# Accuracy of different oxygenation indices in estimating intrapulmonary shunting at increasing infusion rates of dobutamine in horses under general anaesthesia

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## Introduction

Adequate evaluation of gas exchange in anaesthetised patients is crucial for optimal anaesthetic management and assessment of therapeutic strategies. Because of their physiological characteris- tics, anaesthetised horses are prone to cardiovascular and respiratory dysfunction (Moens, 2013), and pulmonary atelectasis and venous admixture (Qs/Qt) are common findings during general anaesthe- sia in healthy equine subjects (Nyman et al., 1990).

Venous admixture is defined as the degree of admixture of mixed venous blood with pulmonary end-capillary blood that would be required to produce the observed difference between the arterial

(PaO$_2$) and the pulmonary end capillary oxygen partial pressure (PcO$_2$) (Lumb, 2010). In other words, Qs/Qt includes mixed venous blood that flows from alveolar units with a low ventilation– perfusion ratio (low V/Q, <1) and from alveoli that are perfused but not ventilated at all (V/Q = 0) (Berggren, 1942; Hedenstierna, 2003).

The Qs/Qt can be estimated with the 'standard' or Berggren shunt equation (Berggren, 1942; Richard et al., 2011) starting from a paired sample of arterial and mixed venous blood collected from the pul- monary artery. Alternatively, less invasive surrogate measures (oxygenation indices, OIs) that require only a peripheral arterial blood sample have been proposed as indicators of Qs/Qt (Covelli et al., 1983; Dean et al., 1985). Oxygen tension-based indices (OTIs) are popular and easy to calculate and include the arterial oxygen tension to fraction of inspired oxygen ratio (P$_a$O$_2$/FiO$_2$), the alveolar to ar- terial oxygen tension difference (P[A − a]O$_2$), the respiratory index (RI) (P[A − a]O$_2$/PaO$_2$), and the arterial to alveolar oxygen tension ratio (P$_a$O$_2$/P$_A$O$_2$) (Covelli et al., 1983).

The F-shunt is an oxygen content-based index (OCI), which is based on the Qs/Qt calculation but implies a fixed arterial to mixed venous oxygen content difference (C[a − v]O$_2$) of 3.5 mg/dL and thus does not require sampling of mixed venous blood (Wandrup, 1995). The accuracy of the OTIs and F-shunt in estimating the Qs/Qt has been evaluated in several studies with controversial results (Cane et al., 1988; Kathirgamanathan et al., 2009). A recent study in an experimental animal (sheep) model demonstrated that OTIs were less accurate in estimating the Qs/Qt at various FiO$_2$s when com- pared with the F-shunt, which, in turn, had a very strong correlation ($r^2 = 0.9$) with the Qs/Qt (Araos et al., 2012). Variations in cardiac output (Qt) may influence the accuracy of the F-shunt in estimat- ing Qs/Qt by altering the C(a − v)O$_2$ from the fixed value assumed by the F-shunt formula, and this can limit the clinical application of this index (Cane et al., 1988; Wandrup, 1995).

In horses, cardiovascular impairment during anaesthesia further worsens lung function (Thurmon, 1990). Intra- anaesthetic man- agement of hypotension includes administration of inotropes and/or vasoactive drugs (Schauvliege and Gasthuys, 2013). Dobutamine is commonly used in equine practice to treat hypotension in anaesthetised horses; its administration is associated with acute modification of the haemodynamic variables of the subject (espe- cially when high doses are used) (Schauvliege and Gasthuys, 2013). Thus, in such circumstances it is critical to know the impact of a sudden haemodynamic change on the accuracy of the OI in pre- dicting Qs/Qt.

The aim of this study was to evaluate the accuracy of different OIs in estimating the Qs/Qt in anaesthetised healthy

horses under different infusion rates of dobutamine. Our hypothesis was that OTIs would be more accurate in estimating venous admixture as com- pared with F-shunt under variable haemodynamic conditions.

## Materials and methods

### Study design

The study was designed as a prospective randomised experimental trial.

### Horses

The study was approved by the Italian Ministry of Health's Ethical Committee (0013843, 20 October 2010). Six healthy experimental Standardbred female horses, $8 \pm 1.5$ years old and weighing $468 \pm 24$ kg, were included. Horses were part of a larger research trial in which the echocardiographic effects of different infusion rates of dobutamine were evaluated (Vitale et al., 2013). All animals were systemically healthy (ASA physical status I, II) on the basis of pre-anaesthetic physical and haematological examinations. Food was withheld for 6 h prior to anaesthesia, but horses had free access to water.

### Premedication and induction of anaesthesia

Forty-five minutes prior to induction of anaesthesia, all horses were premedi- cated with acepromazine IV 0.02 mg/kg (Prequillan 10 mg/mL, Fatro), and after 20–30 min the jugular vein was catheterised with an IV catheter (14 G, 5.5 inches). Xylazine 0.4 mg/kg (Megaxilor 20%, Bio 98) was administered before induction of anaesthesia. General anaesthesia was induced with IV diazepam (Valium 10 mg/2 mL, Roche) 0.1 mg/kg and IV ketamine (Ketavet 100, Intervet Productions) 2.2 mg/kg, and the trachea was intubated with a cuffed oro-tracheal tube (internal diameter 30 mm). Patients were then positioned in left lateral recumbency on a surgical table.

### Maintenance of anaesthesia

The oro-tracheal tube was connected to a large animal anaesthetic circle system and isoflurane (Isoflurane Vet, Merial) in 100% O2 was delivered. All horses were me- chanically ventilated with a large animal ventilator (Ventilatore GA, Samed Elettromedicali) operating in a volume-controlled mode. End-tidal isoflurane con- centration was maintained at levels of 1.2–1.3% during the entire procedure. Ringer's lactate solution (Ringer Lattato, Galenica Senese) was infused intravenously to all horses at a rate of 5 mL/kg/h. At the end of surgery, horses were disconnected from the anaesthetic circuit and placed into a recovery box. All patients received 0.2 mg/kg of xylazine IV, and recovery was assisted by using head and tail ropes.

### Monitoring

The Hb oxygen saturation (SpO2), heart rate (HR), respiratory rate (RR), peak airway pressure (PAWpeak), tidal volume (VT), body temperature (T, nasopharyngeal), and in- spiratory and expiratory gases (CO2, isoflurane, O2) were continuously recorded with a multiparameter monitor (Beneview T5, Mindray). The right transverse facial artery was percutaneously catheterised using an 18 G catheter to sample arterial blood and measure systemic arterial blood pressures. A 9 F introducer (Arrow International) was inserted into the right external jugular vein at the entrance of the thoracic cavity. After the introducer was secured, a 7.5 F Swan–Ganz catheter (Edwards Critical Care Divi- sion) was introduced. The correct position of the catheter into the pulmonary artery was assessed by direct observation of the pressure waveforms and confirmed by ul- trasound. The pulmonary arterial catheter was used to sample mixed venous blood.

### Study protocol

After the instrumentation was complete, all horses received four consecutive infusion rates of dobutamine, always in

the same sequence: 0 (baseline), 2.5 (low), 5 (medium), and 7.5 (high) μg/kg/min. Each infusion rate was maintained for 20 min, and at 15 and 20 min, arterial and mixed venous blood samples were anaerobi- cally collected (heparinised syringes) simultaneously from the facial artery catheter and the distal pulmonary artery port of the Swan Ganz catheter, respectively. At 15 min after the beginning of each infusion rate, HR, mean arterial pressure (MAP, mmHg), respiratory rate (RR, breath/min), end tidal carbon dioxide ($EtCO_2$, mmHg), $SpO_2$ (%), and T (°C) were recorded, and stroke volume (SV, mL) and cardiac output (Qt, L/min) were estimated by means of echocardiography.

Blood gas analysis and derived calculations

Arterial and mixed-venous blood samples were analysed immediately after col- lection with a calibrated blood gas analyser (Stat Profile pHOx Plus L, Nova Biomedical) to measure $PaO_2$, mixed venous $PO_2$ ($PvO_2$), $PaCO_2$, Hb concentration, and pH. Ar- terial and mixed venous oxygen saturation ($SaO_2$ and $SvO_2$, respectively) were calculated by gas analyser calibrated for equine blood. All blood gas results were corrected to the core temperature of the animal at the time of sampling obtained from the Swan–Ganz thermistor.

The Qs/Qt equation was calculated as follows:

$$Qs\ Qt = ([Cc'O_2 - CaO_2][Cc'O_2 - CvO_2]) \times 100$$

where $Cc'O_2$ is the capillary $O_2$ content, $CaO_2$ is the arterial $O_2$ content, and $CvO_2$ is the mixed venous $O_2$ content.

The $O_2$ content-based index (F-shunt) was calculated as:

$$([Cc'O_2 - CaO_2]\ [Cc'O_2 - CaO_2] + 3.5mL\ dL) \times 100$$

where 3.5 mL/dL is a fixed value of $C(a-v)O_2$ (Araos et al., 2012). These values were calculated as reported by Marntell et al. (2005). OTIs calcu- lated in this study included: (Wandrup, 1995) 1) the $PaO_2/FiO_2$ ratio = $PaO_2/FiO_2$, 2) the alveolar-to-arterial $O_2$ tension gradient $P(A-a)O_2 = PAO_2 - PaO_2$, 3) the

$PaO_2/PAO_2$ ratio and 4) the $P(A-a)O_2/PaO_2$ ratio. Echocardiographic measurements

Echocardiographic measurements were performed from 2-D and M-mode images obtained with a 3-MHz sector probe with a 2.5-MHz Doppler translator by using recommended measurement techniques as previously reported (Vitale et al., 2013). Stroke volume (SV) was calculated as SV (mL) = LVVold – LVVols and Qt was calcu- lated as Qt (L/min) = SV × HR, where LVVold is the end-diastole left ventricular volume and LVVols is the end-systole left ventricular volume. For statistical analysis the mean value from three consecutive cardiac cycles was used.

Statistical analysis

Data are reported as means ± SD. Normal distribution was tested with the Kolmogorov−Smirnov test. The respiratory and haemodynamic variables were com- pared at the different time points of the study with analysis of variance for repeated measurements. The relationship between Qs/Qt estimated by the 'gold standard' method and corresponding calculated $O_2$ tension and content-based indices at the different dobutamine infusion rates was evaluated with linear regression analysis (i.e. [Y = a + bX]), where 'a' is a constant, 'b' is the slope, X is the explanatory variable (i.e. Qs/Qt), and Y is the dependent variable i.e. $O_2$ tension or content-based index). The goodness of fit for each calculated formula was evaluated by means of the coefficient of determi- nation ($r^2$). The null hypothesis stating that the slope was equal to zero was tested with Student's t tests, and the statistical significance was set at $P < 0.05$.

The agreement between Qs/Qt and F-shunt was analysed with the Bland− Altman test modified for use with multiple observations per individual (Bland and Altman, 1990). For this test, the bias was calculated from the differences between each pair of observations plotted against their mean ([F-shunt − Qs/Qt]/n). The upper and lower limits of agreement were calculated as bias ± 1.96 times the SD (1.96 SD

of [F-shunt − Qs/Qt]) and defined the range in which it is expected that 95% of the differences between two techniques would lie.

Results

Forty-eight paired venous and arterial samples were obtained and analysed, and their results were used to calculate the differ- ent indices of venous admixture (Table 1). The baseline data were collected at 39.4 ± 12.4 min after the connection to the breathing circuit. The mean ± SD (range) of the OIs during the different infu- sion phases and the coefficient of determination (r2) are summarised in Table 1. Overall, mean ± SD values for Qs/Qt, F-shunt, PaO2/FiO2, P(A − a)O2, PaO2/PAO2, and P(A − a)/PaO2 were as follows: 32.1 ± 11.7%; 25.9 ± 6.6%; 320.9 ± 79.7 mmHg, 325.7 ± 77.1 mmHg, 0.49 ± 0.12, and 1.15 ± 0.60, respectively.

Fig. 1 displays the linear regression relationship and correspond- ing r2 between the results of the evaluated formulas and the respective Qs/Qt obtained during the study at different dobutamine infusion rates. There was a significant linear relationship between Qs/Qt and all the OIs tested in this study (P value for the slope of the linear regression equations < 0.05). Further analysis with r2, however, showed a weak systematic relationship (i.e. r2 = 0.01–0.40) of PaO2/FiO2 (r2 = 0.18), P(A − a)O2 (r2 = 0.17), PaO2/PAO2 (r2 = 0.17), and P(A − a)/PaO2 (r2 = 0.08) as compared with F-shunt (r2 = 0.73). Bland–Altman analysis showed a bias of 0.3%, with limits of agreement at 10.1 and −9.4%, and denoted a strong agreement between Qs/Qt and F-shunt, with 45/48 of the pairwise measurement differences (i.e. 93.7%) falling between the upper and lower limits of agreement (Fig. 2). Fig. 3 represents the scatter plots of F-shunt and Qs/Qt vs. C(a − v)O2 and their respective poly- nomial lines of trend. Physiological data recorded at each study time are reported in Table 2.

Discussion

The results of this study demonstrated that in horses under general anaesthesia, the tested OTIs were very weakly correlated (r2 < 0.2) with the Qs/Qt, whereas the F-shunt demonstrated the strongest correlation (r2 = 0.73), independent of the haemodynamic conditions. The different infusion rates of dobutamine deter- mined a dose-dependent increase of HR, MAP, Qt, SV, and MPAP and a decrease of C(a − v)O2 (Table 1). Qt was estimated by means of transthoracic echocardiography which, as also demonstrated by McConachie et al. (2013), can be used as a monitoring of trend, but the absolute values of Qt should be considered with caution. For the purposes of our study, the accuracy of the measurement of Qt has relative importance since our aim was to test the correlation between different OIs and, by definition, blood sampling was performed at the same Qt condition. Similarly, previous studies on the same topic did not report the Qt values of the patients (Hope et al., 1995; Smith and Jones, 2001).

The F-shunt formula assumes a fixed value for C(a − v)O2 of 3.5 mL/dL, which was derived from a study in human patients (Harrison et al., 1975). The accuracy of this index is strictly depen- dent on a stable cardiovascular condition. In the present study, Qt varied with increasing infusion rates of dobutamine and, as a con- sequence, the calculated C(a − v)O2 ranged between 1.2 and 5.9 mL/dL (mean = 2.8), with the larger values at baseline (4.5 ± 1.0 mL/dL) and the smaller values at the higher infusion rates of dobutamine (1.9 ± 0.3 mL/dL). The C(a − v)O2 constitutes the oxygen extraction by the peripheral tissues and physiologically it is inversely corre- lated with the Qt (Caille and Squara, 2006). In particular at low cardiac output conditions oxygen extraction increases in order to satisfy the oxygen consumption of the tissues in a condition of reduced oxygen delivery (Ringer et al., 2013). This explains the step- wise reduction of C(a − v)O2 observed in this study at increasing infusion rates of dobutamine.

Despite the wide range of C(a − v)O2, the F-shunt showed a similar level of correlation with the Qs/Qt at different phases of the study (r2 = 0.62–0.77, Fig. 1). In Fig. 3, the scatter plots of F-shunt and Qs/Qt vs. C(a − v)O2 show that for values of C(a − v)O2 between 2.5 and 4.5 mL/dL, F-shunt had good agreement with Qs/Qt, whereas there was a tendency for F-shunt to overestimate Qs/Qt for values of C(a − v)O2 > 4.5 mL/dL (low Qt) and to underestimate Qs/Qt for values of C(a − v)O2 < 2.5 mL/dL (high Qt). We speculate that in the vast majority of clinical cases, horses under general anaesthesia have

values of C(a − v)O2 between 2.5 and 4.5 mL/dL (Wetmore et al., 1987), and values outside these limits are found only in specific crit- ical cases in which the use of the F-shunt formula should be considered with caution. Fig. 3 shows also that shunt fraction (in- dependent of the formula used to estimate it) had an inv

correlation with C(a − v)O2. This result is in agreement with docu- mented results in human patients (Lynch et al., 1979).

Agreement between F-shunt and Qs/Qt was further evaluated via the graphic method proposed by Bland and Altman (Myles and Cui, 2007), which revealed that 93.7% of the data points were within the 95% limits of agreement (−9.4 to 10.1), supporting the hypothesis that F-shunt could be an alternative to Qs/Qt measurements. Interest- ingly, visual inspection of the Bland–Altman plots revealed that the majority (81.25%) of the differences of the means of Qs/Qt-F-shunt pairs are within ±5%. The values that were over the 5% limits belong to the medium (5 µg/kg/min) and high (7 µg/kg/min) infusion rate phases when the values of C(a − v)O2 were considerably lower (2.3 ± 0.4 and 1.9 ± 0.3 mL/dL, respectively) than the standard value used in the F-shunt formula (3.5 mL/dL). We should consider also that in the clin- ical scenario, dobutamine is rarely infused at rates higher than 2.5–3 µg/kg/min in horses (Schauvliege and Gasthuys, 2013).

All the OTIs (PaO2/FiO2, P[A − a]O2, PaO2/PAO2, and P[A − a]O2/PaO2) tested demonstrated a poor correlation with the Qs/Qt (r2 < 0.2), in- dependent of the dobutamine infusion rates. To our knowledge, the present study is the first to test the validity of OTIs in horses, despite the fact that these indexes have been used in previous studies and are currently being used in clinical settings, assuming a similarity with other species.

Horses under general anaesthesia develop important pulmo- nary ventilation inhomogeneity with large areas of complete alveolar collapse (atelectasis), areas with partial airway closure and areas with more physiological V/Q ratios (Marntell et al., 2005). In areas of partial or complete airway collapse the PAO2 will be lower than expected or null, determining a prolongation of the time required for equilibration and a lower PcO2 (Lumb, 2005). Moreover, in the specific conditions of our study, the hyperdynamic states deter- mined at the higher infusions rates of dobutamine reduced the time available for equilibration at the alveolar–capillary membrane, further limiting the alveolar–capillary O2 diffusion (Lumb, 2005). Indeed, at the higher infusion rate the r2 for OTIs was lower compared to the other phases of the study.

All of these factors may contribute to the derangement of the linear relationship between FiO2, PAO2 and PaO2, making OTIs less accurate in such conditions to estimate the Qs/Qt as compared to the F-shunt. The latter (in contrast to OTI) relies on the PaO2 and not FiO2 and thus is not strictly dependent on the diffusion process at the alveolar–capillary membrane. Standard infusion rates of dobutamine in horses under general anaesthesia are far below the rate tested in this study and thus further studies are required in order to confirm our results on a larger population of horses and under more physiological cardiovascular conditions.

Conclusions

The results of this study demonstrated that in isoflurane- anaesthetised adult horses, F-shunt is the most reliable OI for the estimation of shunt fraction independent of the haemodynamic con- ditions of the patient. OTIs should be avoided for this purpose because they are weakly correlated with the Qs/Qt. Further studies are needed to better clarify the reason for such poor correlation.

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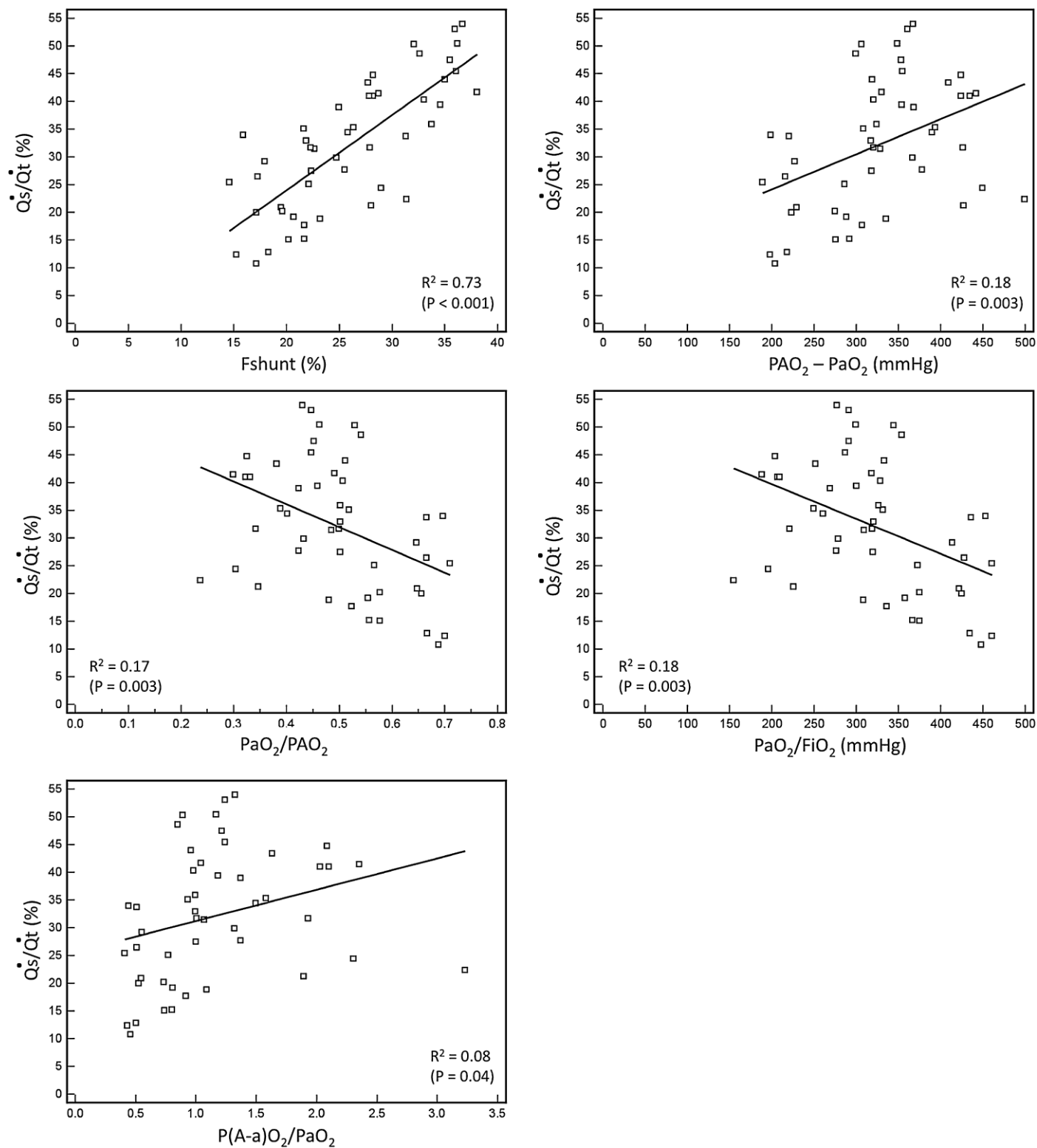
**Fig.1.**
Coefficient of determination ($r^2$) and Cartesian axis plotting of various oxygenation indices as potential indicators of Qs/Qt against the corresponding value in anaesthetised healthy horses ($n = 6$). Calculations were performed on the basis of measurements from 48 paired (simultaneously collected) arterial and mixed venous blood samples ob- tained during administration of different infusion rates of dobutamine (0, 2.5, 5, and 7 μg/kg/min).
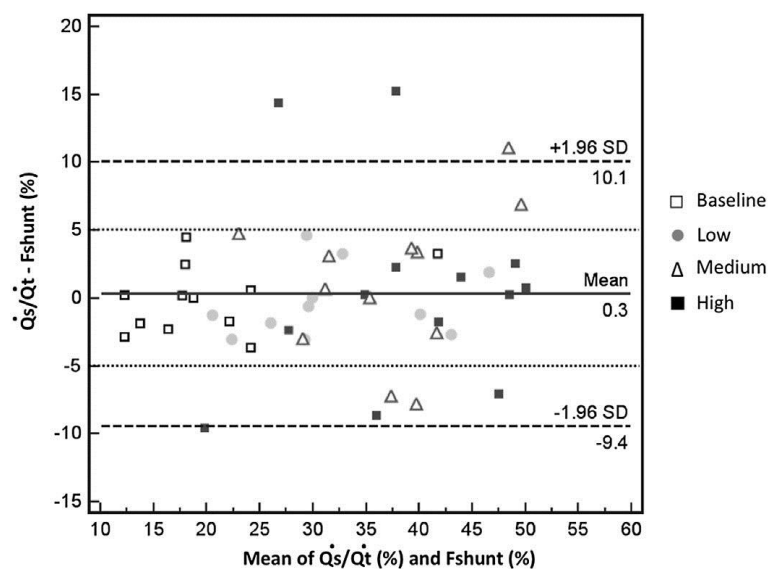
**Fig. 2.** Bland–Altman plot of calculated F-shunt and Qs/Qt values determined via analysis of 48 paired arterial and mixed venous blood samples in isoflurane- anaesthetised healthy horses (*n* = 6). The solid straight line represents the mean of the difference, the dashed lines represent 95% limits of agreement (mean ± 1.96 SD), and the dotted lines represent a difference of ±5%.