Medical Engineering and Physics 000 (2016) 1–9

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta

M.A. Rezaienia[a], G. Paul[a], E.J. Avital[a], S. Mozafari[a], M. Rothman[b], T. Korakianitis[c,*]

[a] School of Engineering and Materials Science, Queen Mary University of London, London E1 4NS, UK
[b] Department of Cardiology, London Chest Hospital, Barts and the London NHS Trust, London E2 9JX, UK
[c] Parks College of Engineering, Aviation and Technology, Saint Louis University, St. Louis, Missouri 63103, USA

ARTICLE INFO

Article history:
Received 8 July 2016
Revised 2 November 2016
Accepted 13 November 2016
Available online xxx

Keywords:
Cardiovascular simulator
Blood pump
MCS
RBP
VAD

ABSTRACT

This study investigates the hemodynamic responses of the cardiovascular system when a rotary blood pump is operating in the descending aorta, with a focus on the cerebral, coronary and renal autoregulation, using our in-house cardiovascular emulator. Several improvements have been made from our previous studies. A novel coronary system was developed to replicate the native coronary perfusion. Three pinch valves actuated by stepper motors were used to simulate the regional autoregulation systems of the native cerebral, coronary and renal circulations. A rotary pump was installed in the descending aorta, in series with the heart, and the hemodynamic responses of the cardiovascular system were investigated with a focus on cerebral, coronary and renal circulation over a wide range of pump rotor speeds. Experiments were performed twice, once with the autoregulation systems active and once with the autoregulation systems inactive, to reflect that there will be some impairment of autoregulatory systems in a patient with heart failure. It was shown that by increasing the rotor speed to 3000 rpm, the cardiac output was improved from 2.9 to 4.1 L/min as a result of an afterload reduction induced by the pressure drop upstream of the pump. The magnitudes of changes in perfusion in the cerebral, coronary and renal circulations were recorded with regional autoregulation systems active and inactive.

1. Introduction

The number of deaths caused by Heart Failure (HF) has decreased during the past decade in developed countries, yet HF is still the leading cause of deaths in the world. In the United States, in a 10 year period from 2001 to 2011, death rates attributable to HF and the actual number of HF deaths declined by 30.8% and 15.5% per year respectively, yet in 2011 HF still accounted for 31.3% of all deaths [1]. Despite all available therapies to this problem, heart transplant is the main option for end-stage HF patients. However, with a limited number of heart donors available annually (2500 for USA, 1400 Europe and 300 other countries [2,3]) the rate of mortality remains very high for patients on and off the waiting list.

As a result, Rotary Blood Pumps (RBP) have become vital for end-stage HF patients as a bridge to transplantation or destination therapy [4,5]. One of the challenges with the traditional RBPs is their highly invasive implantation procedure which makes many elderly and ill patients ineligible for the surgery. This has encouraged many researchers to investigate new approaches with potential for minimally invasive surgery [6,7].

Transaortic or in-series miniature RBPs, distant from the heart, are one minimally invasive solution [8–11]. The implantation of a RBP in the Descending Aorta (DA), in series with the heart, has been of growing interest among various groups [6,8,12–15]. It was reported that the insertion of an RBP device in the descending aorta leads to an improved cardiac output, yet there is a question related to the impact of the pressure drop generated upstream of the pump on blood perfusion in the upper extremities, particularly the brain and heart [6,12,13,16]. In addition, there is a concern associated with the effect of the pressure rise downstream of the pump on lower extremities, particularly the kidneys [17].

The regional autoregulation systems, which maintain a constant flow rate to vital organs during changing local perfusion pressure,

* Corresponding author.
E-mail addresses: korakianitis@alum.mit.edu, theodosios.alexander@gmail.com (T. Korakianitis).

http://dx.doi.org/10.1016/j.medengphy.2016.11.006
1350-4533/

Nomenclature

Subscripts

ao	aortic
dia	diastolic
mean	mean
pp	pulse pressure
sys	systolic

Abbreviations and acronyms

AoP	aortic pressure
AV	aortic valve
C	compliance
CHF	congestive heart failure
CeF	cerebral flow rate
CeP	cerebral pressure
CO	cardiac output
CoF	coronary flow rate
CoP	coronary pressure
CVR	cerebrovascular resistance
DA	descending aorta
F	flow-meter
LA	left atrium
LV	left ventricle
LM	linear motor
LVP	left ventricular pressure
MCS	mechanical circulatory support
MV	mitral valve
P	pressure
PV	pulmonic valve
Q	flow rate
RBP	rotary blood pump
RA	right atrium
ReP	renal pressure
ReF	renal flow rate
RV	right ventricle
RVP	right ventricle pressure
SCVL	simulator of cardiovascular loops
SyF	systemic flow
TV	tricuspid valve

are present in many organs of the native cardiovascular system, however these are most pronounced in the heart, brain and kidneys [18]. The cerebral autoregulation is a vital homeostatic mechanism to maintain the blood supply to the brain in the event of changing perfusion pressure. For a healthy person, the cerebral circulation is autoregulated within wide limits of mean aortic pressure from 60 to 120 mmHg [19,20]. The coronary circulation maintains the blood supply to the heart and is autoregulated within 45–130 mmHg in a healthy person [21]. The renal autoregulation has been extensively investigated in prior studies [22,23]. In a native human body the renal blood supply is relatively constant when the mean arterial pressure varies between 90 and 180 mmHg [22]. It must be noted that various pathological conditions, including hypertension, hypotension and a change in arterial CO_2 level can alter the upper and lower limits of the autoregulated region [24].

The aim of this study is to investigate the hemodynamic responses of the cardiovascular system when a rotary pump is operating in the descending aorta with a focus on the cerebral, coronary and renal circulation. Since the regional autoregulation can be impaired in heart failure patients, the hemodynamic response is investigated with intact and impaired regional autoregulation. An expected outcome is to estimate what level of support is feasible while avoiding the previously mentioned risk of drops in perfusion to the coronary and cerebral circulations.

The objectives of this study are met using our in-house multi-chamber Simulator of Cardio-Vascular Loops (SCVL). Cardiovascular simulators offer a more controlled and inexpensive platform to evaluate the performance of existing blood-contacting devices as well as new medical concepts, prior to in-vivo studies. In recent years, much progress has been made in the design and development of cardiovascular simulators with close similarity to a native system for research and training [25–28].

In the present study, several improvements have been made from our previous studies [6,12,13,29]. The coronary perfusion mechanism which causes the heart to be perfused only during diastole was implemented using a solenoid valve. In addition, the coronary and renal autoregulation circulations, similar to the cerebral autoregulation mechanism presented in our previous study [29], were integrated into the SCVL system, with autoregulation limits determined from the clinical data.

2. Methodology

The native cardiovascular system of an adult human was emulated using our in-house SCVL system, as shown in the schematic diagram of Fig. 1.

Four elastic rubber chambers were used to model the native heart chambers. The left and right ventricles (LV and RV) had a volume of 100 mL and the left and right atrium (LA and RA) had a volume of 50 mL. Four linear motors (P01-37× 120 from LinMot, Spreitenbach, Switzerland) were employed to simulate the contraction and dilation of the ventricle and atrium chambers. Two trajectory time-varying functions extracted from the real time left ventricle and left atrium volume, as described in our previous study [29], were employed to actuate the four linear motors. Fig. 2 shows the simultaneous graphs of trajectory time-varying functions of the ventricles and atria for an intact heart. Each function can be scaled up or down in order to replicate various physiological and pathological conditions.

Four prosthetic heart valves (Medtronic, Minneapolis, Minnesota, USA) modelling the aortic, mitral, pulmonary and tricuspid valves were used to ensure unidirectional flow in the vicinity of each chamber. The systemic and pulmonary circulations are replicated using 24 mm diameter rubber tubing, while smaller arteries are replicated using 12 mm diameter rubber tubing. A blood analog solution comprising of 65 wt% water and 35 wt% glycerol was used as the working fluid, as in the study conducted by Pantalos et al. [27].

Five pressure transducers (PMP 5074, precision ± 0.1 FS BSL) from General Electric, Billerica, MA, USA were used to simultaneously measure the Left Ventricle Pressure (LVP), Aortic Pressure (AoP), Right Ventricle Pressure (RVP), Cerebral Pressure (CeP) and Renal Pressure (ReP). The Coronary Pressure (CoP) was defined as equal to the AoP.

A number of Hoffman clips were used to manually control the systemic and pulmonary resistance level to allow tuning of the SCVL system. Three electromagnetic flow-meters (SITRANS F M MAG 1100 F, precision 0.4% ± of reading, from Siemens, Munich, Germany) were employed to measure the Cerebral Flow (CeF), Coronary Flow (CoF) and Renal Flow (ReF), respectively and an ultrasonic flow-meter (Cynergy UF Flow, C3, precision 3% of reading) (Cynergy UF Flow, C3) was used to measure the Systemic Flow (SyF). The sum of these flows gives the Cardiac Output (CO). The vascular distensibility of the systemic and pulmonary circulations was replicated using a number of compliance units developed in our previous experiment [29]. The compliance level for each unit can be adjusted to match the vascular distensibility of a native system for various pathological conditions.

A parallel configuration of a solenoid valve and narrow tubing was used to model the coronary perfusion mechanism, as shown

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

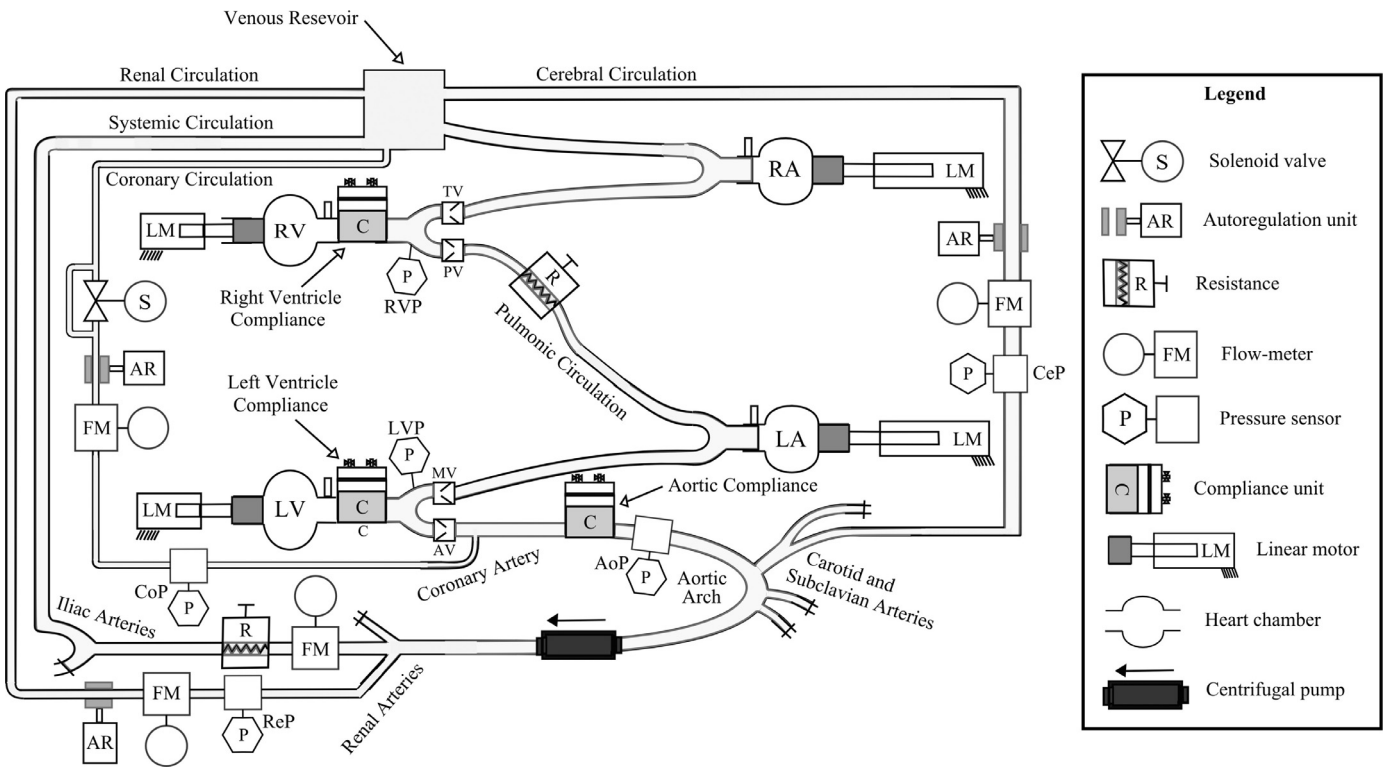

Fig. 1. Schematic diagram of the SCVL system with the coronary, cerebral and renal autoregulation units and an RBP device in the descending aorta.

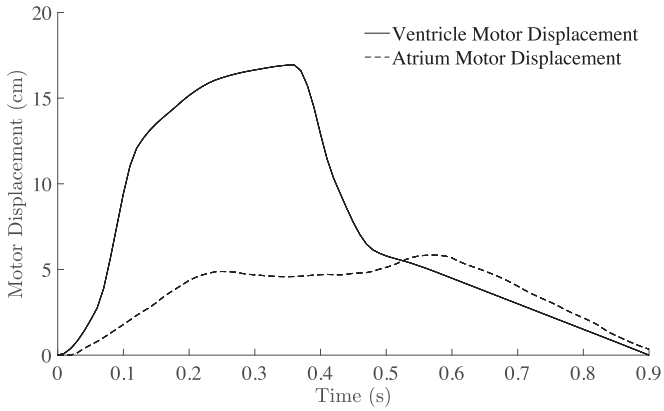

Fig. 2. The predefined time-varying trajectory functions of the ventricles and atria, adopted from the study conducted by Rezaienia et al. [29].

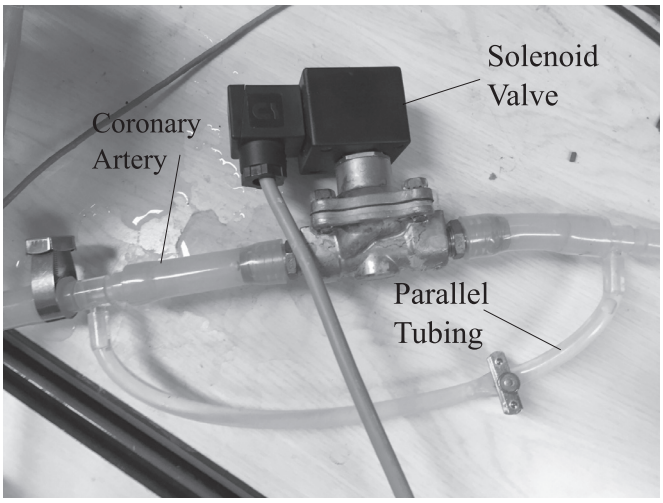

Fig. 3. Photograph of the coronary perfusion mechanism incorporating a parallel configuration of a solenoid valve and tubing.

in Fig. 3. In a native system, coronary blood flow occurs predominantly during diastolic phase when the heart muscles are relaxed and thereby the lumen of the coronary arterioles are fully open [30]. The solenoid valve was programmed to be closed during systole and remain open during diastole. This allows a small portion of the coronary flow to bypass the valve via the tubing during the systolic phase, but the larger portion of the flow occurs via the solenoid valve during the diastolic phase.

Three autoregulation units were attached to the carotid, coronary and renal arteries, as shown in Fig. 1. Each unit takes the form of a pinch valve driven by a stepper motor, as shown in Fig. 4, and applies dilation and constriction to the cerebral, coronary, and renal arteries as occurs in a native system. The flow is adjusted to the autoregulated level when the pressure is within the regulated region, using the appropriate flow-meter as feedback for the control system. Outside of the autoregulated region, the pinch valve is at maximum or minimum dilation depending on whether the pressure is below or above the autoregulated region respectively. Clinical data for each autoregulation unit's pressure/flow profile was taken from suitable in-vivo studies [19,21,31].

3. Results

3.1. SCVL performance

A healthy condition and a HF condition were replicated in order to evaluate the efficacy of SCVL system. For the healthy condition, the four linear motors were operating in full scale according to the trajectory functions shown previously in Fig. 2. Modelling

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

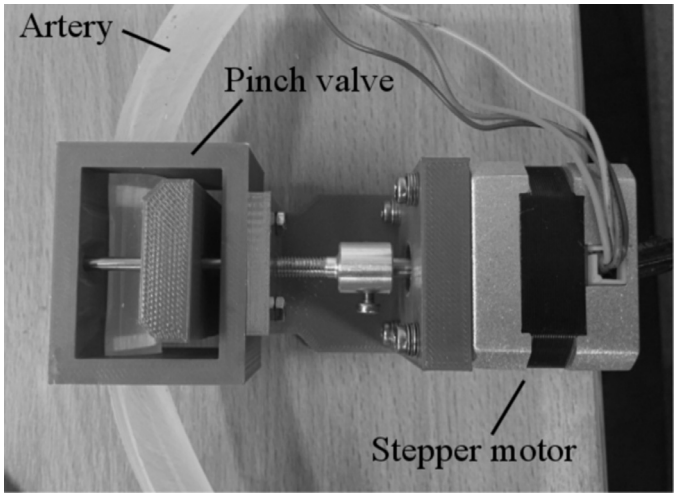

Fig. 4. Photograph of the autoregulation unit using the stepper motor.

of the HF condition is more difficult, since in this condition the heart's chambers deform, the LV dilates and mechanism of contraction changes. For this study, the HF condition was reproduced by decreasing the minimum displacement of the LV linear motor, replicating an increased diastolic LV volume, and decreasing the maximum displacement of the LV linear motor, replicating a reduced LV pumping ability. The LV dilation was modelled by integrating a compliance unit upstream of the aortic valve, as shown in Fig. 1, and increasing its compliance. In addition, the vascular distensibility was decreased by reducing the compliance level to simulate a stiffer vascular system and the systemic resistance was increased slightly.

The SCVL was tuned so that the pressure and flow rate in healthy and HF conditions matched the corresponding clinical data extracted from suitable clinical publications [30,32–34].

Fig. 5 (a, b) shows the experimental AoP, LVP and RVP for the healthy and HF conditions respectively. The measured AoP, LVP and RVP waveforms for the healthy condition are 120/82, 120/5 and 30/5 mmHg respectively. The measured AoP, LVP and RVP waveforms for the HF condition are 107/74, 107/25 and 48/25 mmHg respectively. It is evident that the dicrotic notch (incisura), occurring due to a slight back-flow into the native left ventricle, has been reflected clearly on the descending limb of the simulated AoP waveform. The small pressure bump appearing just before the ascending limb of the LVP waveform is due to the systolic contraction of the atrium as occurs in the native system [30].

The CO for the healthy and HF conditions were recorded as 5.1 L/min and 2.9 L/min and the AoP_{mean} for the healthy and HF condition are 95 and 85 mmHg, respectively. The SCVL correctly simulates the main physiological features of the pressure waveforms in good agreement with clinical data [30,32–34]. A smooth waveform is obtained without any signal filtering because the valve closing pressure spikes often present in cardiovascular simulators [35] are dampened by the compliance units.

3.2. Coronary perfusion mechanism

Fig. 6(a, b) shows AoP and CoF with the SCVL operating in the healthy condition. During the systolic phase CoF drops to 50 ml/min and during the diastolic phase it rises to a maximum of 400 ml/min. This is in agreement with the observed coronary perfusion in a native system [21,30].

3.3. Autoregulation units

The performance of the cerebral, coronary and renal autoregulation units are evaluated by applying a number of stepwise pressure reductions in the systemic artery and subsequently recording the steady state CeF_{mean}, CoF_{mean} and ReF_{mean}. For this study, the performance of only the cerebral autoregulation unit is presented on the basis that the other two units have the same functionality but different autoregulated ranges.

Initially, the AoP_{mean} was set at 125 mmHg. In systemic resistance incremental reductions were introduced into the SCVL system. For each step the AoP_{mean} and CeF_{mean} were recorded after 10 s to ensure that the transient flow was settled. The step period on the stepper motor was adjusted to ensure the autoregulation response is typically around 5 s as observed in the clinical study [36], although this varies slightly depending on the magnitude of the pressure change.

Fig. 7 shows the cerebral autoregulation pressure–flow curve and the corresponding CerebroVascular Resistance (CVR). As shown

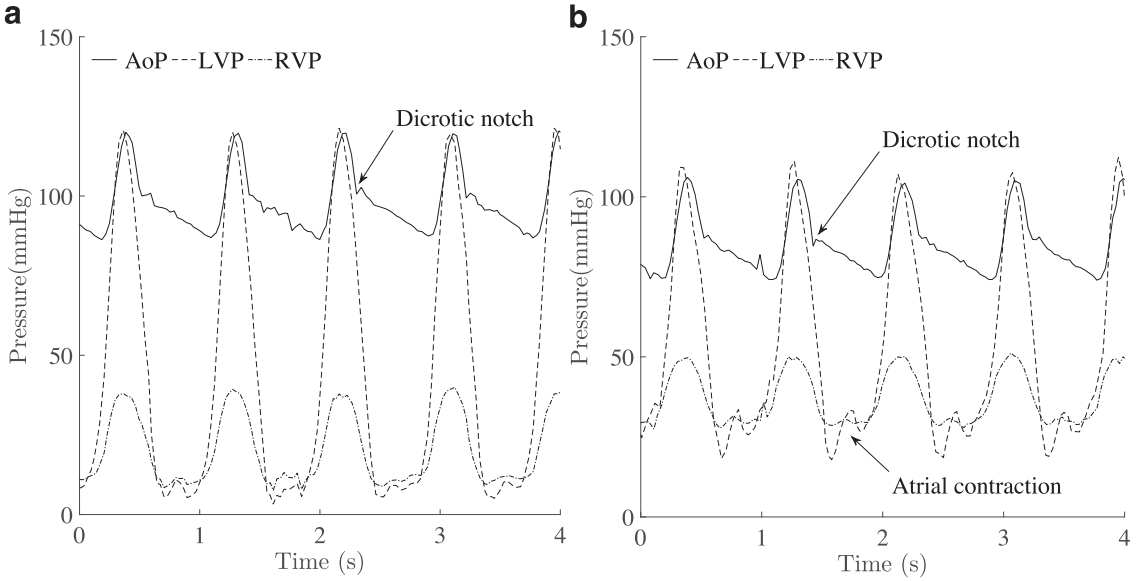

Fig. 5. (a) The experimental AoP, LVP and RVP waveforms for the healthy condition. (b) The experimental AoP, LVP and RVP waveforms for the heart failure condition.

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

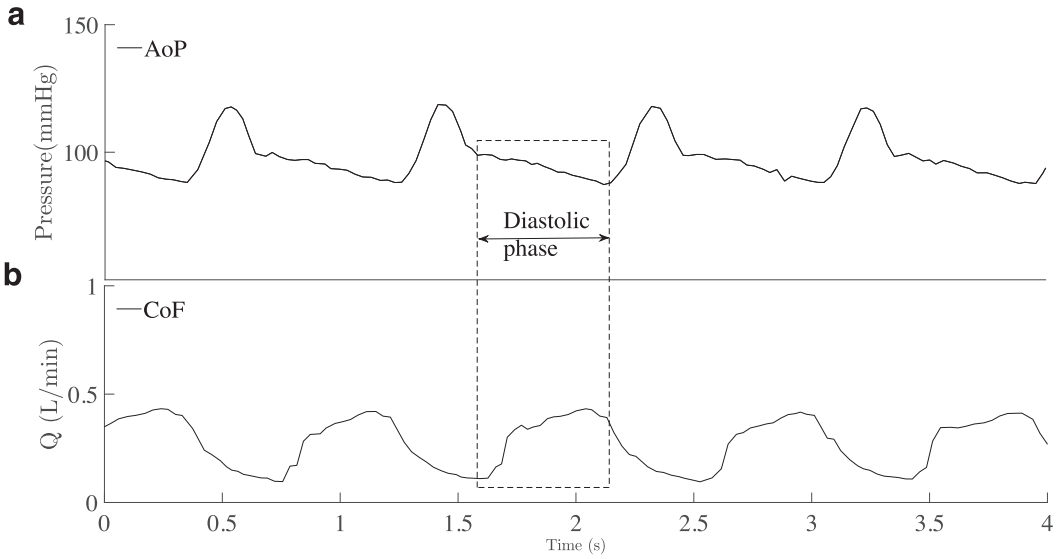

Fig. 6. (a) The experimental AoP waveforms for the healthy condition. (b) The experimental CoF waveform for the healthy condition.

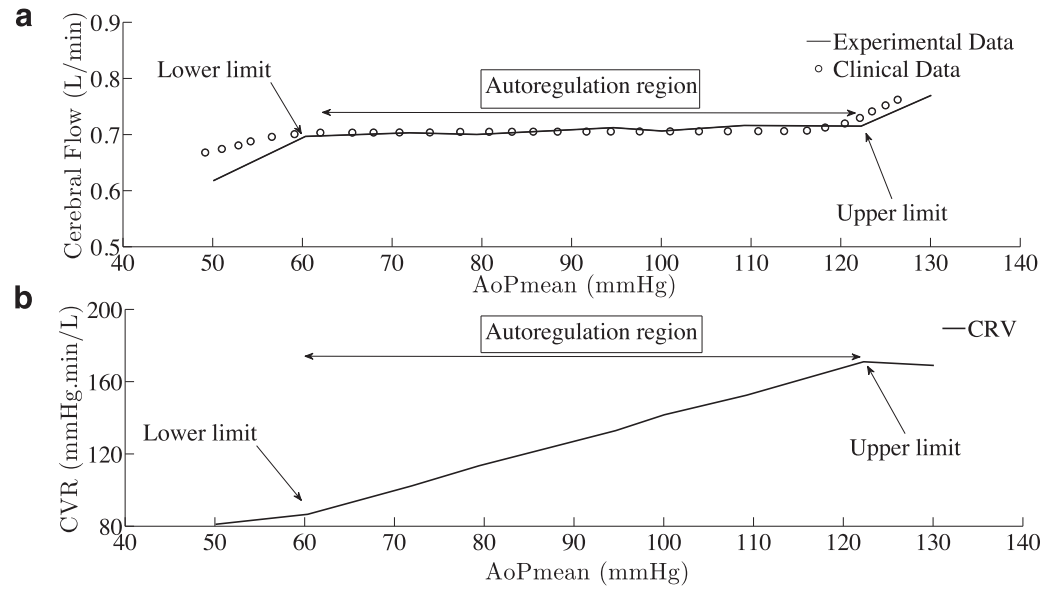

Fig. 7. The performance of the cerebral autoregulation unit from 60 to 120 mmHg, adopted from the study conducted by Rezaienia et al. [29]. (a) Cerebral flow in the SCVL compared with clinical data [24] and (b) the CVR from the same experiment.

in Fig. 7(a), the autoregulated CeF_{mean} is set at 0.71 L/min, as measured in the clinical study conducted by Ford et al. [37] for a normotensive human. It is evident that within the autoregulated region, 60–120 mmHg, the cerebral flow remains unchanged. However, outside the autoregulated region the CeF_{mean} level is proportional to the AoP_{mean} level, with the autoregulated artery at a maximum dilation or a maximum contraction. Fig. 7(b) shows that as the AoP_{mean} level gradually decreases, the CVR decreases to ensure that the cerebral flow remains unchanged within the autoregulated region.

3.4. Integration of a rotary pump in the descending aorta

A HF condition was reproduced in which the AoP_{mean} and the CO are 85 mmHg and 2.9 L/min respectively. A rotary pump simulating a RBP device was implemented in the descending aorta above the renal arteries, in series with the heart, as shown in Fig. 1. The pump is an in-house bench-top centrifugal pump with the hydrodynamic characteristics of 70 mmHg against 5 L/min at 3000 rpm. Five experiments were conducted in which the hemodynamic responses of pressures AoP, LVP, CoP, CeP and ReP as well as flow rates SyF, CeF, CoF, ReF and CO were recorded with the pump operating over rotor speeds from 0 to 4000 rpm in increments of 1000 rpm. This was repeated with the regional autoregulation systems active and inactive. The results are summarised in Tables 1 and 2.

There is an improvement in CO whether or not the regional autoregulation system is active. At 3000 rpm the CO has increased by 42%. Since there is a large resistance downstream of the pump, the pressure drop upstream of the pump in the aortic arch (see CeP and CoP) is relatively small (−13% at 3000 rpm with autoregulation inactive) compared to the pressure rise downstream of the pump (see ReP) which is far larger (+106% at 3000 rpm with autoregulation inactive).

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

Table 1
SCVL hemodynamic characteristics with active regional autoregulation systems for the healthy and HF conditions with an MCS device in the DA operating from 0 to 4000 rpm.

Condition	Healthy, 0 rpm	HF, 0 rpm	HF, 1000 rpm	HF, 2000 rpm	HF, 3000 rpm	HF, 4000 rpm	Units
ΔP	–	–	5	36	82	130	mmHg
AoP_{mean}	95	85	82	78	74	68	mmHg
AoP_{sys}	116	107	104	101	98	95	mmHg
AoP_{dia}	82	75	71	67	62	55	mmHg
CoP_{mean}	95	85	82	78	74	68	mmHg
CeP_{mean}	105	94	92	89	88	80	mmHg
ReP_{mean}	90	80	97	125	170	220	mmHg
CeP_{pp}	34	32	33	34	36	41	mmHg
ReP_{pp}	27	25	28	29	41	45	mmHg
CeF_{mean}	0.71	0.71	0.71	0.71	0.71	0.70	L/min
CoF_{mean}	0.22	0.22	0.22	0.22	0.22	0.21	L/min
ReF_{mean}	1.21	1.20	1.19	1.19	1.21	1.46	L/min
SyF_{mean}	2.97	0.77	0.97	1.13	1.98	2.25	L/min
CO	5.11	2.90	3.09	3.25	4.12	4.62	L/min

AoP_{error}=CoP_{error}=CeP_{error}=ReP_{error} = ±0.1 mmHg, CeF_{error}=CoF_{error}=ReF_{error} = $\pm 4e^{-3}$ $\frac{L}{min}$, CO_{error} = $\pm 3e^{-2}$ $\frac{L}{min}$.

Table 2
SCVL hemodynamic characteristics with inactive regional autoregulation systems for the healthy and HF conditions with an RBP device in the DA operating from 0 to 4000 rpm.

Condition	Healthy, 0 rpm	HF, 0 rpm	HF, 1000 rpm	HF, 2000 rpm	HF, 3000 rpm	HF, 4000 rpm	Units
ΔP	–	–	5	36	82	130	mmHg
AoP_{mean}	95	85	81	78	73	65	mmHg
AoP_{rmsys}	116	107	102	100	96	90	mmHg
AoP_{dia}	82	75	71	65	59	47	mmHg
CoP_{mean}	95	85	81	78	73	65	mmHg
CeP_{mean}	105	94	93.5	90	85	75	mmHg
ReP_{mean}	90	80	98.3	119	165	215	mmHg
CeP_{rmpp}	34	32	27.9	32	36	44	mmHg
ReP_{rmpp}	27	25	25.2	31	32	30	mmHg
CeF_{mean}	0.71	0.70	0.69	0.65	0.59	0.49	L/min
CoF_{mean}	0.22	0.22	0.22	0.20	0.17	0.13	L/min
ReF_{mean}	1.21	1.21	1.31	1.60	2.06	2.6	L/min
SyF_{mean}	2.97	0.78	0.91	0.94	1.22	1.37	L/min
CO	5.11	2.91	3.13	3.39	4.04	4.59	L/min

AoP_{error}=CoP_{error}=CeP_{error}=ReP_{error} = ±0.1 mmHg, CeF_{error}=CoF_{error}=ReF_{error} = $\pm 4e^{-3}$ $\frac{L}{min}$, CO_{error} = $\pm 3e^{-2}$ $\frac{L}{min}$.

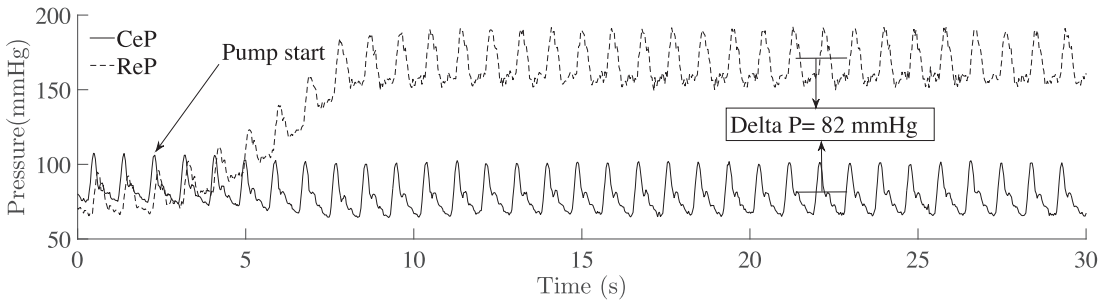

Fig. 8. The transient responses of CeP and ReP with the pump operating at 3000 rpm at T = 3 s.

Fig. 8 shows the ReP and CeP waveforms as the pump accelerated to 3000 rpm, at which point a pressure rise of 82 mmHg is recorded across the pump. The dashed line represents the measured ReP waveform downstream of the pump and the solid line represents the CeP waveforms upstream of the pump. At T = 3 s, when the pump is switched on, the CeP gradually decreases over the course of 10 s until CeP_{mean} reaches a steady level of 88 mmHg. In contrast, ReP_{mean} is increased from 80 mmHg for HF condition until it reaches the steady level of 170 mmHg. It is also shown that upon insertion of the pump, the cerebral pulse pressure (CeP_{pp}), and renal pulse pressure (ReP_{pp}), determined by subtracting the systolic from the diastolic pressure at these circulations, rise by 12% and 30% respectively.

Fig. 9 shows the transient responses of the CoF, CeF, ReF and CO when the pump is switched on at 3000 rpm and regional autoregulation systems are active. Fig. 9(a) shows that with the pump at 3000 rpm there is no variation in CoF. Fig. 9(b) shows that the CeF drops by 8% at T = 12 s, however since CeP remains within the cerebral autoregulated region (60–120 mmHg), the CeF is autoregulated and returns to the initial steady state level of 0.71 L/min at T = 28 s. It is evident that at T = 18 s there is a slight overshoot in the CeF, before reaching the steady state level. Aaslid et al. [36] in a clinical study on humans demonstrated that the CeF overshoot occurs due to the delay in the autoregulation system compensating for a change in the aortic pressure. Fig. 9(c) shows that the ReF rises by 45% at T = 13 s to 1.65 L/min, however, since ReP_{mean} remains within the renal autoregulated region (90–180 mmHg), the autoregulation system compensates and the CeF returns to the initial level of 1.2 L/min by T = 28 s. Fig. 9(d) shows that with the pump operating at 3000 rpm, CO gradually increases

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

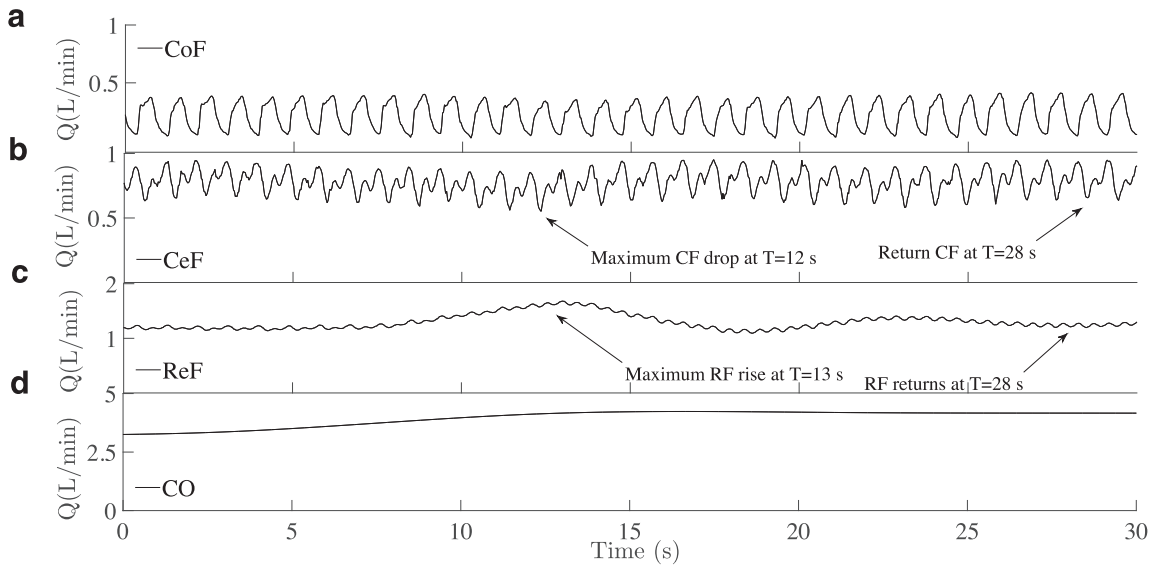

Fig. 9. (a) The transient responses of the CoF waveforms (b) CeF waveforms, (c) ReF waveforms, (d) CO with the pump operating at 3000 rpm.

from 2.9 L/min and reaches the steady level of 4.1 L/min over the course of 25 s. The perfusion pressure to the cerebral and coronary circulations remained within the autoregulated regions at all levels of support, so when the autoregulation systems were active there was no drop in CoF or CeF.

At 4000 rpm AoP_{mean} falls by around 20%. The fall in AoP_{mean} can result in reduced perfusion to vital organs when regional autoregulation systems are inactive in this scenario. CeF falls 31% at 4000 rpm, from 0.71 L/min to 0.49 L/min, while CoF falls 41% from 0.22 L/min to 0.13 L/min. The drop in CoF is larger than the drop in CeF because of the increased pulsatility; AoP_{dia} falls by more than AoP_{mean}, so the drop in coronary perfusion, which primarily occurs in diastole, is exacerbated. The large pressure increase downstream of the pump causes an increase in renal perfusion. When the autoregulation systems are on, renal flow is unaffected at speeds from 0 to 3000 rpm, however at 4000 rpm there is an increase of 22%. When the autoregulation systems are inactive, the renal flow increases proportional to the pressure.

4. Discussion

The SCVL was used to accurately replicate clinical pressure waveforms and flow rates for healthy and HF conditions. The novel parallel configuration of a solenoid valve and narrow tubing ensured the coronary was primarily perfused in diastole, as in the native system. The autoregulation units, when active, successfully maintained clinically accurate flow rates in cerebral, coronary and renal circulations and this technique can be used to simulate arterial constriction and dilation in other parts of the body, such as skeletal muscles or intestines [18].

With an integrated RBP, operating over a wide range of rotor speeds in the DA, it was observed that the pressure rise generated downstream of the pump was several times higher than the pressure drop generated upstream of the pump. This is because the resistance in lower extremities was much larger than the resistance between the LV and the pump. As demonstrated in previous studies [6,12,13,29], the pressure drop induced by the pump reduces the afterload pressure and thus improves the CO. It was reported in our previous work [13] that the afterload reduction due to a pump operating in the descending aorta results in a greater ejection with the same LV contractile energy, leading to an improvement in LV performance.

If the comparatively low pressure drop in the aortic arch is replicated in-vivo, it suggests that a beneficial level of support could be applied without significant perfusion drops in cerebral and coronary circulations. With regional autoregulation inactive, a 3000 rpm pump speed resulted in a 42% increase in CO with drops of 17% and 23% in CeF and CoF. Any regional autoregulation activity would reduce these perfusion drops. The pressure rise downstream of the pump improves perfusion to the kidneys. Studies on HF patients showed that the mortality rate is more closely associated with the worsening of renal function than any other established risk factor such as left ventricular ejection fraction [38]. It is reported the worsening renal function is strongly related to the hemodynamic stability of the renal blood flow [39]. Clinical data on the kidney's response to sustained high pressure in humans could not be obtained although it is noted that the renal circulation has a high upper limit to its autoregulation system, at 180 mmHg, which was exceeded in our experiment only at the 4000 rpm level of support.

With the rotary pump operating in series with the heart, it was observed that the flow pulsatility in all circulations was improved. This is in contrast to the traditional LVAD implantation, where increasing the level of pump support attenuates the pulsatility [6]. Clinical studies show that the flow pulsatility has a positive effect on recovery of cerebral, renal, and coronary systems functionality in patients with HF [40–42]. However, the pulsatility also results in a lower AoP_{dia} which presents a risk to coronary perfusion. A larger perfusion drop was observed in the coronary circulation than in the cerebral circulation during RBP support in the SCVL with regional autoregulation inactive.

In this paper the response of the SCVL to a rotary pump in the descending aorta with and without regional autoregulation systems is compared. The debate of whether and to what extent autoregulation systems are impaired in HF is still ongoing and there was no clear answer from the authors' literature search. Descending aorta RBP has been investigated in animals [16] and man [8] by Reitan et al. They found that with their percutaneous catheter-based pump in the descending aorta of calves, no variation in the coronary perfusion was observed. A drop of 15% in CeF was observed, however in the same study the author emphasised on existing differences between the human and animal cerebral functionality and they predicted that the human cerebral autoregulation system would ensure a sufficient blood supply down to

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

AoP_{mean} of 60 mmHg. In the study in man, such invasive measurements could not be taken.

No other studies on the regional autoregulation involve in-series RBP device insertion. There are studies [43,44] showing clearly that the regional autoregulations, particularly cerebral autoregulation is partially impaired in severe HF. However, other studies [45] claim that many patients with moderate to severe HF condition have a normal regional autoregulation due to the redistribution of the blood flow in the cardiovascular system. In addition, there are studies [44,46] show that, in some cases after the RBP implantation or heart transplantation, the impaired regional autoregulation has been improved, following CO re-establishment. Whether or not regional autoregulation is impaired due to heart failure, this study has indicated that the pressure drop in the upper extremities is relatively low (10–12 mmHg at 3000 rpm) even without regional autoregulation.

There are many advantages, compared to the existing LVAD in-parallel configuration, that makes this approach worthy of investigation. Implantation in the descending aorta is less invasive and possibly can be performed via a left thoracotomy. As a result, the operation would be less expensive and potentially can be done in district general hospitals. Also, this technique may reduce the chance of stroke. For the in-parallel configuration, the thrombi released from the LVAD outlet graft, can be transported along the blood stream through the ascending aorta toward the brain, thereby increasing the chance of stroke [47]. With a RBP in the descending aorta, thrombi would be directed to the lower extremities rather than upper extremities, thus reducing the chance of stroke. However there are some concerns about the in-series implantation which needs further examination through more in-vitro and in-vivo tests. For instance, the level of support should clearly be limited to avoid excessive pressure drops upstream and rises downstream, otherwise perfusion in the cerebral, coronary, and renal circulations may become more impaired than before implantation.

5. Limitations

One limitation of this study is the lack of appropriate clinical data on impairment of regional autoregulation in HF. How these systems are affected during HF is an unresolved question which has significant implications for the suitability of descending aorta RBP support. Consequently, we repeated our experiment with and without regional autoregulation systems active to give a best-case and worst-case scenario for in-series support. While the data used here for cardiovascular parameters were collected from a variety of sources, it was not possible to collect all required data from a single individual and the resulting simulations accurately replicate the cardiovascular system of a typical human adult.

For this study the preload (Frank–Starling mechanism) and afterload (autonomic nervous system) sensitivity of the ventricles were not modelled in the SCVL. Preload and afterload sensitive motors have been implemented into other cardiovascular simulators [25,26,28]. Implementation of these features in the SCVL is necessary to give a more comprehensive understanding of the hemodynamic effects of an RBP device in the DA. Theoretically, in a native system pressure rise generated downstream of the pump, would cause a high preload pressure in the right atrium which would lead to further improved cardiac output due to the Frank–Starling mechanism. In addition, the pressure drop upstream of the pump, would trigger the autonomic nervous mechanism which consequently would lead to the redistribution of blood toward the upper extremities as a result of increased vasoconstriction in the major arterial system [45]. In this study the effect of a rise in hydrostatic pressure due to the horizontal position of the system was not considered. In a supine position, an increased hydrostatic pressure leads to a rise in preload which consequently improves the cardiac output, provided that the Frank–Starling is intact [18].

Although the previous studies show that the improvement in renal flow may have a positive impact on renal functionality [39,48,49], yet the clinical consequence of an the increased renal pressure observed in this study is not known. An in-vivo study [50] on a dog showed that the incremental increase in renal pressure, directly affects the peritubular capillaries in the kidneys and that leads to a rise in urine flow and subsequently urinary sodium excretion. In-vivo tests are mandated in order to evaluate the effect of the pressure rise and extra renal perfusion on kidney functionality.

6. Conclusions

This study showed the use of a novel coronary mechanism and autoregulation units in the SCVL. The improved SCVL system is able to emulate the behaviour of the heart during healthy and HF conditions in close agreement to the existing clinical data and allows measurement of pressure and flow in cerebral, coronary and renal circulations. Certainly, having more clinical data, for instance on impairment of the regional autoregulation, would improve the results. The perfusion in these regional circulations may be affected by an RBP device operating in the descending aorta. The extent of changes in perfusion is determined by the level of support and the efficacy of the regional autoregulation systems. Our work suggests that a beneficial level of support is possible at 3000 rpm without detrimental effects on the cerebral and coronary perfusion, but only with unimpaired regional autoregulation. In a future study, we will replicate impaired cerebral, coronary and renal autoregulation in the SCVL once suitable clinical data has been obtained. It is our intention to integrate the autonomic and Frank–Starling mechanisms to the SCVL system and investigate the hemodynamic responses of the whole system in detail with an RBP operating in the descending aorta.

Conflict of interest

None.

Acknowledgements

This report is independent research funded by the National Institute for Health Research [i4i, Turbocardia, II-LB-1111-20007]. Principal Investigator for the grant is Professor T. Korakianitis. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

References

[1] Mozaffarian D, Benjamin EJ, Go AS. Executive summary: heart disease and stroke statistics—2015 update a report from the American heart association. Circulation Jan 27 2015;131(4):434–41.
[2] Lund LH, Edwards LB, Kucheryavaya AY. The registry of the international society for heart and lung transplantation: thirty-first official adult heart transplant report-2014; focus theme: retransplantation. J Heart Lung Transplant Oct 2014;33(10):996–1008.
[3] Adler ED, Goldfinger JZ, Kalman J, Park ME, Meier DE. Palliative care in the treatment of advanced heart failure. Circulation Dec 22 2009;120(25):2597–606.
[4] Griffith BP, Kormos RL, Borovetz HS, Litwak K, Antaki JF, Poirier VL, et al. Heartmate II left ventricular assist system: from concept to first clinical use. Ann Thorac Surg March 2001;71(3S):116–20.
[5] Christiansen C, Klocke A, Autschbach R. Past, present, and future of long-term mechanical cardiac support in adults. J Cardiac Surg Dec 2008;23(6):664–76.
[6] Rezaienia MA, Rahideh A, Rothman MT, Sell SA, Mitchell K, Korakianitis T. In vitro comparison of two different mechanical circulatory support devices installed in series and in parallel. Artif Organs 2014;38(9):800–9.
[7] Schmitto JD, Rojas SV, Hanke JS, Avsar M, Haverich A. Minimally invasive left ventricular assist device explanation after cardiac recovery: surgical technical considerations. Artif Organs June 2014;38(6):507–10.

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006

[8] Smith EJ, Reitan O, Keeble T, Dixon K, Rothman MT. A first-in-man study of the Reitan catheter pump for circulatory support in patients undergoing high--risk percutaneous coronary intervention. Catheteriz Cardiovasc Interven June 2009;73(7):859–65.
[9] Okamoto E, Yano T, Shiraishi Y, Miura H, Yambe T, Mitamura Y. Initial acute animal experiment using a new miniature axial flow pump in series with the natural heart. Artif Organs 2016;39(8):701–28.
[10] Bhayana JN, Scott SM, Sethi GK, Takaro T. Effects of intra-aortic balloon pumping on organ perfusion in cardiogenic shock. J Surg Res 1979;26(2):108–13.
[11] Korakianitis T, Rezaienia MA, Paul GM, Rahideh A, Rothman MT, Mozafari S. Optimization of centrifugal pump characteristic dimensions for mechanical circulatory support devices. ASAIO J 2016;62(5):545–51.
[12] Ruiz P, Rezaienia MA, Rahideh A, Keeble TR, Rothman MT, Korakianitis T. In vitro cardiovascular system emulator (bioreactor) for the simulation of normal and diseased conditions with and without mechanical circulatory support. Artif Organs Jun 2013;37(6):549–60.
[13] Rezaienia MA, Rahideh A, Hamedani BA, Bosak DEM, Zustiac S, Korakianitis T. Numerical and in vitro investigation of a novel mechanical circulatory support device installed in the descending aorta. Artif Organs June 2015;39(6):502–13.
[14] del Rio C, Clifton W, Heuring J, Hertzog B, Ueyama Y, Youngblood B, et al. Aortix, a novel catheter-based intra-vascular assist device, provides cardio-renal support while improving ventriculo-arterial coupling and myocardial demand in sheep with induced chronic ischemic heart failure. In: Poster Presented in 64th Annual Conference of ACC. 15 in San Diego, California; March 2015.
[15] Wang Y, Hsu PL, Love HC, Timms DL, McMahon RA. In vitro study of an intra-aortic VAD: effect of reverse-rotating mode on ventricular recovery. In: 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2015. p. 274–7.
[16] Reitan O, Steen S, Ohlin H. Hemodynamic effects of a new percutaneous circulatory support device in a left ventricular failure model. ASAIO J 2003;49(6):731–6.
[17] Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: “Guyton revisited”. Eur Heart J 2005;26(1):11–17.
[18] Guyton AC. Textbook of medical physiology. W. B. Saunders Company; 1986.
[19] Mchenry LC, West JW, Cooper ES, Goldberg HI, Jaffe ME. Cerebral autoregulation in man. Stroke 1974;5(6):695–706.
[20] Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metabol Rev 1990;2(2):161–92.
[21] Pijls NHJ, De Bruyne B. Coronary Pressure. Springer; 2013.
[22] Marsh JM, Holstein NH. Renal blood flow regulation and arterial pressure fluctuations: a case study in nonlinear dynamics. Physiol Rev 1994;74(3):637–81.
[23] Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Failure Rev 2012;17(2):161–75.
[24] Strandgaard S. Autoregulation of cerebral blood-flow in hypertensive patients—modifying influence of prolonged antihypertensive treatment on tolerance to acute, drug-induced hypotension. Circulation 1976;53(4):720–7.
[25] Crosby JR, DeCook KJ, Tran PL, Smith RG, Larson DF, Khalpey ZI, et al. Physiological characterization of the syncardia total artificial heart in a mock circulation system. ASAIO J May 2015;61(3):274–81.
[26] Gregory SD, Stevens M, Timms D, Pearcy M. Replication of the frank-starling response in a mock circulation loop. In: 2011 International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2011. p. 6825–8.
[27] Pantalos GM, Ionan C, Koenig SC, Gillars KJ, Horrell T, Sahetya S, et al. Expanded pediatric cardiovascular simulator for research and training. ASAIO J 2010;56(1):67–72.
[28] Jansen-Park SH, Mahmood MN, Müller I, Turnhoff LK, Schmitz-Rode T, Steinseifer U, et al. Effects of interaction between ventricular assist device assistance and autoregulated mock circulation including Frank–Starling mechanism and baroreflex. Artif Organs 2015;40(10):981–91.
[29] Rezaienia MA, Gordon P, Avital E, Rahideh A, Rothman MT, Korakianitis T. In--vitro investigation of cerebral-perfusion effects of a rotary blood pump installed in the descending aorta. J Biomech 2016;49(9):1–8.
[30] Guyton AC, Hall JE. Textbook of medical physiology. Elsevier Saunders; 2006.
[31] Palmer BF. Renal dysfunction complicating the treatment of hypertension. New Engl J Med 2002;347(16):1256–61.
[32] Fischer EIC, Armentano RL, Pessana FM, Graf S, Romero L, Christen AI, et al. Endothelium-dependent arterial wall tone elasticity modulated by blood viscosity. Am J Physiol—Heart Circul Physiol 2002;282(2):389–94.
[33] Lin ACW, Lowe A, Sidhu K, Harrison W, Ruygrok P, Stewart R. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. J Hypertens September 2012;30(9):1743–50.
[34] Denardo SJ, Nandyala R, Freeman GL, Pierce GL, Nichols WW. Pulse wave analysis of the aortic pressure waveform in severe left ventricular systolic dysfunction. Circul—Heart Failure 2010;3(1):149–56.
[35] Ferrari G, Lazzari CD, Kozarski M, Clemente F, Gorczynska K, Mimmo R, et al. A hybrid mock circulatory system: testing a prototype under physiologic and pathological conditions. ASAIO J 2002;48(5):487–94.
[36] Rune A, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;56(36):45–53.
[37] Ford MD, Alperin N, Lee SH, Holdsworth DW, Steinman DA. Characterization of volumetric flow rate waveforms in the normal internal carotid and vertebral arteries. Physiol Measure August 2005;26(4):477–88.
[38] Schmieder RE, Mitrovic V, Hengstenberg C. Renal impairment and worsening of renal function in acute heart failure: can new therapies help? The potential role of serelaxin. Clin Res Cardiol March 2015;104(8):621–31.
[39] Smilde TDJ, Damman K, Harst PVd, Navis G, Westenbrink BD, Voors A, et al. Differential associations between renal function and modifiable risk factors in patients with chronic heart failure. Clin Res Cardiol: Official J German Cardiac Soc 2009;98(2):121–9.
[40] Kim HK, Son HS, Fang YH, Park SY, Hwang CM, Sun K. The effects of pulsatile flow upon renal tissue perfusion during cardiopulmonary bypass: A comparative study of pulsatile and nonpulsatile flow. ASAIO J January 2005;51(1):30–6.
[41] Undar A. Myths and truths of pulsatile and nonpulsatile perfusion during acute and chronic cardiac support. Artif Organs May 2004;28(5):439–43.
[42] Sezai A, Shiono M, Orime Y, Nakata K, Hata M, Iida M, et al. Major organ function under mechanical support: comparative studies of pulsatile and nonpulsatile circulation. Arti Organs March 1999;23(3):280–5.
[43] Saha M, Muppala MR, Castaldo JE, Gee W, Reed JF, Morris DL. The impact of cardiac index on cerebral hemodynamics. Stroke: J Cereb Circul 1993;24(11):1686–90.
[44] Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen S, Thomsen G, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke: J Cereb Circul. 2001;32(11):2530–3.
[45] Rappaport H, Bruce D, Langfitt T. The effect of lowered cardiac output on cerebral blood flow. Cereb Circul Metabol 1975;4:14–17.
[46] Cornwell WK, Levine BD. Patients with heart failure with reduced ejection fraction have exaggerated reductions in cerebral blood flow during upright posture. Heart Failure 2015;3(2):176–9.
[47] Wilhelm MJ, Hammel D, Schmid C, Rhode A, Kaan T, Rothenburger M, et al. Long-term support of 9 patients with the Debakey vad for more than 200 days. J Thorac Cardiovasc Surg Oct 2005;130(4):1122–9.
[48] Metra M, Cotter G, Gheorghiade M, Dei CL, Voors AA. The role of the kidney in heart failure. Eur Heart J 2012;3(17):2135–42.
[49] Hillege HL, Girbes AR, Kam PJ, Boomsma F, Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102(2):203–10.
[50] Aperia C, Broberger CGO, Surgery P. Relationship and tubular between sodium renal artery perfusion pressure reabsorption. Am J Physiol 1971;220(5):1205–12.

Please cite this article as: M.A. Rezaienia et al., In-vitro investigation of the hemodynamic responses of the cerebral, coronary and renal circulations with a rotary blood pump installed in the descending aorta, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.11.006