly in association with the Smartcan. It will considerably reduce the distance between CAD and the perfused artery (Z3).

Similarly, an improvement in the microcirculation of the myocardium has been observed in an ischemic model by permanent ligation of the left anterior descending coronary artery (LAD), after applying shear forces generated by pulsatile catheter inserted in the pulmonary artery forming part of the right circuit of the heart.

Given the very short lifetime of nitric oxide, it cannot reach zone that are remote from the site where it is secreted, since it is necessarily absorbed by hemoglobin before reaching said remote zones. Thus, it has been found that at least one mediator mechanism other than those that are already known and secreted by the endothelium is capable of triggering the opening of microcirculation. The devices and methods of the present concept advantageously enable such secretion to take place.

As a priority, assistance should be provided to the right portion of the heart. It is known that the right heart "dominates" the left heart and controls hemodynamics by pulmonary resistances (Nour S 2008). Isolated ventricular assistance, on the left or right, can then be envisaged in accordance with the present disclosure; and after that assistance for the left heart.

The method makes it possible to restore the endothelial function progressively by maintaining quasi-physiological shear forces on the endothelium; consequently, there is a significant improvement in the function of myocardium, thus making it possible avoid subsequent transplants.

Alternatively, the pulsatile catheter prototype, when applied in the clinic, could be implanted into the pulmonary artery through a central venous line (ongoing study), in hospital settings, it could be connected to a small portable-implantable driving device. Patients with catheter device set implants would benefit from real-time hemodynamic measurements and simultaneous therapeutic pulmonary pulsation. Thus, this approach promises to be cost-effective.

By providing immediate improvement of myocardial microcirculation, the device could become a first priority in IHD as well as PAH managements.

In future investigations, the device could be inserted through the PA (ongoing study) or coronary sinus, either associated or not with an absorbable stent, to test for enhancements in the restoration of endothelial function.

Over the long term, shear stress-induced endothelial regulation, alone or in combination with progenitors and angiogenic factors could promote cardio-circulatory rehabilitation and accelerate cardiogenesis. This approach might eliminate the need for interventional or surgical procedures.

Finally, as far as the concept has been proven therapeutic efficiencies, there were some study limits that should be resolved in the future. This includes the severe vasodilatation as a result of direct intravascular endothelial stimulations by the intrapulmonary pulsatile catheter as well as the pulsatile tube as a LVAD.

Interestingly, the application of the pulsatile tube alone as a LVAD without perfusion pump induced severe vasodilatation after impressive improvement of MI (please refer to operative movie). This is proving the hypersensitivity of the pulmonary endothelium as well as the LV endocardium that were responded rapidly to the unsynchronized tube pulsations.

A similar phenomenon has been observed with Nicorandil, an exogenous NO donor used for angina pectoris relief (Falase BA, et al., 1999), (Blanc P, et al., 2001).

Meanwhile, vasodilatation that could be induced by exogenous NO donors, leads to hypovolemic-cardiogenic shock. In contrast, the observed study hypovolemia, was preceded by general improvement of hemodynamic and organ microcirculation. This was manifested by the increased renal output manifested by a vesical globe that was released spontaneously in the pulsatile group animal models, which could be easily compensated by IV fluids. Currently we reduced the frequencies of pulsatile time (5-10 min), interrupted by interval pause guided by hemodynamic monitors, particularly systemic BP.

There was no observed severe vasodilatation with the externally stimulated endothelial devices (the pulsatile trouser and mask). By caution, as the mechanism of vasodilatation is still undiscovered, also the improved microcirculation became almost steady after 15-20 min of external endothelial stimulations, our recommendation for the pulsatile suit sessions is: 20-30 min. Furthermore, it is unnecessary to apply high-pressure pulsatile volume. A low pressure (1.2-2 bars) is sufficient to stimulate the superficial intravascular blood volume, covered by their endothelial stocks.

Contraindications of the pulsatile suit, are more or less relatives as a non-invasive device, meanwhile cautions may be considered with some patients (e.g. hepatic cirrhosis, malignancy, open fractures, 3rd degree burns, colostomy, cerebral accidents, malignancy). Under all circumstances, Clinicians will determine contraindications according to the obtained results.

Currently, clinical programs of the non-invasive devices will start very soon, with (Type A, & C) endothelial dysfunction patients (e.g. CHF, resistant arterial hypertension, cerebral atherosclerosis, etc.) and others with healthy persons (Type C) e.g. bedridden, athletes.

12. Conclusion

A promising therapeutic approach for CVD and circulatory disorders management with more physiological cost effective manners compared to current therapies. According to physics, it consists of: a shear rate intravascular enhancement device (catheter); a steady flow transformer device (tube) and an accessory circulatory driving forces enhancement and/or replacement device (suit). Drawbacks of the invasive devices could be overruled through accurate mathematical calculations of the induced momentum according to individual body surface area and the stimulated sites (blood column). Means, optimum devices performances could be achieved with computational models and biomedical engineering, to define the accurate device geometries as well as materials.

13. Acknowledgements

14. Sources of funding

15. References

Abrams, J (1988). A reappraisal of nitrate therapy. *JAMA, Vol.*259, No.3, (January 1988) 396-401.
Al-Ghazali, W (1989). Evidence of redistribution of cardiac output in asymmetrical growth retardation. *Br J Obstet Gynaecol*, Vol. 96, No. 6, (June 1989), pp.697-704.
Anderson, RM. (1999). *The Gross Physiology of the Cardiovascular System,* Racquet Press 4625. San Carlos PL. Tucson, Arizona 85712, USA.
Aron EA, et al (2003). *Angiogenesis. Genetics and Embryology Textbook.* Australia; pp.83.
Adamo L. (2009). *Biomechanical control of hematopoiesis,* Ph.D., HARVARD UNIVERSITY. ISBN: 3385549, Boston, USA.
Abshire, TC (2009). Bleeding risks with cardiac disease.Transfusion Medicine and Hemostasis, Academic Press, (April 2009), pp. 577-580. ISBN. 9780123744326
Burton, AC (1954). Relation of structure to function of the tissues of the wall of blood vessels. *Physiol Rev*, Vol.34, No.4, (October 1954), pp. 619-42.
Bick, RL (1976). Alterations of hemostasis associated with cardiopulmonary bypass. *Thrombosis Research*, Vol.8, No.3, (March 1976), pp. 285-302.
Busch, T (1997). Vascular complications related to intraaortic balloon counterpulsation: an analysis of ten years experience. *Thorac Cardiovasc Surg,* Vol.45, No.2, (April 1997), pp. 55-59.

Berger, PB (1999). One-year survival among patients with acute myocardial infarction complicated by cardiogenic shock, and its relation to early revascularization: results from the GUSTO-I trial. *Circulation,* Vol. 99, No.7, (February 1999), pp. 873-8.

Bolotin, G (2001). Hemodynamic evaluation of descending aortomyoplasty versus intraaortic balloon pump performed in normal animals: an acute study. *Eur J Cardiothorac Surg*, Vol. 19, No. 2, (February 2001), pp.174-8.

Bolli, R (2001). Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research. *J Mol Cell Cardiol,* Vol.33, No.11, (November 2001), pp.1897-1918.

Bonetti, PO (2003). Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *J Am Coll Cardiol*, Vol. 41, No.10, (May 2003), pp.1761-8.

Box, FM (2005). The influence of flow, vessel diameter, and non-newtonian blood viscosity on the wall shear stress in a carotid bifurcation model for unsteady flow. *Invest Radiol*, Vol.40, No.5, (May 2005), pp. 277-94.

Buckberg, GD. (2006). The ventricular septum: the lion of right ventricular function, and its impact on right ventricular restoration. *Eur J Cardiothorac Surg*, Vol.29, No.1, (Apr 2006), pp.272–8.

Burkhoff, D (2006). A randomized multicenter clinical study to evaluate the safety and efficacy of the Tandem Heart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J,* Vol. 152, No. 3, (September 2006), pp. 469.e1-8.

Bauer, NR (2007). Rodent models of PAH: are we there yet? *Am J Physiol Lung Cell Mol Physiol*, Vol. 293, No.3, (September 2007), pp. 580–582.

Clark, EB. (1987). Mechanisms in the pathogenesis of congenital cardiac malformations. In: *The Genetics of Cardiovascular Disease,* Pierpont MEM, Moller JH, editors. Nijhoff Publishing, Boston, 1987:3–11.

Calvert, JB. (2000). Bernoulli's Equation « The most useful relation in engineering hydraulics is really three ». (August 2000), (11/09/20011), available from: <http://www.du.edu/~jcalvert/tech/fluids/bernoul.htm>

Chachques, JC (2005). Cellular cardiomyoplasty for myocardial regeneration. *Asian Cardiovasc Thorac Ann*, Vol.13, No.3, (September 2005), pp. 287-296.

Cooper, JR Jr (2006). Fatal pulmonary microthrombi during surgical therapy for end-stage heart failure: possible association with antifibrinolytic therapy. *J Thorac Cardiovasc Surg*, Vol.131, No.5, (May 2006), pp. 963-968.

Chatzizisis, YS (2007). Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol,* Vol.49, No.25, (June 2007), 2379-2393.

Couzens, GF (2009). Surviving a Heart Attack, Succumbing to Heart Failure. *The New Yourk Times*-Iside Health, (January 2009), available from:
http://www.nytimes.com/ref/health/healthguide/esn-heart-failure-ess.html

Carpentier, A. (2011). Building human hearts on an assembly line (CARMAT). *European hospital*, (Aug 2011), available from: http://www.european-hospital.com/en/article/8917-Building_human_hearts_on_an_assembly_line.html

Dhombres, J. (1989). "La théorie de la capillarité selon Laplace: mathématisation superficielle ou étendue" (in French). Revue d'Histoire des sciences et de leurs applications, Vol.42, No.42 (1989), pp. 43–70, available from: <http://www.persee.fr/web/revues/home/prescript/article/rhs_0151-4105_1989_num_42_1_4134>

Depre, C (1997). Activation of nitric oxide synthase by ischaemia in the perfused heart. *Cardiovasc Res*, Vol. 33, No.1, (January 1997), pp. 82-87.

Doherty, DH (1998). Rate of reaction with nitric oxide determines the hypertensive effect of cell-free hemoglobin. *Nat Biotechnol,* Vol.16, No.7, (July 1998), pp. 672-676.

Dangas, G (2001). Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. *J Am Coll Cardiol,* Vol.38, No.3, (September 2001), pp. 638-641.

Davignon, J (2004). Role of endothelial dysfunction in atherosclerosis. *Circulation*, Vol.109, No.23 Suppl 1, (June 2004), pp. III27-32.

D'Alto, M. (2007). Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, 1 clinical, and haemodynamic effect. *Heart, Vol.93, No.5, (May 2007),* pp. 621-625.

Endemann, DH. (1983). Endothelial Dysfunction. *J Am Soc Nephrol,* Vol.15, No.8, (August 2004), pp. 1983-92.

Gorge, G. (1989). Microvascular and collateral adaptation in swine hearts following progressive coronary artery stenosis. *Basic Res Cardiol,* Vol.84, No.5, (September-October 1989), pp. 524-35.

Geankoplis, CJ. (2005). Principles of Momentum Transfer and Applications. 4th edition, ISBN 13: 9780131013674;

Gershlick, T.(2007). PCI or CABG: which patients and at what cost? *Heart, Vol.93*, No.10, (October 2007), pp.1188-90.

Gravlee, GP. (2008). Cardiopulmonary bypass: principles and practices. Lippincott Williams & Wilkins, a Wolters Kluwer business. ISBN 978.0.7817.6815.3.

Fahraeus R, Lindquist T (1931). The Viscosity of the blood in narrow capillary tubes. *Am J Physiol,* Vol. 96, No.3 (March 1931), pp. 562-568.

Furchgott, RF. (1980). The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature,* Vol.288, No.5789, (November 1980), pp. 373–376.

Feynman, R P. (2005). The Feynman Lectures on Physics. Vol. 1 (2nd ed.). Pearson/Addison-Wesley. ISBN 0805390499.

Humbert, P (1947). L'OEuvre scientifique de Blaise Pascal, Paris, Albin Michel, '1947), available from: <http://www.persee.fr/web/revues/home/prescript/article/rhs_0048-7996_1948_num_1_3_2649>.

Hutchins, GM. (1988). Development of the coronary arteries in the embryonic human heart. *Circulation,* Vol.77, No.6, (June 1988), pp. 1250-7.

Hoeks, APG. (1995). Noninvasive Determination of Shear-Rate Distribution Across the Arterial Lumen. *Hypertension,* Vol.26, No.1, (July 1995), pp. 26-33.

Huang, W (1998). Zero-stress states of human pulmonary arteries and veins. *J Appl Physiol*, Vol.85, No.3, (September 1998), pp. 867-73.

Haji, SA. (2000). Right ventricular infarction--diagnosis and treatment. *Clin Cardiol,* Vol.23,No.7, (July 2000), pp. 473-82.

Heilmann, L. (2005). Fetal hemorheology in normal pregnancy and severe preeclampsia. *Clinc Hemorheol Microcirc*, Vol.32, No.3, (2005), pp. 183-90.

Heinzel, FR. (2008). Inducible nitric oxide synthase expression and cardiomyocyte dysfunction during sustained moderate ischemia in pigs. *Circ Res,* Vol.103, No.10, (November 2008), pp.1120-7.

Haddad, F. (2011). Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail*, Vol.4, No.6, (Nov 2011), pp. 692-9.

Ignarro, LJ. (2002). Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview. *Circ Res,* Vol.90, No.1, (January 2002), pp. 21-28.

Ishida, K. (2004). Heparin-induced thrombocytopenia after coronary artery bypass grafting with cardiopulmonary bypass: report of a case. *Surg Today*, Vol.34, No.12, (2004), pp. 1041-1043.

Jones, SP. (2006). The ubiquitous role of nitric oxide in cardioprotection. *J Mol Cell Cardiol,*Vol.40, No.1, (January 2006), pp. 16-23.

Koller, A. (1993). Role of shear stress and endothelial prostaglandins in flow- and viscosity induced dilation of arterioles in vitro. *Circulation Research*, Vol.72, No.6, (June 1993), pp. 1276-84.

Kessler, DP. (1999). Momentum, Heat, and Mass Transfers Fundamentals. Marcel Dekker, Inc. ISBN 0-8247-1972-7.

Kadoi, Y (2000). Balloon pump-induced pulsatile perfusion during cardiopulmonary bypass does not improve brain oxygenation. *J Thorac Cardiovasc Surg*, Vol. 11ç, No.1, (January 2000), pp. 189-90.

Kozák-Bárány, A. (2001). Development of left ventricular systolic and diastolic function in preterm infants during the first month of life: a prospective follow-up study. *J Pediatr*, Vol.139, No.4, (October 2001), pp. 539-45.

Katz, AM (2002). Ernest Henry Starling, his predecessors, and the "Law of the Heart". *Circulation*, Vol. 106, No.23, (December 2002), pp. 2986-92.

Kapur, A. (2007). Mortality after myocardial infarction in patients with diabetes mellitus. *Heart,* Vol.93, No.12, (December 2007), pp. 1504-1506.

Kusama, Y. (2011). Variant angina and coronary artery spasm: the clinical spectrum, pathophysiology, and management. *J Nihon Med Sch*, Vol.78, No.1, (2011), pp. 4-12.

Letsou, GV. (1993). Pulmonary artery balloon counterpulsation: safe after peripheral placement. *Ann Thorac Surg,* Vol.55, No.3, (March 1993), pp.741-746.

Lam, CF (2006). Increased blood flow causes coordinated upregulation of arterial eNOS and biosynthesis of tetrahydrobiopterin. *Am J Physiol Heart Circ Physiol,* Vol.290, No.2, (February 2006), pp. H786-793.

Limaye, V. (2007). The vascular endothelium: structure and function. Mechanisms of Vascular Disease: A Textbook for Vascular Surgeons. ISBN: 9780521860635.

Mital, S. (2002). Endogenous endothelium-derived nitric oxide inhibits myocardial caspase activity: implications for treatment of end-stage heart failure. *J Heart Lung Transplant,* Vol.21, No.5, (May 2002), pp. 576-585.

Martini, J. (2006). Mechanotransduction and the homeostatic significance of maintaining blood viscosity in hypotension, hypertension and haemorrhage. *J Intern Med*, Vol.259, No.4, (April 2006), pp. 364-72.

McCrindle, BW. (2007). Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements *Circulation*, Vol.116, No.2, (July 2007), pp. 174-9.

Meyers, K. (2007). Fetal Development: 10 Stages. Biology 156: Online Lab Seven. 2OO7. 1-6. http://desertfiddlekate.blogspot.com/2007/07/online-lab-seven-fetaldevelopment-10.html

Neri Serneri, GG. (1981). Pathophysiological aspects of platelet aggregation in relation to blood flow rheology in microcirculation. *Ric Clin Lab*, Vol.11, No.1, (1981), pp.39-46.

Nour, S. (2003). Étude préliminaire sur un nouveau dispositif de circulation extra corporelle pédiatrique pulsée. DEA de Sciences Chirurgicales . Université de Paris XI (Octobr 2003).

Newburger, JW. (2004). Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation,* Vol.110, No.17, (October 2004), pp. 2747-2771.

Nour, S. (2008). DISPOSABLE PULSE PIPE. Patent application, WO 2008/000110, available from:
http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submitted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY=gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2008). NEONATE OR INFANT PULSATING WEAR. Patent application, WO 2008/000111 available from:
http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submitted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY=gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2008). Shear stress, energy losses and costs: the resolved dilemma of pediatric heart lung machines with a pulastile tube (abstract). The 16th annual meeting of the Asian Society for Cardiovascular & thoracic surgery. Singapore 14-16 March.

Nour, S. (2008). De l'ECG au coeur artificiel (Lecture). Module Instrumentation Biomédicale. Ecole Central de Paris. 10/03/2008.

Nour, S. (2009). Instrumentation pour les secteurs de cardiologie et de chirurgie cardiaque (Lecture). Module Instrumentation Biomédicale. Ecole Central de Paris. 17/02/2009.

Nour, S. (2009). Flow and rate: almost all we need to trigger, restore and maintain the Cardio-endothelial system (video presentation). The 17th annual meeting of the Asian Society for Cardiovascular & thoracic surgery. Taipei, Taiwan 5-8 March.

Nour, S. (2009). The forgotten driving forces in right heart failure: new concept and device. *Asian Cardiovasc Thorac Ann*, Vol.17, No.5, (October 2009), pp. 525-30.

Nour, S. (2009). NOVEL PULSATING MEDICAL DEVICE. Patent application, WO 2009/136035, available from:

http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submi
tted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY
=gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nardell, K. (2009). Risk factors of bleeding in pediatric post-cardiotomy patients requiring
    ECLS. *Perfusion*, Vol.24, No.3, (May 2009), pp. 191-197.
Nour, S. (2010). PULSATILE AND NON-INVASIVE DEVICE FOR CIRCULATORY AND
    HAEMODYNAMIC ASSISTANCE. WO 2010/070018, available from:

http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submitted=true
    &DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY=gb&LG
    =en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2010). PULSATILE MEDICAL DEVICE DESIGNED TO BE USED IN
    EXTRACORPOREAL SURGERY. Patent application WO 2010/066899, available
    from:
    http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submi
    tted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY
    =gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2011). SINGLE-USE CARDIOVASCULAR DEVICE FOR MEDICO-SURGICAL
    OPERATION. Patent application, WO 2011/089162, available from:
    http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submi
    tted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY
    =gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2011). EQUIPMENT THAT MAKES IT POSSIBLE TO APPLY A DETERMINED
    PULSATILE PRESSURE TO A MEDICAL DEVICE. Patent application, US
    2011/166515, available from:
    http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submi
    tted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY
    =gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour S (2011). NOVEL MEDICAL PULSATING DEVICE. Patent application, US
    2011/021987, available from:
    http://worldwide.espacenet.com/searchResults?bookmarkedResults=true&submi
    tted=true&DB=EPODOC&locale=en_gb&IA=NOUR+SAYED&sf=q&FIRST=1&CY
    =gb&LG=en&&st=IA&kw=NOUR+SAYED&Submit=SEARCH&=&=&=&=&=

Nour, S. (2011). A THERAPEUTIC AND SURGICAL TREATMENT METHOD FOR
    PROVIDING CARDIOPULMONARY AND CIRCULATORY ASSIST DEVICE. US
    patent application in pending.
Nour, S. (in press). Forgotten driving forces in right heart failure (Part II): experimental
    study. Asian Cardiovasc Thorac Ann. DOI: 10.1177/0218492312440567.
Nour, S. (in press). Intrapulmonary Shear Stress Enhancement: a New Therapeutic
    Approach in Pulmonary Arterial Hypertension. Pediatr Card [PEDC-D-11-
    00290R1].
Onuzo, OC. (2000). Heterotopic cardiac transplantation and Batista operation. *Ann Thorac
    Surg,* Vol.70, No.1, (July 2000), pp. 285-287.
Olufsen, MS. (2004). On deriving lumped models for blood flow and pressure in the
    systemic arteries. *Math Biosci Eng*, Vol.1, No.1, (June 2004), pp. 61-80.
Onorati, F. (2007). A randomized trial of pulsatile perfusion using an intra-aortic ballon
    pump versus nonpulsatile perfusion on short-term changes in kidney function

during cardiopulmonary bypass during myocardial reperfusion. *Am J Kidney Dis*, Vol.50, No.2, (August 2007), pp. 229-38.

Pelc, LR. (1987). Preferential increase in subendocardial perfusion produced by endothelium dependent vasodilators. *Circulation*, Vol. 76, No. 1, (July 1987), pp. 191–200.

Petrovic, D. (2000). Apoptosis and proliferation of cardiomyocytes in heart failure of different etiologies. *Cardiovasc Pathol,* Vol.9, No.3, (May-June 2000), pp.149-152.

Palmieri, V. (2001). Aortic root dilatation at sinuses of valsalva and aortic regurgitation in hypertensive and normotensive subjects: The Hypertension Genetic Epidemiology Network Study. *Hypertension*, Vol37, No.5, (May 2001), pp.1229-35.

Pereira, NL (2005). Cardiac transplant following failed Fontan or Glenn procedures. J Am Coll Cardiol, Vol.46, No.7, (October 2005), pp. 1374-5; author reply 1375-6.

Park, SJ. (2005). Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg,* Vol.129, No.1, (January 2005), pp. 9-17.

Pouard, Ph. (2006). Normothermia becomes more practiced during CPB perfusion with less morbidity normothermic cardiopulmonary bypass and myocardial cardioplegic protection for neonatal arterial switch operation. *Eur J Cardiothorac Surg, Vol.30, No.5, (November* 2006), pp. 695-699.

Potapov, EV. (2007). Ventricular assist devices in children: current achievements and future perspectives. *Pediatr Transplant*, Vol.11, No.3, (May 2007), pp. 241-55.

Poelmann, RE. (2008). The development of the heart and microcirculation: role of shear stress. *Med Biol Eng Comput*, Vol.46, No.5, (May 2008), pp. 479-84.

Prutkin, JM. (2008). Percutaneous right ventricular assist device as support for cardiogenic shock due to right ventricular infarction. *J Invasive Cardiol*, Vol.20, No.7, (July 2008), pp. E215-E216.

Prendiville, TW. (2010). Heterotaxy syndrome: defining contemporary disease trends. *Pediatr Cardiol*, Vol.31, No.7, (Oct 2010), pp. 1052-8.

Pagonas, N. (2010). Assessment of the effect of external counterpulsation on myocardial adaptive arteriogenesis by invasive functional measurements--design of the arteriogenesis network trial 2. *Int J Cardiol*, Vol.145, No.3, (December 2010), pp. 432-7.

Rao, PS. (1994). Hypoplastic left heart syndrome. In: Kambam J (ed.). *Cardiac Anesthesia for Infants and Children*. St. Louis, MO: Mosby-Year Book,; 1994:296-309. ISBN0801672899, 9780801672897

Rothenberg, F. (2003). Sculpting the cardiac outflow tract. *Birth Defects Res C Embryo Today*, Vol.69, No.1, (Feb 2003), pp. 38-45.

Roselli, RJ. (2003). Redesigning a biomechanics course using challenge-based instruction. *IEEE Eng Med Biol Mag*, Vol. 22, No. 4, (July-August 2003), pp.66-70.

Robbins, IM (2004). Advancing Therapy for Pulmonary Arterial Hypertension : Can Animal Models Help? *Am J Respir Crit Care Med*, Vol.169, No.1, (January 2004), pp. 169:5-6.

Rastan, AJ. (2008). Moderate vesrsus deep hypothermia for the arterial switch operation: experience with 100 consecutive patients. *Eur. J. Cardiothorac. Surg*, Vol.33, No.4, (April 2008), pp. 619 – 625.

Roussel, JC. (2009). CardioWest (Jarvik) total artificial heart: a single-center experience with 42 patients. *Ann Thorac Surg*, Vol.87, No.1, (January 2009), pp. 124-9.

Stern Lc (1875). Ebers G. ed (in German). *Papyros Ebers: Das hermetische Buch uber die Arzeneimittel der alten Ägypter in hieratischer Schrift, herausgegeben mit Inhaltsangabe und Einleitung versehen von Georg Ebers, mit Hieroglyphisch-Lateinischem Glossar von*

Ludwig Stern, mit Unterstützung des Königlich Sächsischen Cultusministerium. 2 (1 ed.).Leipzig: W. Englemann. Retrieved 2010-09-18.

Sanfelippo, PM. (1987). Vascular complication associated with the use of intra-aortic ballon pumping. *Texas Heart Inst J*, Vol.14, No.2, (June 1987) pp.187-5.

Sollano, J. (1998). Do we need another cardiac assist device? Assessing the feasibility of a new cardiac compression device for the treatment of cardiogenic shock. Paper presented at: Annu Meet Int Soc Technol Assess Health Care Int Soc Technol Assess Health Care Meet, 1998.

Samet, I. and Lelkes, PI. (1999): "Mechanical Forces and Endothelium"; 2-11; Harwood academic publishers; The Netherlands.

Schmauss, D. (2008). Cardiac allograft vasculopathy: recent developments. *Circulation*, Vol.117, No.16, (April 2008), pp. 2131-2141.

Senzaki, H. (2008). Sedation of hypercyanotic spells in a neonate with tetralogy of Fallot using dexmedetomidine. *J Pediatr (Rio J)*, Vol.84, No.4, (Jul-Aug 2008), pp. 377-80.

Seyfarth, M. (2008). A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol*, Vol.52, No.19, (November 2008), pp. 1584-1588.

Shroyer, AL. (2009). On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*, Vol.361, No.19, (November 2009), pp.1827-37.

Samady, H. (2011). Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. *Circulation*, Vol.124, No.7, (August 2011), pp. 779-88.

Thom, Th. (2006). Heart Disease and Stroke Statistics—2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, Vol.113, No.8, (February 2006), pp. e85 - e151.

Tumkosit, M (2007). Left ventricular spherical remodeling and apical myocardial relaxation: cardiovascular MR imaging measurement of myocardial segments. *Radiology*, Vol.244, No.2, (August 2007), pp. 411-8.

Unger, F. (1988). Artificial heart and cardiac transplantation: report on the first European combined procedure. *Artif Organs.* Vol.12, No.1, (February 1988), pp. 51-55.

Ündar, A. (1999). Effects of perfusion mode on regional and global organ blood flow in a neonatal piglet model. *Ann Thorac Surg*, Vol.68, No.4, (October 1999), pp.1336-43.

Ündar, A. (2001). Comparison of six pediatric bypass pumps during pulsatile and nonpulsatile perfusion. *J Thorac Cardiovasc Surg*, Vol.122, No.4, (October 2001), pp. 827-9.

Undar, A. (2006). Quantification of perfusion modes in terms of surplus hemodynamic energy levels in a simulated pediatric CPB model. *ASAIO J*, Vol.52, No.6, (November-December 2006), pp. 712-7.

Undar, A. (2007). Pulsatile Perfusion During Cardiopulmonary Bypass Procedures in Neonates, Infants, and Small Children. *ASAIO J*, Vol.53, No.6, (November-December 2007), pp. 706 –709.

Vroom, MB. 1996). Myocardial stunning, hibernation, and ischemic preconditioning. *J Cardiothorac Vasc Anesth*, Vol.10, No.6, (October 1996), pp. 789-799.

Vincent, JL. (2008). Defining sepsis. *Clin Chest Med*, Vol.29, No.4 (Dec 2008), pp. 585-90.

Voss, B. (2010). Cardiopulmonary bypass with physiological flow and pressure curves: pulse is unnecessary!. *Eur J Cardiothorac Surg,* Vol.37, No.1, (January 2010), pp. 223 − 232.

Wilmot, I. (2011). Effectiveness of mechanical circulatory support in children with acute fulminant and persistent myocarditis. *J Card Fail*, Vol.17, No.6, (June 2011) pp. 487-94.

Walsh, JH. (2003). Exercise training improves conduit vessel function in patients with coronary artery disease. *J Appl Physiol,* Vol.95, No.1, (July 2003), pp. 20-25.

Wu, KH. (2006). Cellular therapy and myocardial tissue engineering: the role of adult stem and progenitor cells. *Eur J Cardiothorac Surg.* Vol.30, No.5, (November 2006), pp. 770-781.

Yacoub, MH. (1995). Two hearts that beat as one. *Circulation*, Vol.92, No.2, (Jul 1995), pp.156-7

Yeager, SB. (2002) Prenatal role of the ductus arteriosus in absent pulmonary valve syndrome. *Echocardiography*, Vol. 19, No.6, (Aug 2002), pp.489-93.

Zickmund, SL. (2006). Congestive heart failure patients report conflict with their physicians. *J Card Fail*. Vol.12, No.7, (September 2006), pp. 546-53.

Zhang, Y. (2007). Enhanced external counterpulsation inhibits intimal hyperplasia by modifying shear stress responsive gene expression in hypercholesterolemic pigs. *Circulation,* Vol.116, No.5, (July 2007), pp. 526-534.

Biophysics

Edited by Dr. Prof. Dr. A.N. Misra

Biophysics is a vast cross-disciplinary subject encompassing the fields of biology, physics and computational biology etc in microbes, plants, animals and human being. Wide array of subjects from molecular, physiological and structural are covered in this book. Most of these chapters are oriented toward new techniques or the application of techniques in the novel fields. The contributions from scientists and experts from different continents and countries focuss on major aspects of biophysics. The book covers a wide range of topics reflecting the complexity of the biological systems. Although the field of biophysics is ever emerging and innovative, the recent topics covered in this book are contemporary and application-oriented in the field of biology, agriculture, and medicine. This book contains mainly reviews of photobiology, molecular motors, medical biophysics such as micotools and hoemodynamic theory.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sayed Nour (2012). "Flow and Rate": Concept and Clinical Applications of a New Hemodynamic Theory, Biophysics, Dr. Prof. Dr. A.N. Misra (Ed.), ISBN: 978-953-51-0376-9, InTech, Available from: http://www.intechopen.com/books/biophysics/-flow-and-rate-concept-and-clinical-applications-of-a-new-hemodynamic-theory

INTECH
open science | open minds