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Cover Letter

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Geneva, 2016-01-06

Dear Editors,

Hereby we would like to submit our original research article entitled "*Surgical repair of mitral valve disease in children: perioperative changes in respiratory function*" for publication to Journal of Cardiothoracic and Vascular Anesthsia.

The authors agree with and are responsible for the data presented. The authors have no conflicts of interest related to the present study.

We all state that this work is original and has not been submitted for publication elsewhere or published in any significant part in any other journal. Furthermore, this paper will not be submitted elsewhere before a decision has been taken as to its acceptability by the journal.

We thank you for considering the manuscript for reviewing and we hope that you will find this work of high enough interest and quality.

Sincerely yours,

Iliona Malaspinas
Ferenc Petak
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*Title Page (complete with Author details)

SURGICAL REPAIR OF MITRAL VALVE DISEASE IN CHILDREN: PERIOPERATIVE CHANGES IN RESPIRATORY FUNCTION

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ABSTRACT

Objective: To assess the profile of changes in airway (Raw) and respiratory tissue mechanics within a follow-up study performed in children with mitral valve disease, before and after surgical valve repair.

Design and Setting: Perioperative measurements in a prospective consecutive cross sectional study.

Participants: 24 children with congenital or post rheumatic mitral valve insufficiency.

Interventions: Input impedance of the respiratory system during spontaneous breathing was measured before, at 5 days and 3 weeks after mitral valve surgery. In addition, airway and respiratory tissue mechanics and pulmonary arterial pressure (Ppa) were also assessed under general anesthesia pre- and immediately postoperatively. Raw and respiratory tissue elastance were estimated from forced oscillatory impedance data by fitting an appropriate model.

Measurement and main results: Relating airway and respiratory tissue mechanics to age-matched healthy controls revealed abnormal respiratory function (135±6.2% and 148±13% in respiratory elastance and resistance, respectively, $p<0.001$). Improvement in the airway properties was observed immediately after surgery (-15.2±3.4%, $p<0.005$) and lasted for the study-period (-19±4.1%, $p<0.001$). Respiratory tissue elastance, which was correlated preoperatively to the diastolic Ppa, decreased only 5 days postoperatively (-20.6±4.1%, $p<0.005$). However, there was no evidence for a clear immediate effect of surgery on the tissue mechanical parameters measured intraoperatively despite a decrease in diastolic pulmonary pressure.

Conclusions: The role of the close cardiopulmonary interactions was evidenced from the present findings in the presence of mitral valve disease. Different underlying mechanisms responsible for the alterations in the compromised airway and respiratory tissue function can be inferred from these results.

Key words: pulmonary hypertension, children, respiratory mechanics

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INTRODUCTION

Among the valvular heart diseases, mitral valve insufficiency is the most frequent malfunction encountered in clinical practice. While this disease is often the consequence of cardiac ischemia in adults, acute rheumatic fever due to group A streptococcal tonsillopharyngitis and the subsequent infectious pancarditis is the main cause of mitral valve disease in children [1]. This anomaly has a large public health impact in emerging countries with lack of available antibiotics [2].

The cardiopulmonary interaction is exerted via complex interdependences either on the alveolo-capillary compartment or at the level of the bronchial tree closely surrounded by the pulmonary vessels. An expression of this interaction can be appreciated by the adverse respiratory symptoms in patients suffering from low left ventricular ejection fraction and congestive heart failure [3, 4]. The resulting pulmonary vascular congestion compromises the airway and lung tissue mechanics [5, 6], which is manifested in the development of clinical symptoms, such as dyspnea, orthopnea, and wheezing [7].

Numerous mechanisms may contribute to the respiratory clinical manifestations of mitral valve disease. The increase in postcapillary pulmonary pressure may lead to the development of interstitial edema with consequent uncoupling of the airways from the lung parenchyma and adverse alterations in the lung visco-elasticity [8]. Concomitantly, vascular engorgement in the pulmonary vascular bed may compress the bronchial wall and decrease the airway lumen [5, 6, 9]. As a long term consequence of lung congestion, chronic mitral valve disease may lead to cellular remodeling of the alveolar and bronchial walls, further compromising the lung function [4, 6, 10-13]. While several studies have demonstrated the potential beneficial effect of decrease in postcapillary pulmonary pressure on the improvement in lung function [14, 15], it is

still unknown whether the decrease in capillary overload and/or the relief of the airway compression are responsible for this acute beneficial effect following surgical repair of mitral valve. Defining the primary mechanism may help the clinician understanding the clinical symptoms exerted by the patient and targeting the treatment accordingly.

Thus, we aim at characterizing the perioperative profile of the airway and respiratory tissue mechanics in children undergoing surgical repair of their mitral valve. We postulate that assessing the airway and tissue mechanical parameters separately will reveal different processes responsible for their contribution to the lung function alteration. We therefore hypothesize that airway and respiratory tissue mechanics exert different profile after reestablishing the mitral valve function, which decreases interstitial vascular engorgement.

METHODS

Study population

The measurement protocol was approved by the Pediatric Ethics Committee (No. 09-042 matped) of the University Hospitals of Geneva. All children included in the present study were of African origin and supported by a humanitarian mission (Terre des Hommes). They were from French-speaking African countries and were able to understand the information provided by the investigators, and participated freely in the study. The parent were aware and gave authorization of the possible involvement of their children into clinical studies, and the ethics committee agreed that the consent is given by the children's tutor or the medical director of the humanitarian charity on behalf of the parents. Thus, a written informed consent was obtained from the medical referee. Children were included in the study in a consecutive case series design, and those who refused participation were excluded without further consequences. Inclusion criteria consisted of the diagnosis and subsequent elective surgical

repair of mitral valve disease. Children with chronic pulmonary diseases, obtained by clinical history, were excluded from the protocol.

Forced oscillatory measurements in spontaneously breathing children

The forced oscillatory technique (FOT) measurements were performed in accordance with the European Respiratory Society (ERS) guidelines [16]. A custom made device was applied to measure the input impedance of the respiratory system (Zrs_{sp}) while the child performed normal breathing. Briefly, a loudspeaker generated a pseudorandom broad-band forcing signal between 4 and 26 Hz, which was led through a plexiglass wave tube (ID 14 mm, OD 20 mm, L=17 cm) attached to a disposable bacterial filter and mouthpiece. The bias tube of the system was flushed with 100% oxygen during the measurements to reduce rebreathing. Lateral pressures were measured at the loudspeaker end (P_1) and the distal end (P_2) of the wave-tube with miniature pressure transducers (ICS model 33NA002D, ICSensors, Milpitas, CA). These signals were low-pass filtered (25 Hz) and digitized (128 Hz). The pressure transfer function (P1/P2) was calculated by fast Fourier transformation from the 12-s recordings and the Zrs_{sp} was computed as the load impedance of the wave-tube [17].

During the data recording periods, the children were asked to wear a nose clip and to sit in an upright position. They were asked to breathing quietly through the mouthpiece while supporting their cheeks with their palms during these maneuvers in order to minimize upper airway shunting. Four to six technically acceptable measurements were made at each occasion and were ensemble-averaged for further analyses.

The resistive and elastic properties of the respiratory system were evaluated by fitting a simple resistance-compliance model of the respiratory system to the Zrs_{sp} spectra [18]. The resistive parameter of this model reflects the flow resistance of the airways (Raw_{sp}), while the compliance ($Crs=1/Ers_{sp}$, where Ers_{sp} is the respiratory elastance) is related to the respiratory tissue stiffness. The parameters Raw_{sp} and Ers_{sp} were related to reference values obtained in

healthy children by using similar methodology [18]. Since the children involved in the present study were severely underweight, reference equations based on the age were applied.

Anesthesia and mechanical ventilation

One day after completing the first set of Zrs_{sp} measurements, children received oral midazolam for (0.5 mg/kg) 30 min before anesthesia induction. Induction of anesthesia was achieved by either inhalation of sevoflurane (up to 6%) or intravenously with etomidate (2-3 mg/kg). Endotracheal intubation with a cuffed tube was performed following the iv administration of atracurium (0.5 mg/kg). Analgesia was provided by iv administration of a bolus of of sufentanil (0.5 µg/kg) and ketamine (0.15 mg/kg), followed by the continuous infusion of sufentanil (0.5 to 1 µg/kg/h) and ketamine (0.1 µg/kg/h). In addition, anesthesia was maintained with iv midazolam (0.2 mg/kg/h). Additional iv boluses of atracurium (0.3 mg/kg) were administered to ensure neuromuscular blockade.

Children were mechanically ventilated in pressure-regulated mode (VT 8 ml/kg), while maintaining a positive end-expiratory pressure (PEEP) of 5 cmH_2O, an inspired oxygen fraction (FiO_2) of 0.5, and setting the respiratory rate to achieve an end-tidal partial pressure of CO_2 in the expired gas around 5.5 kPa.

Low-frequency Forced oscillatory measurements in anesthetized children

The measurement apparatus used for the respiratory impedance (Zrs_{OR}) measurements in the anesthetized, mechanically ventilated children was detailed previously [19]. Before starting the oscillatory measurements, the lungs were inflated to a pressure of about 30 cmH_2O to standardize the volume history. The ventilation was suspended at end-expiration and the ET-tube was switched into communication with the forced oscillatory equipment. In the resulting 8-sec apneic period, small-amplitude (<2 cmH_2O peak-to-peak) pseudorandom pressure excitations incorporating multiple frequency components (0.4-12 Hz) were delivered by a

loudspeaker into the trachea. The pressure in the loudspeaker chamber was set to 5 cmH_2O prior to the measurements to maintain the PEEP level during recordings.

A 12-mm-ID screen pneumotachograph connected to a differential pressure transducer (ICS model 33NA002D, ICSensors, Milpitas, CA) was used to measure the tracheal flow (V'). The tracheal pressure (Ptr) was measured with an identical pressure transducer through a polyethylene catheter (1.5-mm-OD). To exclude the ET tube impedance from the measurements, the tip of the intratracheal catheter (having several lateral holes) was positioned 1.5-2 cm beyond the distal end of the ET tube.

Four-to-six 8-s data epochs were collected at a mean transrespiratory pressure of 5 cmH_2O both immediately before sternotomy and after chest closure. In the latter case, the chest drain tubes were clamped to ensure a closed chest cavity. At least 1-min periods of mechanical ventilation were interposed between successive measurements. The signals of the transducers were low-pass filtered (25 Hz), and digitized (256 Hz). Zrs_{OR} spectra were calculated from the Ptr and V' signals (Zrs_{OR}=Ptr/V'). The impedance curves collected before or after the surgery were ensemble-averaged in each child. The potential biasing effects of leak on the oscillatory measurements were excluded by checking the equality of the inspiratory and expiratory tidal volumes during mechanical ventilation and by monitoring the lack of a gradual fall in Ptr during the data collection.

To separate the airway and tissue mechanics, a model containing a frequency-independent airway resistance (Raw_{OR}) and inertance (Iaw_{OR}) in series with a constant-phase tissue model [20] including damping (G_{OR}) and elastance (H_{OR}) was fitted to the Zrs spectra by minimizing the differences between the measured and modeled impedance values. Impedance data at frequencies coinciding with the heart rate and its harmonics were omitted from the model fitting.

Hemodynamic measurements

To assess the systolic (Ppa_{sys}), diastolic (Ppa_{dia}) and mean (Ppa_{mean}) pulmonary artery pressure values, the pulmonary artery is directly punctured by the surgeon via a 24G needle immediately before cannulation of the aorta and after decannulation when the patient is weaned from cardiopulmonary bypass (CPB).

Study protocol

The study period covered 22 days with Zrs_{sp} measurements performed under spontaneous breathing the day before the surgery, and at 5 days postoperatively before clearance from the ward (Fig. 1). The last spontaneous FOT assessment was performed at day 21 in the outpatient setting during postoperative cardiology assessment and prior to return to their countries. The first set of Zrs_{OR} measurements took place in the operating room under steady state conditions and before chest opening. The initial assessment of pulmonary hemodynamics was performed prior to aortic cannulation. Following mitral valve surgery, a second hemodynamic reading was made prior to sternal closure. The second set of Zrs_{OR} was collected after chest closure and before transferring the child to intensive care. All respiratory mechanics were performed 1 minute following a sigh (obtained by applying a pressure of 30 cmH_2O for 10 seconds) to ensure a standardized volume history.

Statistical analyses

The scatters in the parameters were expressed by the SEM values. The Lilliefors test was used to test data for normality. All examined parameters or their log transformations were normally distributed (all $p>0.11$). The effects of time on the data obtained during spontaneous breathing were evaluated by one-way repeated measured ANOVA with time as repeated measures (within-subject) factor. Pairwise comparisons were performed on estimated marginal means

by taking into account the presence or absence of interaction, p-values for multiple comparisons were corrected by the Holm-Sidak method. Respiratory mechanical or pulmonary hemodynamic data obtained in the anesthetized children were analyzed by using paired t-tests, as these data were all normally distributed ($p>0.19$). The Spearman correlation test was applied to test the strength of associations between the variables. Statistical tests were carried out with the significance level set at $p<0.05$ by using SigmaPlot (version 12, Systat Software, Chicago, IL, USA).

RESULTS

Twenty-four children we enrolled into the study with (17 female and 7 males) aging 12.7±0.5 years (8-16 years), with a height of 148±2.4 cm (127-167 cm), weighing 33.9±1.8 kg (19.6-49 kg), and having a body mass index of 15.2±0.5 kg/m^2(11.3-19.7 kg/m^2).

From the 24 children enrolled into the study, spontaneous FOT could not be obtained in one child because of lack of cooperation and for half of them the 21-day assessment could not be performed because of loss of follow-up. For one child, we were unable to collect intraoperative data because of technical failure, and the second set of intraoperative forced oscillatory data was incomplete in three patients due to OR turnover. Finally, pulmonary hemodynamics was missed in 7 children for surgical reasons. Despite these missing values, we decided to include all consecutively enrolled patients in order to avoid sampling bias.

Table 1 summarizes the demographic parameters and clinical features of the children enrolled in the study. All children had clinical symptoms and were classified as New York Heart Association (NYHA) grade II and III. The most frequent etiology of their mitral valve disease was related to acute rheumatic fever. Postoperative transthoracic echocardiography revealed

adequate outcome of the surgical repair with no-to-mild residual leak in all patients except 2 (F and P) who required a redo for mitral valve replacement.

Perioperative changes in the airway and respiratory tissue mechanical parameters obtained during spontaneous breathing and during mechanical ventilation are demonstrated on Fig. 2. Parameters related to the flow resistance of the airways exhibited significant decreases both under spontaneous breathing ($p<0.001$) and in the operating theatre immediately after surgical repair of mitral diseases ($p<0.005$). The improvement in the airway properties was still detectable at 21 days postoperatively ($p=0.002$). The postoperative changes in the tissue elasticity were less consistent with H_{or} increasing significantly immediately after the surgery ($p=0.02$), and an evidence for an improvement in Ers_{sp} 5 days postoperatively ($p<0.005$). The postoperative changes in G_{OR} immediately after the surgery did not reach statistical significance ($p=0.064$).

Figure 3 demonstrates pulmonary arterial pressures before and immediately after the surgical correction of mitral valve diseases. Significant decreases in Ppa_{dia} were observed postoperatively ($p<0.02$), whereas no statistically significant changes were detectable in Ppa_{sys} or Ppa_{mean} ($p=0.95$ and 0.35, respectively).

Resistance and elastance expressed as percentage of reference values obtained in the children in the perioperative period during spontaneous breathing are depicted on Fig. 4. Before the surgical correction of the mitral valve disease, the values of both Raw_{sp} and Ers_{sp} were significantly higher than those expected in age-matched healthy controls ($p<0.001$ for both). Furthermore, both mechanical parameters decreased significantly 5 days postoperatively ($p<0.001$ and $p=0.014$ for Raw_{sp} and Ers_{sp}, respectively), approaching the reference values

obtained in healthy children. While at 21 days, there was still evidence for a statistical significant decrease in Raw_{sp} ($p<0.005$), the postoperative values of Ers_{sp} at this time point did not differ significantly from the preoperative or normal values.

The associations between the magnitude of the airway and respiratory tissue parameters and the amount of their postoperative change are summarized on Fig. 5. The changes in both resistive and elastic parameters obtained during spontaneous breathing 5 days after the surgery exhibited close correlation with their preoperative initial levels. Postoperative changes in the mechanical parameters measured in the anesthetized children showed no close correlations with their preoperative initial values.

Since Ppa_{dia} showed clear improvements after the surgery, the preoperative respiratory mechanical abnormalities were related to this pulmonary hemodynamic variable. Figure 6 panels A-B summarize these relationships by depicting the preoperative Rrs_{sp} and Ers_{sp} values expressed as percentage of reference values against the corresponding preoperative levels of Ppa_{dia}. No clear tendency was obvious between Ppa_{dia} and Raw_{sp} (Panel A), whereas Ppa_{dia} exhibited significant correlations with Ers_{sp} (panel B). No clear associations were observed between the perioperative changes in Ppa_{dia} and those in Raw_{sp} (panel C), Ers_{sp} (panel D) and Raw_{OR} (panel E). The changes in the airway properties measured during spontaneous breathing and during mechanical ventilation exhibited no close association either (Panel F).

DISCUSSION

In the present study, we attempted to assess changes in the mechanical properties of the airways and the respiratory tissues following surgical repair of mitral valve disease. We demonstrated that airway properties improved significantly and immediately after surgery and

remained in the normal range 21 days postoperatively. This improvement was correlated to the preoperative airway tone, but no correlation could be evidenced with the pulmonary hemodynamics. Conversely, respiratory tissue stiffness, which was correlated preoperatively to the diastolic pulmonary pressure, demonstrated an improvement only 5 days postoperatively. Moreover, this beneficial change correlated significantly with the preoperative respiratory elastance. However, there was no evidence for a clear immediate effect of surgery on the tissue mechanical parameters measured intraoperatively despite a decrease in diastolic pulmonary pressure.

Previous studies addressed the pulmonary consequences of surgical correction of mitral valve diseases via evaluating the lung functional changes by using spirometry or by estimating lung diffusion capacity [21-24]. To our knowledge, this is the first investigation that provides specific information about the perioperative trends in the airway and respiratory tissue mechanics. Well validated techniques were applied before, immediately after and in the follow-up period to measure airway and respiratory tissue mechanics in children under spontaneous breathing [18] and during mechanical ventilation [14, 19, 25]. While the two methods have common features, they differ in many aspects in estimating the respiratory mechanics. While Zrs_{OR} excludes the upper airways and the trachea and is measured in supine position under general anesthesia with muscle relaxation, Zrs_{sp} is measured in sitting position with the involvement of the upper airway mechanics. Thus, direct comparison of the airway and tissue mechanical parameters would not be straightforward, but their within-subject changes reflect alterations in these compartments accurately. Taking into account the age-dependence of the respiratory mechanical parameters, the values obtained in this study in children with post-capillary pulmonary hypertension are in line with those obtained previously in children with pulmonary hypertension resulting from left to right shunt (VSD) [14, 25].

One of the main finding of the present study is the instantaneous improvement in the airway resistance measured in the mechanically ventilated patients, and this beneficial change remained throughout in the follow-up period. Nevertheless, the lack of association between the magnitude of decreases between the airway resistance estimates under mechanical ventilation and spontaneous breathing children (Fig. 6, Panel F) suggests the presence of different processes behind these improvements. While the routine use of inotropes following CPB (dobutamine, adrenaline, milrinone) may have contributed to the airway smooth muscle relaxation [26-28], it is unlikely that these effects remained 5 days postoperatively. This finding suggests that postoperative changes in the airway properties can only be assessed reliably after maintaining a time gap between the cease of inotropes allowing their clearance.

It is noteworthy, that these children had abnormally high airway resistance prior to the surgery (Fig. 4), which returned to the normal range after weaning from postoperative cardiorespiratory support. Furthermore, this improvement was proportional to the severity of preoperative airway obstruction (Fig. 5) suggesting that this postoperative improvement has greater importance in the children with marked preoperative bronchoconstriction. In agreement with previous results [29, 30], no clear association between the pulmonary hemodynamic improvement and the amount of airway dilation could be evidenced (Fig. 6). Thus, it is unlikely that a direct cardiopulmonary interdependence is responsible for this finding. The improvement in airway patency is rather due to the postoperative elevation in functional residual capacity [31, 32], which than provides greater mechanical support to the airways walls, thereby increasing their lumen.

In contrast with the consistent changes in the airway properties, tissue mechanical parameters exhibited dissociated changes postoperatively when they were assessed under mechanical

ventilation immediately after CPB, or days after the correction surgery (Fig. 2). While the surgery diminished vascular engorgement as evidenced by the decreased Ppa_{dia} (Fig. 3), these beneficial changes were not reflected in the tissue mechanical parameters obtained in the immediate postoperative period. This apparent inconsistency can be explained by the inflammatory consequence of CPB, which leads to interstitial water extravasation with consequent increase in respiratory tissue stiffness [14, 26, 33-35]. This phenomenon may mask the beneficial effect of decreased vascular engorgement on the viscoelastic properties of the respiratory system. The lack of change in G_{OR} despite the improvement in Raw_{OR} can also be attributed to the opposing effects of diminished postcapillary overload and the detrimental effects of CPB. Consequently, the decreased Raw_{OR} associated with increased H_{OR} demonstrate the postoperative development of ventilation heterogeneities following CPB, which is independent of the valve repair *per se* [14].

Five days after the surgery, when all these confounding effects of CPB faded, the Ers_{sp} improved significantly, particularly in the children with highly elevated preoperative respiratory tissue stiffness (Fig. 5). The close correlation between the preoperative level of Ers_{sp} and Ppa_{dia} and the consistency between their beneficial postoperative changes (Fig. 6) suggest the presence of a close association between pulmonary hemodynamics and tissue mechanics in children with mitral disease. This finding is in line with earlier results demonstrating the presence of increased tissue stiffness in children with mitral valve disease and its reversal following the correction surgery [31, 32]. However, we cannot exclude the additive effect of postoperative diuretics and negative fluid balance in these children in the improvement of tissue elastance obtained 5 days after the surgery. The tendency for a stiffening of the respiratory tissues 21 days postoperatively despite the success of mitral valve surgery (Figs 2 and 4) suggests the presence of irreversible pulmonary interstitial changes, at

least in the follow-up time frame. This rebound is consistent with earlier results demonstrating that despite the temporal decongestion of the pulmonary interstitium, a sustained remodeling of the alveolar wall structure remains in the presence of a chronic heart disease with postcapillary pulmonary overload [21].

In summary, perioperative assessment of airway and respiratory tissue mechanics revealed that children with mitral valve disease exhibit abnormal airway and respiratory tissue mechanics when these lung function parameters are related to age-matched healthy controls. The adverse alteration in the respiratory elastance was directly related to the pulmonary heamodynamical impairment, whereas the diminished airway properties showed no clear associations with the severity of the pulmonary hypertension. Both airway and tissue mechanical parameters exerted beneficial short-term improvements 5 days postoperatively. Nevertheless, sustained enlargement of the airway caliber remained 21 days postoperatively while persistence of tissue stiffness was still detected in the late follow-up. These findings indicate that clinical symptoms related to airway narrowing (wheezing, cough) are expected to be alleviated postoperatively, whereas impairment in lung function may persist even after weeks due to residual lung tissue stiffening.

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Table 1 — Physical and Clinical Data of Patients

Children	Age (year)	Height (cm)	Weight (kg)	Preoperative Treatment	Diagnosis (Preoperative ultrasound)	Inotrope after bypass	Postoperative treatment
A	14	153.5	30	F, S	Severe MI , Moderate AI	M, A	F, S, E
B	14	153.5	29.6	F, S	Severe MI, Moderate AI Mild TI	M, Do	F, S, E
C	16	152	44	none	ASD, VSD* Severe MI, Mild TI	Do	F, E
D	15	167	49	F, S	Severe MS and MI Moderate AI	none	F, S, E
E	13	162	33	F	Severe MS, Mild MI	Do	F, S, E
F	14	147	32	F, S, E	Severe MI	M, P	F, S
G	8	142.5	28.3	F, E	Severe MI, Mild TI*	Do	F, S, E
H	8	130	22.8	F	Severe MI*	A, Ne	F, S, E
I	12	148	30	F, E	Severe MI*	Do	F, S, E
J	15	153	39.5	F, S, E	Severe MI, Moderate TI Mild AI	M, A, P	F, S, E
K	14	133	24.3	F, S	Severe MI, Mild TI	Do	F
L	14	158	42	F, S	Severe MI	Do	F, S, E
M	12	148	30	F, S, E	Severe MI	M	F, S, E
N	13	131	24.4	F, S, E	Severe MI, Moderate AI	Not documented	
O	12	153	46	F, S	Severe MI, Severe IA	Am, M	F, S, E
P	10	143	43	F, S	Severe MI	A, M	F, S, E
Q	11	136	27.6	none	Severe MI	Do	F, S, E
R	15	163	39.9	E	Severe MI, Mild AI	Do	F, S, E
S	13	160	36.7	S, T	Severe MS and MI, moderate TI	M, Do	F, S, E
T	11	132.5	31	none	Severe MI*	M	F, S
U	13	127	19.6	F, S, E	Severe MI, Severe TI*	Do	
V	15	159	32	F, S, E	Severe MI, Moderate TI	none	F, S, E
W	15	163	49	T, S, E	Moderate MI Severe AI,	Not documented	F, S, E
X[1]	13	145	30	F, D	Severe MI, Severe TI	none	F, E

MI = Mitral insufficiency; MS = mitral stenosis; AI = aortic insufficiency; TI = tricuspid insufficiency; VSD = ventricular septal defect; ASD = atrial septal defect. * = congenital etiology of mitral valve disease.

Pre- and postoperative treatment: F: furosemide, S: spironalactone, E: enalapril, D: digoxin, T: thiazide.

Inotrope after weaning from bypass: Do = Dobutamine, M = Milrinone, A = Adrenaline, Am = amiodarone, Ne = norepinephrine; P = Phenylephrine.

1 = latent tuberculosis

FIGURE CAPTIONS

Figure 1: Scheme of the experimental protocol. Zrs_{sp}: forced oscillatory input impedance measurement during spontaneous breathing. Zrs_{OR}: forced oscillatory input impedance measurement during mechanical ventilation under general anesthesia. Ppa: assessment of pulmonary arterial pressure.

Figure 2: Airway and respiratory tissue mechanical parameters obtained in spontaneously breathing children (Raw_{sp}: airway resistance, Erssp: respiratory system elastance) and during mechanical ventilation (Raw_{OR}: airway resistance, G_{OR}: tissue damping, H_{OR}: tissue elastance) on the day before the surgery (D0), immediately before and after the mitral valve surgery in the operating room (Bef, Aft) and 5 (D5) and 21 (D21) days postoperatively. *: significant change vs. the corresponding value at D0 or Bef. Thin lines with various symbols: data points in the individual patients, thick line: group means, box plots: median and 10%, 25%, 75%, and 90% percentiles.

Figure 3: Pulmonary arterial pressure parameters immediately before (Bef) and after (Aft) the mitral valve surgery in the operating room (Bef, Aft). Thin lines with various symbols: data points in the individual patients, thick line: group means, box plots: median and 10%, 25%, 75%, and 90% percentiles. *: $p<0.05$ vs. Bef.

Figure 4: Airway resistance (Raw_{sp}) and elastance (Ers_{sp}) expressed as percentage of healthy age matched controls obtained by forced oscillations during spontaneous breathing on the day before the surgery (D0), and 5 (D5) and 21 (D21) days postoperatively. Thin lines with various symbols: data points in the individual patients, thick line: group means, box plots: median and 10%, 25%, 75%, and 90% percentiles. *: $p<0.05$ vs. D0.

Figure 5: Relationships between the magnitude of the airway resistance and elastance obtained during spontaneous breathing (Raw_{sp}, Ers_{sp}) and during mechanical ventilation (Raw_{OR}, Ers_{OR}) and their postoperative percentage change. Lines: best fit hyperbolas.

Figure 6: Panels A-B: relationships between diastolic pulmonary arterial pressure (Ppa_{dia}) and the airway resistance and elastance obtained during spontaneous breathing (Raw_{sp}, Ers_{sp}, both expressed as % of normal values). Panels C-E: relationships between pperioperative changes in the diastolic pulmonary arterial pressure (Ppa_{dia}) and the airway resistance and elastance obtained during

spontaneous breathing ($dRaw_{sp}$, $dErs_{sp}$) and during mechanical ventilation (Raw_{OR}). Panel F: relationship between airway resistance parameters obtained under spontaneous breathing (Raw_{sp}) and during mechanical ventilation (Raw_{OR}). Lines: linear regression.

Figure

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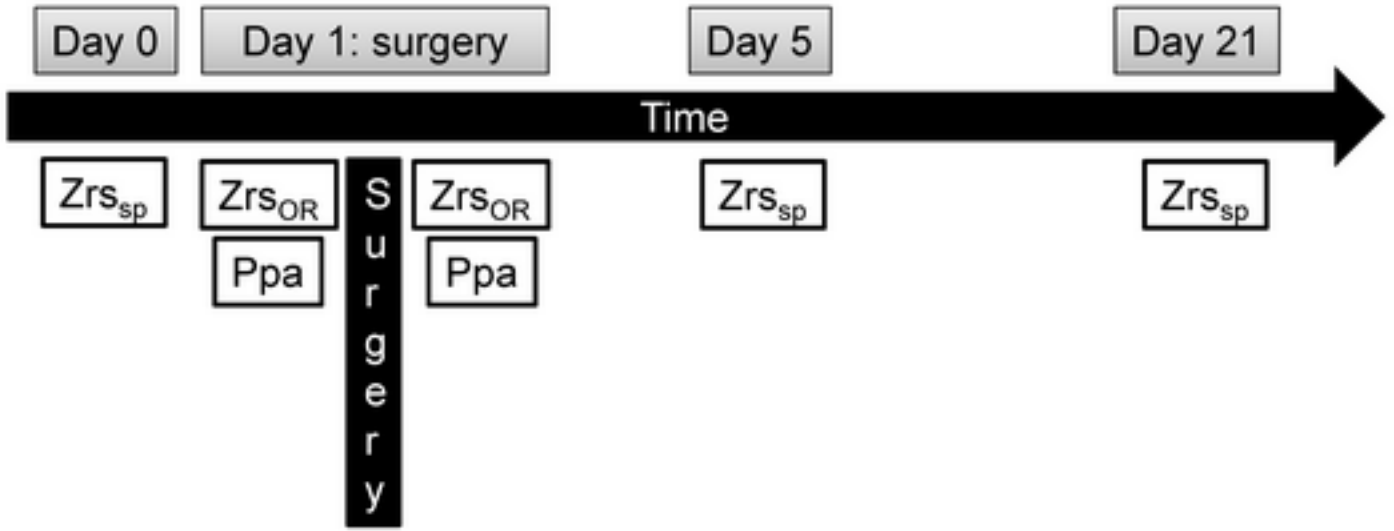

Figure 1

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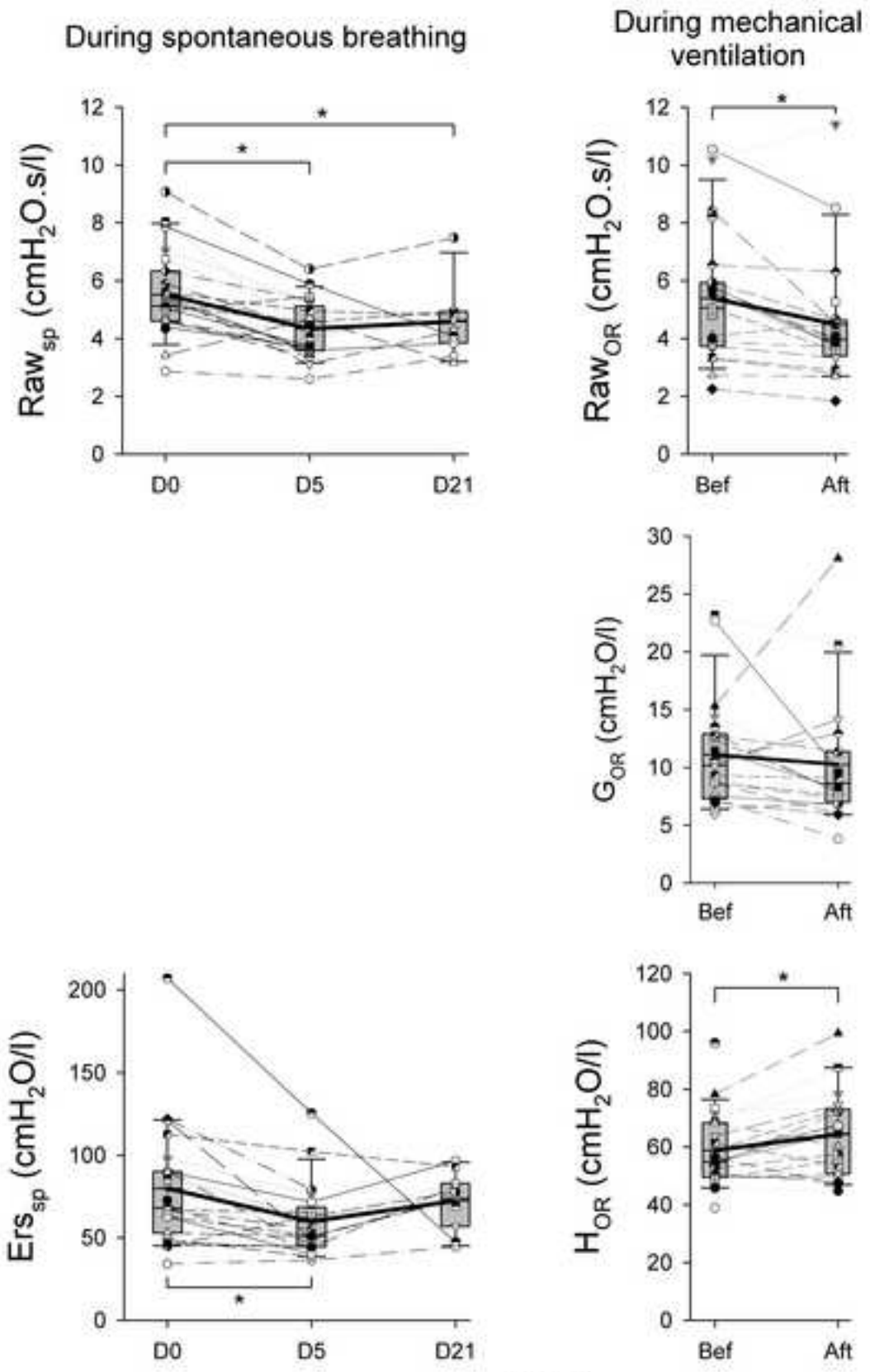

Figure 2

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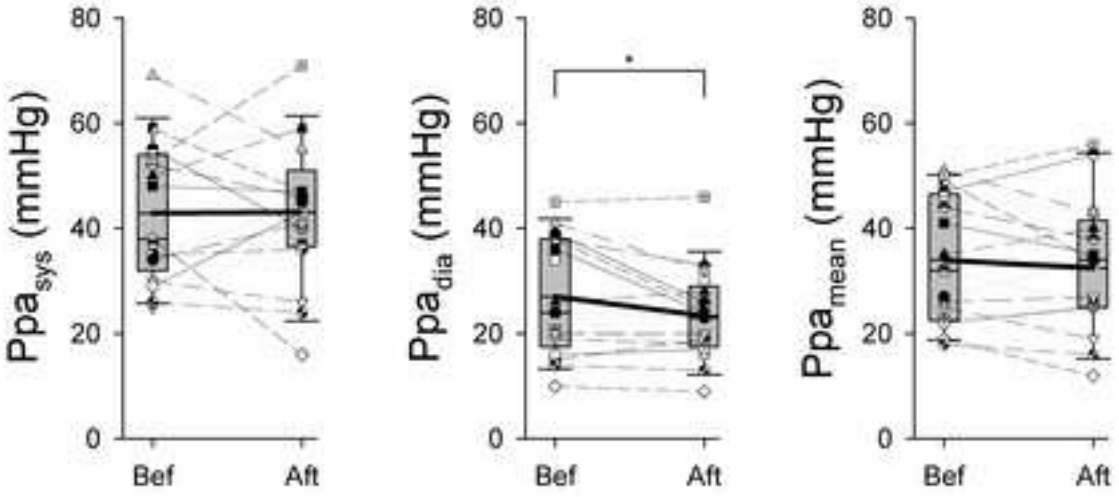

Figure 3

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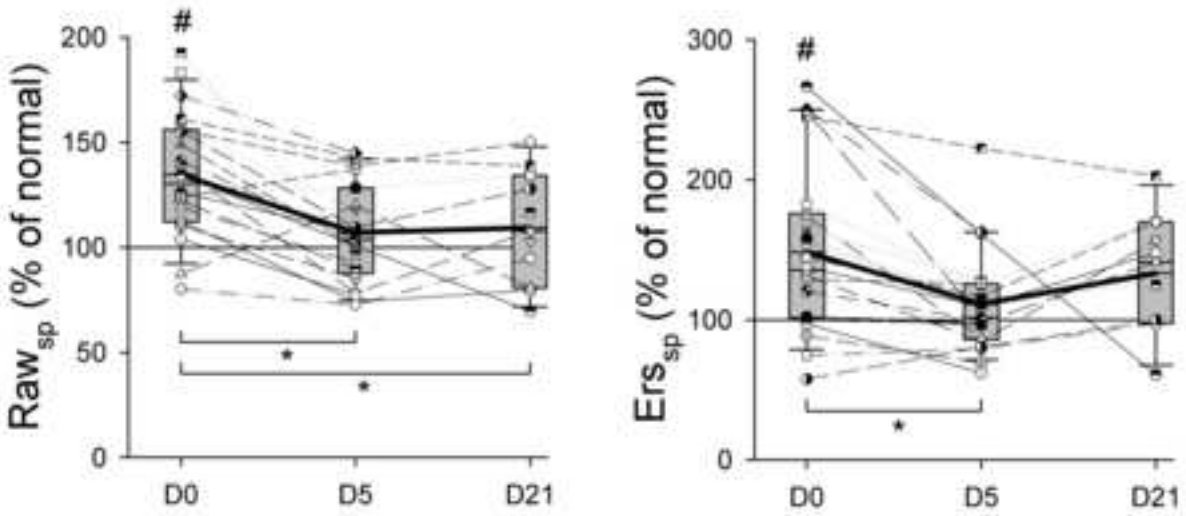

Figure 4

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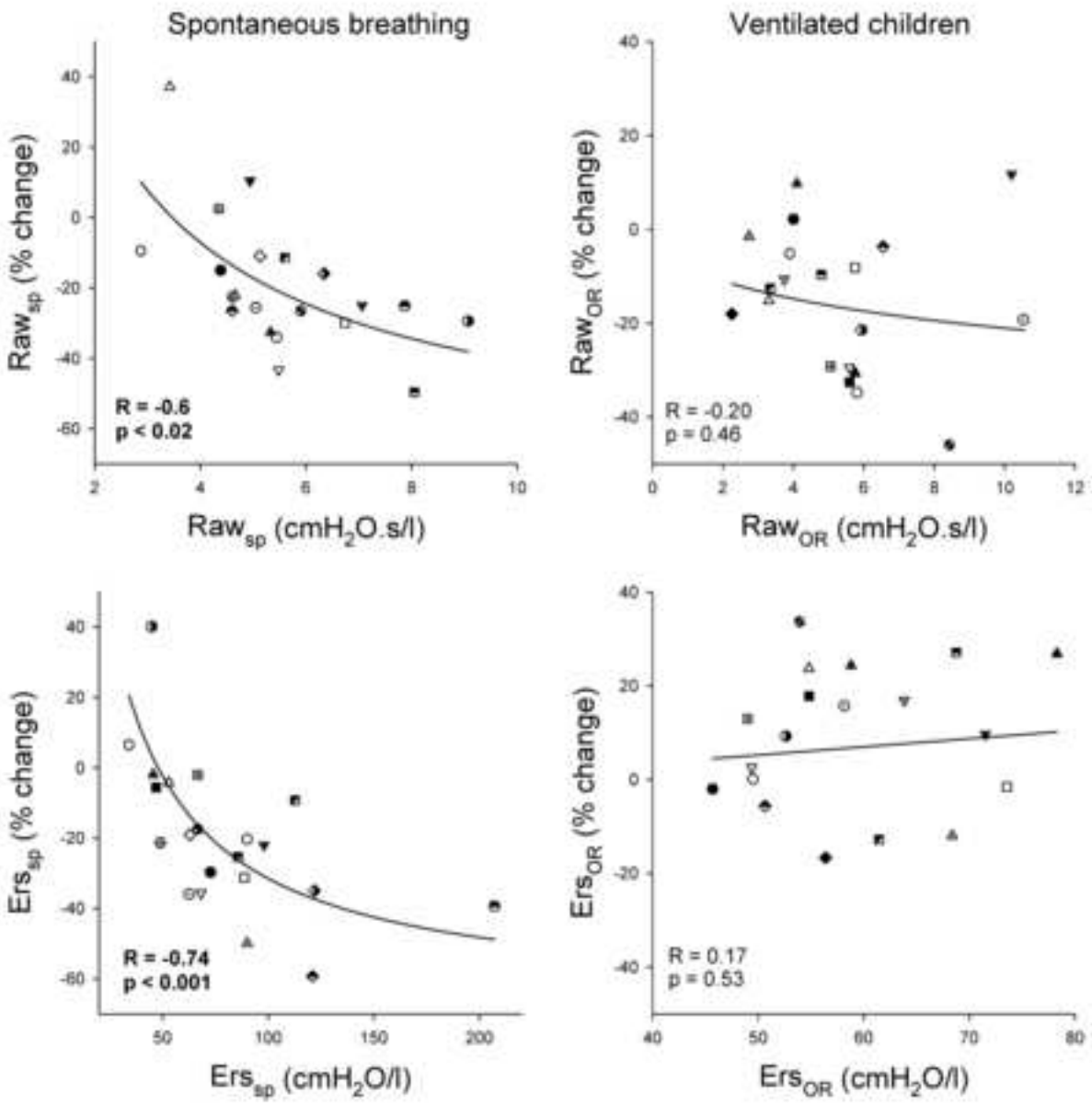

Figure 5

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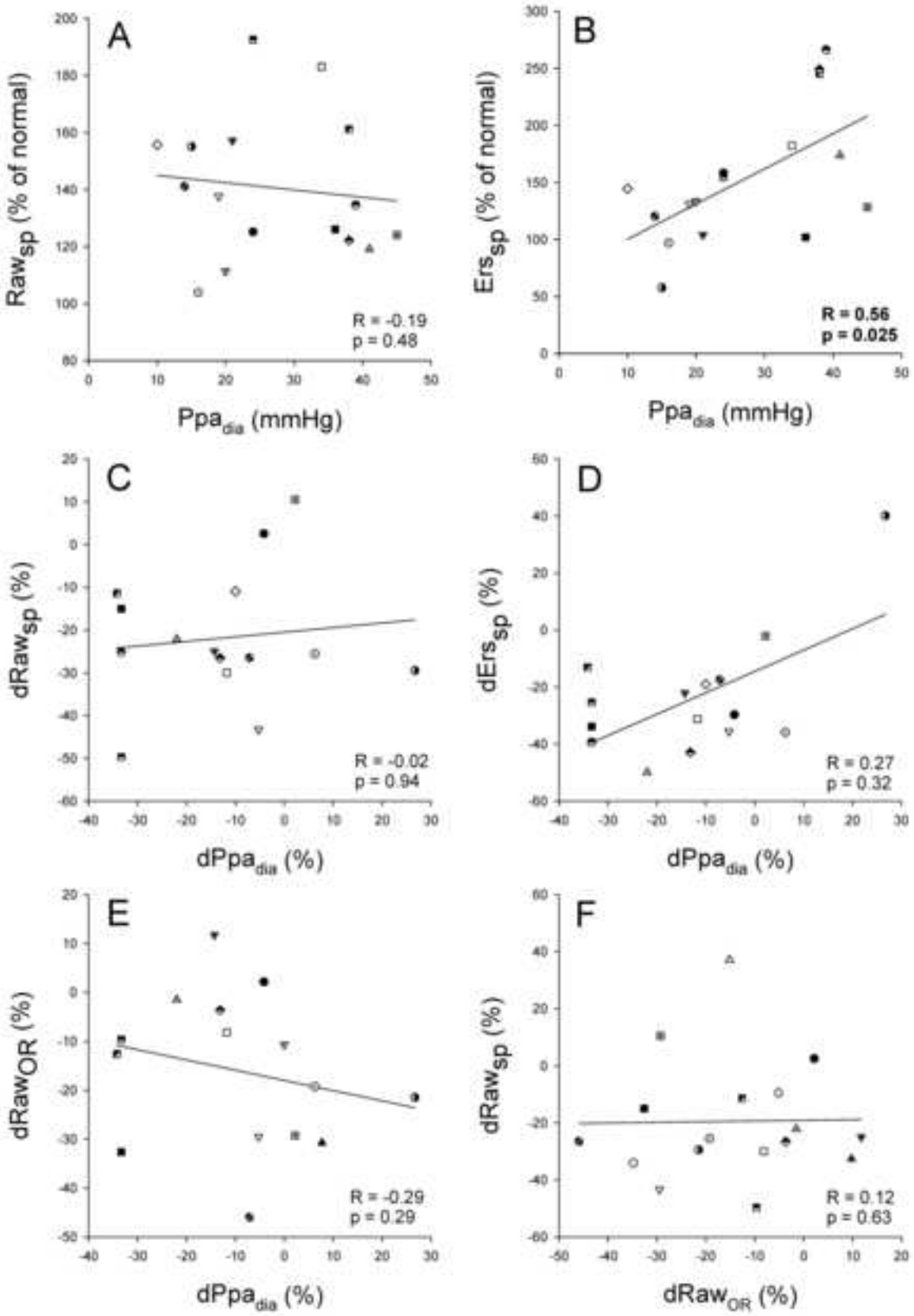

Figure 6