Changes in cerebral hemodynamics during systemic pulmonary shunt and pulmonary artery banding in infants with congenital heart disease

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Authors' contributions

Conceptualization: [Masataka Yamamoto, Yuji Morimoto]; Methodology: [Masataka Yamamoto, Yuji Morimoto]; Formal analysis and investigation: [Yoshifumi Takeda, Yoichi M. Ito, Masataka Yamamoto, Yuji Morimoto]; Writing - original draft preparation: [Yoshifumi Takeda, Yuji Morimoto]; Writing - review and editing: [Nobuyasu Kato, Satoru Wakasa, Koji Hoshino]

Abstract

Palliative surgery is often performed in the treatment of congenital heart disease. Two representative palliative procedures are the systemic pulmonary shunt and pulmonary artery banding. Dramatic changes in cerebral hemodynamics may occur in these operations due to changes in the pulmonary-to-systemic blood flow ratio and systemic oxygenation. However, there seem to be almost no studies evaluating them. Accordingly, we evaluated cerebral perfusion by transcranial Doppler ultrasonography and cerebral oxygenation by near infrared spectroscopy during these procedures.

In the post hoc analysis of a previous prospective observational study, cerebral blood flow velocities of the middle cerebral artery measured by transcranial Doppler were compared between the start and end of surgery as were the pulsatility index and resistance index. The cerebral oxygenation values were also compared between the start and end of surgery.

Twenty-two infants with systemic pulmonary shunt and 20 infants with pulmonary artery banding were evaluated. There were no significant differences of the flow velocities between the start and end of surgery in either procedure. The pulsatility index significantly increased after pulmonary artery banding, which may compete with the

increase in cerebral perfusion due to the increase in systemic blood flow. The cerebral oxygenation decreased in both procedures, possibly due to an increase in body temperature. Arterial oxygen saturation was almost the same before and after both procedures.

Contrary to our expectation, the changes in cerebral hemodynamics in the palliative operations were small if the management of physiological indices such as arterial oxygen saturation was properly performed during the procedures.

Key Words: pediatric cardiac surgery, congenital heart disease, palliative surgery, systemic pulmonary shunt, Blalock Taussig shunt, pulmonary artery banding, transcranial Doppler, cerebral oxygen saturation, near infrared spectroscopy

Statements and Declarations

Funding: None

Conflict of interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Introduction

It cannot be said that brain disorders after surgery for congenital heart disease (CHD) have been overcome, particularly in infants [1]. One of the reasons for this is that the changes in cerebral hemodynamics are not fully understood in surgery for CHD. Recently, transcranial Doppler ultrasonography (TCD) and near infrared spectroscopy (NIRS) have become common perioperative neuromonitoring modalities [2]. These modalities are useful not only for clinical monitoring but also for the study of cerebral hemodynamics during CHD surgery.

Before curative surgery, palliative surgery is often performed in the treatment of CHD. Two representative palliative procedures are systemic pulmonary shunt (SPS) and pulmonary artery banding (PAB). In SPS, a short circuit between the systemic and pulmonary arteries is established by using a vascular graft for patients with a decrease in pulmonary blood flow. The Blalock Taussig shunt (BTS) from the subclavian artery and central shunt from the aorta is the representative procedure. In PAB, inhibition of pulmonary blood flow is attempted by constricting the root of the pulmonary artery in patients with an increase in pulmonary blood flow. Thus, dramatic changes in cerebral hemodynamics may occur in both procedures due to changes in the pulmonary-to-systemic blood flow ratio (Qp/Qs) and systemic oxygenation [3].

It is reported that term infants have functional autoregulation and vasoreactivity, whereas preterm infants have anatomically incomplete and underdeveloped cerebral vasculature that cannot yet autoregulate fully [4]. However, another study demonstrated that even term newborns with CHD showed impaired cerebral autoregulation [5]. In addition, our previous studies also indicated that infants with CHD had immature

cerebral autoregulation because changes in rSO_2 were mostly dependent on the changes in systemic blood pressure [6,7]. Accordingly, through both procedures, the changes in cerebral hemodynamics may be enhanced in infants with CHD.

However, as far as we know, there has been only one report [8] that examined cerebral perfusion and oxygenation in SPS other than a few case reports [9,10]. In that report, however, a Blalock Taussig shunt was performed as a part of the Norwood procedure under deep hypothermic cardiopulmonary bypass [8]. With regard to PAB, there seem to be no such reports until now. In this study, accordingly, we evaluated cerebral perfusion by TCD and cerebral oxygenation by NIRS in SPS and PAB without using cardiopulmonary bypass.

Patients and Methods

This study is a post hoc analysis of a previous prospective observational study approved by the Institutional Review Board of the Hokkaido University Hospital (IRB #016-0505). Written informed consent for the prospective study was obtained from the parents of all subjects. This post hoc analysis was also approved by the Institutional Review Board of the Hokkaido University Hospital (IRB #021-0131) and we employed the opt-out method to obtain consent. The opportunity to opt-out of the study was provided through the Hokkaido University Hospital website. The study was registered at the UMIN Clinical Trials Registry (UMIN000046780).

The patients who underwent SPS or PAB during the registration period of the prospective study (2017/8/10-2020/12/30) were examined. Those who had at least 2 examinations of cerebral perfusion by TCD, at around the start of surgery and at the around end of surgery, were included. Children with intracranial disorders were excluded.

Anesthesia and perioperative management, including ICU care, were conducted according to our institutional practices. In brief, fentanyl (15-25μg/kg) was supplemented with midazolam (0.2-0.5mg/kg) and sevoflurane (1-2%) as tolerated, and neuromuscular blockade was achieved with rocuronium. Remifentanil (0.1-0.5μg/kg/min) was used in some older infants.

Standard monitoring was used, including a femoral artery catheter for measurement of systemic arterial blood pressure and intermittent blood sampling and an internal jugular catheter for measurement of central venous pressure. Cardiopulmonary bypass was not used in any of the patients.

Before the SPS procedure, the fraction of inspiratory oxygen (FIO_2) was maintained at a high concentration to secure pulmonary blood flow except for patients with patent ductus arteriosus. For the latter patients, low FIO_2 was employed to prevent ductus arteriosus occlusion. After the SPS procedure, FIO_2 was regulated by observing the changes in arterial oxygen saturation (SaO_2) to prevent an excessive increase in it, that is, an increase in pulmonary blood flow. For the same purpose, active blood transfusion was performed to keep the hematocrit (Hct) high. Before the PAB procedure, low FIO_2 and high partial pressure of arterial carbon dioxide ($PaCO_2$) were maintained to inhibit the pulmonary blood flow. After the procedure, management of higher FIO_2 and lower $PaCO_2$ levels was performed for the purpose of inhibiting an excessive decrease in pulmonary blood flow. Epinephrine was used in almost all the cases of both procedures during the surgery. Olprinone was also used in many cases together with epinephrine. Prostaglandin E1 was used until the ligation of the ductus arteriosus in the patients with patent ductus arteriosus.

A 2-MHz, range-gated, pulsed-wave transcranial Doppler ultrasonographic probe (Multi-Dop T, DWL Elektronische Systeme GmbH, Sipplingen, Germany) was placed over the right temporal window. As an index of cerebral blood flow, middle cerebral artery blood flow velocity in the proximal (M1) segment of the middle cerebral artery was measured. To ensure a reproducible window, the signal from the artery was adjusted to be accompanied by retrograde anterior cerebral artery flow. The sample volume, gain, and power of ultrasound were kept constant for all measurements. Peak systolic, mean, and peak end-diastolic flow velocities（Vs, Vm, Vd) were recorded at around the start of surgery and the end of it. The pulsatility index (PI) and resistance index (RI) were used as qualitative measures of cerebral vascular resistance and calculated according to the formula: PI=[Vs-Vd]/Vm, RI=[Vs-Vd]/Vs .

In the former part of the experimental period, cerebral tissue oxygen saturation (rSO_2) was measured with an INVOS 5100C (Somanetics, Troy, MI, USA). In the latter part of 2018, the spectroscope was temporarily changed to a ForeSight Elite（CASMED, Irvine, CA, USA). Finally, the spectroscope was changed to a NIRO 200NX (Hamamatsu Photonics, Hamamatsu, Japan). After induction of anesthesia, the sensor was placed on the right side of the forehead. After an accommodation period, data collection was begun every one minute throughout the surgery.

Mean arterial pressure, central venous pressure, and rectal temperature (esophageal temperature in some patients) (body temperature) were also obtained every one minute. Arterial blood gases were analyzed at 37°C intermittently and the arterial oxygen saturation (SaO_2), $PaCO_2$, and Hct were obtained.

Statistics

The primary outcome in this study was to compare the changes in indices of TCD (Vs, Vm, Vd, PI, and RI) between the start and end of surgery. According to one study that evaluated TCD indices in SPS with cardiopulmonary bypass, the standard deviation of Vm before surgery was 10 cm/s [8]. For a two-sided 95% confidence interval with a normal mean, assuming a standard deviation of 10cm/s, a sample size 20 is required to obtain a half-width of at most 4.4cm/s. The secondary outcome was to compare the rSO_2 values between the start and end of surgery. As physiological values, mean arterial pressure, central venous pressure, body temperature, and FiO_2 at the TCD measurement points were compared. Arterial blood gas values (SaO_2, $PaCO_2$, and Hct) at the nearest points of TCD measurement were also compared.

The normality of data was ascertained using the Shapiro-Wilk test. Because a part of

the data indicated non-normality, all the data are expressed as the median (minimum value, maximum value). The values between the start and end of surgery were compared using the Wilcoxon signed-rank test. Statistical analysis was performed using SPSS ver. 25.0 (Armonk, USA). A P-value <0.05 was considered statistically significant.

Results

During the study period, there were 23 patients with SPS and 20 patients with PAB who had at least 2 TCD measurements, at around the start and end of surgery. However, one patient with SPS was excluded due to a previous cerebral hemorrhage. Demographic data are shown in Table 1. Among the 22 infants with SPS, BTS was performed for all except for one with a central shunt. For 10 patients with SPS, ligation of the ductus arteriosus was performed simultaneously. The patients with SPS consisted of 13 newborns and 9 infants, whereas the patients with PAB consisted of 9 newborns and 11 infants.

Table 2 and Figure 1 show the results for TCD indices. There were no significant differences between the start and end of surgery in Vs (P = 0.59 in SPS, P= 0.38 in PAB), Vm (P = 0.27 in SPS, P = 0.37 in PAB) and Vd (P =0.90 in SPS, P = 0.23 in PAB) in either procedure. While PI and RI did not significantly change after SPS (P = 0.68 and P = 0.69, respectively), PI significantly increased after PAB (1.52 vs. 1.89, P = 0.04). There was a trend for RI to also increase (0.75 vs. 0.82, P = 0.07). These changes indicated an increase in cerebral vascular resistance after PAB. Although statistical analysis was not performed, Vs, PI and RI at the start of surgery in SPS seemed to show

high values compared to those in PAB (80 vs. 66 in Vs, 1.87 vs. 1.52 in PI, 0.86 vs. 0.75 in RI).

Table 3 shows the results for rSO_2 values. Because a part of the data for 2 patients with PAB in which rSO_2 was measured by the INVOS 5100C was missing, rSO_2 in PAB was analyzed in the remaining 18 patients. The rSO_2 values significantly decreased in the PAB group (66 vs. 62, P = 0.004) and there was a trend for it to decrease in the SPS group (62 vs. 57, P = 0.13). It has been reported that a change in baseline of more than 20% is associated with hypoxic-ischemic neural injury [11]. Accordingly, its clinical significance may be small, because the degree of the decrease was less than 10%.

Table 4 shows the changes in physiological data. All the data except one for central venous pressure in PAB were obtained. In SPS, SaO_2 values were kept stable during and after the procedure (86 vs. 83, P = 0.72) by regulating FIO_2 and Hct values in accordance with SaO_2 changes. In PAB, SaO_2 values were also kept stable (90 vs. 90, P = 1.00) by regulating FIO_2 and $PaCO_2$ levels. Mean arterial pressure significantly increased in both procedures (P <0.001 in SPS, P= 0.002 in PAB), possibly due to the effect of epinephrine. Central venous pressure significantly increased in SPS (5 vs. 8, P < 0.001), possibly due to the active blood transfusion.

Discussion

As far as we know, this is the first study to evaluate the cerebral perfusion by TCD and cerebral oxygenation by NIRS in SPS and PAB without using cardiopulmonary bypass. Compared to the values at the start of surgery, changes in TCD indices at the end of surgery were small in both procedures. The rSO_2 values decreased after surgery in both procedures. However, the clinical significance of this seemed to be small. Thus, contrary to our expectation, the changes in cerebral hemodynamics in the palliative operations were small if the management of physiological indices such as arterial oxygen saturation was properly performed during the procedures.

There were no significant changes in TCD indices caused by the SPS procedure. With this procedure, Qp/Qs increases, so systemic blood flow may decrease. In addition, systemic oxygenation is improved. These changes may decrease cerebral blood flow [3]. In our routine practice after SPS, FIO_2 was regulated by keeping SaO_2 values stable and active blood transfusion was performed to keep Hct high. In addition, systemic blood pressure was maintained by using epinephrine. These strategies might contribute to the stabilization of cerebral perfusion after SPS. Rather, there was a possibility that cerebral blood flow increased due to a rise in systemic blood pressure. This might also be inhibited by an increase in Hct due to an increase in blood viscosity [3].

There was only one report that evaluated cerebral perfusion and oxygenation in SPS [8]. In that study, however, BTS was performed as a part of the Norwood procedure under deep hypothermic cardiopulmonary bypass [8]. In the Norwood procedure, a new larger aorta is simultaneously made, which may modify the systemic circulation. Therefore, it may be difficult to compare with our results.

There were no changes in cerebral blood velocities, although cerebral vascular resistance was increased by the PAB procedure. As a result of this procedure, Qp/Qs decreases, so systemic blood flow may increase. In addition, SaO_2 decreases. These changes may increase cerebral blood flow [3]. The increase in cerebral vascular resistance that occurs after PAB may compete with an increase in cerebral blood flow. In addition, a lower $PaCO_2$ level may decrease cerebral blood flow because a recent report indicated that CO_2 reactivity was preserved even in infants with CHD [12]. Therefore, cerebral blood flow velocities might not significantly change.

In our study, Vs, PI and RI were high at the start of surgery in the patients with SPS compared to the patients with PAB, although statistical comparison was not performed due to this not being an endpoint of the study. In a study that evaluated the cerebral resistance in fetuses with CHD, the PI in the middle cerebral artery was lower than normal in fetuses with hypoplastic left heart syndrome [13]. On the other hand, the PI was higher in fetuses with right-sided obstructive lesions than in fetuses with hypoplastic left heart syndrome. Another recent paper reported that the PI in the middle cerebral artery was lower in aortic stenosis and higher in pulmonary atresia in fetuses with CHD [14]. Thus, in fetuses, a decrease in cerebrovascular resistance may be seen as an adaptive response to a decrease in carotid blood flow. Because the patients with SPS had low Qp/Qs before the procedure, high systemic blood flow might contribute to high Vs and high PI and RI might compete with it.

The rSO_2 value significantly decreased in the PAB group and there was a trend for it to decrease in the SPS group. It is reported that cerebral oxygen saturation can be expressed as a function of SaO_2, the blood hemoglobin concentration, cerebral blood

flow and cerebral metabolic rate for oxygen [15]. Cerebral blood flow velocities and SaO_2 did not significantly change in either procedure. Hct rather increased in both procedures, which contributed to the increase in rSO_2. Body temperature increased by about 1°C in both procedures. The cerebral metabolic rate changes by 6-7% per 1°C [3]. Accordingly, rSO_2 reduction might be attributable to the increase in body temperature rather than the effects of procedures. This finding may indicate the importance of the intraoperative management of body temperature. In addition, it has been reported that a change in baseline of more than 20% is associated with hypoxic-ischemic neural injury [11]. Accordingly, the clinical significance of the change of less than 10% seen in our study may be small.

Two case reports revealed the usefulness of NIRS for BTS [9,10]. In these reports, rSO_2 dropped due to preferential blood flow to the BTS at the expense of cerebral oxygen delivery [9,10] or right-sided ductal insertion with compromised pulmonary blood flow [9]. Thus, accidental changes in cerebral oxygenation can be detected by rSO_2 monitoring.

There are some limitations in this study. First, we conducted post hoc analysis of the small number of patients in a single center. However, this study seems to be the first study to evaluate the cerebral perfusion by TCD and cerebral oxygenation by NIRS in two representative palliative procedures, SPS and PAB, for CHD in infants and we believe

that our results provide new information for the management of cerebral hemodynamics in these procedures. Next, we used three different spectroscopes for the measurement of cerebral oxygenation. The INVOS 5100C and ForeSight Elite adopt the principle of the modified Beer-Lambert law, whereas the NIRO 200NX adopts the spatial resolved spectroscopy method [16]. However, it has been reported that these devices can be used interchangeably and their data can be compared [17] [18].

In conclusion, we evaluated cerebral perfusion by TCD and cerebral oxygenation by NIRS in SPS and PAB, after which procedures cerebral hemodynamics may dramatically change due to alterations of Qp/Qs and systemic oxygenation. However, our study suggests that these changes are clinically small if the management of physiological indices such as SaO_2 values is properly performed during the procedures.

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Figure legend

Figure 1 Comparison of TCD indices (Vs, Vm, Vd, PI, RI) at the start and end of surgery

a: SPS procedure

b: PAB procedure

Start: start of surgery, End: end of surgery

Unit of Vs, Vm and Vd is cm/s.

*; P = 0.04 between Start and End.

Table 1 Demographic data

	SPS	PAB
Patient number	22	20
Age (weeks)	2.5 (0, 50)	4.0 (0, 29)
Weight (kg)	3.2 (1,9, 10.1)	2.7 (1.5, 4.9)
Male:female	15:7	8:12
Surgery time (min)	150 (83, 260)	81 (47, 135)
Diagnosis		
double outlet right ventricle	6	3
tetralogy of Fallot	6	
ventricle septal defect + atrial septal defect		6
atrioventricular septal defect	1	5
pulmonary atresia/ intact ventricular septum	4	
pulmonary atresia/ ventricle septal defect	1	
transposition of great arteries +pulmonary stenosis	2	
ventricle septal defect + interrupted aortic arch (type B)		2
ventricle septal defect		2
hypoplastic left heart syndrome		2
truncus arteriosus communis	1	
tricuspid atresia	1	
Near infrared spectroscope used		
INVOS 5100C	12	4
ForeSight Elite	2	5
NIRO 200NX	8	9

Table 2 Pre- and post-surgery cerebral blood flow velocity (cm/s), PI and RI

SPS

	Start of surgery	End of surgery	p value
Vs	80 (29, 141)	72 (37, 162)	0.59
Vm	33 (16, 80)	31 (17, 78)	0.27
Vd	10 (5, 41)	12 (6, 36)	0.90
PI	1.87 (0.98, 2.84)	1.72 (1.24, 2.76)	0.68
RI	0.86 (0.60, 0.93)	0.84 (0.70, 0.91)	0.69

PAB

	Start of surgery	End of surgery	p value
Vs	66 (41, 121)	72 (45, 154)	0.38
Vm	35(18, 67)	31 (20, 83)	0.37
Vd	16 (6, 32)	12 (8, 40)	0.23
PI	1.52 (0.98, 2.00)	1.89 (1.03, 2.67)	0.04
RI	0.75 (0.61, 0.91)	0.82 (0. 65, 0.91)	0.07

Table 3 Cerebral tissue oxygen saturation (%) at start and end of surgery

	Start of surgery	End of surgery	p value
SPS (n=22)			
	62 (33, 82)	57 (23, 76)	0.13
PAB (n=18)			
	66 (34, 83)	62 (30. 79)	0.004

Table 4 Pre- and post-surgery physiological data

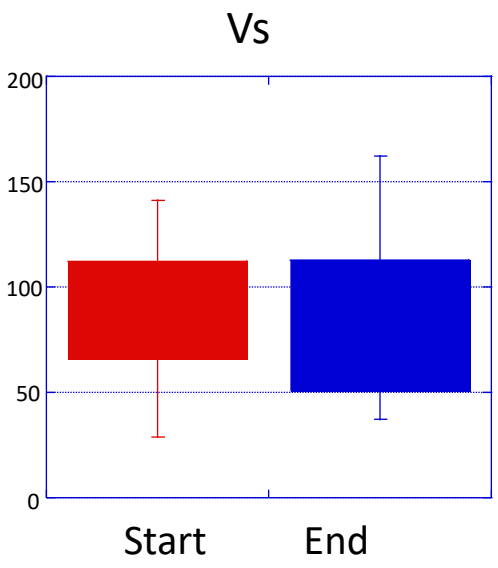
SPS

	Start of surgery	End of surgery	p value
mean arterial pressure (mmHg)	45 (30, 67)	58 (42, 68)	<0.001
central venous pressure (mmHg)	5 (1,15)	8 (2, 14)	<0.001
body temperature (℃)	36,2 (34,6, 37,7)	37.0 (34.3, 39.7)	0.001
$PaCO_2$ (mmHg)	42 (27, 53)	38 (30, 56)	0.09
SaO_2 (%)	86 (71, 96)	83 (71, 99)	0.72
FiO_2 (%)	40 (19, 99)	56 (19, 99)	0.88
Hct (%)	39.7 (31.3, 64.3)	45.6 (35.3, 56,7)	0.02

PAB

	Start of surgery	End of surgery	p value
mean arterial pressure (mmHg)	43 (32, 57)	55 (38, 70)	0.002
central venous pressure (mmHg) (n=19)	5 (2,9)	6 (2, 11)	0.14
body temperature (℃)	36.4 (33.8, 37.6)	37.1 (34.8. 39)	<0.001
$PaCO_2$ (mmHg)	48 (39, 77)	43 (35, 54)	<0.001
SaO_2 (%)	90 (69, 99)	90 (72, 100)	1.00
FiO_2 (%)	21 (20, 21)	33 (20. 92)	<0.001
Hct (%)	37.2 (21.2, 49.8)	38.0 (22.i8. 49.7)	0.003

$PaCO_2$; partial pressure of arterial carbon dioxide, SaO_2, arterial oxygen saturation, FiO_2; fraction of inspiratory oxygen, Hct; hematocrit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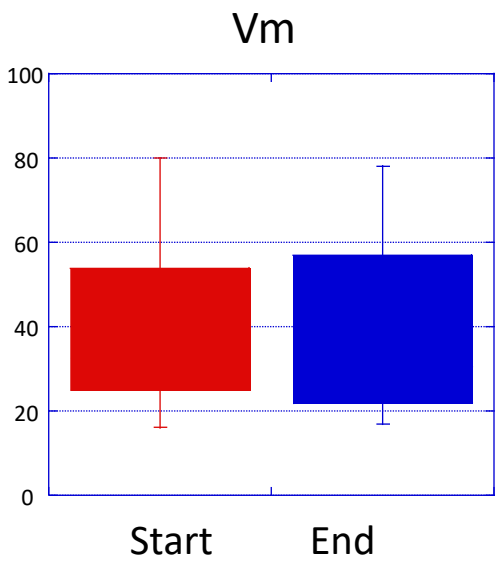
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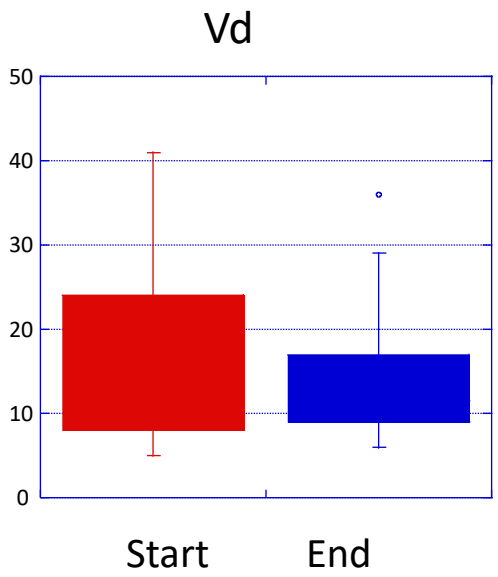
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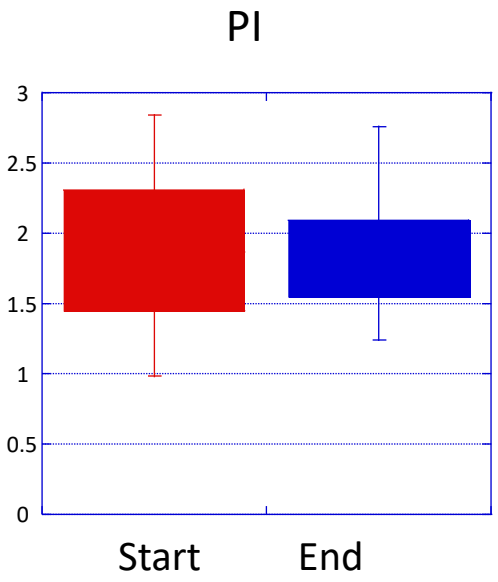
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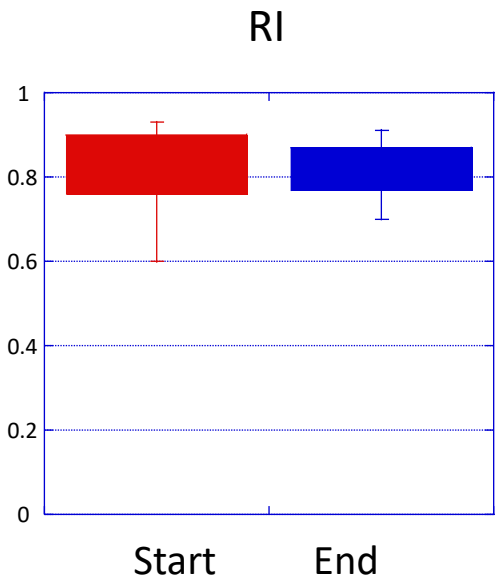
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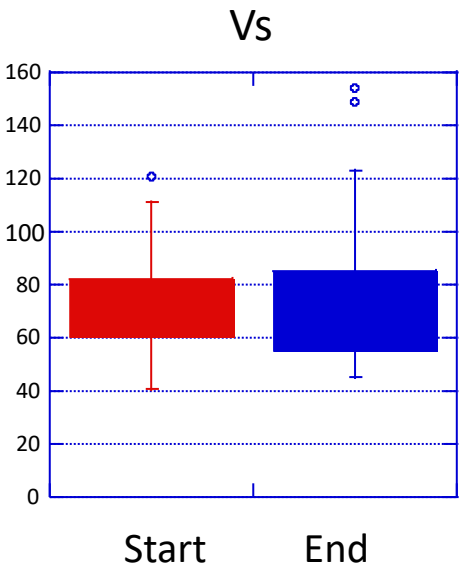
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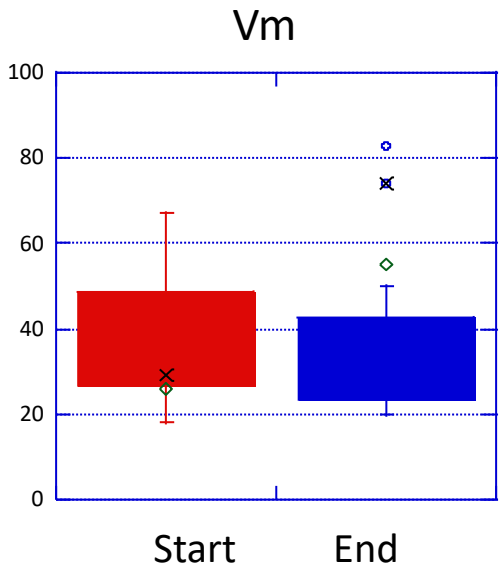
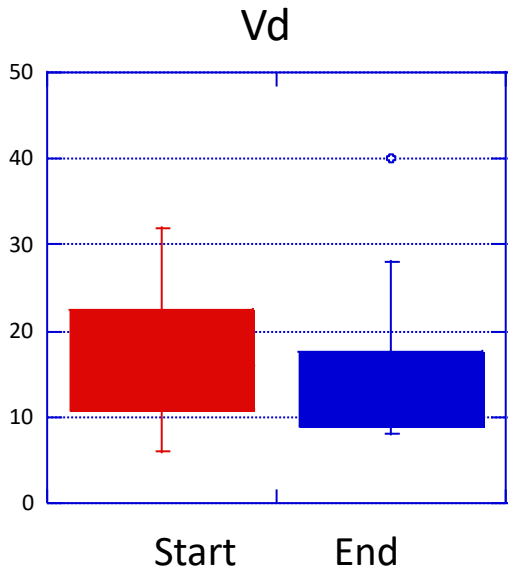
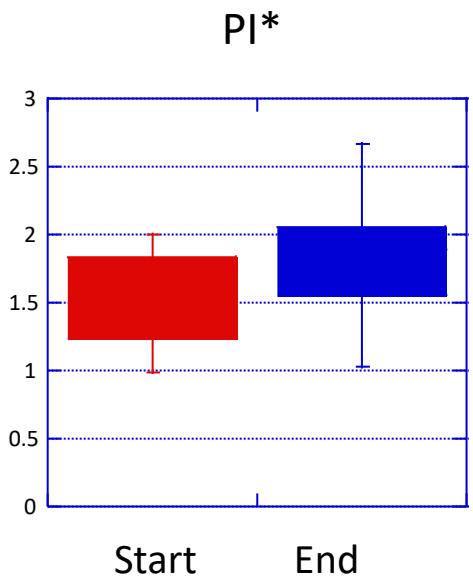
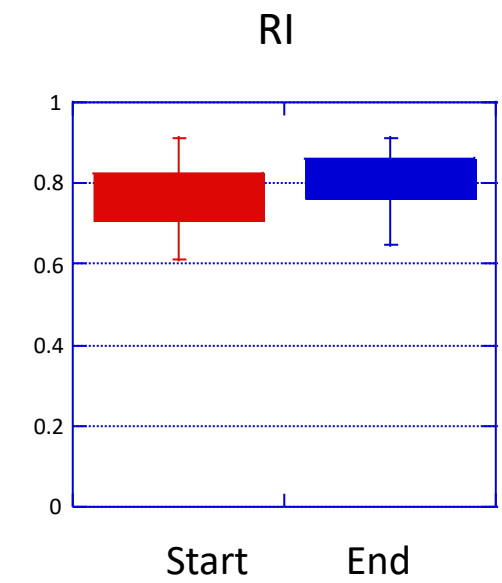
160
140
120
100
80
60
40
20
0
Start
End


Vm
100
80
60
40
20
0
Start
End


Vd
50
40
30
20
10
0
Start
End


PI*
3
2.5
2
1.5
1
0.5
0
Start
End


RI
1
0.8
0.6
0.4
0.2
0
Start
End