

# The sheep as a pre-clinical model for testing intra-aortic percutaneous mechanical circulatory support devices

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## Abstract

The safe deployment of intra-aortic percutaneous mechanical circulatory support devices is highly dependent on the inner aortic diameter. Finding the anatomically and ethically most suitable animal model for performance testing of new pMCS devices remains challenging. For this study, an ovine model using adult ewes of a large framed breed (Swiss White Alpine Sheep) was developed to test safety, reliability, and biocompatibility of catheter-mounted mechanical support devices placed in the descending thoracic aorta. Following the drawback of fluctuating aortic diameter and device malfunction in the first four animals, the model was improved by stenting the following animals with an aortic stent. Stenting the animals with an intra-aortic over the balloon stent was found to standardize the experimental set-up and to avoid early termination of the experiment due to non-device related issues.

## Keywords

Mechanical circulatory support, animal model, sheep, 3R, thoracic aorta, preclinical study

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## Introduction

Over the past years, several percutaneous Mechanical Circulatory Support systems (pMCS) aiming to improve left ventricular (LV) systolic function and cardiac output (CO) have been developed and clinically implemented.<sup>1,2</sup> Currently available devices can generally be assigned to one of three categories: rotary (blood) pumps, centrifugal continuous pumps and axial flow pumps.<sup>1</sup> The latter category comprises of a small variety of devices that are catheter-mounted and are introduced via the femoral artery and either placed in the left ventricle across the aortic valve (intraventricular) or in the mid-thoracic descending aorta (intra-aortic) at the level of the diaphragmatic wall. By pumping the blood from the ventricle into the systemic circulation or by ante grade acceleration of the blood flow in the aorta respectively, they assist LV function in a heart-rhythm independent manner.<sup>3</sup> Both, intraventricular pMCS devices and intra-aortic pMCS devices bear their own risks from aortic valve injury to myocardial infarction and ischaemic cerebrovascular events, to bleeding, vascular injury, thromboembolic events and hemolysis leading to acute kidney injury.<sup>4</sup> Due to the use of large-bore

peripheral arterial access sheaths, the use of either type of pMCS is often associated with access site complications such as bleeding or limb ischaemia.<sup>5</sup> Therefore, one of the challenges in the design and development of axial blood pumps is amongst others to diminish the size of the device to reduce the trauma of implantation without increasing shear stress and hemolysis caused by the very high rotational speeds (up to 51,000 rpm) required to deliver sufficient blood flow.<sup>6–8</sup> Axial flow pumps used in pMCS devices today are therefore size limited and for intra-aortic

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pMCS devices, a safe intra-aortic deployment is furthermore highly dependent on the inner aortic diameter (IAD). While the mid-thoracic descending aortic diameter in humans is described as age and gender dependent, having a diameter of  $27 \pm 2.8$  mm– $28.2 \pm 3$  mm in males and  $24.6 \pm 2.4$  mm– $25.4 \pm 3$  mm in females,<sup>9,10</sup> preclinical studies appear to struggle in finding the most suitable animal model for the testing of new pMCS devices.

In the past, calves at the age of 2–3 months (70–100 kg body weight),<sup>11</sup> have shown to be useful animal models for acute cardiovascular studies and device research, due to their size and their blood volume. Their large peripheral vessels facilitate vascular access for device cannulation and instrumentation and with an average diameter of  $27 \pm 3.1$  mm the mid-thoracic descending aorta of a calf is large enough for current intra-aortic pMCS devices.<sup>12,13</sup> However, when it comes to hemocompatibility testing, that is, blood damage potential and coagulation risks, the use of the calf model has received some criticism in the past.<sup>14</sup> Firstly, infant haemoglobin is known to have different fragility properties than adult haemoglobin.<sup>14</sup> Secondly, the coagulation system of the calf shows a markedly slower fibrinogen activation and platelet stimulation than in man.<sup>15</sup> Further limitations arise in chronic studies due to the calf's fast somatic growth and associated large elevation in CO over the duration of the testing period.<sup>16</sup> Choosing an animal model, not only of comparable anatomy and size but also reflecting comparable age-related physiologic properties in reserve, resilience and resistance to stressors<sup>17</sup> is essential to avoid conducting costly experiments with misleading and meaningless study results lacking transferability. The pig has been widely used as a model in cardiovascular research, including hemodynamic studies of pMCS devices<sup>18–21</sup> and appears to be a valuable alternative to the calf at first glance. Due to the porcine heart bearing a close resemblance to the human heart in terms of size and hemodynamics,<sup>22</sup> it is especially suitable for the testing of intraventricular pMCS devices<sup>19</sup> and with an average mid-descending thoracic aortic diameter of  $15.57 \pm 0.40$  mm<sup>23</sup> smaller intra-aortic balloon pumps expanding to a final diameter of 15–18 mm.<sup>24</sup> However, larger intra-aortic pMCS devices had to overcome the small aortic diameter by placing a Dacron aortic graft<sup>25</sup> demanding rather invasive model modifications.

The adult sheep is another popular animal model in cardiovascular research due to its anatomical structures and physiological functions that are comparable to those of humans, with similar annulus sizes, equivalent heart rate and CO and no consistent differences in coagulation parameters.<sup>16</sup> However, due to the assumed smaller diameter of the mid-thoracic descending aorta (OAD  $21.07 \pm 0.69$  mm, wall thickness  $1.56 \pm 0.07$  mm<sup>26</sup>) the sheep has so far been used predominantly for the development and testing of paediatric pMCS systems.<sup>27</sup>

This paper describes the development and refinement of an adult sheep model for safety, reliability, and

biocompatibility testing of adult size catheter-mounted intra-aortic pMCS devices. From initial difficulties, reconsideration of the animal model to finding a solution.

## Ethical statement

Animal housing and all experimental procedures were approved by the local Committee for Experimental Animal Research (Cantonal Veterinary Office Zurich, Switzerland) under the Licence numbers ZH41/2017 and ZH51/2020, and conform to the European Directive 2010/63/EU of the European Parliament and the Council on the Protection of Animals used for Scientific Purposes, and to the Guide for the Care and Use of Laboratory Animals.<sup>28</sup>

## Material and methods

### Pre-procedural animal selection

A total of 34 female adult Swiss White Alpine (WAS) Sheep were chosen for pre-procedural assessment based on their frame size and bodyweight ( $87 \pm 4.5$  kg). A preselection has been performed through aortic valve diameter measurement by transthoracic ultrasound in the awake sheep (Cx50 xMATRIX, Phillips Healthcare, Germany, S5-1 ultrasound probe). A parasternal long axis image of the aortic root was acquired through the left 4th intercostal space. Sheep with an aortic valve diameter  $>28$  mm were considered suitable based on the assumption, from previous experience with this sheep breed and data found in humans,<sup>29</sup> of mid-thoracic descending aortic diameter to aortic valve annulus ratio of  $>0.76$ . From a total of 19 sheep fulfilling the aortic valve size criteria and undergoing pMCS device testing experiments, 8 sheep were included to describe the animal model development presented here.

### Pre-procedural CT scan

4/8 sheep underwent pre-procedural CT scanning on the day of the experiment. Animals were scanned under general anaesthesia with a third-generation 192-slice dual-source CT machine (SOMATOM Definition Flash, Siemens Healthineers, Forchheim, Germany). The data acquisition was synchronized with the electrocardiogram (ECG) of the animals using retrospective ECG-gating. A total of 0.5–1 ml/kg BW iodinated contrast media (iopromide, Ultravist 370, Bayer Healthcare, Berlin, Germany) was administered intravenously at a flow-rate of 5 ml/s followed by 30 ml of saline chaser at a flow-rate of 3.5 ml/s. Bolus tracking was performed in the mid-thoracic descending aorta.

### Anaesthesia and animal instrumentalization

Anaesthesia was induced by i.v. injection of ketamine hydrochloride (Ketasol<sup>®</sup>-100 ad us. vet.; Dr. E. Graeb AG,

Berne, Switzerland; 3 mg/kg BW) in combination with Midazolam (Dormicum<sup>®</sup>, Roche Pharma (Schweiz) AG, Reinach, Switzerland; 0.2 mg/kg BW) and Propofol (Propofol<sup>®</sup>-Lipuro 1%, B. Braun Medical AG; Sempach, Switzerland 2–4 mg/kg/h; 2–5 mg/kg BW). After intubation anaesthesia was maintained by positive pressure ventilation (fresh gas flow 1–1.5 l/min, 12–15 breaths/min, tidal volume 10–15 ml/kg, FiO<sub>2</sub> 0.5) of 2%–3% Isoflurane in oxygen/air mixture and a continuous infusion pump applying propofol (Propofol<sup>®</sup>-Lipuro 1%, B. Braun Medical AG; Sempach, Switzerland 2–4 mg/kg/h). Throughout the procedure the animals received a continuous intravenous infusion of sufentanil (Sufenta<sup>®</sup> Forte, Janssen-Cilag AG, Zug, Switzerland; 0.05 mg/kg/h). All sheep were anticoagulated with a continuous infusion of Na-Heparin (B. Braun Medical AG, Sempach Crystalloids) to achieve an ACT of 200–210.

In all sheep percutaneous placement of a femoral arterial introducer sheath (10F ( $n=4$ ), 14F ( $n=4$ )), a femoral 2-lumen venous catheter (HighFlow Dolphin Catheter, 13F, Baxter International, Deerfield IL, USA), a carotid arterial line (5F) and a multilumen jugular vein catheter (AeroGuard Blue, Arrow<sup>®</sup>, Teleflex Medical Europe Ltd., Ireland) was performed.

Carotid and femoral arterial blood pressure (ABP) and central venous blood pressure (CVP) were continuously recorded using the DSI Ponemah System V.5.1. (DataScience International, St. Paul, Minnesota, USA).

### *Fluoroscopic measurement of inner diameter (ID) of the thoracic aorta*

Prior to the deployment of the intra-aortic pMCS device, exact location of deployment was determined by angiography. A pigtail catheter (Infiniti 5F PIG 145 .038 125 cm, Cordis Corporation, Miami Lakes, USA) was introduced through the femoral access sheath and advanced to the aortic arch. Contrast agent (30 ml total volume, 15 ml/s, Ultravist<sup>®</sup>-300, Bayer Vital, Leverkusen, Germany) was injected using a power injector.

Thoracic descending aortic diameter measurement were performed at three locations of the intrathoracic aorta (proximal, medial and distal) from the angiographic images using Sante DICOM Editor 3D (Santesoft LTD., Nicosia, Cyprus, Version 4.3.2.). Images were calibrated to the size of the pigtail.

### *Aortic stent*

In 4/8 animals an over a balloon covered aortic stent (Bentley, BeGraft aortic, BGA4824\_2, Hechingen, Germany) was placed in the thoracic descending aorta over a 14F introducer sheath in the femoral artery. The stent was over-expanded to a final size between 23.5 and 24.7 mm. Correct location of the stent was verified with fluoroscopy.

## **Results**

### *Aortic valve diameter*

The average aortic valve diameter of the eight animals included in this study was  $29.23 \pm 0.78$  mm (Figure 1(a)).

### *Mid-descending aorta diameter to aortic annulus ratio*

In 4/8 sheep the diameter of the descending thoracic aorta was assessed with CT scan (proximal:  $27.5 \pm 0.32$  mm, medial:  $26.28 \pm 0.40$  mm, distal:  $24.35 \pm 0.46$  mm ( $n=4$ ) (Figure 1(b) I–III)). In 8/8 sheep the thoracic descending aortic diameter was additionally ( $n=4$ ) or only ( $n=4$ ) assessed with angiography (Figure 1(c)) (proximal:  $25.93 \pm 1.80$  mm, medial:  $24.12 \pm 1.68$  mm, distal:  $22.63 \pm 1.49$  mm) resulting in an average mid-thoracic descending aortic diameter to aortic valve annulus ratio of  $0.83 \pm 0.06$ . Individual results are summarized in Table 1.

### *Step 1: The native model*

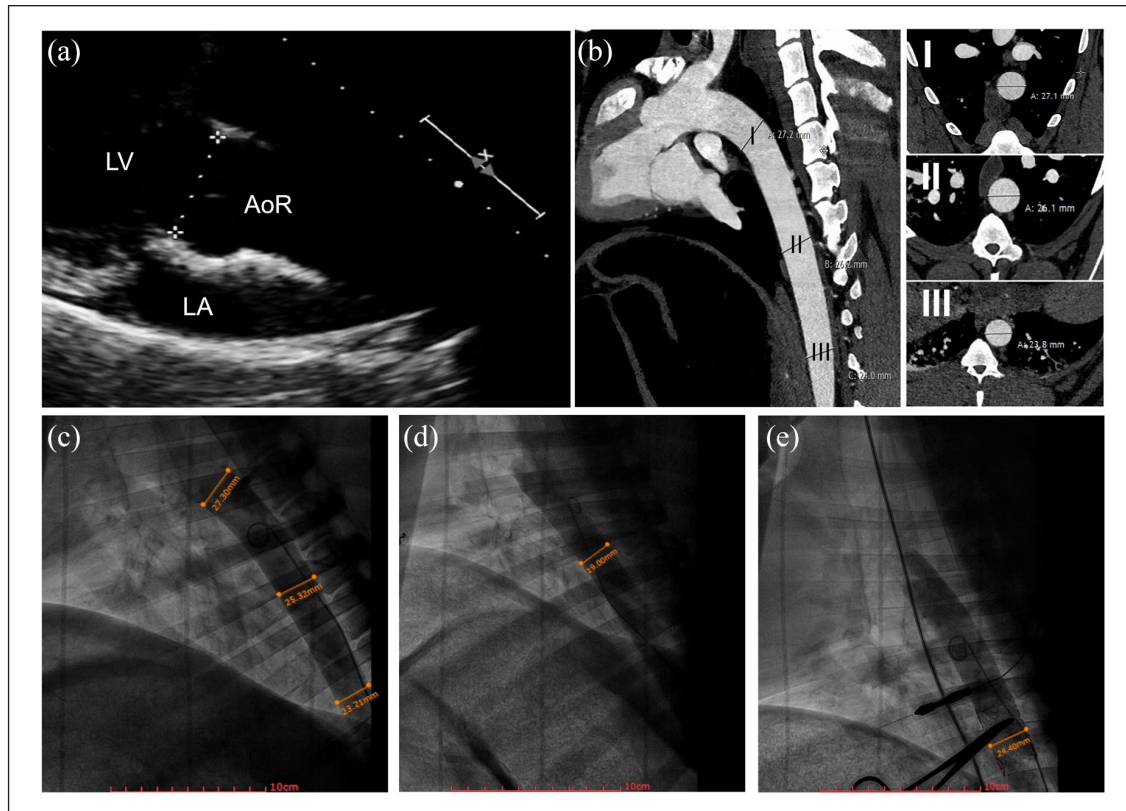
After fluoroscopic determination of exact site of placement, in 4/8 animals the pMCS device was deployed in the thoracic descending aorta with an intended pump running time of 24–30 hours. Proper mechanical function was hampered in all four animals within 3–8 hours of running time of the pMCS device. Control fluoroscopy at the time of the device malfunctioning revealed that the diameter of the mid-descending aorta had markedly reduced ( $20.1 \pm 0.78$  mm (Figure 1(d));  $\Delta -6.64 \pm 0.36$  mm) and was no longer able to support the device size adequately. Aggressive volume substitution and a continuous infusion of noradrenaline (60–200  $\mu$ g/h) was started, which allowed the pMCS device to resume its function.

Malfunctioning of the device re-occurred in Animal 4 after which the trial was terminated prematurely at a pump running time of 9 hours. Animal 2 was discontinued after a pump running time of 21 hours due to volume overload and cardiac arrhythmia.

Decoupling the pMCS device required a complete change and de novo deployment of the pump. The native sheep model was therefore rendered unsuitable for testing pump performance over the duration decisive for save clinical approval. Repeated angiographies throughout the pump running time showed large fluctuations of the aortic diameter in these sheep, which needed to be excavated by improving the initial model.

### *Step 2: The stented model*

To counteract the fluctuations of the descending thoracic aortic diameter the following four animals were stented with an over a balloon aortic stent, which was expanded to 23.5–24.7 mm (Figure 1(e)). Fluoroscopic determination of exact location of stent placement was performed analogously to the



**Figure 1.** Representative image of: (a) trans-thoracic ultrasound of the aortic root parasternal long axis, LV: left ventricle; LA: left atrium; AoR: aortic root. (b) CT measurement of thoracic aorta: proximal, medial, distal, (b.I.) proximal cross-section thoracic aorta, (b.II) medial cross-section thoracic aorta, and (b.III) distal cross-section thoracic aorta. (c) Angiographic measurement of thoracic aorta at the beginning of the procedure: proximal, medial, distal. (d) Angiographic measurement of the medial thoracic aorta at time of device decoupling and (e) Intra-aortic stent placement.

native model. In order to assure precise device positioning and to prevent distal migration due to the forward aortic flow, high dose adenosine (12–60 mg) was used in the first sheep to induce temporary high degree AV block as described in humans.<sup>30</sup> As no significant cardiovascular effect was achieved with the application of Adenosine, a bolus of propofol (1 mg/kg) was administered, causing a significant drop in mean arterial blood pressure (mean  $\Delta$ -11.10  $\pm$  3.407 mmHg,  $p$ =0.03) immediately prior to stent deployment.

The pMCS device was then placed to run within the stent. In all four animals the 30 hour testing period was completed without any device malfunction.

#### Mean Arterial blood pressure (ABP), heart rate (HR) and central venous blood pressure (CVP)

No significant difference was found in mean ABP at the time point of pMCS deployment between the native and the stented group (76.54  $\pm$  6.87 mmHg in the native group vs 82.65  $\pm$  5.15 mmHg in the stented group;  $p$ =0.219). No significant difference was found in heart rate (85.94  $\pm$  3.87 bpm in the native group vs 101.11  $\pm$  12.33 bpm in the stented group,  $p$ =0.290) at the time of point of pMCS deployment. Furthermore CVP was comparable at

that time point between the two groups with no significant difference (7.44  $\pm$  1.80 mmHg in the native vs 10.45  $\pm$  2.12 mmHg in the stented group;  $p$ =0.002).

Mean ABP significantly decreases over time in the stented group ( $m$ =-0.525,  $p$ <0.0001). A decrease of mean ABP is also observed in the native group, however, not significantly ( $m$ =-0.013,  $p$ =0.898) (Figure 2(a)). There is a significant decrease of heart rate in the stented group ( $m$ =-0.525,  $p$ <0.0001) while heart rate in the native group significantly increases ( $m$ =0.797,  $p$ <0.0001) (Figure 2(b)). CVP increases significantly in both groups ( $m$ =0.074,  $p$ <0.0001 in the stented group,  $m$ =0.206,  $p$ <0.0001 in the native group respectively) (Figure 2(c)).

At the time of mechanical constriction of the pMCS device the mean ABP showed a marked decrease in three out of four animals (Animal 1:  $\Delta$ -17.008 mmHg, Animal 3:  $\Delta$ -8.781 mmHg, Animal 4:  $\Delta$ -15.545), in Animal 2 mean ABP showed a slight increase of mean ABP at the time of mechanical decoupling ( $\Delta$ +5.121 mmHg).

## Discussion

Intra-aortic axial flow pumps used in adult pMCS today are size limited and their safe intra-aortic deployment is

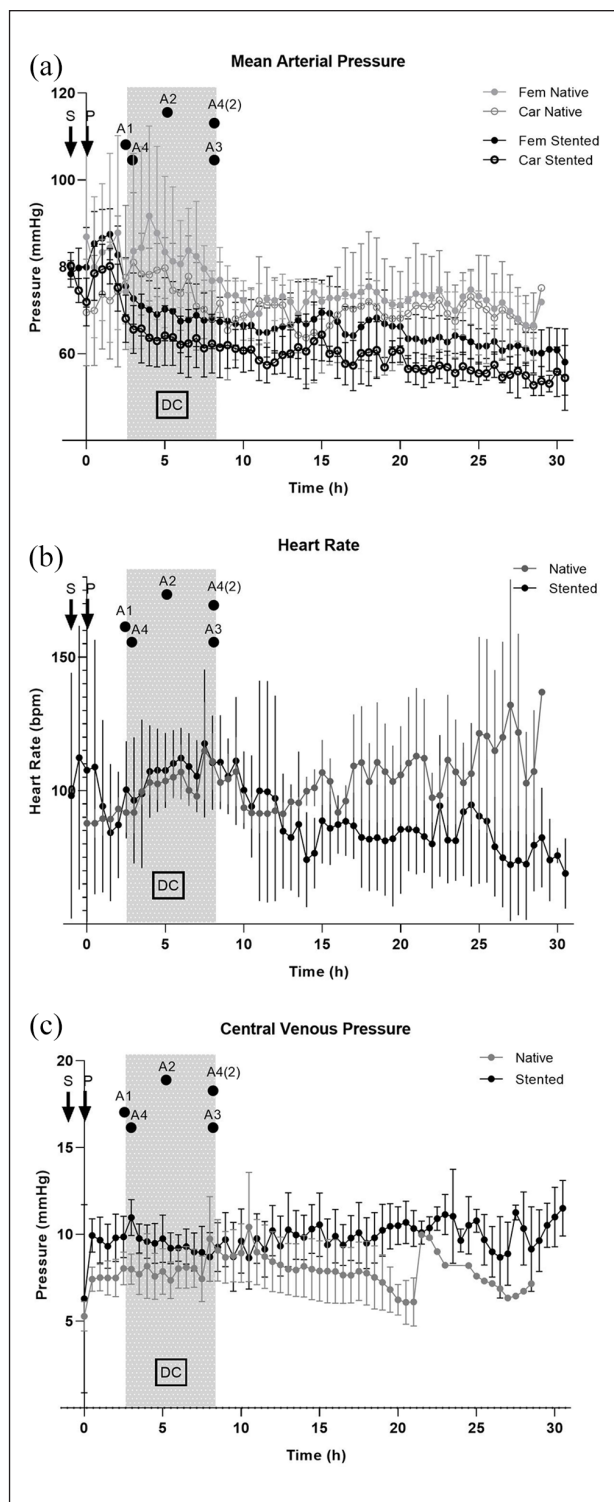
**Table 1.** Overview of conducted measurements.

	Animal no	Body weight (kg)	Aortic valve diameter (mm)	Descending thoracic aorta CT (mm) proximal-medial-distal	Descending thoracic aorta angiography (mm) proximal-medial-distal	Aortic stent expansion size (mm)	Ratio aortic valve to mid-thoracic descending aorta
Native	Animal 1	85.5	30	27.3 25.7 24.7	26.16 25.95 23.77	n.a.	0.86
	Animal 2	88.0	30	27.9 26.4 23.8	27.14 26.64 24.15	n.a.	0.88
	Animal 3	80.0	29.7	27.1 25.6 24.0	27.54 24.37 24.00	n.a.	0.82
	Animal 4	90.0	30.1	27.7 26.8 24.9	27.05 22.73 22.59	n.a.	0.75
Stented	Animal 5	91.5	28.7	n.a.	23.63 21.60 20.61	24.4	0.75
	Animal 6	87.5	28.2	n.a.	26.29 23.94 22.87	23.6	0.84
	Animal 7	88.5	28.1	n.a.	27.32 25.32 23.21	24.7	0.90
	Animal 8	91.0	29.0	n.a.	22.28 22.37 19.84	23.5	0.77

highly dependent on the inner diameter of the descending thoracic aorta (IAD). Choosing the appropriate animal model for preclinical pMCS device testing remains therefore a challenge. In this study, adult sheep of a large-framed breed (Swiss White Alpine Sheep) were used, with the intention of replacing the calf, with its juvenile characteristics, as an animal model in pMCS device testing. Although the initially assessed diameter of the descending thoracic aorta was large enough in all sheep for a safe device deployment, mechanical malfunction occurred in 4/8 sheep due to an apparent fluctuations of the aortic diameter during the experiment. In both, human and sheep, an exponential pressure-diameter relationship curve of the aorta is described under physiologic conditions.<sup>26,31,32</sup> However, with the lack of obvious hemodynamic events at first glance, one may only propose a few hypothesis about the underlying cause leading to the significant diminishment of the inner aortic diameter over time. Firstly, autonomic vascular tone modulation: An acute pressure gradient between the carotid artery and the femoral artery caused by the axial turbine pump accelerating the blood flow in the aorta ante gradely is observed. This phenomenon possibly causes a baroreceptor reflex in the carotid sinus, thus, activating the sympathetic nervous system inducing vasoconstriction in the descending aorta and

peripheral arteries, as well as an increase in heart rate and contractility (26). Furthermore, the acute volume expansion experienced by the kidneys, again due to the accelerated blood flow in the aorta ante gradely, will lead to a release of atrial natriuretic peptides (ANP) Type C from the endothelial cells, causing systemic vasodilation and an increase in diuresis and consequently loss of volume (27). Increased urine production was seen in all four native animals after approximately 4.5 hours (data not shown) following pMCS device deployment, demanding increased volume substitution.

Secondly, venous blood pooling: Left-sided pMCS devices have shown to increase venous return to the right ventricle (RV) (28). At the same time, acute unloading of the left ventricle is described to cause a septal shift altering RV shape and size, thereby affecting its contractility (29, 30). Reduced right ventricular cardiac output will cause venous blood pooling by redistribution of volume to the peripheral veins (31) leading to relative hypovolemia (32). The second hypothesis may explain the response to noradrenaline, as noradrenaline is known to increase mean systemic pressure by restoring venous vascular tone and to improve contractility of the heart (33) by stimulation of adrenergic receptors. Although the continuation of the device test under noradrenaline initially seemed possible,



**Figure 2.** (a) Continuous measurement of mean arterial blood pressure (ABP) in the carotid and the femoral artery of the native ( $n=4$ ) and the stented group ( $n=4$ ), (b) continuous measurement of heart rate (HR) in the native ( $n=4$ ) and stented group ( $n=4$ ) and (c) continuous measurement of the central venous pressure (CVP) in the native ( $n=4$ ) and stented group ( $n=4$ ).

S: stent placement; P: pump start; DC: decoupling period; A1: animal 1; A2: animal 2; A3: animal 3; A4: animal 4.

successful pMCS device performance testing was further hampered by the rapid reduction in response to continued noradrenaline administration caused by receptor desensitization and down-regulation.<sup>33</sup>

In humans an age-dependent increase in arterial wall stiffness has been described in both healthy and diseased populations.<sup>34</sup> Patients intended to profit from pMCS devices are commonly of advanced age, presenting with acute decompensated heart failure and often a variety of comorbid diseases such as diabetes, anaemia, peripheral vascular disease and renal dysfunction.<sup>35,36</sup> These comorbidities in conjunction with an increase of aortic wall stiffness increases the prevalence of systolic hypertension in these patients<sup>34</sup> and in turn may render the occurring issues in the healthy sheep model irrelevant for the clinical setting. The scientific significance of testing pMCS devices in healthy adult sheep, as presented in this study, is therefore currently limited to the demonstration of device safety, reliability and biocompatibility only.<sup>12</sup> Placing an intravascular stent in the descending thoracic aorta at the pMCS deployment site, somewhat mimicking aortic wall stiffness in patients, successfully eliminated device malfunction due to mechanical constriction and allowed for an uninterrupted device performance testing over 30 hours.

In conclusion, we find the described sheep model to be a suitable animal model for pMCS device testing in regards of device safety, reliability and biocompatibility. There is of course a consensus in the field, that clinical effectiveness is critical in the development of novel pMCS devices and thus relevant large animal heart failure models are required. However, traditional heart failure models, such as models of ischaemia, volume- or pressure overload or rapid pacing models, are known to lack reproducibility due to high mortality rates and inconsistent manifestations of heart failure. A novel refined closed chest sheep model of cardiogenic shock recently described by Rienzo et al.<sup>37</sup> not only attenuates the shortcomings of previously described large animal heart failure models but reducing the invasiveness of intervention over all. We are convinced that, by complementing our model with a reliable heart failure model in the future will allow us to use the adult sheep not only for device safety testing but also for pre-clinical efficacy and effectiveness studies of novel pMCS devices.

Pre-selection of sheep by trans-thoracic aortic annulus diameter assessment is highly recommended. We believe it allows for a sufficient conclusion regarding the mid-thoracic descending aortic diameter, thus avoiding undersizing or extreme oversizing of the stent. Both scenarios will hamper the success of the preclinical study, consequently leading to an increased number of study animals needed. As public concern about animal welfare in biomedical research rises it remains our ethical, legal and scientific obligation to plan and carry out studies in accordance with the 3R principles.<sup>38</sup>

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## Author contributions

MW: Study coordination, ethics approval, animal selection, preparation and monitoring of animals, conducting experiments, data analysis, writing of manuscript. MK: Animal selection, preparation and monitoring of animals, conducting experiments, critical revision of manuscript. TG: Study concept/design, data collection/ analysis/interpretation, critical revision of manuscript. TW: Conducting experiments, study concept/design, data analysis/interpretation, critical revision of manuscript. NC: Project acquisition, Animal model concept/design, animal selection, critical revision of manuscript.

## Declaration of conflicting interests

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