Regional Tissue Oximetry Reflects Changes in Arterial Flow in Porcine Chronic Heart Failure Treated With Venoarterial Extracorporeal Membrane Oxygenation

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Summary

Venoarterial extracorporeal membrane oxygenation (VA ECMO) is widely used in treatment of decompensated heart failure. Our aim was to investigate its effects on regional perfusion and tissue oxygenation with respect to extracorporeal blood flow (EBF). In five swine, decompensated low-output chronic heart failure was induced by long-term rapid ventricular pacing. Subsequently, VA ECMO was introduced and left ventricular (LV) volume, aortic blood pressure, regional arterial flow and tissue oxygenation were continuously recorded at different levels of EBF. With increasing EBF from minimal to 5 l/min, mean arterial pressure increased from 47±22 to 84±12 mm Hg (P<0.001) and arterial blood flow increased in carotid artery from 211±72 to 479±58 ml/min (P<0.01) and in subclavian artery from 103±49 to 296±54 ml/min (P<0.001). Corresponding brain and brachial tissue oxygenation increased promptly from 57±6 to 74±3 % and from 37±6 to 77±6 %, respectively (both P<0.01). Presented results confirm that VA ECMO is a capable form of heart support. Regional arterial flow and tissue oxygenation suggest that partial circulatory support may be sufficient to supply brain and peripheral tissue by oxygen.

Key words

Extracorporeal membrane oxygenation • Chronic heart failure • Swine • Perfusion • Oximetry

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Introduction

Extracorporeal membrane oxygenation in venoarterial settings (VA ECMO) represents a well-established percutaneously introduced circulatory support used in refractory but potentially recoverable cardiogenic shock. It can fully substitute the functions of lungs and heart to maintain sufficient gas exchange and systemic blood circulation (Pranikoff *et al.* 1994, Abrams *et al.* 2014). When applied, VA ECMO forms a circulatory bypass as it drains blood from right atrium and after passing it through the gas exchange unit, the oxygenated blood is returned to the thoracic aorta. VA ECMO is proofed beneficial for improved survival, neurologic outcome and resuscitability (Belohlavek *et al.* 2012, Mlcek *et al.* 2012).

On the other hand, VA ECMO has significant effects on systemic circulation. Increasing VA ECMO flow negatively affects left ventricular (LV) performance and hence it has been recently suggested to use only lowest possible rate of circulatory support (Ostadal *et al.* 2015, Broome and Donker 2016). Especially in this context of increasing LV demands during high bypass flow, evaluation of systemic cerebral and peripheral

arterial flow, its characteristics and regional tissue oxygen supply become important.

VA ECMO has been studied in number of experiments, but to our knowledge, only intact or acute heart failure (HF) models have been used (Bavaria *et al.* 1988, Shen *et al.* 2001, Mlcek *et al.* 2012, Ostadal *et al.* 2013) and therefore the heart and whole cardiovascular system was untouched prior to the investigations. In contrast, significant part of VA ECMO applications from real life are due to acute circulatory decompensation which develops on grounds of previously present chronic heart disease. Furthermore, retrospective clinical studies have also revealed that outcome of patients treated by ECMO differs according to the "acuteness or chronicity" of underlying cardiac disease (Tarzia *et al.* 2015).

Although there are reasons why models of chronic heart failure are being used rarely – their time-consuming preparation, instability of heart rhythm, ethical questions or mortality rate – their advantage is clearly documented as they offer long-term neurohormonal activation, general systemic adaptation and structural and functional alterations of myocytes (Moe and Armstrong 1999). In presented experiment chronic HF model was developed by fast cardiac pacing. This tachycardia-induced cardiomyopathy (TIC), first described by Gossage and Braxton Hicks (1913) and widely used in experiments since 1962 (Whipple *et al.* 1962), reliably mimics decompensated dilated cardiomyopathy with low cardiac output which persists also after cessation of pacing (Shinbane *et al.* 1997, Takagaki *et al.* 2002, Schmitto *et al.* 2011).

The aim of our study was to describe cerebral and peripheral blood supply in swine model of decompensated chronic HF supported by increasing flow of VA ECMO in a stepwise protocol. We focused on arterial flow speed, its characteristics represented by pulsatility index and possible association with tissue oxygen saturation. Based on published data it is expected that VA ECMO should be able to supply both cerebral and peripheral tissue adequately, but the optimal flow rate of circulatory support remains unclear. At the same time reduction of pulsatility indices was expected in arterial flow and pressure.

Methods

Experimental protocol was reviewed and approved by the Institutional Animal Expert Committee of First Faculty of Medicine, Charles University and was performed at the University experimental laboratory, Department of Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic, in accordance with Act No. 246/1992 Coll., on the protection of animals against cruelty. All animals were treated and cared for in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

At the completion of each study the animal was sacrificed and a necropsy performed to look for potential cardiac anomalies.

Animal model

According to large evidence, TIC as a form of dilated cardiomyopathy was generated by long-term rapid cardiac pacing (Spinale *et al.* 1990, Nikolaidis *et al.* 2001, Gupta and Figueredo 2014).

Five healthy crossbred female swine (*Sus scrofa domestica*) up to 6 months of age with initial weight of 37-46 kg were included in this experiment. After 1 day of fasting, general anesthesia was initiated by intramuscular administration of midazolam (0.3 mg/kg) and ketamine hydrochloride (15-20 mg/kg). Intravenous boluses of propofol (2 mg/kg) and morphine (0.1-0.2 mg/kg) were administered and animals were provided with oxygen and orotracheally intubated with a cuffed endotracheal tube. Total intravenous anesthesia was then continued by combination of propofol (6-12 mg/kg/h), midazolam (0.1-0.2 mg/kg/h) and morphine (0.1-0.2 mg/kg/h), the doses adjusted according to individual responses. Mechanical ventilation was operated by a Hamilton G5 closed-loop automatic device (Hamilton Medical AG, Switzerland) set to adaptive support ventilation to maintain target end-tidal CO_2 of 38-42 mm Hg and adequate hemoglobin saturation of 95-99 %. All procedures were performed according to standard veterinary conventions.

Under aseptic conditions and antibiotic prophylaxis (cefazolin 1 g) a single pacing lead with active fixation was placed transvenously under fluoroscopic guidance in the apical part of right ventricle and subcutaneously tunneled to connect with an in-house modified heart pacemaker (Effecta, Biotronik SE & Co. KG, Germany) which was then implanted into a dorsal subcutaneous pocket. These arrangements proved to prevent device-related complications and allowed a wide range of high rate pacing frequencies.

Additional permanent catheter (Groshong PICC, Bard AS, USA of Arteriofix, B. Braun, Germany) was inserted through the marginal ear vein; animals were then kept in chronic care facility under the care of veterinary specialist. They were provided with free access to water and continued antibiotic regimen of cefazolin for total of 5 days.

Pacing protocol and chronic heart failure induction

After the necessary resting period of two to five days reserved for recovery from the surgical procedure, the rapid ventricular pacing was initiated. According to publications of previous frequent experiments and our own experience, the pacing protocol was defined and started with pacing rate of 200 beats/min. Subsequently, the frequency was escalated and titrated between 200 and 240 beats/min with respect to the heart failure progression (Moe *et al.* 1988, Chow *et al.* 1990, Hendrick *et al.* 1990, Tomita *et al.* 1991). Veterinary surveillance and clinical check-ups including echocardiographic evaluations were kept regularly. Due to interindividual differences in response to fast pacing, time needed to produce chronic heart failure with profound signs of decompensation varied from 4 to 8 weeks.

At the end of pacing protocol, all animals showed consistently significant symptoms of chronic HF – tachypnea, fatigue, spontaneous sinus tachycardia of >150 beats/min and systolic murmurs. At further investigation ascites, pericardial and pleural effusions, nonsustained ventricular tachycardias, dilation of all heart chambers and significant mitral and tricuspid regurgitations were apparent. Hemodynamics of failing circulation was denoted by arterial hypotension and due to poor contractility and low stroke volume, cardiac output was reduced to approximately 50 % of healthy animal's expected normal value. This developed model of tachycardia induced cardiomyopathy corresponds well to poorly compensated dilated cardiomyopathy and was preserved also after the cessation of pacing (Cruz *et al.* 1990, Takagaki *et al.* 2002, Umana *et al.* 2003). Qualities of prepared model including neurohormonal dynamics, peripheral vascular abnormalities and cardiac dysfunction are reflecting human chronic HF (Power and Tonkin 1999).

Experimental preparation and monitoring

At this stage of decompensated chronic heart failure, again anesthesia and artificial ventilation were administered following principles described above, but dosing was adjusted due to low cardiac output (Roberts and Freshwater-Turner 2007).

Anesthetized animals were then connected to bed-side monitor (Life Scope TR, Nihon Kohden, Japan) and all invasive approaches commenced. Bilateral femoral veins and arteries, jugular vein and left carotid artery were punctured and intravascular approaches ensured by standard percutaneous intraluminal sheaths. Right carotid and subclavian arteries were surgically exposed and circumjacent ultrasound flow probes of appropriate sizes attached (3PSB, 4PSB or 6PSB, Scisense, Transonic Systems, USA) enabling to obtain continuous blood flow measurements.

Intravenous anticoagulation was initiated by unfractionated heparin bolus (100 IU/kg) followed by continual infusion maintaining an activated clotting time (ACT) of 200 s (Hemochron Junior+, International Technidyne Corporation, USA) and following invasive catheters were introduced. A balloon Swan-Ganz catheter through femoral vein to the pulmonary artery allowing thermodilution derived continuous cardiac output (CCO Combo Catheter; Vigilance II, Edwards Lifesciences, USA), mixed venous hemoglobin saturation, pulmonary artery and pulmonary arterial wedge pressure assessments. Through the aortic valve a pressure-volume catheter (7F VSL Pigtail, Scisense, Transonic Systems, USA) was introduced to the LV cavity. Central venous pressure was measured *via* jugular vein using a standard invasive method with pressure transducer (TruWave, Edwards Lifesciences, USA), but a high sensitive pressure sensor equipped pigtail catheter in aortic arch (7F VSL Pigtail, Scisense, Transonic Systems, USA) was used for systemic arterial pressure measurement.

Regional tissue oxygenation was monitored by near-infrared spectroscopy (INVOS Oximeter, Somanetics, USA) with sensors placed on forehead and right arm region representing brain and peripheral tissue oxygen saturation levels (Wolf *et al.* 2007).

Intracardiac and transthoracic echocardiography probes (AcuNav IPX8, Acuson P5-1 and X300 ultrasound system, Siemens, USA) were used for 2D and color Doppler imaging. ECG, heart rate, pulse oximetry, capnometry, rectal temperature, mixed central venous hemoglobin saturation were measured continuously. Blood gas parameters were evaluated by a bedside analysis system (AVL Compact 3, Roche Diagnostics, Germany).

VA ECMO

After intravenous systemic heparinization, extracorporeal circulation was maintained by a femoral venoarterial extracorporeal oxygenation system (VA ECMO) compounded of Levitronix Centrimag console (Thoratec, USA) with centrifugal pump, hollow fiber microporous membrane oxygenator (QUADROX-i Adult, Maquet Cardiopulmonary, Germany) and tubing set with two percutaneous cannulas (Medtronic, USA) introduced by the Seldinger technic through punctures of the unilateral femoral vein and artery (Fig. 1). Tip of venous inflow cannula (23 Fr) was advanced to the right atrium and the tip of arterial outflow cannula (18 Fr) reached the thoracic descending aorta, the position of both being verified by fluoroscopy. Fully assembled ECMO circuit was primed with saline solution and extracorporeal blood flow (EBF) initiated at flow of 300 ml/min being considered the minimal flow necessary to prevent thrombus formation inside ECMO circuit and having a neglectable impact to the systemic circulation at the same time. This rate of EBF was later referred to EBF 0 category. EBF was registered by a separate circumjacent flow probe (ME 9PXL, Transonic Systems, USA) attached to the ECMO outflow cannula.

Blood gas analysis was monitored continuously (CDI Blood Parameter Monitoring System 500, Terumo Cardiovascular Systems Corporation, USA) and the partial oxygen pressure and air flow through the oxygenator adjusted to maintain pO_2 100-120 mm Hg, pCO_2 35-45 mm Hg and pH 7.35-7.45 in the blood leaving the oxygenator throughout the whole experiment.

Experimental protocol

After instrumentation was completed, ventricular pacing was discontinued, so all animals were further studied in sinus rhythm.

Under the conditions of profound chronic HF, ECMO protocol was initiated. Mechanical ventilation was repeatedly adjusted (both partial pressure of oxygen and minute ventilation) to reach hemoglobin saturation in arterial blood of 95-99 % and end-tidal CO_2 between 38-42 mm Hg. Crystalloid infusion was administered (100-500 ml/h) to reach and maintain a mean baseline CVP at least 5 mm Hg, ACT kept in range of 200-300 s by continuous intravenous heparin administration.

According to our standardized ramp protocol, the speed of EBF was set by changing the VA ECMO pump rotation speed. We gradually changed the EBF by steps of 1 l/min every 10-15 min and these stepwise
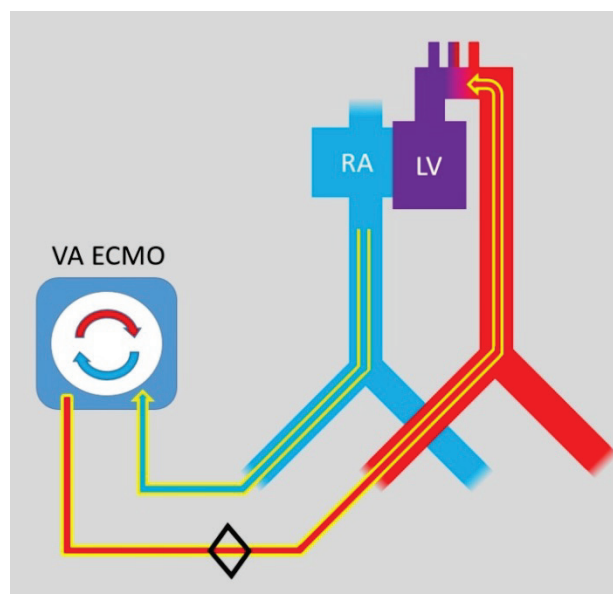

Fig. 1. Femoro-femoral VA ECMO scheme. Venous blood is drawn by inflow cannula from right atrium (RA). It then continuous through the gas exchange unit by the force of centrifugal pump and oxygenated is returned to the descending part of thoracic aorta. LV – left ventricle. Black diamond showing the placement of EBF flow probe.

categories with constant EBF were referred to as EBF 0, 1, 2, 3, 4 and 5.

Data acquisition

In sinus rhythm, time was provided for stabilization of all measured parameters and the baseline values were collected before ECMO introduction. Then ECMO was started and at each EBF step animals were allowed to stabilize for 10-15 min to reach steady state conditions. Parameters were then recorded and sets of data averaged from three end-expiratory time points. If present, premature beats were omitted from the analyses.

Statistical analysis

All data are expressed as mean ± standard error of mean (SEM). Comparisons between different levels of EBF were analyzed by using the Friedman test with Dunn's multiple comparison. Nonparametric Spearman correlation was used for statistical relationship of groups. A P-value of <0.05 was considered statistically significant.

Recordings were sampled at 400 Hz by PowerLab A/D converter and continuously recorded to LabChart Pro Software (ADInstruments, Australia), statistical analyses and graphical interpretations were performed in GraphPad Prism 6 (GraphPad, USA) and Excel (Microsoft, USA).
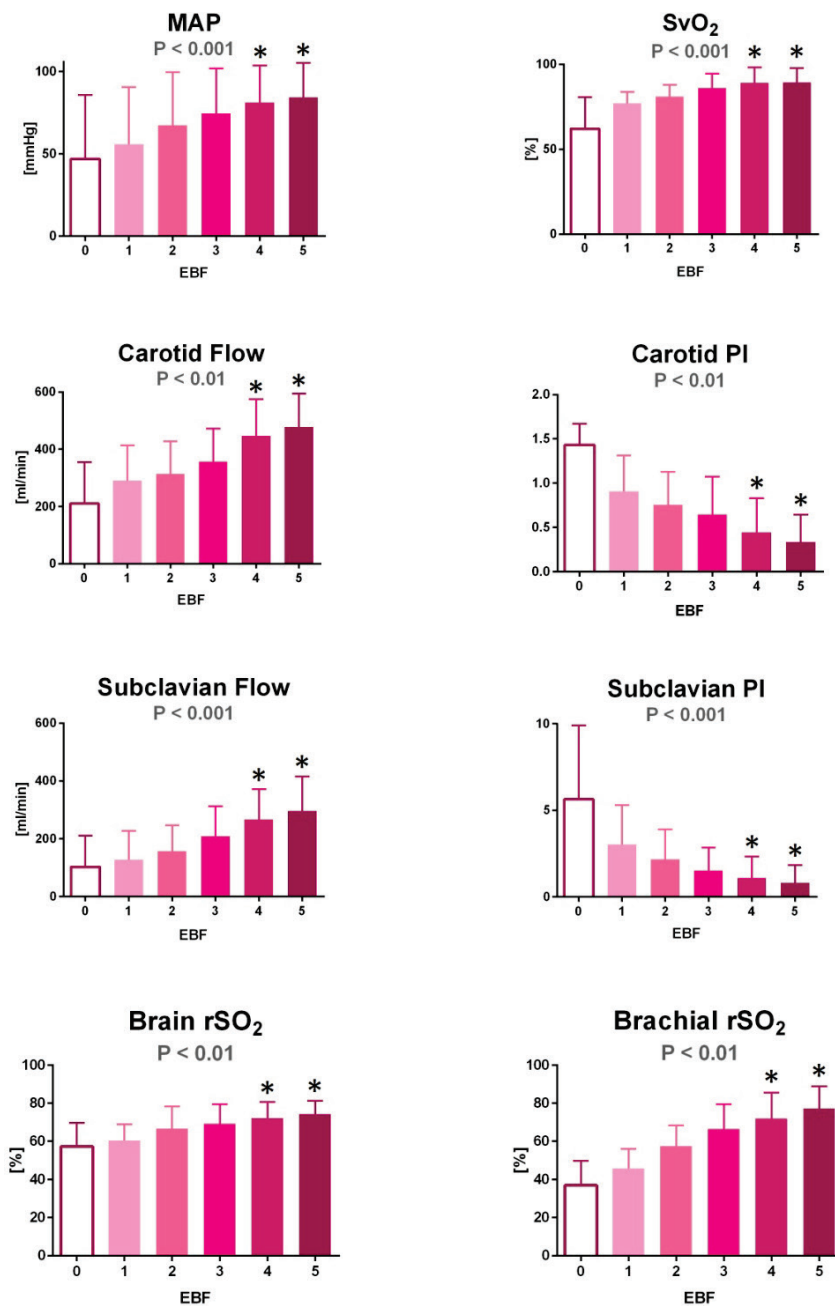
Fig. 2. The effect of venoarterial extracorporeal membrane oxygenation blood flow (EBF) on selected hemodynamic parameters in a porcine model of chronic heart failure. * marks significant change from EBF 0. MAP – mean aortic pressure, SvO$_2$ – mixed venous oxygenation, PI – pulsatility index, rSO$_2$ – regional tissue oxygenation.

Results

Detailed results are summarized in Table 1 and Figure 2. In all animals included in our study fast ventricular pacing for 4-8 weeks generated TIC with signs of decompensated heart failure which was denoted by baseline values of cardiac output at rest 2.9±0.4 l/min, severe dilation of all heart chambers and mean aortic pressure 47±22 mm Hg. Left ventricular ejection fraction evaluated by echocardiography and pressure-volume catheter was below 30 % in all animals and initial mean heart rate of sinus rhythm was 100±19 beats/min. Baseline SvO$_2$ value of 62±8 % corresponds with

inadequate tissue oxygen delivery in our model.

With stepwise increase of EBF from minimal to maximal flow, we observed gradual increase in mean aortic blood pressure by 79 % – from baseline 47±22 mm Hg to 84±12 mm Hg (for EBF 0 to EBF 5, P<0.001). Similarly, arterial blood flow increased with every increase of EBF. In carotid artery it changed from 211±72 ml/min to 479±58 ml/min (by 127 % from EBF 0 to EBF 5, P<0.01) and in subclavian artery from 103±49 ml/min to 296±54 ml/min (by 187 % from EBF 0 to EBF 5, P<0.001). For both arteries the pulsatility index (PI) was defined as calculated difference between the peak systolic and minimum diastolic velocities divided

by the mean velocity during each cardiac cycle and as such represents the variability of arterial flow during cardiac cycle. Interestingly, baseline PI was considerably higher in subclavian than in carotid artery. A reduction of pulsatility indices by 76 % (from 1.43±0.12 to 0.34±0.15, P<0.05) in the carotid and by 85 % (from 5.7±1.9 to 0.8±0.5, P<0.001) in the subclavian artery was observed from EBF 0 to EBF 5.

Mean heart rate (HR) tended to decline with every increase in EBF – from 101±22 beats/min to 86±14 beats/min (for EBF 0-5, P=0.34). Left ventricular stroke work (SW) was calculated from measured pressure-volume loops and exhibits flow-dependent increase from 1434±941 mm Hg*ml to 1892±1036 mm Hg*ml (for EBF 0-5, P<0.05), but reaching its maximal value of 2105±1060 mm Hg*ml at EBF 4. Baseline mixed venous blood saturation (SvO_2) was 62±8 %, but increased to

77±3 % with EBF 1 and reached >80 % with all higher EBF steps (P<0.01). With increasing of EBF, the average value of CVP did gradually fall, but not under 7 mm Hg, avoiding ECMO underfilling.

Regional tissue oxygenation (rSO_2) both on forehead and right arm was on low level at baseline, but increased promptly with increase of EBF. Forehead rSO_2 changed by 30 % from 57±6 % to 74±3 % and right brachial rSO_2 changed in total by 108 % from 37±6 % to 77±6 % (both P<0.01).

Graphs of regional perfusion and tissue oxygenation are visualized on Figure 3 and demonstrate linear relationship – carotid flow correlated significantly with brain oxygenation (r=0.75, P<0.001) and subclavian flow correlated significantly with corresponding brachial oxygenation (r=0.94, P<0.001).

Table 1. Hemodynamic parameters and oximetry data for each step of increasing extracorporeal blood flow (EBF in l/min).

Parameter	VA ECMO blood flow						Relative change
	EBF 0	EBF 1	EBF 2	EBF 3	EBF 4	EBF 5	*EBF 0-5*
MAP, mm Hg	47±22	56±20	67±19	75±16	81±13*	84±12*	79 %
Carotid flow, ml/min	211±72	291±62	314±57	356±57	447±64*	479±58*	127 %
Carotid pulsatility index	1.43±0.12	0.91±0.20	0.75±0.19	0.64±0.21	0.44±0.19*	0.34±0.15*	-76 %
Subclavian flow, ml/min	103±49	128±44	158±40	208±47	266±47*	296±54*	187 %
Subclavian pulsatility index	5.7±1.9	3.0±1.0	2.2±0.8	1.5±0.6	1.1±0.5*	0.8±0.5*	-86 %
HR, beats/min	101±22	96±19	93±17	90±13	90±14	86±14	-15 %
*SW, mm Hg*ml*	1434±941	1595±987	1867±1102	2014±1062	2105±1060*	1892±1036	32 %
SvO_2, %	62±8	77±3	81±3	86±4	89±4*	89±4*	44 %
CVP, mm Hg	14±2	11±2	10±2	8±2*	9±2*	8±2*	-43 %
rSO_2 forehead, %	57±6	60±4	67±5	69±5	72±4*	74±3*	30 %
rSO_2 right arm, %	37±6	46±5	58±5	67±6	72±7*	77±6*	108 %

Values expressed as mean ± SEM. Values significantly different from EBF 0 marked with *. MAP – mean aortic pressure, HR – heart rate, SW – left ventricular stroke work, SvO_2 – mixed venous blood oxygenation, CVP – central venous pressure, rSO_2 – regional tissue oxygenation.
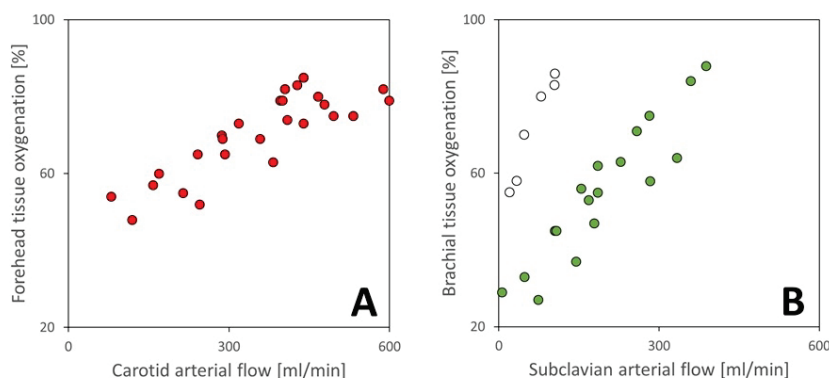

Fig. 3. Correlation of carotid (**A**) and subclavian (**B**) arterial flow and corresponding regional tissue oxygenation. Correlation coefficients r=0.75 (for A) and r=0.94 (for B), P<0.001 for both; omitting one outlying subject – empty circles in B.
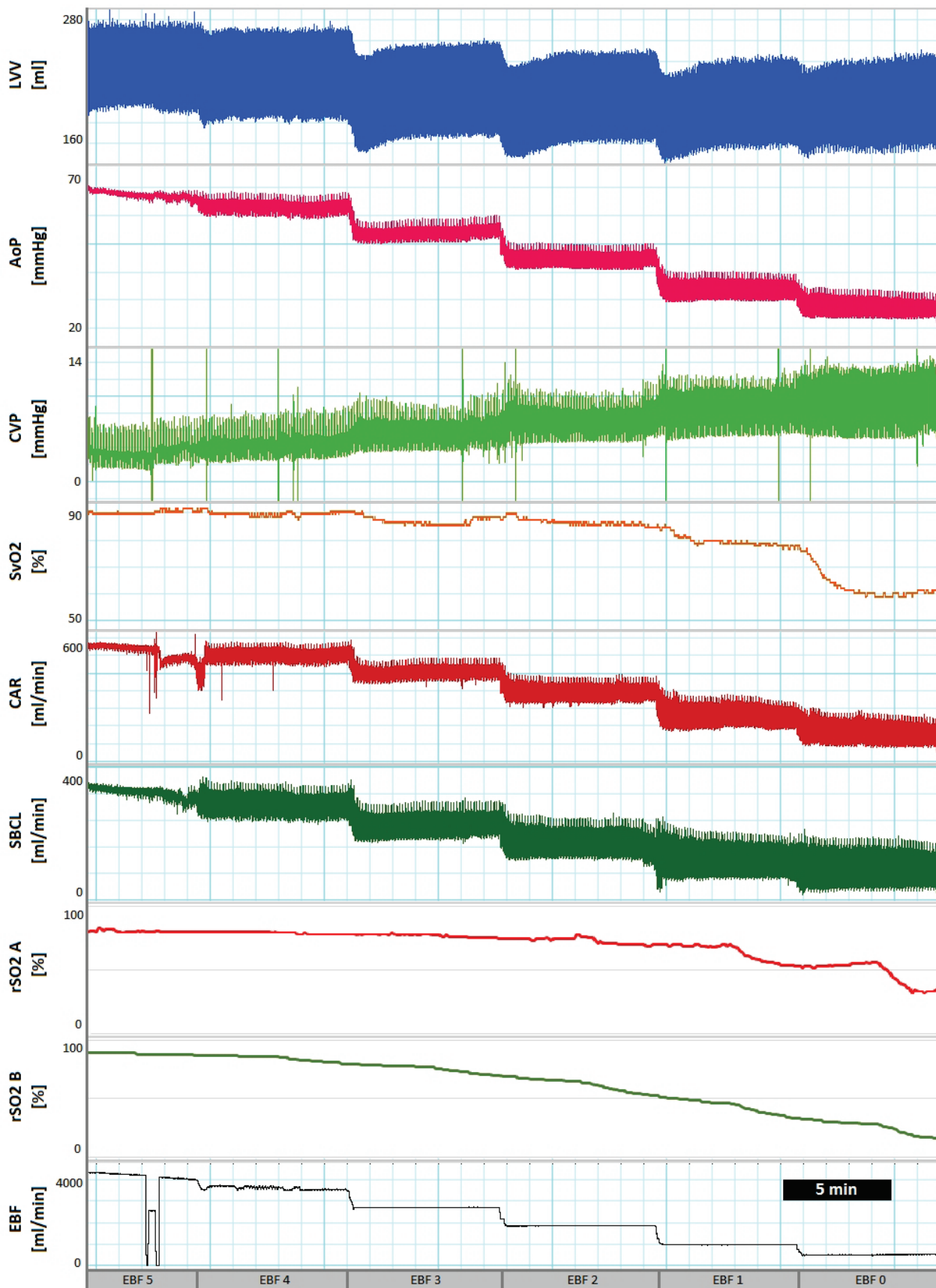
Fig. 4. Continuous data records from one animal (reversed protocol EBF 5-0). With time (horizontal axis) the EBF changed in stepwise manner. LVV – left ventricular volume, AoP – aortic blood pressure, CVP – central venous pressure, SvO_2 – mixed venous blood oxygenation, CAR – carotid arterial flow, SBCL – subclavian arterial flow, rSO_2 A – forehead tissue oxygenation, rSO_2 B – brachial tissue oxygenation, EBF – extracorporeal blood flow.

Continuous data samples acquired from one animal model are shown on Figure 4. After each change of EBF, presented parameters change abruptly, then stabilize during 1-5 min reaching steady-state. Volumetric and hemodynamic parameters demonstrate only partial compensation. Postmortem autopsies did not reveal any shunt or other cardiac anomaly, but significant myocardial hypertrophy (mean heart weight of 471±127 g).

Discussion

VA ECMO serves as an efficient circulatory support in cases of cardiac decompensation. In recent studies, it has been reported that increasing inflow of oxygenated blood from ECMO circuit to the thoracic aorta significantly increases afterload and demands on work of LV and therefore oxygen consumption of the myocardium. By the same authors, setting VA ECMO flow as low as possible was proposed (Ostadal et al. 2015, Broome and Donker 2016). Based on SW measurements, this is in agreement with our observations. On the other hand, adequate vital organ perfusion and tissue oxygenation has to be ensured. Thus, the optimal rate of support from extracorporeal circulation remains unclear. In presented study, we focused on influence of VA ECMO on brain and peripheral arterial flow and corresponding tissue oxygenation in a stepwise protocol of increasing EBF.

As in current healthcare practice, VA ECMO is used to treat acute circulatory decompensation which often develops on grounds of previously present chronic heart disease. The use of a chronic HF model to study effects of VA ECMO on systemic circulation is a novel approach of our experimental work. We chose to individualize the pacing protocol as interindividual differences in response have been reported. For TIC induction we paced the apex of right ventricle of each animal at a rate between 200 and 240 beats/min and the TIC model was developed in a period of 4-8 weeks. After this time, persistent changes of myocardium were expected and circulatory failure persisted after cessation of pacing. Also neurohormonal response and compensatory mechanisms were activated during this period. In agreement with literature mentioned above, this porcine model of tachycardia-induced heart failure represented a form of dilated cardiomyopathy with symptoms of profound circulatory decompensation which was denoted by low-flow heart failure, low central

venous and regional tissue oxygenation.

Brain and peripheral tissue oxygenation levels were represented by near-infrared spectroscopy with sensors placed on forehead and right arm. This transcutaneous technique is widely used for bedside monitoring of relative local oxyhemoglobin concentration changes. As a non-invasive method it has been validated both in experimental and clinical studies for microcirculation assessments (Ito et al. 2012, Ostadal et al. 2014). Blood flow to matching regions was measured by circumjacent probes on right carotid and right subclavian artery.

Overlook of our results confirms that with stepwise increase of the EBF, arterial blood flow in carotid and subclavian artery increase in a manner respecting the increase of mean aortic blood pressure. As both pulsatile systemic and non-pulsatile extracorporeal circulations are concomitantly meeting in the thoracic aorta, with increasing of EBF, the relative contribution of LV ejection to arterial flow is decreasing. Due to the increase of LV end-diastolic pressure, excessive afterload may not be accompanied by an increase in coronary perfusion, which may further contribute to the loss of pulsatility observed in both arteries (Kato et al. 1996).

Whether deficiency of pulsatile flow in arteries negatively affects organ perfusion remains a controversial topic. At baseline before ECMO initiation, pulsatility index of carotid flow was considerably lower compared to subclavian, but with increase of EBF to 5 l/min, the carotid PI dropped less than in subclavian artery (by 76 % vs. 85 %). In general, PI is to be influenced by transaortic LV ejection, vascular resistance, arterial carbon dioxide tension and aortic and arterial wall stiffness, which can be considered low as we studied young animals. To suppress their effects, blood gas parameters were maintained in physiological ranges in extracorporeal and also native circulation. Insufficiency of the aortic valve, another contributor to pulsatility, was present in our model due to the insertion of transaortic catheter. But, according to echocardiography, this was of little significance. Similar gradual decline of PI in newborns was observed at higher EBF and remained low also shortly after the VA ECMO decannulation, suggesting changes in vascular resistance (Van De Bor et al. 1990).

In our results, baseline cerebral perfusion through the right carotid artery was 211±72 ml/min, which is approximately 59 % of flow reported previously in healthy animals with identical methodology (Mlcek et al. 2015). Interindividual variability of carotid flow does

not seem to correlate with body size. Instantaneous increase of arterial flow is provided by setting higher EBF. This increase is again more prominent in subclavian compared to carotid artery (by 187 % vs. 127 %). Similarly, respecting the local flow, baseline regional tissue oxygenation of the arm is lower compared to the forehead (P=0.08), but it increases by 108 % compared to only 30 % increase on the forehead. These observations are reflecting peripheral hypoperfusion and the ability to compensate intracranial circulation at baseline in conditions of cardiogenic shock. Both brain and brachial tissue oxygenation demonstrate linear correlation with local perfusion throughout the whole protocol, which supports the constant local oxygen consumption.

Our results of cerebral perfusion are similar to clinical study reported by Liem *et al.* (1995). In infants undergoing VA ECMO for cardiorespiratory failure, they evidenced increased total cerebral blood flow accompanied by increased cerebral blood volume and also loss of PI assessed by transcranial Doppler ultrasound. On contrary, different observations were reported by Stolar and Reyes (1988) in healthy lambs – two hours of high flow VA ECMO narrowed pulse pressure, but caused no significant changes of carotid flow. The use of healthy animals, absence of increase in mean arterial pressure or cannulas' position can explain this discrepancy. Notably, link of cerebral hyperperfusion and intracranial hemorrhage is suspected (Van De Bor *et al.* 1990).

Mean brain oxygenation in healthy animal is referred to reach 65 % (Xanthos *et al.* 2007). In our work, already during low to mild circulatory support of EBF 2 or 3 l/min, the tissue oxygenation, arterial flow and mixed venous oxygen saturation steeply comes close to normal values. Further increase to high rates of EBF then seems to provide only moderate improvement. These experimental results could imply that in decompensated chronic heart failure of matching severity, low to mild EBF may be of enough circulatory support to cover adequate tissue needs and at the same time protecting the LV from possibly harming overload.

Although the main parameters followed trends significantly, only five animals were included in the study. Despite our maximal effort, presented results should be tempered by several limitations. First, the animal model can represent only one form of decompensated chronic heart failure, but VA ECMO would be employed in broad spectrum of patients who may differ in response. Next, near-infrared spectroscopy provides good information about regional tissue oxygenation, but due to technical limitations, only its relative change in time should be evaluated. Also, we could not measure the total brain perfusion as it is served by both carotid and vertebral arteries. Lastly, because we used circulatory support of VA ECMO only for short-term period of hours, its chronic effects cannot be determined. Upcoming studies can answer some of these interesting questions.

Conclusions

Our results imply that even low to mild circulatory support of VA ECMO provides sufficient cerebral and peripheral perfusion in conditions of decompensated chronic heart failure. In these settings high rates of EBF may not be necessary.

Conflict of Interest
There is no conflict of interest.

Acknowledgements

Abbreviations
CVP – central venous pressure, EBF – extracorporeal blood flow, HF – heart failure, HR – heart rate, LV – left ventricle, PI – pulsatility index, rSO_2 – regional tissue oxygenation, SvO_2 – mixed venous blood saturation, SW – stroke work, TIC – tachycardia-induced cardio-myopathy, VA ECMO – venoarterial extracorporeal membrane oxygenation,.

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