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ORIGINAL ARTICLE

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Hemodynamic evaluation of anesthetized baboons and piglets by transpulmonary thermodilution: Normal values and interspecies differences with respect to xenotransplantation

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Abstract

Background: Transpulmonary thermodilution is well established as a tool for in-depth hemodynamic monitoring of critically ill patients during surgical procedures and intensive care. It permits easy assessment of graft function following cardiac transplantation and guides post-operative volume and catecholamine therapy. Since no pulmonary catheter is needed, transpulmonary thermodilution could be useful in experimental cardiac pig-to-baboon xenotransplantation. However, normal values for healthy animals have not yet been reported. Here, we present data from piglets and baboons before xenotransplantation experiments and highlight differences between the two species and human reference values.

Methods: Transpulmonary thermodilution from baboons (body weight 10-34 kg) and piglets (body weight 10-38kg) were analyzed. Measurements were taken in steady state after induction of general anesthesia before surgical procedures commenced. Cardiac index (CI), mean arterial pressure (MAP), systemic vascular resistance index (SVRI), parameters quantifying cardiac filling (global end-diastolic volume index, GEDI), and pulmonary edema (extravascular lung water, ELWI) were assessed.

Results: Preload, afterload, and contractility parameters clearly correlated with total body weight or body surface area. Baboons had lower CI values than weight-matched piglets (4.2 ± 0.9l/min/m^2 vs 5.3 ± 1.0/min/m^2, $P < .01$). MAP and SVRI were higher in baboons than piglets (MAP: 99 ± 22 mm Hg vs 62 ± 11 mm Hg, $P < .01$; SVRI: 1823 ± 581 dyn*s/cm^{5}*m^2 vs 827 ± 204 dyn*s/cm^{5}*m^2, $P < .01$). GEDI and ELWI did differ significantly between both species, but measurements were within similar ranges (GEDI: 523 ± 103 mL/m^2 vs 433 ± 78 mL/m^2, $P < .01$; ELWI: 10 ± 3 mL/kg vs 11 ± 2 mL/kg, $P < .01$). Regarding adult human reference values, CI was similar to both baboons and piglets, but all other parameters were different.

Andreas Bauer and Jan-Michael Abicht equally contributed to this work.

Conclusions: Parameters of preload, afterload, and contractility differ between baboons and piglets. In particular, baboons have a much higher afterload than piglets, which might be instrumental in causing perioperative xenograft dysfunction and post-operative myocardial hypertrophy after orthotopic pig-to-baboon cardiac xenotransplantation. Most transpulmonary thermodilution-derived parameters obtained from healthy piglets and baboons lie outside the reference ranges for humans, so human normal values should not be used to guide treatment in those animals. Our data provide reference values as a basis for developing algorithms for perioperative hemodynamic management in pig-to-baboon cardiac xenotransplantation.

KEYWORDS

baboon, cardiac transplantation, hemodynamic monitoring, perioperative management, reference range, transpulmonary thermodilution, xenotransplantation

1 | INTRODUCTION

Minimally invasive hemodynamic monitoring has become the standard procedure for critically ill patients undergoing surgery or requiring intensive care. Pulmonary artery catheterization for thermodilution measurement of cardiac output (CO) is still considered the gold standard, but its use has been declining in recent years.[1] Less invasive methods of transpulmonary thermodilution (TPTD), such as the PiCCO system (Pulsion Medical Systems SE), have become an important alternative, especially for children where the use of Swan Ganz catheters is limited by vessel size.[2] CO measured by TPDT has repeatedly been shown to correlate well with CO measured by pulmonary artery catheter in animal experiments, as well as clinical settings in cardiac surgery, acute lung failure, intensive care, transplantation surgery, and pediatrics.[3]

For TPTD, a central venous access and a catheter placed in the femoral artery are required. Arterial blood pressure is monitored continuously via a pressure transducer. After initiating a hemodynamic measurement with a central venous injection of cold saline solution, the thermistor at the tip of the arterial catheter measures the blood temperature change over time. Cardiac output (CO) is measured based on a modified Stewart-Hamilton algorithm.[4,5] Stroke volume (SV) and systemic vascular resistance (SVR) are calculated once heart rate (HR) and the systemic arterial pressure are obtained. Additional hemodynamic parameters are derived from the mean transit time and the exponential downslope time of the thermodilution curve. Global end-diastolic volume (GEDV) describes cardiac preload, and extravascular lung water (EVLW) quantifies pulmonary edema. To enable better comparison between individuals of different size, indexing to body surface area (BSA) is performed for parameters of cardiac output (CI, cardiac index; SVI stroke volume index), volumetric preload (GEDI), and afterload (SVRI); EVLW is indexed to total body weight (TBW). A combined interpretation of these indexed parameters allows a detailed assessment of preload, afterload, contractility, and volume status of critically ill patients, which are pre-requisites for goal-directed volume and catecholamine therapy. The reader is referred to two excellent reviews for further details of clinical and technical aspects of this topic.[6,7]

In xenotransplantation, TPTD has been used to assess CO during pig-to-primate kidney[8] and heart transplantation.[9-11] As for human allotransplantation, comprehensive hemodynamic monitoring and careful therapeutic management are key to a favorable outcome after cardiac xenotransplantation. However, little is known about the normal values in baboons and piglets of the sizes used for these experiments. To our knowledge, no reference tables are as yet available.

2 | METHODS

2.1 | Animals

Hemodynamic data sets from pigs and baboons obtained between August 2006 and October 2018 were analyzed. All baboons were captive-bred (*Papio anubis* and *Papio hamadryas*, n = 47, age 3-11 years, body weight 10-34kg; German Primate Center DPZ, Göttingen, Germany). The piglets were juveniles of the breeds large white/landrace and were "wild type" with no genetic modifications (*Sus scrofa*, n = 45, age approximately 1-4 months, body weight 10-38kg; Institute for Molecular Animal Breeding and Biotechnology, Gene Center, Faculty of Veterinary Medicine, Ludwig-Maximilians-University). The perfusion and xenotransplantation studies of which these animals were a part were carried out according to the European Law on Protection of Animals for Scientific Purposes and were approved by the Government of Upper Bavaria, Germany. Care of the animals was in accordance with the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, 1985) and the German Law for the Care of Experimental Animals (German Legislation for the Welfare of Laboratory Animals, article 5, §7-§9a, revised 2006).

2.2 | Anesthesia

All animals were fasted for 12 hours prior to anesthesia. General anesthesia of both baboons and pigs was induced with intravenous bolus administrations of propofol and fentanyl. Anesthesia was maintained with either continuous infusions of propofol (0.1-0.2 mg/kg/min; baboons and pigs) or inhalation of isoflurane (0.8-1.2 vol%) and sevoflurane (1-2 vol% end-expiratory concentration) for baboons only. Analgesia was maintained with repetitive bolus administrations of fentanyl (2.5-8 μg/kg every 30-45 minutes). After endotracheal intubation, the animals were ventilated mechanically. During anesthesia, ventilation was adjusted to end-tidal CO_2 as necessary, and ECG, blood pressure, and peripheral oxygen saturation were monitored.

2.3 | Invasive hemodynamic monitoring and measurements

For hemodynamic measurements, a central venous catheter was placed in the jugular vein (4Fr, 5.5Fr or 7Fr single/multi-lumen central venous catheter; Arrow International, Reading, PA, USA) and a 3 or 4Fr arterial catheter (Thermodilution Pulsiocath; Pulsion Medical Systems) inserted in either the contralateral carotid artery (pig) or the right femoral artery (baboon).

Hemodynamic evaluation was performed after completion of venous and arterial cannulations after restoring normovolemia during steady state. A minimum of three transpulmonary thermodilution measurements was taken with 5 or 10 mL iced sodium chloride 0.9% injections depending on body weight, in accordance with the manufacturer's recommendations. Data were recorded with PiCCOWin 6.0 software (Pulsion Medical Systems). For the modified hemodynamic treatment algorithm, 2.5% percentiles (CI, GEDI) and 97.5% percentile (ELWI) from the baboon group were used as cutoff values. Calculation of parameters derived from TPDT is presented in Table 1.

2.4 | Offline analysis and statistics

Recorded data were visualized with PiCCOWin 6.0 software. Low-quality measurements were excluded depending on the thermodilution curve, according to clinical standards. Data were then processed with Excel (Microsoft). To normalize the absolute values to body surface area (BSA), the formulas $0.0734 \times TBW^{0.656}$ (pigs), $0.078 \times TBW^{0.664}$ (female baboons), or $0.083 \times TBW^{0.639}$ (male baboons) were used, where TBW is total body weight in kg.[12,13] Data analysis was performed with GraphPad Prism 7.0 (GraphPad Software Inc). Where applicable, human reference values are presented for comparison.[14,15] Data are presented as mean ± standard deviation, median, and 95% interval. Hemodynamic measurements from pigs and baboons were compared using the Mann-Whitney rank sum test. Exact p-values are given for each test; for correlations, Pearson's r is indicated. Statistical significance was assumed when $P < .05$.

TABLE 1 Parameters assessed by transpulmonary thermodilution

Definitions		Calculation
CO	Cardiac output	$[(T_b - T_i) \times V_i \times K]/AUC$
SV	Stroke volume	CO/HR
SVR	Systemic vascular resistance	[(MAP − CVP)/CO] × 80
ITTV	Intrathoracic thermal volume	CO × MTt
PTV	Pulmonary thermal volume	CO × DSt
GEDV	Global end-diastolic volume	ITTV-PTV
ITBV	Intrathoracic blood volume	1.25 × GEDV
EVLW	Extravascular lung water	ITTV-ITBV

Note: The following parameters were measured directly: T_b, blood temperature; T_i, injectate temperature; V_i, injectate volume; AUC, area under the thermodilution curve; HR, heart rate; MTt, mean transit time; DSt, exponential downslope time; MAP, mean arterial pressure; CVP, central venous pressure; K, correction constant (comprises specific weight and specific heat of blood and injectate fluid).

3 | RESULTS

Results from hemodynamic monitoring and TPTD measurements are summarized in Tables 2 and 3. Measurements from 47 baboons and 45 pigs were analyzed. Mean body weights of the two groups were 19.1 ± 5.2 kg and 17.3 ± 4.8 kg ($P = .0601$).

3.1 | Correlation of absolute parameters with body weight and body surface area

Figure 1 shows parameters of cardiac output (A, CO), afterload (B, SVR) and preload (C, GEDV), and pulmonary edema (D, EVLW), correlated with BSA or TBW, respectively. The overall correlation was significant; the correlation coefficient was higher in measurements from piglets compared with those from baboons (Pearson r as indicated in Figure 1; $P < .01$). SVR had a negative correlation coefficient ($r = -0.4435$ and $r = -0.5858$; $P < .01$), indicating decreasing resistances with increasing BSA.

3.2 | Hemodynamic monitoring

Table 2 shows the results from hemodynamic monitoring. MAP was 60% higher in baboons than piglets (Figure 2). Systolic (SAP, 49%) and diastolic arterial pressures (DAP, 68%) were also higher in baboons. Baboons had a 14% slower heart rate than pigs. Central venous pressure (CVP) was not significantly different between the two species.

3.3 | Transpulmonary thermodilution measurements

CI was 20% lower in baboons than pigs (Table 3, Figure 2). Since SVI was similar in both species, the increased CI must be due to an

TABLE 2 Results of hemodynamic monitoring in baboons (n = 47) and piglets (n = 45), presented as mean ± SD, median and 95% interval

	Baboon				Piglets			Human
	Mean ± SD	Median	95% interval	*P*	Mean ± SD	Median	95% interval	Reference
SAP (mm Hg)	124 ± 24	125	77-167	<.0001	83 ± 11	81	64-107	<120
DAP (mm Hg)	79 ± 20	84	43-113	<.0001	47 ± 12	44	30-78	<80
MAP (mm Hg)	99 ± 22	102	62-136	<.0001	62 ± 11	59	42-93	70-90
HR (bpm)	93 ± 13	92	71-126	.0006	108 ± 22	107	64-164	50-100
CVP (mm Hg)	8 ± 5	5	1-17	.2938	6 ± 3	6	1-15	2-6

Note: Statistical differences tested with the Mann-Whitney rank sum test ($P < .05$). Adult human reference ranges are shown for comparison.[14,15] SAP, systolic blood pressure; DAP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

TABLE 3 Indexed parameters derived from transpulmonary thermodilution measurements in baboons (n = 47) and piglets (n = 45), presented as mean ± SD, median and 95% interval

	Baboon				Piglets			Human
	Mean ± SD	Median	95% interval	*P*	Mean ± SD	Median	95% interval	Reference
CI (l/min/m^2)	4.2 ± 0.9	4.2	2.5-6.1	<.0001	5.3 ± 1.0	5.3	3.7-7.1	3.0-5.0
SVI (mL/m^2)	47 ± 15	44	24-93	.0674	51 ± 11	50	28-77	40-60
SVRI (dyn*s/cm^5*m^2)	1823 ± 581	1873	766-2986	<.0001	827 ± 204	805	372-1205	1700-2400
GEDI (mL/m^2)	523 ± 103	519	340-776	<.0001	433 ± 78	430	314-705	680-800
ELWI (mL/kg)	10 ± 3	9	5-15	.001	11 ± 2	11	8-18	3-7

Note: Statistical differences tested with the Mann-Whitney rank sum test ($P < .05$). Adult human reference ranges are shown for comparison.[14] CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; GEDI, global end-diastolic volume index; ELWI, extravascular lung water index.

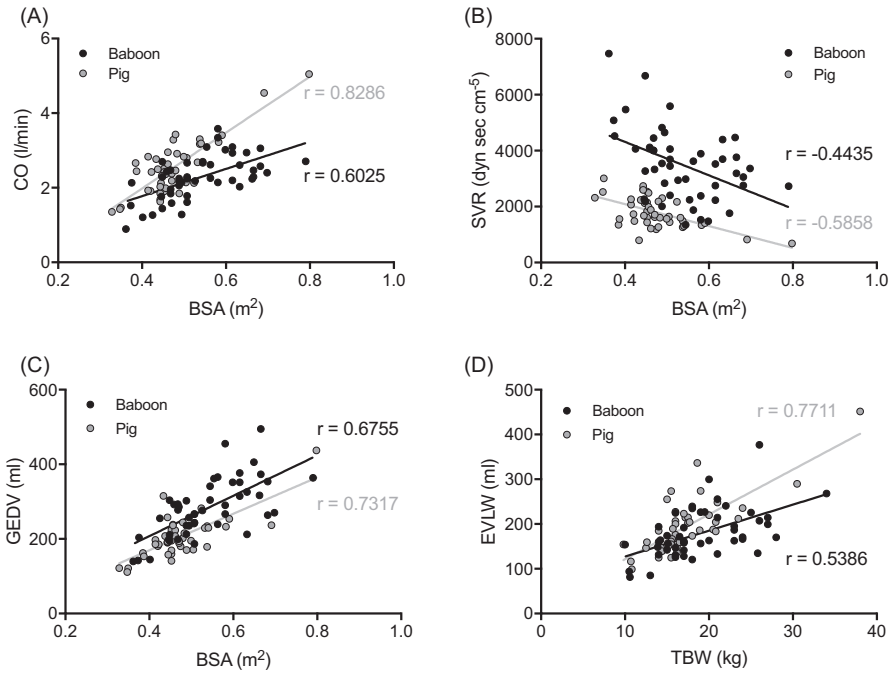

FIGURE 1 Correlations between body surface area (BSA) or total body weight (TBW) and parameters of transpulmonary thermodilution: A, cardiac output (CO); B, systemic vascular resistance (SVR); C, global end-diastolic volume (GEDV); D, extravascular lung volume (EVLW). Pearson r as indicated; $P < .01$

increased heart rate in piglets. SVRI was 120% higher in baboons than in pigs. The volumetric parameter of cardiac preload GEDI was 21% higher in baboons than pigs, whereas the extravascular lung water index (ELWI) was 15% lower.

3.4 | Comparison with human reference values

With the exception of CI and SVI (Table 2, Figure 3A), adult human reference values differed in all other parameters from the

measurements taken from baboons and piglets. MAP and HR of baboons were higher than human reference ranges (Table 2). In comparison, piglets had lower MAP and higher HR. SVRI measured in baboons was within the human reference range, but SVRI in piglets was approximately half that in humans and well below the reference range (Table 2, Figure 3B). The volumetric preload parameter GEDI was lower in both pigs and baboons than in humans (Table 3, Figure 3C), whereas the parameter of pulmonary edema (ELWI) was above human references values (Figure 3D).

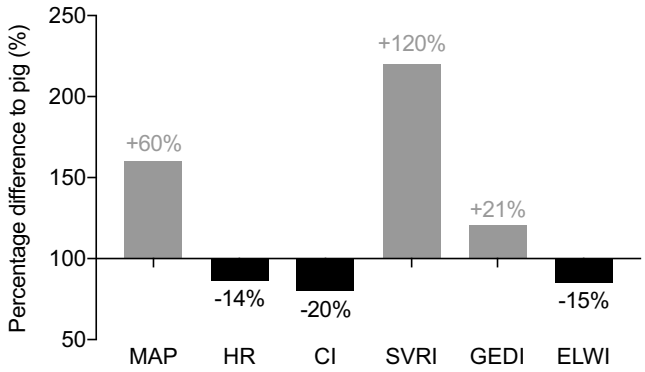

FIGURE 2 Percentage difference of hemodynamic and TPTD parameters of baboons with respect to piglets. Pig parameters are set to 100%. Mean arterial pressure (MAP), cardiac preload, and afterload (GEDI, SVRI) are higher in baboons than pigs, heart rate (HR), cardiac index (CI), and extravascular lung water index (ELWI) are lower. GEDI, global end-diastolic volume index; SVRI, systemic vascular resistance index

4 | DISCUSSION

4.1 | Cardiac output and afterload

Our study has revealed significant differences in the hemodynamic parameters of cardiac output and afterload of normovolemic, anesthetized, weight-matched baboons, and piglets. Cardiac output measurements from baboons and pigs correspond well to those from previous reports.[16-21] Differences in blood pressures have been described by authors working with juvenile pigs[19-22] and baboons.[16-18] Older studies also confirm the twofold difference in systemic vascular resistance between baboons[17,23,24] and pigs[19-22,25] with body sizes similar to the animals we examined.

Discussion of pigs as organ donors for humans has mainly focused on adult donors and recipients.[26,27] Full-grown pigs have cardiac output and arterial blood pressure values comparable to, or even higher than, adult humans.[26-28] Systemic vascular resistance—as well as pulmonary vascular resistance—in adult pigs has been reported as twice that in humans, supposedly giving the transplanted pig heart an advantage in pumping against lower resistance.[26,27]

In contrast, transplanting a juvenile porcine heart accustomed to low vascular resistance into an adolescent baboon with twice the resistance challenges the pig heart's ability to adapt to higher afterload. For most xenotransplantation experiments, clinically approved ischemic preservation is used for organ storage. In 40%-60% of these experiments, the grafts fail within 48 hours due to perioperative xenograft dysfunction (PCXD).[29] We hypothesize that ischemia/reperfusion injury caused by ischemic storage impairs the

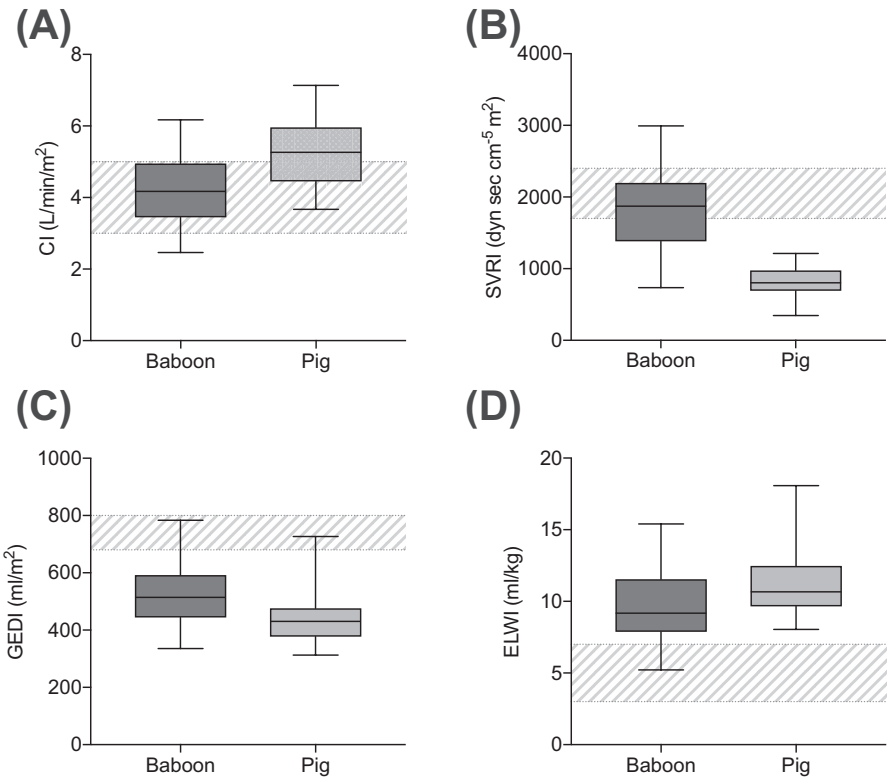

FIGURE 3 Transpulmonary thermodilution measurements in baboons and pigs and comparison with human reference ranges: A, cardiac index (CI); B, systemic vascular resistance index (SVRI); C, global end-diastolic volume index (GEDI); D, extravascular lung volume index (ELWI). Data are presented as box and whisker plots indicating mean, interquartile range, and minimum to maximum, striped areas represent adult human reference ranges[14]

ability of the pig heart to cope with increased systemic afterload, similar to acute right ventricular failure due to pulmonary hypertension in human allotransplantation. This could explain why PCXD is potentially reversible with time (recovery from ischemia/reperfusion injury)[29] and why PCXD does not occur when the porcine grafts are preserved by continuous non-ischemic organ perfusion (prevention of ischemia/reperfusion injury).[9]

Moreover, chronically elevated afterload triggers pressure overload-induced cardiac hypertrophy in humans patients.[30] When compensatory mechanisms fail, concentric myocardial hypertrophy eventually leads to diastolic pump failure. Recently, we observed a similar phenomenon in baboons that had undergone orthotopic xenotransplantation of porcine hearts.[9] Diastolic pump failure was prevented with a combination of anti-hypertensive and anti-proliferative treatments, indicating that chronically elevated afterload might, at least in part, explain excessive graft growth after cardiac xenotransplantation.

4.2 | Cardiac preload and extravascular lung water

For many years, perioperative volume therapy has been guided by central venous (CVP) and pulmonary artery occlusion pressures. However, these parameters do not accurately reflect cardiac preload.[31] TPTD provides the volumetric parameter global end-diastolic volume index (GEDI), which represents the sum of end-diastolic volumes of all four heart chambers. GEDI has been shown to be superior to filling pressures for guiding cardiac preload.[7] TPDT also provides the parameter ELWI, which reflects the fluid that is contained within the perfused regions of the lungs.[7] Elevated ELWI is typically found in pulmonary edema[6] and has been used as a therapeutic guide after cardiac surgery.[32]

To allow proper fluid management in xenotransplantation experiments, normal values are required for donor and recipient animals. The results from our baboon and piglet groups indicate that their normal GEDI values are much lower than reference values for adult human patients (680-800 mL/m^2). In contrast, ELWI is higher in both baboons and infant pigs than in adult humans (3-7 mL/kg). Low GEDI and high ELWI values have also been reported for other animals and human infants: In pediatric patients (n = 101 children, age 0-18 years), median GEDI was between 366 and 479 mL/m^2 and median ELWI between 10 and 12 mL/kg.[33-35] In Maryland minipigs (n = 38, 8-16 kg), López-Herce et al observed mean values of 198 mL/m^2 for GEDI and 16 mL/kg for ELWI, respectively.[36] ELWI values determined by gravimetry in newborn healthy lambs were more than twice as high as in adult sheep (13.3 vs 6.1 mL/kg).[37]

Lemson et al proposed that the lower GEDI values and higher ELWI values in younger children were a result of age-related changes in the ratio of lung weight to body weight and in the ratio of heart weight to BSA.[38] The greater lung weight in infants has consequences for calculating the (non-indexed) EVLW, for which the intrathoracic blood volume (ITBV) is needed. Historically, intrathoracic volumes were measured using the transpulmonary double-indicator (thermo-dye) dilution technique with two different indicators (cold and indocyanine green). Sakka et al empirically found ITBV, the sum of GEDV and pulmonary blood volume, to be ~1.25 × GEDV.[39] This linear relationship was incorporated into the single indicator methodology for TPTD. In children, this multiplier varies from 1.5 in the newborns to 1.2 in adults.[33] Therefore, application of the adult formula underestimates ITBV and overestimates EVLW. Similar to human infants, Rossi et al found ITBV to be 1.52 × GEDV + 49.7 (mL) for landrace piglets (24-32 kg), thus greatly improving the accuracy of estimating EVLW.[40] For baboons, the exact relationship is unknown.

These findings emphasize that human reference values of TPTD parameters for volumetric preload and lung water are age- and species-dependent and cannot be simply adopted in pig-to-baboon xenotransplantation. The normal values provided by this study may serve as a reference for both baboons and pigs, but we caution that comparisons should be restricted to animals of the same species and similar age and body size.

4.3 | TPTD parameters in xenotransplantation—modified hemodynamic decision model

TPTD provides data on many hemodynamic parameters. These require thoughtful interpretation and can be overwhelming for researchers unfamiliar with the method. To facilitate the use of TPTD for pig-to-baboon xenotransplantation experiments, we modified the manufacturer's hemodynamic treatment algorithm (PiCCO, Pulsion Medical Systems) with easily memorable values according to results from the baboon group. Figure 4 represents a simple theoretical decision model for a goal-directed therapy.

CI is the most important global parameter of circulatory function. Circulatory failure, indicated by a severe decrease in CI, results in insufficient peripheral oxygen delivery and must be treated promptly (Figure 4A). Treatment options are mainly volume therapy and catecholamines/vasoactive drugs.

- Low preload (GEDI < 350 mL/m^2) indicates decompensated hypovolemia and must be primarily treated with volume (crystalloid/colloid infusions, blood products in case of bleeding).
- Low preload and signs of pulmonary edema (ELWI > 15 mL/kg) are typical for inflammatory pulmonary disease with septic shock and not common in xenotransplantation experiments. Volume therapy should be applied cautiously and accompanied by catecholamine therapy.
- Low CI in the context of adequate preload (GEDI > 350 mL/m^2) after cardiac transplantation indicates left ventricular insufficiency and the need for catecholamine support (noradrenaline/adrenaline).
- Adequate preload and pulmonary edema (ELWI > 15 mL/kg) are signs of volume overload in severe left ventricular failure and must be treated with inotropic support and volume withdrawal (diuretics).

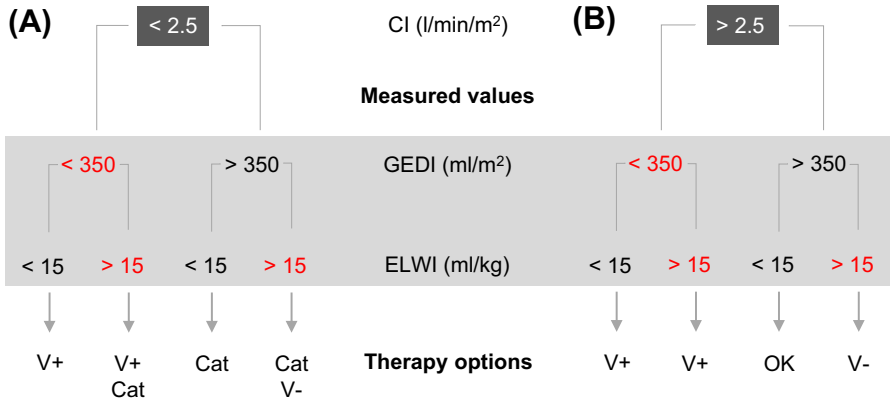

FIGURE 4 Hemodynamic decision model for cardiac pig-to-baboon xenotransplantation based on the manufacturer's recommendations for human adults (PiCCO, Pulsion Medical Systems), modified with normal values obtained from anesthetized baboons. See text for detailed explanations. CI, cardiac index; GEDI, global end-diastolic volume index; ELWI, extravascular lung water index; V+, volume loading; V−, volume withdrawal; Cat, catecholamines or vasoactive agents

Normal CI indicates a compensated circulatory function and does not usually require immediate therapeutic intervention. However, TPTD can help fine-tune or maintain an adequate drug therapy (Figure 4B).

- Low preload (GEDI < 350 mL/m^2) indicates compensated hypovolemia and must be primarily treated with volume (crystalloid/colloid infusions, blood products in the case of bleeding).
- Low preload and signs of pulmonary edema (ELWI > 15 mL/kg) are typical for inflammatory pulmonary disease and not common in xenotransplantation experiments. Volume therapy should be applied cautiously.
- Adequate preload (GEDI > 350 mL/m^2) and low ELWI are the aims of goal-directed therapy. Current volume and catecholamine therapy can be maintained.
- Adequate preload and pulmonary edema (ELWI > 15 mL/kg) are signs of compensated left ventricular insufficiency and should be treated with volume withdrawal.

TPDT measurements should be repeated regularly, especially after treatment changes or when hemodynamic parameters suddenly deteriorate. Circulatory insufficiency (CI < 2.5l/min/m^2) should always lead to a search for possible causes. TPDT can identify circulatory impairment and helps with therapeutic decision-making but cannot substitute for thorough investigation such as echocardiographic imaging. As for all hemodynamic monitoring, it is advisable to interpret absolute values with caution. This is especially so for ELWI, the calculation of which is based on a constant derived from adult human patients and cannot be directly translated to other species. Also, perioperative TPTD parameters should be compared with baseline measurements. A steady deterioration of one parameter, even if still within the reference range, usually indicates the need for intervention.

4.4 | Limitations

All measurements were taken under general anesthesia prior to surgical intervention. Anesthetics and analgesics, mainly propofol, iso/sevoflurane, and fentanyl, have various degrees of vasodilatory, negative inotropic, and negative chronotropic effects. As such, our findings do only apply to laboratory animals under general anesthesia and differ from alert animals. However, hemodynamic monitoring with TPTD is most useful during and shortly after surgery, when the animal is still anesthetized. Subsequent monitoring would be most desirable, but it is not feasible to have an intraarterial catheter in an awake animal.

Our study includes data from several experimental study protocols with different personnel performing anesthesia and surgery. Different anesthesia protocols seem to have only negligible effects on hemodynamic parameters. Bauer et al demonstrated that intravenous and inhalational anesthetics provide equal hemodynamic stability before surgery.[41] Although the choice and dosage of anesthetic (intravenous vs inhalational) did differ, pooling data from different study groups should provide reliable normal values.

Finally, we measured normal values for piglets in wild-type animals, while xenotransplantation experiments generally use genetically modified animals. In our experience, the typical genetic modifications (α1,3-galactosyltransferase knockout, human CD46, and human thrombomodulin) have no influence on hemodynamic parameters. Because of the scarcity of transgenic animals and their value for xenotransplantation experiments, we performed TPDT measurements in only a few animals with different genetic modifications (n = 8, data not shown). These revealed no significant differences as compared to wild-type animals, other than a slightly higher mean ELWI. All measurements were within the 95% interval presented in this study.

5 | SUMMARY

In summary, we present normal values for TPTD measurements in anesthetized baboons and piglets used for xenotransplantation experiments. There are important differences between these

animals with regard to systemic arterial pressure and vascular resistance, the latter being twice as high in baboons as in juvenile pigs. Elevated cardiac afterload may in part explain two phenomena that have been observed in the orthotopic pig-to-baboon cardiac xenotransplantation model: perioperative xenograft dysfunction and post-operative cardiac overgrowth. TPDT is a powerful tool to guide hemodynamic treatment after surgery, but human reference values and algorithms provided by the manufacturer should not be applied. For the purpose of pig-to-baboon cardiac xenotransplantation, we have modified the algorithm for a perioperative goal-directed therapy guideline.

DISCLOSURE

Mark Konrad is Head of Medical of Pulsion Medical Systems, Getinge.

AUTHOR CONTRIBUTIONS

Matthias Längin, Mark Konrad, Andreas Bauer, and Jan-Michael Abicht contributed to concept design, conducted experiments, data collection, data analysis, and drafted the article. Tanja Mayr, Stephanie Vandewiele, Johannes Postrach, Maren Mokelke, Julia Radan, and Paolo Brenner conducted experiments and data collection, contributed to data analysis, and approved the final draft. Bruno Reichart secured fundings, conducted experiments, and critically revised the article.

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REFERENCES

1. Rubenfeld GD, McNamara-Aslin E, Rubinson L. The pulmonary artery catheter, 1967–2007: rest in peace? *JAMA*. 2007;298:458-461.
2. Skowno JJ, Broadhead M. Cardiac output measurement in pediatric anesthesia. *Paediatr Anaesth*. 2008;18:1019-1028.
3. Reuter DA, Huang C, Edrich T, Shernan SK, Eltzschig HK. Cardiac Output monitoring using indicator-dilution techniques: basics, limits, and perspectives. *Anesth Analg*. 2010;110:799-811.
4. Stewart GN. Researches on the circulation time and on the Influences which affect it. *J Physiol (Lond)*. 1897;22:159-183.
5. Hamilton WF, Moore JW, Kinsman JM, Spurling RG IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Studies on the Circulation. *Am J Physiol* 1931;99:534-551.
6. Laight NS, Levin AI. Transcardiopulmonary thermodilution-calibrated arterial waveform analysis - a primer for anesthesiologists and intensivists. *J Cardiothorac Vasc Anesth*. 2015;29:1051-1064.
7. Sakka SG, Reuter DA, Perel A. The transpulmonary thermodilution technique. *J Clin Monit Comput*. 2012;26:347-353.
8. Przemeck M, Loss M, Vangerow B, et al. Perioperative monitoring of cardiac function during discordant pig-to-primate kidney xenotransplantation using transpulmonary thermodilution. *Transplant Proc*. 2000;32:1086.
9. Längin M, Mayr T, Reichart B, et al. Consistent success in life-supporting porcine cardiac xenotransplantation. *Nature*. 2018;564:430-433.
10. Mayr T, Bauer A, Reichart B, et al. Hemodynamic and perioperative management in two different preclinical pig-to-baboon cardiac xenotransplantation models. *Xenotransplantation*. 2017;24(3):e12295.
11. Bauer A, Baschnegger H, Abicht JM, et al. hDAF porcine cardiac xenograft maintains cardiac output after orthotopic transplantation into baboon–a perioperative study. *Xenotransplantation*. 2005;12:444-449.
12. VandeBerg J, Williams-Blangero S, Tarif S, eds. *The baboon in biomedical research*. New York, NY: Springer; 2009.
13. Swindle MM, Makin A, Herron AJ, Clubb FJ Jr, Frazier KS. Swine as models in biomedical research and toxicology testing. *Vet Pathol*. 2011;49:344-356.
14. Pulsion Medical Systems SE *PiCCO Technology*. Getinge, 2018.
15. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021-3104.
16. Zarins CK, Virgilio RW, Smith DE, Peters RM. The effect of vascular volume on positive end-expiratory pressure-induced cardiac output depression and wedge-left atrial pressure discrepancy. *J Surg Res*. 1977;23:348-360.
17. Rosen AL, Gould S, Sehgal LR, et al. Cardiac output response to extreme hemodilution with hemoglobin solutions of various P50 values. *Crit Care Med*. 1979;7:380-384.
18. Rogers GG, Rosendorff C, Shimell CJ, Coull A, Bomzon L. Effect of peroral administration of sotalol on the hemodynamics of the baboon. *J Cardiovasc Pharmacol*. 1982;4:197-204.
19. Salomão E, Otsuki DA, Correa AL, et al. Heart rate variability analysis in an experimental model of hemorrhagic shock and resuscitation in pigs. *PLoS ONE*. 2015;10:e0134387.
20. Bail DHL, Steger V, Heinzelmann U, et al. Administration of brain natriuretic peptide improves cardiac function following operations using extracorporeal circulation in an animal model. *Clin Sci*. 2007;112:315-324.
21. Jormalainen M, Vento AE, Wartiovaara-Kautto U, et al. Recombinant hirudin enhances cardiac output and decreases systemic vascular resistance during reperfusion after cardiopulmonary bypass in a porcine model. *J Thorac Cardiovasc Surg*. 2004;128:189-196.
22. Pfeiffer N, Ebner J, Thaden von, et al. Evaluation of acute cardiovascular effects of propofol on hemodynamic function in pigs. *OAAP*. 2012;4:9-19.
23. Bredenberg CE, Nomoto S, Webb WR. Pulmonary and systemic hemodynamics during hemorrhagic shock in baboons. *Ann Surg*. 1980;192:86-94.
24. Van Aken H, Fitch W, Graham DI, Brüssel T, Themann H. Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon. *Anesth Analg*. 1986;65:565-574.
25. Kates RA, Zaggy AP, Norfleet EA, Heath KR. Comparative cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia in swine. *Anesthes*. 1984;61:10-18.
26. Ibrahim Z, Busch J, Awwad M, et al. Selected physiologic compatibilities and incompatibilities between human and porcine organ systems. *Xenotransplantation*. 2006;13:488-499.
27. Thein E, Hammer C. Physiologic barriers to xenotransplantation. *Curr Opin Organ Transplant*. 2004;9:186-189.
28. Essen GJ, Hekkert ML, Sorop O, et al. Cardiovascular function of modern pigs does not comply with allometric scaling laws. *Sci Rep*. 2018;8:792.
29. Byrne GW, McGregor CGA. Cardiac xenotransplantation: progress and challenges. *Curr Opin Organ Transplant*. 2012;17:148-154.
30. Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. *Heart*. 2003;89:1104-1109.
31. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134:172-178.
32. Lenkin AI, Kirov MY, Kuzkov VV, et al. Comparison of goal-directed hemodynamic optimization using pulmonary artery catheter and

transpulmonary thermodilution in combined valve repair: a randomized clinical trial. *Crit Care Res Pract*. 2012;2012:821218.
33. Lemson J, Backx AP, van Oort AM, Bouw TPWJM, van der Hoeven JG. Extravascular lung water measurement using transpulmonary thermodilution in children. *Pediatr Crit Care Med*. 2009;10:227-233.
34. Nusmeier A, Cecchetti C, Blohm M, et al. Near-normal values of extravascular lung water in children. *Pediatr Crit Care Med*. 2015;16:e28-33.
35. Grindheim G, Eidet J, Bentsen G. Transpulmonary thermodilution (PiCCO) measurements in children without cardiopulmonary dysfunction: large interindividual variation and conflicting reference values. *Paediatr Anaesth*. 2016;26:418-424.
36. López-Herce J, Rupérez M, Sánchez C, García C, Garciá E. Estimation of the parameters of cardiac function and of blood volume by arterial thermodilution in an infant animal model. *Paediatr Anaesth*. 2006;16:635-640.
37. Brigham KL, Sundell H, Harris TR, et al. Lung water and vascular permeability in sheep. Newborns compared with adults. *Circ Res*. 1978;42:851-855.
38. Lemson J, Merkus P, van der Hoeven JG. Extravascular lung water index and global end-diastolic volume index should be corrected in children. *J Crit Care*. 2011;26:432.e7-432.e12.
39. Sakka SG, Rühl CC, Pfeiffer UJ, et al. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med*. 2000;26:180-187.
40. Rossi P, Wanecek M, Rudehill A, et al. Comparison of a single indicator and gravimetric technique for estimation of extravascular lung water in endotoxemic pigs. *Crit Care Med*. 2006;34:1437-1443.
41. Bauer A, Baschnegger H, Renz V, et al. Comparison of propofol and isoflurane anesthesia in orthotopic pig-to-baboon cardiac xenotransplantation. *Xenotransplantation*. 2007;14:249-254.

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