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In-vitro investigation of the effect on cerebral perfusion of a rotary blood pump installed in the descending aorta

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Abstract

This study describes use of a cardiovascular simulator to replicate the hemodynamic responses of the cerebrovascular system with a mechanical circulatory support device operating in the descending aorta. To do so, a cerebral autoregulation unit was developed which replicates the dilation and constriction of the native cerebrovascular resistance system and thereby regulates the cerebral flow rate within defined limits. The efficacy of the replicated autoregulation mechanism was investigated by introducing a number of step alterations in mean aortic pressure and monitoring the cerebral flow. The steady responses of the cerebral flow to changes in mean aortic pressure were in good agreement with clinical data. Next, a rotary pump, modelling a mechanical circulatory support device, was installed in the descending aorta and the hemodynamic responses of the cerebral system were investigated over a wide range of pump operating conditions. Insertion of a mechanical circulatory support device in the descending aorta presented an improved cardiac output as a result of afterload reduction. It was observed that the primary drop in cerebral flow, caused by the pump in the descending aorta, was compensated over the course of five seconds due to a gradual decrease in cerebrovascular resistance. The experimental results suggest that the implantation of a mechanical circulatory support device in the descending aorta, a less invasive procedure than typical mechanical circulatory support implantation, will not have an adverse effect on the cognitive function, provided that the cerebral autoregulation is largely unimpaired.

Introduction

Heart Failure (HF) is one of the leading causes of death in Western countries. More than 7 million people in North America and Europe are diagnosed with heart failure, among whom nearly 6% are categorized as having New York Heart Association class IV heart failure . As a result, the role of mechanical circulatory support (MCS) devices as a bridge to transplantation and as destination therapy has become vital . One challenge of traditional MCS devices is their highly invasive implantation procedure which makes many elderly and ill patients ineligible for the surgery. An MCS device in series configuration with the heart, which could be implanted without a median

sternotomy and thereby with a less invasive implantation procedure, has been examined in prior studies.

Reitan, et al., 2003 showed that with their percutaneous axial pump in the descending aorta, the pressure drop upstream of the pump reduces the afterload pressure in the arterial system and thereby minimizes the ventricular wall stress. This leads to more convenient unloading of the ventricle chamber, causing an improved cardiac output (CO) and recovery of damaged myocardial cells. Also, the pressure rise downstream of the pump may improve renal function in patients suffering from renal impairment, as demonstrated by .

A concern reported in the previous in-vivo studies in an animal trial and in-vitro studies using cardiovascular emulators on the descending aorta implantation, is the potential risk of blood perfusion disturbances to the brain caused by the pressure drop generated upstream of the pump. However, Reitan, et al., 2003 in the same study claimed that the cerebral perfusion drop, observed in their animal trial would be autoregulated in human cardiovascular system.

The cerebral autoregulation is a vital homeostatic mechanism to maintain the nutrient and oxygenated blood flow to the brain in the event of changing perfusion pressure. The concept of cerebral autoregulation was established by Lassen, (1959). Prior in vivo studies demonstrated a distinct difference between the regional cerebral autoregulation response and the sympathetic nervous reaction. The cerebral autoregulation involves changes in small cerebrovascular resistances, induced by a myogenic mechanism, whereas the sympathetic nervous system has an impact on the larger arterial characteristics and triggered largely by the baroreceptors in the carotid sinus and aortic arch. This results in a quicker response from the cerebral autoregulation system to local pressure changes than the sympathetic nervous system . For a healthy person, the cerebral system is autoregulated within wide limits (60 to 120 mmHg) of mean aortic pressure (AoP_{mean}) , however any pathological condition, particularly changes in arterial CO_2 level, can shift the limits of the autoregulated region.

The design and implementation of mechanical cardiovascular simulators is motivated by the necessity of in-vitro tests of various artificial devices prior to in-vivo testing. Although in vivo tests are more reliable and necessary for an MCS device to be deployed, in vitro tests offer a controlled environment where measurements of pressure and flow can be taken easily. There has been remarkable progress in design and development of cardiovascular emulators with the capability of replicating various physiological conditions. Gregory, et al. modelled the Frank-Starling mechanism and investigated the altered contractility of the ventricles with changing preload in comparison with clinical data. Jansen-Park, et al. modelled the Frank-Starling responses and the baroreflex autoregulation mechanisms in their cardiovascular simulator and studied the hemodynamic responses of the cardiovascular system interacting with an MCS device.

The aim of this study is to investigate the effect of a rotary pump installed in the descending aorta on cerebral perfusion with the assumption that the regional cerebral autoregulation is intact. The objectives of this investigation are met using an in-house multi-chamber Simulator of Cardio-Vascular Loops (SCVL) with adjustable compliance and cerebral autoregulation systems. Firstly, the performance of the improved SCVL system was evaluated by simulating healthy and heart failure conditions for a supine human and comparing to clinical data. Secondly, the efficacy of the simulated cerebral autoregulation was examined by changing AoP_{mean} and comparing the cerebral response against corresponding clinical data. Finally, a rotary pump is installed in the descending aorta and operated over a range of rotor speeds, and the effect on cerebral perfusion is examined.

Methodology

The SCVL system is used to simulate the native cardiovascular system. Figure 1 shows the schematic diagram of the SCVL.

Figure 1 – The SCVL system set up to examine cerebral perfusion with a pump in the proximal descending aorta showing flow meters (FM), linear motors (LM), compliances (C), and manually adjustable resistances (R).

Four rubber gaiters were used to model the heart chambers with appropriate sizes. The left and right ventricles (LV and RV) had a volume of 120 mL and the left and right atrium (LA and RA) had a

volume of 50 mL. Two trajectory time varying functions, extracted from real-time clinical data of the left ventricle and atrium volumes, were employed to actuate the four linear motors (P01-37x120 from LinMot, Spreitenbach, Switzerland) which contract and dilate the ventricles and atria. Figure 2 shows the simultaneous graphs of the real time left ventricle and left atrium volume with their corresponding motor displacement, simulating volume changes in an intact heart. This is an improvement from previous work where COS functions were used to actuate the linear motors. These trajectory functions can be scaled and offset to replicate various pathological conditions, such as reduced stroke volume.

Figure 2 – Trajectory functions for the motors actuating ventricles and atria with a heart period of 0.9 s. Extracted from and respectively.

Four mechanical heart valves were used as in the native system to ensure unidirectional flow in the vicinity of each chamber; Mitral (MV), Pulmonary (PV), Tricuspid (TV) and Aortic Valve (AV). These mechanical heart valves are 29 mm diameter Hall Easy-Fit valves (Medtronic). The systemic and the pulmonary vasculature are reproduced by using 24 mm diameter rubber tubing, while smaller arteries use 12 mm diameter tubing. A blood analog solution (water 65%/wt, glycerol 35%/wt) was used as the working fluid. Three pressure transducers (PMP1400 Druck) are used to simultaneously measure the left ventricle pressure (LVP), aortic pressure (AoP), and pulmonic pressure (PuP). The resistance of the pulmonary and systemic circulations are controlled by Hoffman clips. Two electromagnetic flow-meters (SITRANS F M MAG 1100 F) are employed to measure the CO and cerebral flow (CF), respectively. For this paper, the renal and coronary arteries were closed off so that there are only two paths through the systemic circulation; one through the right carotid artery modelling cerebral perfusion and one through a resistance in the descending aorta modelling the downstream systemic circulation.

The vascular distensibility is modelled using novel compliance units with adjustable compliance levels. Each compliance unit consists of two chambers separated by a thin latex diaphragm. The upper chamber is filled with compressed air and the lower chamber is connected to the vascular

system. The compliance level is altered by changing the pressure in the upper chamber via a sphygmomanometer. Four compliance units are used; in the ascending aorta, the pulmonary circulation and two in the superior and inferior vena cava, as described in studies by Shi & Korakianitis, 2006 and Shi, et al., 2010.

An autoregulation unit was developed to replicate the dilation and constriction of the cerebrovascular system. This unit takes the form of an adjustable clamp on the right carotid artery driven by a stepper motor. Other arteries in the aortic arch are closed off. This simulates cerebrovascular resistance changes occurring due to the dilation and constriction of the cerebroarteriolars in a native system as reported by Strandgaard, et al. (1973). Clinical data for the autoregulation unit's pressure/flow profile were taken from research conducted by Strandgaard, in which flow is shown to be regulated between 60 and 120 mmHg. A time delay between each motor step was set to 100 ms to match the autoregulation response period of 5 to 6 seconds reported by Aaslid, et al. (1989). The autoregulation unit in the SCVL is shown in Figure 3.

Figure 3 – The autoregulation unit attached to the right carotid artery.

The pump is used in this study is an in-house centrifugal pump connected to an external electric motor (Maxon EC motor) with an acceleration of 1000 rpm/s, see Figure 4(a). The experimentally measured pump pressure-flow characteristic shown in Figure 4(b).

Figure 4– (a) The picture of the rotary pump, (b) The experimentally measured pressure-flow characteristics of the pump

Results:

The performance of the SCVL system was evaluated with simulations of healthy and heart failure conditions. The experimental measurements for the simulated healthy and the heart failure condition were compared with clinical data. In each case the AoP, LVP, PuP as well as the CO and CF were recorded as these are the gold standard of cardiac condition assessment.

To reproduce heart failure pathology several changes were made to the system. Vascular compliances were decreased slightly to mimic a stiffer vascular system. The minimum left ventricle volume is increased and the stroke volume is decreased with the purpose of mimicking the reduced pumping ability of the left ventricle. The left ventricle dilation was modelled by increasing the distensibility of the compliance unit in series with the left ventricle chamber, upstream of the aortic valve.

Figure 5(a,b) show the experimental AoP and LVP for the healthy and diseased conditions respectively, as well as the clinical data used for SCVL tuning and comparison extracted from Fischer, et al. (2002) and Denardo, et al., (2010) respectively. The clinical data was extracted using a Matlab image analysis program.

Figure 5 – A comparison between the experimental pressure traces in the SCVL with the clinical AoP trace (a) for a healthy human and (b) for a human with heart failure .

The cardiac period in the healthy condition was set at 0.9 s (67 bpm) and the cardiac period in the HF condition was set to 0.8 s (75 bpm) to match clinical data .

For the healthy condition, the measured AoP is 130/76 while the clinical AoP is 133/74. The experimental LVP is 130/5 mmHg. The measured CO and CF for the healthy condition are 5.1 L/min and 0.72 L/min respectively, compared to clinical values of 5 and 0.731 L/min by Guyton & Hall, 2006 and Ford, et al. (2005).

For the HF condition, the measured AoP is 102/65 while the clinical AoP is 101/67. The experimental LVP is 101/30 mmHg. A comparison between Figure 5(a) and 5(b) indicates that for the HF condition the end-diastolic LVP has increased from 5 mmHg for the healthy condition to 30 mmHg. A high end-diastolic LVP represents a depressed heart pumping action . The measured CO and CF for the heart failure condition were 2.1 L/min and 0.71 L/min respectively compared to the clinical values of 3 and 0.731 L/min by Mullens, et al.(2009) and Ford, et al. (2005). A CO of 2.1 L/min is lower than the typical CO of a patient with heart failure, and was the flow rate in our test rig due to limited power and acceleration of the linear motors used to actuate the chambers.

The SCVL is able to capture the main physiological features of the pressure waveforms in good agreement with the clinical data. These include: dicrotic notch due to valve closure, increased pulse pressure during systolic phase and diastolic pressure decay.

Table 1 summarises the measured hemodynamic values for healthy and heart failure conditions.

Table 1 – Hemodynamic values measured from the SCVL in healthy and heart failure modes.

Parameter	Healthy	HF	Unit
Heart period (s)	0.9	0.8	s
Heart rate	67	75	bpm
AoP_{sys}	130	102	mmHg
AoP_{dia}	76	65	mmHg
AoP_{mean}	92	77	mmHg
LVP_{sys}	130	102	mmHg
LVP_{dia}	5	30	mmHg
R_{ao}	0.075	0.11	mmHg.min/L
R_{pu}	0.015	0.04	mmHg.min/L
PuP_{mean}	5	30	mmHg
CF_{mean}	0.72	0.71	L/min
CO	5.1	2.1	L/min

The efficacy of the emulated cerebral autoregulation mechanism is evaluated by introducing a number of stepwise pressure reductions in the aortic arch and recording the steady state CF_{mean} after the transient flow has settled. The baseline AoP_{mean} is set to 92 mmHg, replicating the healthy condition. Each step reduction in AoP_{mean} was implemented by a slight drop in the systemic resistance. Figure 6(a) shows the cerebral autoregulation pressure-flow curve and the corresponding clinical data over a wide range of AoP_{mean}, and Figure 6(b) shows the measured CerebroVascular Resistance (CVR) in the same experiment. Due to the non-dimensionality of the clinical CF_{mean} data in the clinical manuscript , for this study the CF_{mean} within the autoregulated region is set to be 0.71 L/min, from the study conducted by Ford, et al. (2005) for a normotensive human.

Figure 6 – The performance of the simulated cerebral autoregulation mechanism from 60 to 120 mmHg. (a) Cerebral flow in the SCVL compared with clinical data , and (b) cerebrovascular resistance (CVR) from the same experiment.

Within the autoregulated region (60-120 mmHg) there is a nearly constant flow. However, outside the autoregulated region, the CF_{mean} level becomes proportional to the AoP_{mean} level, with the autoregulated artery at maximum dilation or contraction. The delay on the stepper motor ensures the response of the autoregulation system is around 5 seconds. Figures 7(a,b,c) show the transient response of the CF (Figure 7(b)) and CVR (Figure 7(c)) to a drop in AoP_{mean} from 105 to 76 mmHg (Figure 7(a)) while the SCVL is running. The autoregulation unit responds to the drop in AoP_{mean} by dilating the carotid artery until CF returns to the regulated level. This matches the clinical data obtained by Aaslid, et al. (1989).

Figure 7– Response of the cerebral autoregulation to a step drop in AoP_{mean} from 105 to 76 mmHg. (a) LVP and AoP, (b) CF and (c) CVR.

The pump was then inserted into the SCVL in the proximal descending aorta, above the renal arteries, as shown in Figure 1. A heart failure condition was reproduced in which AoP_{mean} and CO are 80 mmHg and 2.1 L/min, respectively. Five experiments were conducted in which the steady and transient responses of CO and CF to the pump operating over rotor speeds of 1000 to 5000 rpm were investigated.

Table 2 summarises the steady hemodynamic responses of AoP, CO and CF with the pump operating from 1000 to 5000 rpm.

Table 2 - Hemodynamic characteristics of the SCVL with the MCS device integrated in the descending aorta operating from 0 to 5000 rpm, including pressure gradient across the pump (ΔP_{MCS}), aortic pulse pressure (AoP_{puls}), and cerebral pulse flow (CF_{puls})

Condition	ΔP_{MCS}	AoP_{mean}	AoP_{puls}	CO_{mean}	CF_{mean} (min)	CF_{mean} (return)	CF_{puls}
Units	mmHg	mmHg	mmHg	L/min	L/min	L/min	L/min
Baseline (HF)	-	80	41	2.1	-	-	0.24
MCS(1000 rpm)	18	78	43	2.35	0.71	0.71	0.26
MCS(2000 rpm)	51	76.5	45	2.6	0.69	0.71	0.28
MCS(3000 rpm)	80	74	48	2.8	0.685	0.71	0.3
MCS(4000 rpm)	95	70	52	3.45	0.67	0.72	0.31
MCS(5000 rpm)	110	65	58	4.1	0.66	0.72	0.33

Figure 8(a,b,c) show the transient responses of AoP, CO, and CF respectively when the pump was switched on at t = 2s to 5000 rpm.

Figure 8- The transient response of cerebral flow to a pump in the descending aorta running at 5000 rpm. (a) AoP, (b) CO and (c) CF.

Figure 8(a) shows that when the pump is switched on to 5000 rpm, the AoP decreases over the course of five seconds until AoP_{mean} reaches 65 mmHg. The aortic pulse pressure AoP_{pulse}, determined by subtracting the systolic aortic pressure (AoP_{sys}) from the diastolic aortic pressure (AoP_{dia}), increases by 40% from 41 mmHg at the baseline to 58 mmHg at 5000 rpm.

Figure 8(b) shows that CO gradually improves from 2.1 L/min to the steady level of 4.1 L/min. This is as a result of the generated pressure drop upstream of the pump, reducing afterload pressure and leading to a successful CO re-establishment.

Figure 8(c) shows that CF_{mean} drops by 7% at T = 6 s, however since AoP_{mean} remains within the prescribed autoregulated region, the autoregulation mechanism compensates and the CF returns to the initial level of 0.71 L/min.

It is evident from Figure 8(c) that there is a flow overshoot occurring just before CF_{mean} returns to the initial level. Aaslid, et al. (1989) reported in their clinical study on humans that this overshoot is likely to be due to the delay in autoregulation response compensating for changes in AoP. Another aspect of the hemodynamic CF response to a pump operating in the descending aorta is that the CF pulsatility (CF_{puls}), which is determined by subtracting the systolic cerebral flow (CF_{sys}) from the diastolic cerebral flow (CF_{dia}), rises by 37% from 0.24 L/min at the baseline to 0.33 L/min at 5000 rpm.

Discussion:

The results show the multi-chamber SCVL can reproduce the hemodynamic parameters for healthy and HF condition. However, for the replicated HF condition a higher CO at these pressures was not achieved due to the limited power of our linear motors. With a more appropriate CO but the same

AoP_{mean}, the same effect on cerebral perfusion is expected since the cerebral circulation is autoregulated within AoP_{mean} of 60-120 mmHg.

When the pump operates at its maximum speed of 5000 rpm, a pressure of 110 mmHg is created across the pump but AoP_{mean} only falls by 15 mmHg (80 to 65 mmHg) because the resistance downstream of the pump is much larger than the resistance upstream. The implication is that the downstream pressure will increase significantly, causing an excess of flow to the renal, splanchnic and lower radial circulations. It would also cause a high preload pressure at the right atrium, possibly improving cardiac output through the Frank-Starling mechanism, if unimpaired. Subsequent research will examine in detail the effects of the descending aorta MCS implementation downstream from the pump by implementing a renal autoregulation unit and a Frank-Starling mechanism into the SCVL.

Figure 8(c) shows that while CF_{mean} returns to its initial level, CF_{puls} increases by 37% at 5000 rpm. The change in CF_{puls} was induced by a rise in AoP_{puls} caused by the pressure drop generated by the pump. It has been reported that flow pulsatility aids recovery of cerebral, renal, and myocardial blood perfusion in patients with HF.

There is a concern that pressure drop during diastolic phase may reduce coronary flow perfusion. The study of the coronary circulation was not part of this in vitro investigation, so the coronary circulation was closed off. The coronary circulation is effectively a parallel branch with the cerebral circulation upstream of the pump. It would be expected that the effects on the coronary perfusion to be the same as those on the cerebral, although it is noted that the coronary circulation has a wider autoregulation range (45-150mmhg) . So, at 5000 rpm when the arterial pressure drops to 65 mmHg, a potential risk of coronary perfusion drop could be compensated by a functioning coronary autoregulation system. Supporting our hypothesis, a prior animal study with a pump in the descending aorta showed that although there was a drop in diastolic coronary perfusion, no reduction was observed in net coronary flow. Further in vivo and in vitro studies are required to investigate this.

In this paper, it is presumed that the autoregulation curve for the replicated heart failure condition is unimpaired. There are studies showing clearly that the CF decreases with severe HF. Gruhn, et al. (2001) observed a drop of 30% in CF in severe heart failure patients before heart transplantation.

However, other investigations suggest that the the improved cardiac output may minimize the chance of blood drop in the upper extrimities. Cornwell & Levine (2015) have shown that for HF patients supported by MCS support, the cerebral blood flow is restored upon the return to higher CO. Also, the study conducted by Gruhn, et al. (2001) shows an improvement in CF upon heart transplantation.

If the cerebral autoregulation was completely impaired, for instance at 5000 rpm, a pressure drop from 80 to 65 mmHg would result in a proportional drop in perfusion of 18.75%. This indicates that any perfusion to the upper extremities may not become significantly more impaired than before implantation, especially if cardiac function recovers with the pump operating in the descending aorta.

In addition, it must be noted that in a native system the main arterial system is autoregulated via the sympathetic nervous system and in many patients with moderate to severe heart failure, the blood flow is redistributed toward the brain and away from the other organs such as skeletal muscles as a result of increased vasoconstriction of systemic arteries . This would minimise the risk of substantial cerebral flow drop, even if the cerebral autoregulation was impaired.

Although there are clearly concerns with the descending aorta implantation compared to existing MCS implantation techniques, there are also several advantages that make this approach worthy of investigation. Most prominent of these:

- Less traumatic and minimally invasive implantation, possibly through the left thoracotomy, which could make the procedure suitable for patients currently considered too sick for highly invasive MCS implantation.
- Increased pulsatility in all of the circulation, which can aid recovery.
- The placement of the pump makes it far easier for a surgeon to access, for initial implantation or pump replacement.

Conclusion:

The results from the present study demonstrated the use of new trajectory functions extracted from real-time clinical data and the use of compliance units to simulate heart dilation and vascular distensibility. The improved SCVL emulated physiological and pathological conditions in close agreement to clinical data. The experimental hemodynamic responses of the emulated cerebral autoregulation mechanism also showed good agreement with the corresponding clinical data. The experimental results from the pump insertion suggest that the implantation of an MCS device in the descending aorta will not have an adverse effect on the cerebral functionality, provided that the cerebral autoregulation is not significantly impaired. In future work, it is our intention to emulate impaired cerebral autoregulaton in the SCVL once suitable clinical data is obtained.

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Conflict of Interest

None

Reference

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