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Cardiovascular performance of adult breeding sows fails to obey allometric scaling laws[1]

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ABSTRACT: In view of the remarkable decrease of the relative heart weight (HW) and the relative blood volume in growing pigs, we investigated whether HW, cardiac output (CO), and stroke volume (SV) of modern growing pigs are proportional to BW, as predicted by allometric scaling laws: HW (or CO or SV) = a·BW^b, in which a and b are constants, and constant b is a multiple of 0.25 (quarter-power scaling law). Specifically, we tested the hypothesis that both HW and CO scale with BW to the power of 0.75 (HW or CO = a·$BW^{0.75}$) and SV scales with BW to the power of 1.00 (SV = a·$BW^{1.0}$). For this purpose, 2 groups of pigs (group 1, consisting of 157 pigs of 50 ± 1 kg; group 2, consisting of 45 pigs of 268 ± 18 kg) were surgically instrumented with a flow probe or a thermodilution dilution catheter, under open-chest anesthetized conditions to measure CO and SV, after which HW was determined. The 95% confidence intervals of power-coefficient b for HW were 0.74 to 0.80, encompassing the predicted value of 0.75, suggesting that HW increased proportionally with BW, as predicted by the allometric scaling laws. In contrast, the 95% confidence intervals of power-coefficient b for CO and SV as measured with flow probes were 0.40 to 0.56 and 0.39 to 0.61, respectively, and values obtained with the thermodilution technique were 0.34 to 0.53 and 0.40 to 0.62, respectively. Thus, the 95% confidence limits failed to encompass the predicted values of b for CO and SV of 0.75 and 1.0, respectively. In conclusion, although adult breeding sows display normal heart growth, cardiac performance appears to be disproportionately low for BW. This raises concern regarding the health status of adult breeding sows.

Key words: breeding sow, cardiovascular system, domestication, pig, scaling law

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INTRODUCTION

Domestication of pigs started about 9,000 yr ago and has resulted in marked differences in anatomy and physiology between domesticated pigs and their ancestor, the wild boar (Darwin, 1868; Hemmer, 1990; Jones, 1998; Giuffra et al., 2000). During the last century in particular, pig breeding has been dominated by selection based on meat quantity and other economic aspects, yielding remarkable increases in BW, muscularity, and litter size (Müller et al., 1999; Saunders and McLeod, 1999), which has inadvertently resulted in alterations of anatomy and physiology of the cardiovascular system of the domesticated pig, including reduced relative heart weight (**HW**), blood volume, and hemoglobin concentrations (von Engelhardt, 1966; Huisman, 1969; Schürmann, 1984). This process has raised concerns regarding cardiovascular capacity and adaptability of modern pigs to stress (von Engelhardt, 1966), and the increased risk of circulatory insufficiency might even contribute to edema disease and transport-associated health problems (Niewold et al., 2000).

In wild animals, HW and cardiac output (**CO**) have been shown to scale with BW to the power of 0.75, blood volume scales with BW to the power of 0.25, and stroke volume (**SV**) scales with BW to the power of

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1.00 (West et al., 1997; Yang and Lin, 1997; West and Brown, 2005). Recently, we tested the scaling hypothesis for CO and SV in growing domesticated pigs with BW ranging from 22 to 75 kg at rest and during strenuous exercise (van Essen et al., 2009) and found that, in domestic pigs with a BW that is within the range of their wild ancestors, CO and SV scaled to BW as predicted by the quarter scaling laws [null hypothesis (**H_0**): $CO = a \cdot BW^{0.75}$; and H_0: $SV = a \cdot BW^{1.0}$). Whether CO and SV scale proportionally with BW in pigs with BW of 200 to 350 kg has not been studied to date. This is important, because these heavy pigs appear more prone to health problems (Niewold et al., 2000).

Consequently, in the present study we investigated the proportionality of the cardiovascular system in pigs over a wide range of BW, including adult breeding sows with a BW of 3 to 4 times the average BW of an adult female wild boar. Specifically, we tested the hypothesis that HW and CO scale with BW to the power of 0.75 ($HW = a \cdot BW^{0.75}$ and $CO = a \cdot BW^{0.75}$) and SV scales with BW to the power of 1.00 ($SV = a \cdot BW^{1.0}$).

MATERIALS AND METHODS

All studies were performed in accordance with the Council of Europe Convention (ETS123)/ Directive (86/609/EEC) for the protection of vertebrate animals used for experimental and other scientific purposes, and with approval of the Animal Care Committees of the Erasmus University Medical Center Rotterdam (group 1) and the Animal Science Group of Wageningen University and Research Centre (ASG of WUR; group 2).

Experimental Groups

Studies were performed in 2 groups of pigs. Group 1 consisted of 157 growing Yorkshire × Landrace pigs of either sex (female or neutered male; age 2 to 6 mo; BW 23 to 97 kg) that were studied in Rotterdam. Group 2 consisted of 45 sows (TOPIGS; age 11 to 43 mo; BW 170 to 338 kg; parity 1 to 11) that were studied in Lelystad. The Rotterdam data were obtained as part of several ongoing studies of cardiovascular variables under general anesthesia (van Kats et al., 2000; van der Velden et al., 2004; Sorop et al., 2008; Duncker et al., 2009; te Lintel Hekkert et al., 2010). The Lelystad data were obtained from a group of pregnant sows delivering full-term piglets by a caesarean section under general anesthesia for the porcine specific-pathogen-free unit.

Pigs of group 1 arrived at Rotterdam 1 wk before surgery and were denied access to food starting 12 h before surgery. The pregnant sows of group 2 arrived at the Lelystad operation theater from different breeding farms in the early morning of the surgery day. They were kept until premedication without access to food in a pen in the preparation department of the surgery room.

Surgical Instrumentation and CO Measurements

Group 1. Pigs were sedated with ketamine [20 mg/kg, intramuscularly (**i.m.**)] and midazolam (0.5 mg/kg, i.m.), anesthetized with sodium pentobarbital [15 mg/kg, intravenously (**i.v.**)], and intubated for ventilation with O_2 and N_2 [1:2 (vol/vol); van der Velden et al., 2004; Sorop et al., 2008; Duncker et al., 2009; te Lintel Hekkert et al., 2010]. A catheter was inserted into a jugular vein and advanced into the superior caval vein for infusion of sodium pentobarbital (10 to 15 mg/kg per hour, i.v.) to maintain anesthesia. In 37 pigs, a Swan-Ganz thermodilution catheter (Corodyn, Braun, Melsungen, Germany) was inserted into a femoral vein, advanced into the pulmonary artery, and connected to a CO computer (Edwards Lifesciences, Irvine, CA) for measurement of CO (Sorop et al., 2008; Duncker et al., 2009). In 93 other pigs, the chest was opened via the sternum, and an electromagnetic flow probe (Skalar, Delft, the Netherlands) was positioned around the ascending aorta for measurement of CO. After stabilization, CO measurements were obtained by thermodilution (using injections of 10 mL of ice-cold saline; measurements were performed in triplicate) or with the Skalar electromagnetic flow probe. In 70 pigs (in 44 of which CO was also measured), the heart was excised, rinsed, and weighed.

Group 2. Sows received azaperone (2 mg/kg, i.m.) as a premedication 15 min before induction of general anesthesia. Ten minutes later, sows were cleaned and prepared for surgery, including local infiltration anesthesia of the left abdominal wall with about 100 to 150 mL of lidocaine (2 mg/mL, i.m.). After induction with propofol (1 mg/kg, i.v.), sows were intubated and mechanically ventilated (tidal volume 13 mL/kg and 13 breaths/min) with a mixture of air and O_2 (3:2; vol/vol) and 2.5% sevoflurane. The sows were delivered by a caesarean section via a mid lateral incision in the left lateral abdominal wall. Uterine and abdominal incisions were closed with sutures and sows were turned on their back for CO measurements. Anesthesia was maintained with 2.5% sevoflurane, midazolam (5 mg/g per hour, i.v.), and sufentanyl (1 μg/kg per hour, i.v.). A Swan-Ganz thermodilution catheter (131HF7, Edwards Lifesciences) connected to a CO computer (Edwards Lifesciences) was inserted into the right jugular vein and advanced into the pulmonary artery of 7 of the 45 sows. The chest was opened via a sternotomy, the pericardial space was opened, and a transit-time CO flow probe (20A; Transonic Systems Inc., Ithaca, NY) was placed around the ascending aorta. The pericardial space was filled with 0.9% NaCl to carry out reliable CO measurements. A pulse-oximetry sensor was placed on the auricle to measure oxygen saturation and heart rate.

After stabilization, 10 thermodilution measurements were obtained per sow (10 mL of saline solution at room

Table 1. Anatomical and hemodynamic data[1]

Item	Group 1: Rotterdam (n = 157)	Group 2: Lelystad (n = 45)
Anatomical study	(n = 70)	(n = 45)
BW, kg	47 ± 3	243 ± 5[a]
HW, g	199 ± 10	717 ± 20[a]
HW/BW, g/kg	4.4 ± 0.1	3.0 ± 0.1[a]
Flow probe studies	(n = 93)	(n = 7)
BW, kg	49 ± 1	268 ± 18[a]
Heart rate, bpm	102 ± 2	104 ± 7
CO_{FP}, L/min	3.6 ± 0.1	8.0 ± 1.1[a]
CO_{FP}/BW, mL/min per kg	76 ± 2	30 ± 4[a]
SV_{FP}, mL	36 ± 1	84 ± 21[a]
SV_{FP}/BW, mL/kg	0.75 ± 0.02	0.32 ± 0.07[a]
Thermodilution studies	(n = 37)	(n = 7)
BW, kg	40 ± 2[b]	268 ± 18[a]
Heart rate, bpm	119 ± 2[b]	104 ± 7
CO_{TD}, L/min	4.2 ± 0.2[b]	9.9 ± 1.2[a,b]
CO_{TD}/BW, mL/min per kg	109 ± 4[b]	38 ± 5[a,b]
SV_{TD}, mL	36 ± 2	101 ± 20[a,b]
SV_{TD}/BW, mL/kg	0.92 ± 0.03[b]	0.39 ± 0.08[a,b]

[a] $P < 0.05$: group 2 versus corresponding variable in group 1.

[b] $P < 0.05$: thermodilution studies versus corresponding value in flow probe studies.

[1] Data are mean ± SE. HW = heart weight; CO = cardiac output; SV = stroke volume; FP = flow probe; TD = thermodilution.

temperature for injection into the Swan-Ganz catheter with a 2-min interval) simultaneously with the CO measurements. At the end of each saline injection, the CO value on the flow meter was simultaneously recorded to allow direct comparison of the 2 techniques. At the same moment, heart rate was registered using the pulse-oximeter and these values were checked against the simultaneously counted heartbeats, visible via the open chest. After completion of these measurements, these 7 sows, as well as the 38 other sows that underwent caesarean delivery (but without hemodynamic measurements), were killed. After measurement of the postpartum BW, the heart was removed and the large vessels were cut nearest to the heart base and the atria, after which HW was determined.

Statistical Analysis

Inter- (group 1 vs. group 2) and intra-group (flow probe vs. thermodilution) comparisons were performed using unpaired and paired *t*-tests as appropriate. The scaling coefficients of the relationships between BW as an independent variable and CO, SV, and HW as dependent variables were determined using a linear mixed model. Experimental study location (Rotterdam vs. Lelystad) was treated as a random effect and assumed to have a normal distribution. To linearize the function $CO = a \cdot BW^b$, the natural logarithm was taken: $\log(CO) = \log(a) + b \cdot \log(BW)$. The same transformation was applied to SV and HW. The Akaike information criterion was used to select the best model. The assumptions for this model were checked by studying the residuals. Cardiac output and SV were analyzed separately for the measuring technique (flow probe and thermodilution). The library NLME (Pinheiro et al., 2007) of the statistical package R version 2.7.0 (R Development Core Team, 2007) was used for the analysis. Data are presented as mean ± SE unless otherwise stated.

RESULTS

Table 1 shows the characteristics of groups 1 and 2 for the anatomical and hemodynamic studies. Pigs in group 2 had considerably greater BW, HW, CO, and SV than pigs in group 1 (all $P < 0.001$), whereas heart rates were similar in both groups ($P = 0.80$). Moreover, in both groups, CO values as measured with the thermodilution technique were greater than those obtained with the flow probe technique in both group 1 ($P = 0.001$) and group 2 ($P = 0.03$). These differences can be attributed, at least in part, to the position of the flow probe around the ascending aorta distal to the coronary arteries (which encompass about 5% of CO), but may also be related to slight overestimation of flow by the thermodilution technique (see Discussion section below).

Relative values (normalized to BW) of HW, and particularly of CO and SV, were consistently less (all $P < 0.001$) in the adult sows of group 2 compared with the younger pigs of group 1 (Table 1), confirming earlier observations (von Engelhardt, 1966; Huisman, 1969; Schürmann, 1984; Niewold et al., 2000). To test the hypothesis that HW, CO, and SV of modern growing pigs and adult sows are proportional to BW as predicted by the quarter scaling laws (H_0 of HW: b = 0.75; H_0 of CO: b = 0.75; H_0 of SV: b = 1.0), HW, CO, and SV were plotted as a function of BW. Figure 1 shows an increase of HW that is commensurate with the increase in BW according to the formula $HW = a \cdot BW^{0.75}$, indicating that HW follows natural scaling laws. Table 2 also shows that the expected exponent of HW of 0.75 is well within the 95% confidence interval. In contrast, Figure 2 shows that CO and SV in the adult sows were less than expected based on BW, with estimated values of b being close to 0.50 for both CO and SV. Furthermore, the expected exponent of SV of 1.00 and the expected exponent of CO of 0.75 are well outside the 95% confidence intervals of value b (Table 2), irrespective of the technique that was used to measure CO and SV.

DISCUSSION

von Engelhardt (1966) and Niewold et al. (2000) reported relatively small HW, small blood volume, and reduced hemoglobin concentrations of growing pigs and raised concern about the cardiovascular stability and adaptability of modern fattening pigs. However, information regarding the cardiovascular system of the pig in relation to BW is fragmentary, and CO measurements, especially in growing pigs, are lacking to date. Recently, we (van Essen et al., 2009) addressed this question by collecting and analyzing CO and SV data of 60 growing pigs, with BW ranging from 22 to 75 kg, both at rest

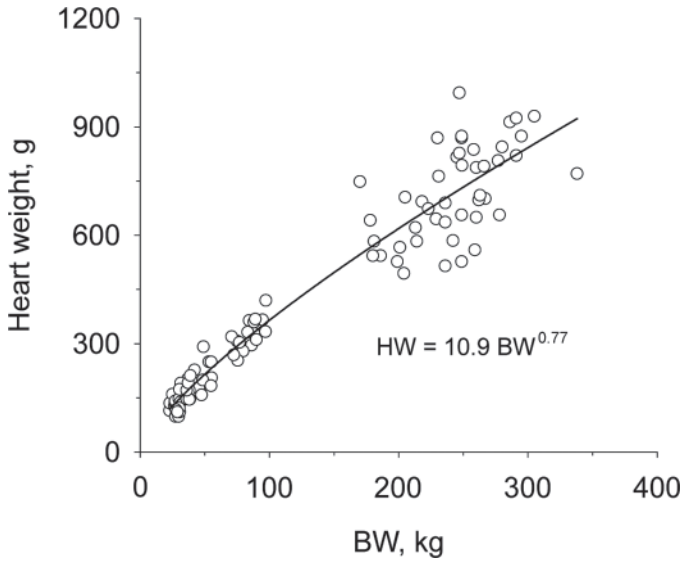

Figure 1. Relation between BW and heart weight in 115 pigs.

and during strenuous treadmill exercise. The results of that study showed for the first time that both CO and SV obeyed allometric scaling laws in pigs up to 75 kg, not only under resting conditions, but also during treadmill exercise. However, in that study, BW of the pigs remained well below the range of BW reached in modern farming, with pigs that reach 100 to 120 kg for meat production and to 250 kg in the case of breeding sows. Consequently, the aim of the present study was to test the hypothesis that HW, CO, and SV of growing pigs and adult pregnant sows are proportional to their body size, as predicted by the quarter scaling laws as proposed by West and Brown (2005). Specifically, we tested the hypothesis that HW and CO scale with BW raised to the power of 0.75 ($HW = a \cdot BW^{0.75}$ and $CO = a \cdot BW^{0.75}$) and SV scales with BW raised to the power of 1.00 ($SV = a \cdot BW^{1.0}$).

Many physiological processes scale with animal size in a surprisingly simple fashion. The cardiovascular system and its components, such as HW, CO, SV, and blood volume have been proposed to scale allometrically with BW (West et al., 1997; Agutter and Wheatley, 2004; West and Brown, 2005; Dewey et al., 2008). The observed scaling is typically a simple power law: $Y = a \cdot BW^{b}$, where Y is an observed variable; for example, CO, a is a constant, and the exponent b almost invariably approximates a multiple of 0.25 (West et al., 1997; Agutter and Wheatley, 2004; West and Brown, 2005), although the value of exponent b is subject to debate (Agutter and Wheatley, 2004; Painter, 2005; Glazier, 2008). For example, several early interspecies studies indicated that HW scales with BW to an exponent value of 1.0 (see Brown et al., 1997), whereas intraspecies studies have shown that HW scales with BW to a scaling power of 0.75. Thus, in wild pigs (von Engelhardt, 1966), as well as in cross-bred domestic pigs up to 110 kg (Yang and Lin, 1997) or 100 kg (present study), HW was found to scale allometrically with BW to a scaling exponent of 0.70 (von Engelhardt, 1966), 0.75 (Yang and Lin, 1997), and 0.80 with a 95% confidence interval of 0.73 to 0.87 (present study), respectively. The present study showed that the 95% confidence interval of the coefficient b for HW of all pigs also encompassed the predicted value of 0.75, demonstrating that in pigs well over 100 kg, HW also continues to scale to BW raised to a power of 0.75.

Table 2. Confidence intervals of coefficient b[1]

Item	Lower	Mean	Upper
HW, g	0.74	0.77	0.80
CO_{FP}, L/min	0.40	0.48	0.56
CO_{TD}, L/min	0.34	0.44	0.53
SV_{FP}, mL	0.39	0.50	0.61
SV_{TD}, mL	0.40	0.51	0.62

[1]Shown are the 95% confidence intervals for and the mean value of exponent b for HW ($HW = a \cdot BW^{b}$), CO ($CO = a \cdot BW^{b}$) and SV ($SV = a \cdot BW^{b}$). HW = heart weight; CO = cardiac output; SV = stroke volume; FP = flow probe; TD = thermodilution.

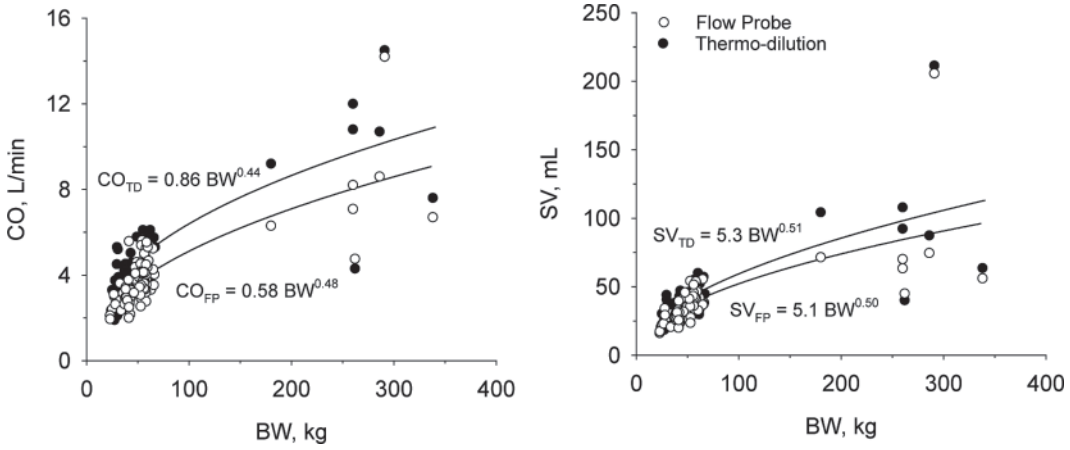

Figure 2. Relations between BW and cardiac output (CO) and stroke volume (SV) as measured by using a thermodilution (TD) catheter in the pulmonary artery (●; n = 44) or a flow probe (FP) around the ascending aorta (○; n = 100).

In contrast, the 95% confidence intervals of exponent b for CO and SV failed to encompass the predicted values of 0.75 and 1.0, respectively (West and Brown, 2005). The mean estimate of exponent value b for CO was 0.48 for flow probe measurements and 0.44 for thermodilution measurements. The calculated mean estimates of exponent b for SV were 0.50 for flow probe data and 0.51 for thermodilution data. Taken together, these data indicate that, whereas HW scales with BW according to the allometric scaling law: $HW = a \cdot BW^{0.75}$, neither CO nor SV scale with BW according to the 0.75 and 1.00 allometric scaling laws, respectively. Thus, cardiac performance of adult pregnant sows is clearly less than expected based on their BW. It should be acknowledged that the exact value of exponent b with which metabolism (and thus CO) scales to BW (being either 0.75 or 0.67) is subject to debate (West et al., 1997; Agutter and Wheatley, 2004; West and Brown, 2005; Painter, 2005; Glazier, 2008). However, irrespective of whether the exponent b is closer to 0.75 or 0.67, it is important to note that the upper limits of the 95% confidence intervals of exponent b for both CO and SV were well below the value of 0.67. In contrast, analysis of pigs of group 1 alone yielded average values of exponent b for CO and SV, as determined by flow probe of 0.63 and 0.74, respectively, with 95% confidence intervals of 0.45 to 0.81 and 0.54 to 0.94, respectively, encompassing both the values 0.67 and 0.75. Taken together, these findings indicate that CO and SV were low in the large pigs relative to their BW.

The consequent increased risk of circulatory insufficiency or failure may contribute to persistent pig diseases such as edema disease and transport-associated health problems (Niewold et al., 2000). In the present study, we did not determine regional blood flows to investigate which organs and tissues experienced hypoperfusion. However, visceral organs such as the small intestine, to which blood flow is reduced even during physiological stress such as exercise (Armstrong et al., 1987), are particularly prone to hypoperfusion during exercise in the presence of circulatory insufficiency (Haitsma et al., 2001). In addition, evidence exists that skeletal muscle composed of principally oxidative fibers displays a decreased vascular flow capacity in animals with circulatory insufficiency and appears to be more sensitive than skeletal muscle composed principally of fast glycolytic fibers (McAllister et al., 1993). Future studies are required to investigate the consequences for regional organ and tissue perfusion of the relatively low CO in large pigs.

Several methodological aspects of the present study need to be taken into account when interpreting our data sets. These include intergroup differences in 1) CO measurement techniques, 2) physiology due to pregnancy of sows in group 2, and 3) anesthesia regimen, and 4) potential intergroup differences in body fat percentage. First, studies were performed in 2 experimental centers and using different flow probe systems. Thus, in group 1, CO was assessed using an electromagnetic flow probe, whereas in group 2, transit-time flow probes were used. There is evidence that electromagnetic flow probes may yield slightly (~15%) greater flows than transit-time flow probes (Hartman et al., 1994; Buffington and Nystrom, 2004; Flynn et al., 2006), which could have resulted in a smaller b value. However, the thermodilution technique that was used in both centers yielded very similar results in terms of b values compared with the flow probe data, indicating that flow probe results were not due to differences in flow probe measurement techniques. Second, studies were performed under different anesthesia regimens in groups 1 and 2. In group 1, measurements were performed under pentobarbital anesthesia, whereas in group 2, pigs were anesthetized with midazolam, sufentanyl, and sevoflurane. We have previously shown that in pigs, pentobarbital (van Kats et al., 2000) is more cardiodepressive (in terms of negative inotropic effects) than the combination of midazolam-fentanyl anesthesia (van Woerkens et al., 1992), although CO was only slightly (<10%) lower under pentobarbital than under midazolam-fentanyl anesthesia. Yet these small differences are unlikely to have had a significant effect on our estimation of b, but if anything, will tend to overestimate it, because CO would be expected to be less in the sows if they had been studied under pentobarbital anesthesia as well. A third confounding factor could be the effects of pregnancy on hemodynamics. Thus, all mature sows in group 2 had just delivered, as opposed to the adolescent growing pigs in group 1. Indeed, gestation causes an increase of blood volume, mainly in the last third of gestation (Anderson et al., 1970). This physiological volume loading results in increases of cardiac preload and a 15 to 30% increase in cardiac muscle mass (Mone et al., 1996; Schannwell et al., 2002) that together serve to produce a 10 to 35% increase in CO and SV by the end of pregnancy, which is principally directed toward the uterus and fetuses (Reynolds et al., 1985). In the present study, these cardiovascular adaptations in the pregnant sows may have resulted in overestimations of HW, CO, and SV. Hence, a disproportional increase in HW compared with BW (i.e., a smaller b value) may have been masked by the pregnancy-induced increase in HW in the sows. Conversely, the smaller b value of CO and SV may actually have been underestimated by the pregnancy-induced increases in CO and SV, indicating that a discrepancy between HW and CO or SV is clearly present. Furthermore, by adding the random effect for "experiment" (Rotterdam vs. Lelystad) in the statistical model, differences in experimental circumstances were taken into account for the estimation of effects. Taken together, the differences between the experimental setups in Rotterdam and Lelystad may have resulted in masking of a disproportionate increase in HW (i.e., due to the pregnancy status of the adult sows), but cannot explain the disproportionately small increase in CO and SV in adult sows.

Finally, it could also be argued that a progressive increase in fat percentage in larger pigs may have contributed to a smaller value of exponent b for CO and SV, because metabolic demands and hence perfusion are less in fat than in most other body tissues (Armstrong et al., 1987). Body and carcass composition of modern growing pigs changes considerably during growth, and the fat percentage appears to increase from about 14% at 20 kg of BW to about 22% at 70 kg (Fowler et al., 1992; Mitchell et al., 2001). Interestingly, the line of sows that was used in our study has an estimated fat percentage in the range of 20 to 24%, which is much less than the 40% fat values reported in earlier studies in pigs of 145 kg (Shields et al., 1983), and likely reflects breeding selection over the past 20 yr to further increase meat percentage (up to 60% in the TOPIGS lines). Thus, we conclude that the decreased CO in the large sows was not the result of an increase in fat percentage.

In conclusion, we previously reported that the proposed disproportionate development of the cardiovascular system in modern fattening pigs is not apparent in growing pigs with BW up to 75 kg, even when the cardiovascular system is stressed during submaximal exercise (van Essen et al., 2009). The present study in young growing and adult pigs demonstrates for the first time that adult sows exhibit CO and SV that are disproportionately low for their BW. Future studies in groups of young growing and (nonpregnant) adult pigs studied in the unanesthetized state are needed to establish to what extent the reduced cardiac performance is exaggerated under stress conditions, such as treadmill exercise. Such studies should also include animals in the BW range of 100 to 120 kg to assess cardiovascular performance in pigs at slaughter weight.

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