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Synchronously counterpulsating extracorporeal life support enhances myocardial working conditions regardless of systemic perfusion pressure

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Abstract

Objective: A new pulsatile extracorporeal life support (pECLS) system has entered the market. We wanted to investigate what potential advantages pECLS may have over current non-pulsatile systems (NPS). Our research was focused on the pump's functional interaction with the left ventricle and the coronary circulation. **Methods:** Extensive hemodynamic measurements were performed during asynchronous and synchronous pECLS in 10 calves. The two extremes regarding LV afterload, namely systolic arrival (SA) and diastolic arrival (DA) of the pump pulse were studied. **Results:** SA was associated with increased oxygen consumption (+57%) and decreased diastolic coronary perfusion (−43%). DA increased left ventricular output (DA: 4.5 ± 2.4 l/min vs SA: 3.5 ± 2.2 l/min), LV ejection fraction (+10%), and ventricular efficiency (+17%). Mean aortic pressure and mean coronary flow were only marginally affected by pulse incidence. Systolic impairment was more pronounced with higher bypass flows. These results indicate that myocardial working conditions can be optimized by phasing pECLS ejection into cardiac diastole. **Conclusion:** We conclude that during pECLS, myocardial working conditions can be improved by avoidance of systolic impairment. Synchronously counterpulsating pECLS could be a more economic and versatile alternative to NPS or NPS combined with intra-aortic balloon pumping. The potential benefits of synchronously counterpulsating pECLS over the current alternatives remain to be investigated.

Keywords: Extracorporeal life support; Hemodynamics; Pressure–volume relation; Counterpulsation; Myocardial energetics

1. Introduction

From 1965 onwards, adult extracorporeal membrane oxygenation (ECMO) or more generically in literature referred to as extracorporeal life support (ECLS) has provided a means to support patients suffering from postcardiotomy cardiopulmonary failure with typical durations that range from a few hours to a couple of weeks [1,2]. More recently, the use of ECLS to assist high-risk minimally invasive surgical procedures has gained more interest [3–5].

In today's clinical practice, mostly, non-pulsatile ECLS circuits are employed. As set forth by Wright [6] and others [7], the choice for this technology is bound to a historical context. In the early years, pulsatile circuits were bulky and expensive systems, which required elaborate setup and tuning. The advent of roller pumps and later centrifugal pumps paved the way for smaller, cheaper, and easier to setup non-pulsatile systems. However, little scientific evidence was available to back up the trend towards continuous flow perfusion because research efforts lagged behind the technological progress. Today, the debate remains controversial, as solid evidence is still void [6,7].

The application of (continuous flow) centrifugal pumps in ECLS systems has gained widespread use clinically. Whereas continuous flow technology has valuable features like good reliability and lower cost; ECLS therapy is frequently combined with intra-aortic balloon pumping (IABP), which suggests that the specific cardiac/coronary demands cannot always be met by the extracorporeal circuit alone [1,5,8].

We sought to investigate the mechanics of pulsatile extracorporeal life support (pECLS) and specifically the hemodynamic interaction with the left ventricle and coronary circulation. Our hypothesis is that left ventricular function is impaired when extracorporeal pulse flow occurs during cardiac systole and that this will adversely affect myocardial working conditions.

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2. Methods

2.1. Animal preparation

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 86-23, 1985 revision; National Institutes of Health, USA). Ten calves weighing 75 ± 26 kg (mean $\pm$ SD) were premedicated with atropine (0.05 mg/kg, s.c.). Anesthesia was induced with sodium thiopental (bolus 20 mg/kg, i.v.) and maintained with a 1:2 mixture of O_2:N_2O and halothane (1.5%). After administration of analgesic buprenorfine (bolus 0.01 mg/kg, i.v.) and muscle relaxant suxamethonium (bolus 0.1 mg/kg, i.v.), a left thoracotomy was performed while maintaining a peak end-expiratory pressure of 5 cmH_2O. Coagulation was controlled through administration of heparin (bolus 200 IU/kg, i.v.) and monitored by activated clotting time (ACT) measurements. ACT was kept above 480 s during the experiment. Monitoring included ECG, blood pressure, oxygen saturation, and capnography. The animal was sacrificed through a pentobarbital overdose (bolus 80 mg/kg, i.v.). The study was approved by the animal ethical committee of the University of Maastricht.

2.2. Circulatory support

The T-PLS system is a recently developed ECLS system (NewheartBio Corporation, Seoul, Korea) that features two tubular shaped pumping chambers in push–pull configuration [9,10]. The pumps fill passively and are emptied by an undulating pendulum, which pushes the sacs in alternating mode. The maximum volume of the chambers is 70 ml. The pump rate is specified as selectable from 20 to 120 bpm in steps of 1 bpm but cannot be synchronized by external inputs. The system features a suction alarm and a feedback circuit that reduces pump rate to avoid severe suction.

The ECLS system was configured as a femoro-femoral veno-arterial ECMO circuit, which was primed through the use of a venous reservoir. During support, the reservoir was bypassed. Femoral arterial access was via a 21 Fr cannula (Jostra, Hirrlingen, Germany). A femoral vein, a jugular vein, or both were cannulated for venous drainage (24–27 Fr or 32/40 Fr double stage venous cannulae). An external pressure sensor (Baxter International Inc., Deerfield, IL) and an ultrasonic flow probe (Transonic Systems, Ithaca, NY) were placed on the arterial cannula to measure pump output pressure and flow. Pump output was adjusted to 40–60% of total output. Fig. 1 sketches the basic experimental arrangement and presents the idea of interacting pulses from the heart and the extracorporeal circuit.

2.3. Instrumentation

A Swan-Ganz thermodilution catheter (Arrow International, Reading, PA) was advanced into the pulmonary artery via a femoral vein. An external pressure transducer was placed on the central venous lumen (Baxter International Inc.). A conductance catheter, incorporating a pressure sensor (CD Leycom, Zoetermeer, the Netherlands), was positioned in the left ventricle via left femoral arterial access. The conductance catheter was connected to a Sigma 5DF conductance processor (CD Leycom), which was used in dual-field mode [11]. Solid-state pressure catheters (CD Leycom) were placed in the ascending aorta via the left carotid artery and in the left atrium through a purse-string suture. Ultrasonic flow probes (Transonic Systems) were placed on the ascending aorta and on a side branch of the left anterior descending coronary artery. All hemodynamic data were acquired and stored using a 16-channel acquisition system (Conduct-PC, CD Leycom).

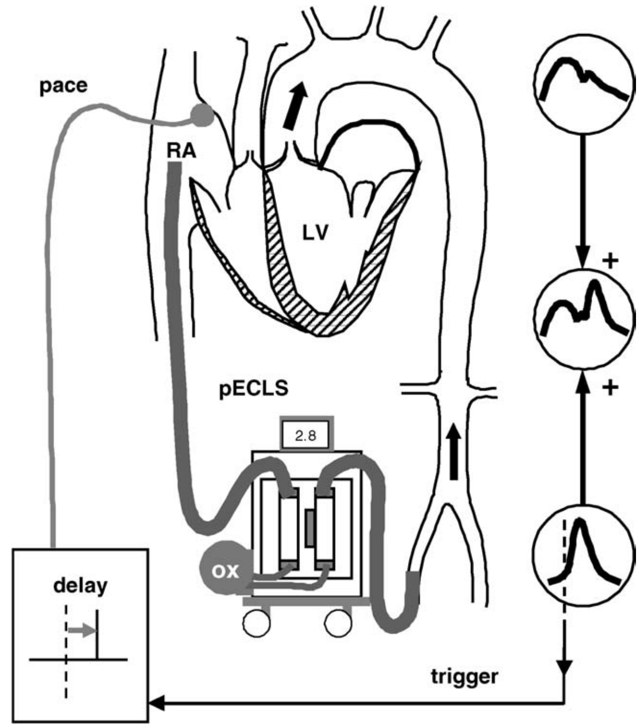

Fig. 1. Basic experimental setup. RA, right atrium; LV, left ventricle; pECLS, pulsatile extracorporeal life support system. The diagram gives an interpretation of how a pulse coming from the extracorporeal system is superimposed on the cardiac pulse. For synchronization purposes a pacing loop was configured as follows: A trigger was derived from the pump outflow signal, which was then converted to an atrial pace stimulus after the application of a selectable delay.

2.4. Conductance calibration

Parallel conductance was determined by injecting 7.5 ml of 6.5% hypertonic saline into the pulmonary artery [12]. A 5 ml blood sample was collected in a sampling cuvette for blood resistivity measurement (CD Leycom). The gain calibration factor was determined by comparing conductance derived left ventricular output (LVO) with the aortic flow at baseline. The conductance data were analyzed with the Circlab 2000 software package (Paul Steendijk, Leiden University Medical Center, Leiden, the Netherlands).

2.5. Measurements and analysis

2.5.1. Asynchronous protocol

Animal heart rate was greater than 90 bpm, and the pump rate was set between 60 and 80 bpm. Hereby, asynchronous support was established. After stabilization of bypass flow and cardiac output, hemodynamic recordings of 30 s duration were made. To differentiate between the effects of systolic arrival (SA) and diastolic arrival (DA) of the pECLS pulse at the aortic valve, the associated beats were selected and averaged (at least > 5 beats of each type).

2.5.2. Synchronous protocol

As the T-PLS system supplied for investigation did not provide any means to synchronize its output with the heart beat, the reverse option was employed. A custom cardiac pacing loop was designed around the setup shown in Fig. 1 and implemented in LabView (National Instruments, Austin, TX). A trigger pulse was derived from the upward slope of the pump outflow signal and subjected to a selectable delay. The delayed signal was then fed to the trigger input of a cardiac pacing unit. Atrial pacing was employed to ensure homogenous cardiac activation. By this arrangement, heart rate was synchronized with pumping frequency.

The simultaneous ejection of the heart and the pump was defined as the zero delay setting. Consecutively, the pace pulse was delivered in delayed fashion covering the entire cardiac cycle in steps of 50 ms. With every run hemodynamics were allowed to stabilize before recordings were made.

The following hemodynamic indices were calculated. An estimate of external left ventricular work (EW) was calculated from $(Vlv_{ED} - Vlv_{ES})(Plv_{PEAK} - Plv_{ED})$. LV potential energy (PE) was estimated by $\frac{1}{2}Vlv_{ES}(Plv_{PEAK} - Plv_{ED})$. The total pressure—volume area (PVA) was calculated from PVA = EW + PE [13]. The ratio of EW over PVA was calculated as a measure of ventricular efficiency. From the synchronous data the percentage of coronary flow during diastolic (DCF, in %) was calculated. Statistical comparison was performed by application of the non-parametric Wilcoxon signed-ranks test ($n = 10$). Significance was assumed if p-values were lower than 0.05.

3. Results

Asynchronous measurements were obtained successfully in all animals. During support, the T-PLS system pumped 1.9 ± 0.3 l/min (mean $\pm$ SD) while mean total cardiac output was 5.6 ± 2.4 l/min. Among the individual animals total cardiac output varied considerably and thus a substantial range in bypass ratios was covered (pump flow/total cardiac output; range 18—82%, mean 34%). The intended limited range of 40—60% could not be achieved. During pump installment and operation it was evident that the period available for venous filling (half the pump cycle length) and the bore of the venous cannula were the primary factors limiting venous return and pump output. At high pump rate settings (>90 bpm), the T-PLS system effectively reduced its rate to prevent suction. The maximally attainable pump rate in these experiments was therefore only 80 bpm. In the synchronous protocol these limitations necessitated the use of a β-blocker agent (Inderal, Propanolol, AstraZeneca, Zoetermeer, the Netherlands) to enable pacing at a rate of 80 bpm. In five animals the procedure proved successful, and stable synchronization of the heart beat to the pECLS system was obtained. During synchronous support, the pECLS delivered a flow of 1.9 ± 0.4 l/min while the left ventricular output amounted to approximately 1.8 ± 4.0 l/min. The details and data of both protocols are presented separately below.

Table 1
Hemodynamic effect of asynchronous support

	Units	Pump off	Pump on
Qpump	l/min	–	1.9 (0.3)
LVO	l/min	4.4 (2.9)	3.7 (2.4)
CO	l/min	4.4 (2.9)	5.6 (2.4)
Qcor	ml/min	61 (36)	79 (48)*
Plv_{PEAK}	mmHg	79 (24)	97 (27)*
$Pasc_{PEAK}$	mmHg	78 (25)	103 (27)*
Pasc	mmHg	62 (17)	81 (23)*
Pcv	mmHg	11.6 (6.8)	9.3 (4.3)*

Values are mean (SD), $n = 9$. Qpump, bypass pump flow; LVO, left ventricular output; CO, total cardiac output; Qcor, coronary artery flow; Plv_{PEAK}, peak left ventricular pressure; $Pasc_{PEAK}$, peak ascending aortic pressure; Pasc, ascending aortic pressure; Pcv, central venous pressure.
* $p < .05$ versus pump off.

3.1. Pump system on—off

In Table 1 the hemodynamic effects of unsynchronized support have been summarized. With the pECLS system switched on, central venous pressure decreased and aortic pressure and coronary flow increased significantly: Pcv: −20%; Pasc: +30%; and Qcor: +30% ($p < .05$). Plv_{PEAK} increased from 79 ± 24 mmHg to 97 ± 27 mmHg ($p < .05$). Peak aortic pressure was elevated beyond peak left ventricular pressure ($Pasc_{PEAK}$ 103 mmHg $>$ Plv_{PEAK} 97 mmHg). Fig. 2 shows a typical hemodynamic recording of asynchronous pECLS support. Aortic pressure becomes biphasic with the pECLS pressure pulse arriving in diastole (beats C—E). Left ventricular pressure is higher when the pulse arrives at the aortic valve during systole (beats A and B). Both systolic and diastolic left

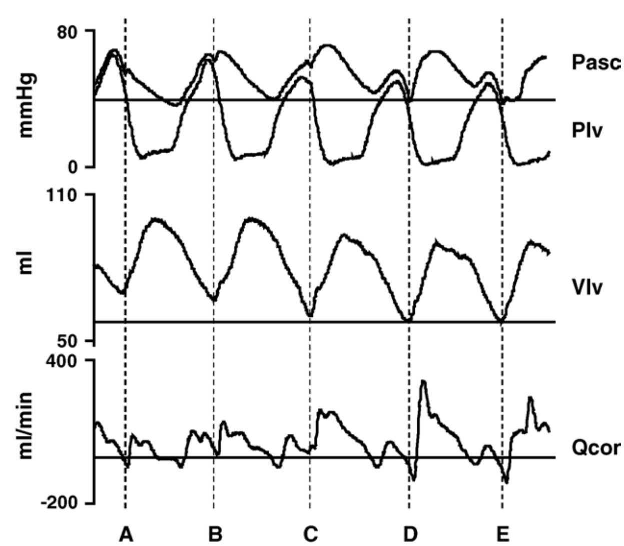

Fig. 2. Five consecutive cardiac beats with various coincidences of the pump pulse during asynchronous support. Pump rate is lower than heart rate. The vertical dotted lines indicate aortic valve closure (start of diastole). Pasc, ascending aortic pressure; Plv, left ventricular pressure; Vlv, left ventricular volume; Qcor, coronary artery flow.

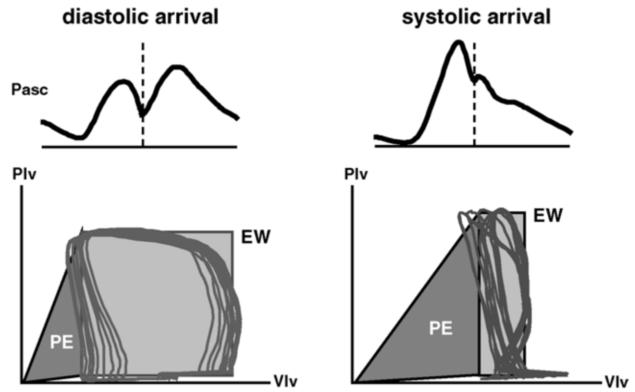

Fig. 3. Pressure—volume (PV) data obtained during an episode of asynchronous support in which pump rate and heart rate were such that every other heart beat experienced systolic arrival following diastolic arrival. Here, these pseudo-stable SA and DA loops are depicted separately for the sake of PV area analysis. Top: Classification of asynchronous beats into DA and SA of the pump pulse. Bottom: Corresponding effect on left ventricular function. First-order approximations of left ventricular external work (EW) and potential energy (PE) are shown within the pressure—volume planes. Pasc, ascending aortic pressure; Plv, left ventricular pressure; Vlv, left ventricular volume.

Table 2
Acute phase-dependent effect of asynchronous pumping on left ventricular function

	Units	SA	DA
Qpump	l/min	2.6 (0.8)	2.4 (0.6)
LVO	l/min	3.5 (2.2)	4.5 (2.4) [a]
CO	l/min	6.2 (2.3)	6.9 (2.0)
Plv_{PEAK}	mmHg	107 (27)	92 (25) [a]
$Pasc_{PEAK}$	mmHg	111 (29)	104 (22) [a]
Pasc	mmHg	83 (23)	84 (21)
Pcv	mmHg	8.8 (4.3)	8.9 (4.3)
Pla	mmHg	8.8 (2.8)	8.3 (2.7) [a]
Vlv_{ED}	ml	110 (61)	109 (59)
Vlv_{ES}	ml	79 (45)	69 (42) [a]
Qcor	ml/min	73 (49)	79 (46) [a]
PVA	N m	1.03 (0.72)	0.91 (0.58) [a]
EW/PVA	%	48 (22)	57 (22) [a]

Values are mean (SD), n = 10. DA, diastolic arrival; Qpump, bypass pump flow; LVO, left ventricular output; CO, total cardiac output; Plv_{PEAK}, peak left ventricular pressure; $Pasc_{PEAK}$, peak ascending aortic pressure; Pasc, ascending aortic pressure; Pcv, central venous pressure; Pla, left atrial pressure; Vlv_{ED}, end-diastolic left ventricular volume; Vlv_{ES}, end-systolic left ventricular volume; Qcor, coronary artery flow; PVA, total pressure—volume area; EW/PVA, ventricular efficiency.

[a] $p < .05$ versus SA (systolic arrival).

ventricular volumes are higher during these beats as well. The changes in the coronary artery flow pattern correspond to those in aortic pressure. Progressively from beats A to E, systolic coronary flow is reduced while diastolic flow is augmented. Diastolic coronary flow peaks early in diastole, which is associated with the upward slope of the pECLS pressure pulse. Beats similar to type A were selected for analysis of systolic arrival. Similarly, D-type beats were averaged for diastolic arrival data. Fig. 3 illustrates both beat types and the corresponding left ventricular pressure—volume loops. With systolic arrival ventricular ejection is decreased and pressure development is higher. The ratio of external work over potential energy is greater with diastolic arrival.

3.2. Asynchronous data

Table 2 compares the hemodynamic and cardiac indices after differentiation of the phase of arrival. Compared to systolic arrival left ventricular output is significantly higher during diastolic arrival: SA: 3.5 ± 2.2 l/min versus DA: 4.5 ± 2.4 l/min. Peak left ventricular pressure is significantly lower (−14%) during DA, but there is no significant difference in mean aortic pressure. Only end-systolic left ventricular volume is lower during DA (−13%), which amounts to an increase in ejection fraction from roughly 30% to 40%. Mean coronary artery flow is slightly larger during DA than during SA. Total pressure—volume area was 12% smaller during DA (DA: 0.91 N m vs SA: 1.03 N m). Ventricular efficiency (EW/PVA) proved to be about 10% lower during systolic arrival of the pECLS pulse ($p < .05$).

3.3. Synchronous evaluation

In Fig. 4 the results of synchronized pumping have been illustrated. The graph shows the sensitivity to pulse arrival of four determinants of myocardial working conditions in two

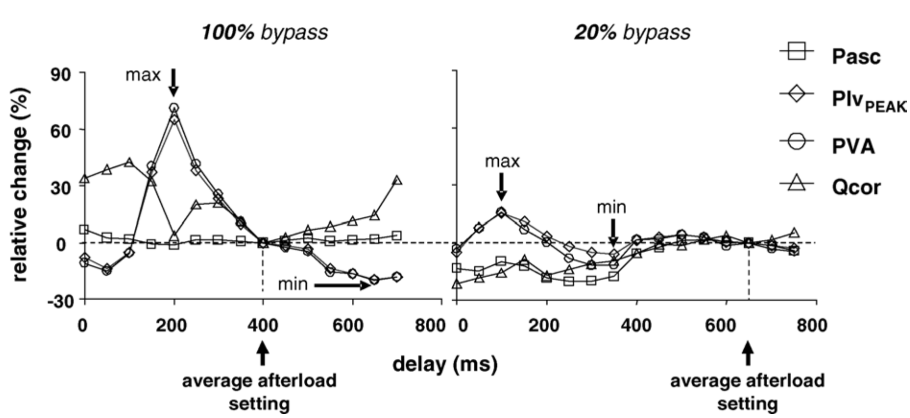

Fig. 4. Synchronous evaluation of pump pulse arrival: Two distinct examples with respect to bypass flow ratio are presented. A delay of 0 ms complies with the simultaneous ejection of blood from the left ventricle into the aorta and from the pump into the femoral artery. Every subsequent step on the horizontal axis adds another 50 ms to the delay in cardiac ejection. The vertical axis represents the relative change of each variable with respect to the average afterload setting (left, at 400 ms; right, at 650 ms). For each example the maximum and minimum afterload levels are indicated. Pasc, mean ascending aortic pressure; Plv_{PEAK}, peak left ventricular pressure; PVA, pressure—volume area; Qcor, coronary artery flow.

Table 3
Hemodynamic indices at both extremes of LV afterload obtained with synchronized measurements

	Units	Maximum afterload	Minimum afterload
Plv_{PEAK}	mmHg	70 (36)	45 (35)
Pasc	mmHg	51 (23)	46 (20)
Qpump	l/min	2.0 (0.4)	1.8 (0.4)
LVO	l/min	1.9 (4.2)	1.7 (3.9)
Vlv_{ED}	ml	123 (69)	89 (78)
Vlv_{ES}	ml	96 (41)	61 (49)
Qcor	ml/min	33 (36)	31 (41)
DCF	%	53 (12)	93 (19)
PVA	N m	0.74 (1.0)	0.47 (0.81)
EW/PVA	%	28 (22)	45 (27)

Values are mean (SD), $n = 5$. Plv_{PEAK}, peak left ventricular pressure; Pasc, ascending aortic pressure; Qpump, bypass pump flow; LVO, left ventricular output; CO, total cardiac output; Vlv_{ED}, end-diastolic left ventricular volume; Vlv_{ES}, end-systolic left ventricular volume; Qcor, coronary artery flow; DCF, diastolic coronary flow; PVA, total pressure–volume area; EW/PVA, ventricular efficiency.

individual subjects. The data were processed as follows: the Plv_{PEAK} values of all delay settings were averaged. The delay setting corresponding with this average afterload was selected as the benchmark setting. The relative changes with respect to this benchmark are plotted on the vertical axis (Fig. 4). For instance, in the 100% bypass case the Qcor trend shows only positive values. All delay settings produced an increase in coronary flow with respect to the coronary flow at the average afterload setting. The benchmark setting may be regarded as representative of non-synchronized pECLS or even continuous flow ECLS.

In the fully bypassed animal, manipulation of the timing of pECLS pulse incidence produced marked changes in peak left ventricular pressure, pressure–volume area, and coronary flow (Fig. 4). At the point of maximum afterload, PVA was increased by 70% while coronary flow was not enhanced (<5%). However, coronary flow increased more than 30% with pulse arrivals corresponding to minimum afterload and decreased PVA (−20%). Ascending aortic pressure was only marginally affected by the variation in pulse arrival. In the low bypass case (Fig. 4, right panel) both negative and positive deviations do not exceed 15%. Furthermore, a less strong correlation between the indices is noted.

In Table 3, the grouped hemodynamic differences between the afterload extremes have been summarized ($n = 5$). At maximum afterload, marked increases in left ventricular volume (+35 ml) and PVA (57%) were measured. Concomitantly, the diastolic coronary fraction and the ventricular efficiency showed a strong decline: DCF decreased from 93% to 53% and EW/PVA was compromised (28% vs 45% at minimum load).

4. Discussion

Intra-aortic counterpulsation during non-pulsatile ECLS is commonly employed to address specific myocardial demands. However, the use of IABP during ECLS or CPB has not been firmly protocolized, and the effects on myocardial recovery have only been investigated in limited applications [14]. Most clinical investigations only report the use of conjunct IABP with ECLS without further specification and allegedly ascribe favorable outcomes to counterpulsation and pulsatile perfusion [1,5,15,16]. In the present study, we focused on the potential of pulsatile ECLS systems to address myocardial support requirements.

The synchronous evaluation of pECLS indicated a pronounced effect of pulse incidence on ventricular function. Spot on systolic arrival was unambiguously associated with the highest left ventricular afterload (Fig. 4). Systolic impairment clearly compromises ventricular efficiency and the oxygen demand–supply balance (Table 3). Diastolically phased pECLS featured decreased LV afterload and oxygen demand, increased diastolic coronary perfusion, and improved ventricular efficiency (Fig. 4, Table 3). Other investigators have found similar attributes under experimental conditions as well as in clinical practice [1–3,5,17–20]. Corday et al. [17], showed that veno-arterial pulsatile partial bypass had greater efficacy in augmenting (diastolic) coronary flow than IABP alone. Moreover, their setup incorporated additional end-diastolic arterial suction as a means to actively reduce left ventricular afterload. However, they found that in experiments in dogs as well as in selected clinical cases, active afterload reduction by pulsatile ECLS was associated with elevated renal flow resistance and morbidity [18]. Synchronously counterpulsating pECLS as presented in this paper does not actively reduce afterload.

Asynchronous pECLS support produced an increase in both coronary and systemic perfusion pressure. The observed peak aortic pressure exceeded peak left ventricular pressure (Table 1). Apparently, the greater number of pECLS pulses arrived at the aortic valve during diastole. This could have been expected because diastole takes up more than 50% of the cardiac cycle period. If we consider the effect, well-aligned diastolic arrival pulses have (type D; Fig. 2), an enhanced aortic to ventricular pressure difference is noted (104 over 92 mmHg mean; Table 2). The DA data from the asynchronous protocol thus serve as a model of pulsatile ECLS, as if it were phased to the diastolic period. However, these analyses depend on specific beat selections from asynchronous recordings, and therefore only describe the acute, pseudo steady-state differences between SA and DA.

4.1. Oxygen demand and supply

Mechanical cardiac support and specifically myocardial preservation are aimed at creating favorable myocardial working conditions. To achieve this, either a reduction in work (demand) or an augmentation of coronary flow (supply), or both are mandatory [8,15,19,21]. The results of the present study showed no dependence of mean coronary flow on pulse incidence. The insensitivity of mean coronary flow to these changes in perfusion pressure has been found in other studies and is associated with intact coronary autoregulation [17,19,20]. Nonetheless, diastolic coronary perfusion did change dramatically with varying delays of synchronized ejection (Fig. 2, Table 3). The perfusion of subendocardial layers is known to depend strongly on diastolic flow [15,22]. To satisfy metabolic demands during partial bypass, the heart entirely depends on coronary flow reserve, which normally is limited to 20–30%. This suggests that in pathological situations little headroom is left to fulfill myocardial oxygen requirements [8].

Left ventricular myocardial work was significantly affected by systolic arrival of the pECLS pulse (Tables 2 and 3, Figs. 3 and 4). Pressure—volume area has been identified as an appropriate measure of myocardial oxygen consumption [23]. Avoidance of systolic impairment provided a reduction of 57% in oxygen consumption (Table 3). This capability to unload the myocardium while maintaining coronary flow and increasing subendocardial perfusion proves that synchronously counterpulsating pECLS is an interesting cardiac assist option when regarding myocardial working conditions. Failure to establish proper myocardial oxygen balance during ECLS may lengthen the therapeutic time path or may even lead to expansion of the ischemic/stunned myocardial mass [14,15]. Pappas et al. [14] studied the use of intra-aortic balloon pumping during cardiopulmonary bypass in both low-risk and high-risk patients. They found an immediate postoperative improvement of LV ejection fraction for the CPB plus IABP group. In the CPB only group, however, postoperative low output syndrome occurred and inotropic support and diuretics were necessary. Metabolic evaluations showed significantly higher myocardial lactate production in the CPB only group. Apparently, IABP support during CPB improved the myocardial oxygen balance, which resulted in better outcome.

4.2. Alternative to standard ECLS?

The implantation and management of both ECLS and IABP systems make the combined therapy invasive, complex (logistically), and costly. Synchronously counterpulsating pECLS may combine the attributes of IABP with those of extracorporeal partial bypass in a single system. The augmentation of cardiac output and aortic pressure and the simultaneous reduction of LV afterload suggest that myocardial oxygen consumption and peripheral perfusion pressure can be decoupled by phasing pECLS ejection into diastole (Tables 2 and 3, Figs. 3 and 4). In contrast, with nonpulsatile ECLS left ventricular afterload is directly related to bypass flow, which should fit the perfusion demand of all systemic organs [1,2,5,14]. This finding implies that phased ejection pECLS has an advantage over continuous flow ECLS. The potential benefit of synchronously counterpulsating pECLS over continuous flow ECLS plus IABP in terms of economy and simplicity remains to be investigated, preferably in a comparative (pre-) clinical trial.

The pump system used in this investigation was not equipped for synchronous support. Further technological developments in this direction should include a sync input (ECG), a selectable delay option, and dedicated monitoring of aortic pressure. The initial setup and calibration may be facilitated by catheterization or 2D-echo. The adjustment procedure of the pump ejection delay would be similar to that with ordinary intra-aortic balloon pumping [20,24]. Due to the inertia inherent in the current pump design beat-to-beat adaptation of ejection timing may not be feasible; IABP features faster pumping technology that may cope better with rapid adjustments. In most clinical applications timing optimization over several cardiac beats would probably suffice and should be aimed at avoiding spot on systolic impairment (Fig. 4). An important requirement for stable synchronization is that the propagation delay of the pump pulse from the femoral artery to the aortic arch remains constant over time. During our acute measurements this delay did not vary. With aortic cannulation this propagation delay and its variance would be negligible.

4.3. Clinical context

Recognizing the potential of phased ejection pECLS, it is important to identify where the advantages of this support modality fit in the therapeutic timeline. The patient suffering from reversible cardiogenic shock will be considered as a model in the following discussion [2,3,8]. In the early stages of treatment veno-arterial bypass flow will be nearly 100% of the total cardiac output, and the minimal volume loading of the heart will ensure low absolute myocardial oxygen requirement allowing for stabilization of basal metabolism. However, in compromised areas of the myocardium the oxygen balance remains crucial, as pressure work still requires sufficient oxygen delivery (Figs. 3 and 4) [13]. Stunned myocardium would be the most vulnerable in this stage of support [8,22]. As soon as global systemic organ function has improved up to an acceptable level, cardiopulmonary activity should be increased as a first step in rehabilitation [25]. This second stage involves lower assist ratios and consequent increased myocardial loading. Synchronously counterpulsating pECLS can be particularly helpful to optimize myocardial working conditions and controlling them independently of global perfusion (Tables 2 and 3, Fig. 4). The presence of working myocardium and increased coronary perfusion make this stage apt for the launch of adjunctive therapies [22]. When further progress is made towards weaning off ECLS, hemodynamic challenges can be employed to study cardiac and overall circulatory functional stability. Phased pECLS offers an alternative to specifically evaluate cardiac function by a simple switch over to the asynchronous mode or even timed systolic impairment for brief trial periods. Eventually, actual weaning can take place, and the patient can be treated off mechanical support or bridged to transplantation or an assist device.

4.4. Study limitations

Left ventricular function with synchronized pECLS was studied in five animals only. Solid statistical evidence could therefore not be produced, but these results did, however, prove consistent with the rest of the data and peer findings [5,14,17,18].

In the present study, we did not evaluate aortic arterial cannulation. In clinical practice, ECLS is applied with thoracic cannulation but mostly in the immediate postoperative setting. For long-term support and minimal invasive cases, peripheral cannulation is employed more widely. The avoidance of systolic impairment is more critical during long-term ECLS, which is associated with partial bypass.

Because the curves as presented in Fig. 4 would merely shift in a cyclic fashion with an arbitrary propagation delay, the results of synchronized operation are considered to remain applicable in case of aortic cannulation.

The extracorporeal circuit setup we used had a limited capability in terms of pump rate (max. 80 bpm) and flow (1.9 ± 0.3 l/min). This was due to the small size of the cannulae and the limited filling time—both appear to be inherent to the pulsatile ECLS concept. The drainage of venous blood was essentially passive and depended on the gravitational effect and the elastic recoil of the TPLS pumping chamber only. In this study, we chose to straightforwardly evaluate the properties of the TPLS system as a unit. In clinical practice, drainage may be enhanced by the use of kinetic or vacuum assisted drainage techniques. With sufficient venous drainage, the use of β-blocker could have been dispensed with in our protocol, because the pump would not have limited its rate in order to avoid suction.

A representative model of cardiac failure was not included in this study's design, as our focus was on the mechanical interaction of pECLS with the left ventricle. The results show that bypass flow ratio is a key determinant of how much impact pulse arrival has on ventricular function. A full range of possible bypass situations was covered in this investigation, which proved useful in determining in which stage of clinical application synchronization would pay off. We believe that the basic findings of this study can be extrapolated to pathological conditions and associated assist modes. However, the therapeutic effect of synchronized counterpulsation remains to be investigated in a long-term, failing myocardium setting.

5. Conclusion

Asynchronous pulsatile extracorporeal life support may be modified to enhance myocardial working conditions regardless of systemic perfusion by phasing pump ejection into cardiac diastole. Synchronously counterpulsating pECLS provides an opportunity to optimize current ECLS practice.

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