Restrained cerebral hyperperfusion in response to superimposed acute hypoxemia in growth restricted human fetuses with established brain-sparing blood flow

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ABSTRACT

Objective: To investigate the cerebral circulatory response to superimposed acute hypoxemia in growth-restricted fetuses with established brain-sparing flow (BSF) during basal conditions.

Material and methods: 76 term fetuses suspected of growth restriction were exposed to Doppler velocimetry in the umbilical artery (UA) and middle cerebral artery (MCA), and in 38-39 cases also in Galen's vein (GV), straight sinus (SS), and transverse sinus (TS), before and during an oxytocin challenge test (OCT), and simultaneous to electronic fetal heart rate monitoring. Nonparametric statistical analyses compared presence/absence of established BSF (MCA-to-UA pulsatility index [PI] ratio < 1.08) with a two-tailed $P < 0.05$ considered significant.

Results: The OCT (positive/negative) was not different in the BSF group (BSFG, N = 16) and the normal flow group (NFG, N = 60) ($P = 0.2$). During uterine contractions, the MCA PI decreased in the NFG, but not in the BSFG. *De novo* GV pulsations and increase of GV maximum flow velocity occurred during contractions in the NFG, but not in the BSFG. Significant SS flow velocity waveform changes were found in neither group and TS flow changes in the BSFG only.

Conclusions: Fetuses without established brain-sparing flow during basal conditions responded with both arterial and venous brain-sparing flow during acute hypoxemia, whereas in fetuses with established brain-sparing flow the cerebral circulatory responses were absent or equivocal. Fetuses with established brain-sparing flow may have a limited capacity of further cerebral hyperperfusion during superimposed acute hypoxic stress.

INTRODUCTION

Human fetuses have developed sophisticated mechanisms to resist hypoxia. An increased extraction of oxygen from erythrocytes in peripheral tissues[1,2], metabolic down-regulation[3], mobilization of glucose from glycogen stores[4], and redistribution and priority of blood flow to vital organs such as the heart, brain and adrenal glands [5-7] are then important defense mechanisms. In cerebral vessels, the redistribution of blood flow is recorded by Doppler velocimetry as a decrease of the vascular flow resistance in the fetal middle cerebral artery (MCA)[8]. This phenomenon implies a cerebral hyperperfusion, called 'brain-sparing flow' (BSF), and is prevalent in intrauterine growth restricted (IUGR) fetuses sustaining chronic hypoxemia[9,10].

In general, fetal brain-sparing flow predicts perinatal problems[9,10]. Fetuses with chronic brain-sparing flow are more often delivered prematurely, have a lower birthweight, are less vigorous at birth, and neonatal problems are more frequent than in fetuses with normal cerebral blood flows.

In contrast to circumstances during chronic hypoxemia, during acute hypoxic stress we have found that BSF occurs also in vigorous babies[11]. This suggests BSF is a physiological response to acute transient hypoxemia. However, fetuses showing an impaired ability to resist acute hypoxic stress respond with a more profound cerebral vasodilatation than unaffected fetuses, and also with a centralization of blood flow at the expense of placental blood flow[11].

We have performed a series of studies using the oxytocin challenge test (OCT) as an experimental model to study acute circulatory changes in human fetuses at risk[11-13]. In

the present study, we addressed the question as to what extent a growth restricted fetus showing BSF already during basal conditions has an intact ability to further increase its cerebral circulation when exposed to superimposed acute hypoxic stress. For this purpose, both arterial and venous cerebral circulations were studied during uterine contractions.

MATERIAL AND METHODS

The study comprised a consecutive series of 76 women with a singleton pregnancy at a gestational age of ≥ 36 weeks, a fetus suspected of IUGR, and with a clinical indication to perform an OCT. The managing obstetricians' uncertainty about the optimal time and mode of delivery was a prerequisite to perform the OCT. The experiments with simultaneous Doppler velocimetry and electronic fetal heart rate (FHR) recordings during the OCT were approved by the Lund University Research Ethics Committee and all participating women gave their informed consent. The results of the basal umbilical artery (UA) blood flow measurements were revealed to the obstetrician, but other flow results were concealed.

Ultrasound screening for dating in the early second trimester and for fetal growth in weeks 32-33 is routine at our department. Suspected IUGR was defined as an ultrasonographically estimated fetal weight deviation (WD) below the gestational age-adjusted mean weight minus 22 %, corresponding to mean minus 2 standard deviations (SD) according to reference values[14], or a fall of ≥ 10 % WD between two ultrasound measurements. Newborns with a birthweight less than mean – 2 SD were classified as small-for-gestational age (SGA).

The UA pulsatility index (PI)[15] was increased (> mean + 2 SD according to reference values[16]) in 26 cases, but end-diastolic flow was maintained in all cases. Since absent or reversed end-diastolic flow in the UA is an indication for a cesarean section (CS) at our unit in term or near term pregnancies, such cases were not exposed to an OCT.

The procedure of simultaneous Doppler velocimetry and OCT has previously been described[11-13]. Basal measurements with Doppler velocimetry in the UA, MCA, vein of Galen (Galen's vein, GV, or *v. cerebri magna*), straight sinus (SS, *sinus rectus*), and transverse sinus (TS, *sinus transversus*) were performed during uterine and fetal quiescence immediately before the OCT started. To mimic labor contractions, an intravenous oxytocin infusion was applied and increased stepwise until three uterine contractions per 10-minute period occurred. Doppler velocimetry was then performed during contractions and relaxations and the FHR patterns interpreted relative to contractions. The OCT was classified positive (repetitive late FHR decelerations) or negative[17]. Although the OCT may occasionally be false positive, at our department a CS is promptly performed in cases of positive OCT. In cases of negative OCT, labor was induced or spontaneous labor was awaited. The median time from OCT to delivery in the latter group was 5 days (range 0-21).

The blood flow measurements were performed by altogether four specially trained expert ultrasound technicians operating an Acuson Sequoia 512 real-time ultrasound scanner (Acuson, Mountain View, CA, USA) with an automatic step-less 2.5 to 6 MHz probe with pulsed and color flow Doppler options. This equipment has an automatic adjustment of the high-pass filter. During the OCT, blood flow velocities and flow velocity waveforms (FVWs) were recorded during the peak of contractions and during relaxations. For quantitative variables (see below) the mean of three consecutive FVWs was calculated from recordings performed during basal conditions, during one uterine contraction, and during one relaxation period, respectively. For qualitative variables, i.e. venous pulsations, the 'worst ever' recorded FVW was chosen.

FVWs in the UA was recorded in a free-floating part of the cord. By color flow mapping the MCA was identified as a major lateral branch of the Circle of Willis, and FVWs were identified with the sampling volume placed in the middle portion of the vessel at an insonation angle close to 0°.

The FHR correlates negatively with the UA PI[18,19] and to allow statistical comparisons the PI values for both the UA and MCA were adjusted for changes of heart rate according to the equation 'Corrected PI = observed PI - constant • (mean FHR – observed FHR)' in case a significant linear correlation existed between FHR and PI. Each type of measurements was analyzed individually (basal, contraction, relaxation) in each group, and at a significant correlation the PI was adjusted to a FHR close to the mean value in the group.

BSF was defined as a cerebral-to-umbilical artery vascular resistance ratio ([MCA PI]/[UA PI]) of < 1.08 recorded at basal measurements[9]. This definition could be used only for basal measurements and not for the dynamic changes occurring during the OCT, since the UA PI is likely to increase during uterine contractions in OCT positive cases[12,20].

The Doppler blood flow velocimetry technique for recordings in cerebral veins have been described in detail previously[11] and the anatomy is illustrated in Fig. 1. FVWs were recorded in the GV after identification of the vessel with color Doppler flow mapping, and the Doppler shift sampling volume was placed halfway upstream in the GV. The blood flow pattern in the GV is in 92 % of normal fetuses non-pulsatile[21], and venous pulsations was defined as a deviation of flow velocity of > 15 % from the

baseline maximum velocity (V_{max}), i.e., a > 15 % reduction of flow velocity since venous pulsations are caused by a counter-current pressure wave. The V_{max} was recorded for both pulsatile and non-pulsatile GV flows.

In the SS, FVWs were obtained for recordings of maximum and minimum velocities (V_{min}) after automatic adjustment for the insonation angle. Pulsations were defined as for the GV. In the TS, the triphasic flow velocity patterns was characterized by calculation of the PI for veins (PIV)[22]. As with PI for arteries, the PIV was adjusted for FHR variations when indicated.

The blood flow changes during the OCT were compared with regard to the presence or absence of brain-sparing flow during basal conditions (BSF group, BSFG, vs. the normal flow group, NFG). Birth asphyxia was defined as a 5-minute Apgar score < 7 and/or umbilical cord arterial blood pH < 7.10 and/or venous blood pH < 7.15. In OCT negative cases, allowed a trial of vaginal delivery, also operative delivery for fetal distress (ODFD: CS, ventouse or forceps delivery due to abnormal FHR pattern) was an outcome parameter.

The Chi-square test and Fisher's exact test were used for comparison of discrete variables, the McNemar test with continuity correction for comparison of discrete paired variables, the Mann-Whitney *U* test for comparison of cross-sectional non-paired continuous variables, and the Wilcoxon matched-pairs signed-rank test ('Wilcoxon's test') for comparison of continuous variables recorded longitudinally. Simple linear regression analysis was used to show relationships between variables. *P* values were corrected for ties and a two-tailed *P* value < 0.05 was considered significant. Statistics

were performed manually or with aid of StatView® (SAS Institute, Cary, NC, U.S.A.) and MedCalc® (MedCalc Software, Mariakerke, Belgium) computer software.

RESULTS

During basal conditions, 16 fetuses showed a BSF. BSF was not more common in the OCT positive group (N = 11) than in the OCT negative group (N = 65) (4/11 vs. 12/65; Fisher's exact test, $P = 0.2$).

There was no case of birth asphyxia at all. Among cases allowed a trial of labor (OCT positive cases excluded), there were 1 case of ODFD in the BSFG and 4 cases in the NFG (1/12 vs. 4/53; Fisher's exact test, $P = 1.0$).

During uterine contractions, but not during basal conditions and relaxations, the MCA PI was negatively correlated with FHR in the NFG (simple linear regression analysis, $P = 0.007$). For recordings obtained during contractions, in the NFG the MCA PI was therefore in each individual case adjusted to a FHR of 137 beats/min. No significant relationships between FHR and MCA PI were found in the BSFG during any condition. During basal conditions and relaxations, but not during contractions, the MCA PI was lower in the BSFG (Fig. 2). In the BSFG, the MCA PI did not change significantly during contractions and relaxations compared with basal measurements, whereas in the NFG the PI decreased significantly during both contractions and relaxations (Fig. 2).

Galena vein FVWs were obtained in 38 cases (BSFG, N = 6; NFG, N = 32; Chi-square test, $P = 0.4$). During basal conditions, the presence of GV pulsations was not different between the groups (1/6 vs. 4/32; Fisher's exact test, $P = 1.0$). In the NFG, but not in the BSFG, *de novo* pulsations occurred during both contractions (McNemar test, $0.001 < P < 0.005$) and relaxations (McNemar test, $0.025 < P < 0.05$). During basal conditions, the GV V_{max} was higher in the BSFG than in the NFG, but the difference did not reach

statistical significance (Mann-Whitney *U* test, $P = 0.1$) (Fig. 3). In the NFG, but not in the BSFG, the GV V_{max} increased during contractions and relaxations. In contrast, in the BSFG there was a non-significant decrease of GV V_{max} during relaxations (Wilcoxon's test, $P = 0.07$).

Straight sinus FVWs were obtained in 39/76 cases (BSFG, N = 7; NFG, N = 32; Chi-square test, $P = 0.7$). There was no difference between the BSFG and NFG regarding any of the investigated parameters during any condition. In comparison with basal measurements, the SS V_{max} increased non-significantly during contractions in both the BSFG and NFG (Wilcoxon's test, $P = 0.09$ for both), whereas the SS V_{min} showed an increase in the BSFG only ($P = 0.08$).

Transverse sinus FVWs were obtained in 7/16 cases in the BSFG and 31/60 cases in the NFG (Chi-square test, $P = 0.8$). No significant relationships were found between FHR and PIV during any condition. During basal conditions as well as during contractions and relaxations, there were no differences in TS PIV between the groups (Mann-Whitney *U* test, $P = 0.3$-0.9) (Fig. 4). In the BSFG, the TS PIV decreased from basal conditions to contractions, and in the NFG from basal conditions to relaxations ($P = 0.06$).

DISCUSSION

This study demonstrated different cerebral circulatory responses to hypoxic stress in fetuses with and without brain-sparing flow established already during basal conditions. In contrast to fetuses having a normal cerebral arterial circulation, fetuses with an established brain-sparing flow showed no further ability of decreasing the vascular flow resistance in the middle cerebral artery during uterine contractions. This indicates an already maximally utilized circulatory brain-sparing capacity and limited ability to further increase cerebral blood flow during acute hypoxic stress. However, positive OCT and operative delivery for fetal distress were not different between cases with and without established brain-sparing flow, suggesting a restrained capacity to acutely respond with cerebral hyperperfusion might have a weak relationship with the ability to sustain hypoxic stress.

In the normal flow group, a cerebral hyperperfusion during contractions was indicated by Doppler recordings not only in the arterial circulation, but also in the Galena vein, straight sinus and transverse sinus. The findings confirm the ability of Doppler flow recordings in the cerebral venous circulation to detect acute blood flow changes due to hypoxic stress. In the brain-sparing flow group, venous blood flow changes were discrete and equivocal. Signs of a hyperperfusion were demonstrated in the straight sinus and transverse sinus, but in the Galena vein the tendency was towards a lower flow velocity rather than a higher velocity. The seemingly paradoxical venous flow changes in the brain-sparing flow group might be due to a deranged physiological circulatory response, or to a statistically low power in the study.

In the normal flow group, the appearance of a brain-sparing flow with hyperperfusion of the brain was detected in combination with *de novo* pulsations in the Galena vein. In central veins, a pulsatile flow is a normal finding due to retrograde pressure waves transmitted from atrial contractions[23]. Cheema *et al*.[21] discussed the etiology of Galena vein pulsations, or rather the absence of pulsations during normal conditions, since Galena vein pulsations would normally be expected. The Galena vein is part of the systemic venous circulation and there is no known anatomical sphincter that would neutralize retrograde pressure waves from the heart. Although Galena vein pulsations in chronically hypoxemic fetuses suggest fetal compromise[24], the present results indicate that such pulsations may occur in an acute sequence and be an epiphenomenon to brain-sparing flow during transient mild to moderate fetal hypoxemia.

In summary, this study demonstrated signs of acute hyperperfusion in both the arterial and venous vascular systems of the fetal brain in response to hypoxic stress provoked by uterine contractions. Arterial Doppler blood flow velocimetry in fetuses with established brain-sparing flow already during basal conditions indicated an already maximally utilized brain-sparing capacity, and in the venous cerebral circulation the equivocal flow changes provoked by hypoxic stress suggest a deranged physiological response.

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LEGENDS TO FIGURES

Figure 1

Lateral view of a midline sagittal plane through the skull, showing the cerebral venous vessels explored in the study: *v. cerebri magna* (Galena vein), *sinus rectus* (straight sinus) and *sinus transversus* (transverse sinus). S*inus transversus* is shown in the figure, but is a pair of veins that each run laterally and anterior from the midline confluence of *sinus rectus* and *sinus sagittalis superior* towards the parietal region to join with the *sinus sigmoideus* and further to form the internal jugular vein.

Figure 2

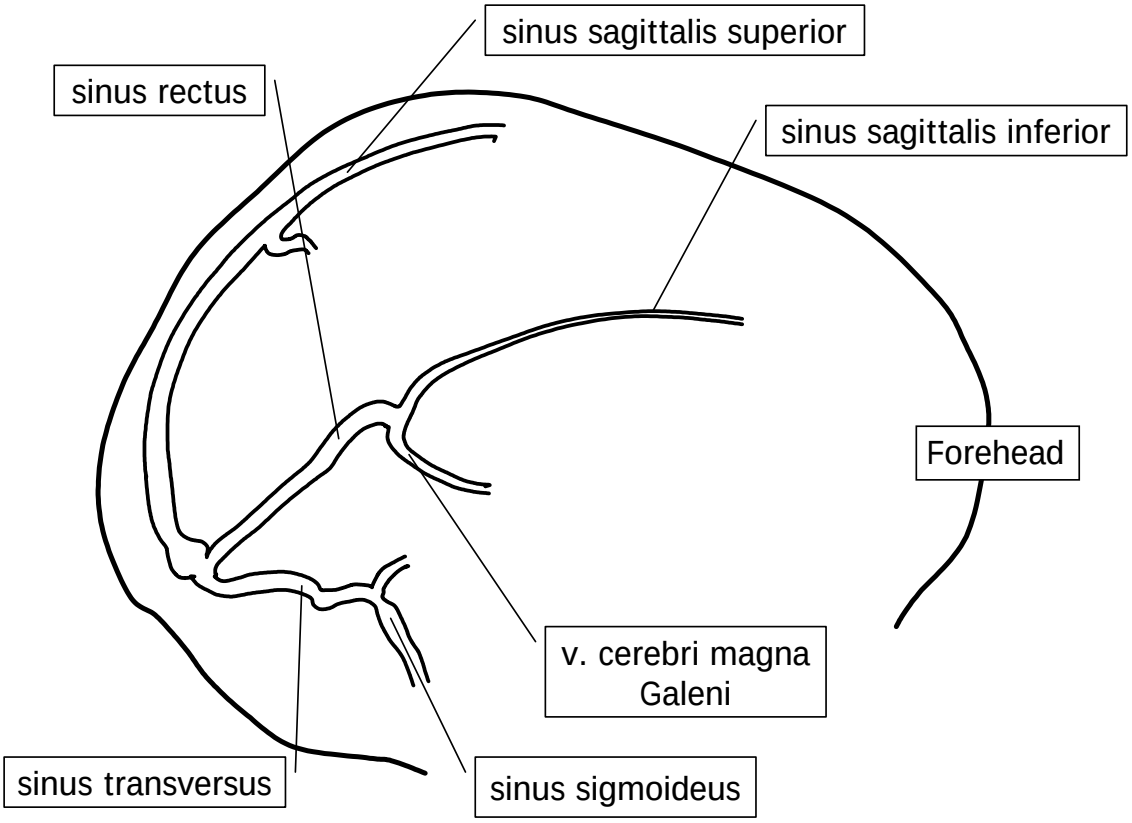
Fetal middle cerebral artery pulsatility index (PI) before and during an oxytocin challenge test (OCT) relative to the presence (brain-sparing flow group, N =16) and absence (normal flow group, N = 60) of a brain-sparing flow during basal conditions. Comparisons between measurements were performed with the Wilcoxon matched-pairs signed-ranks test, and between groups with the Mann-Whitney *U* test. A two-tailed *P* value of < 0.05 is denoted with double-pointing arrows. Mean values and standard deviations are indicated.

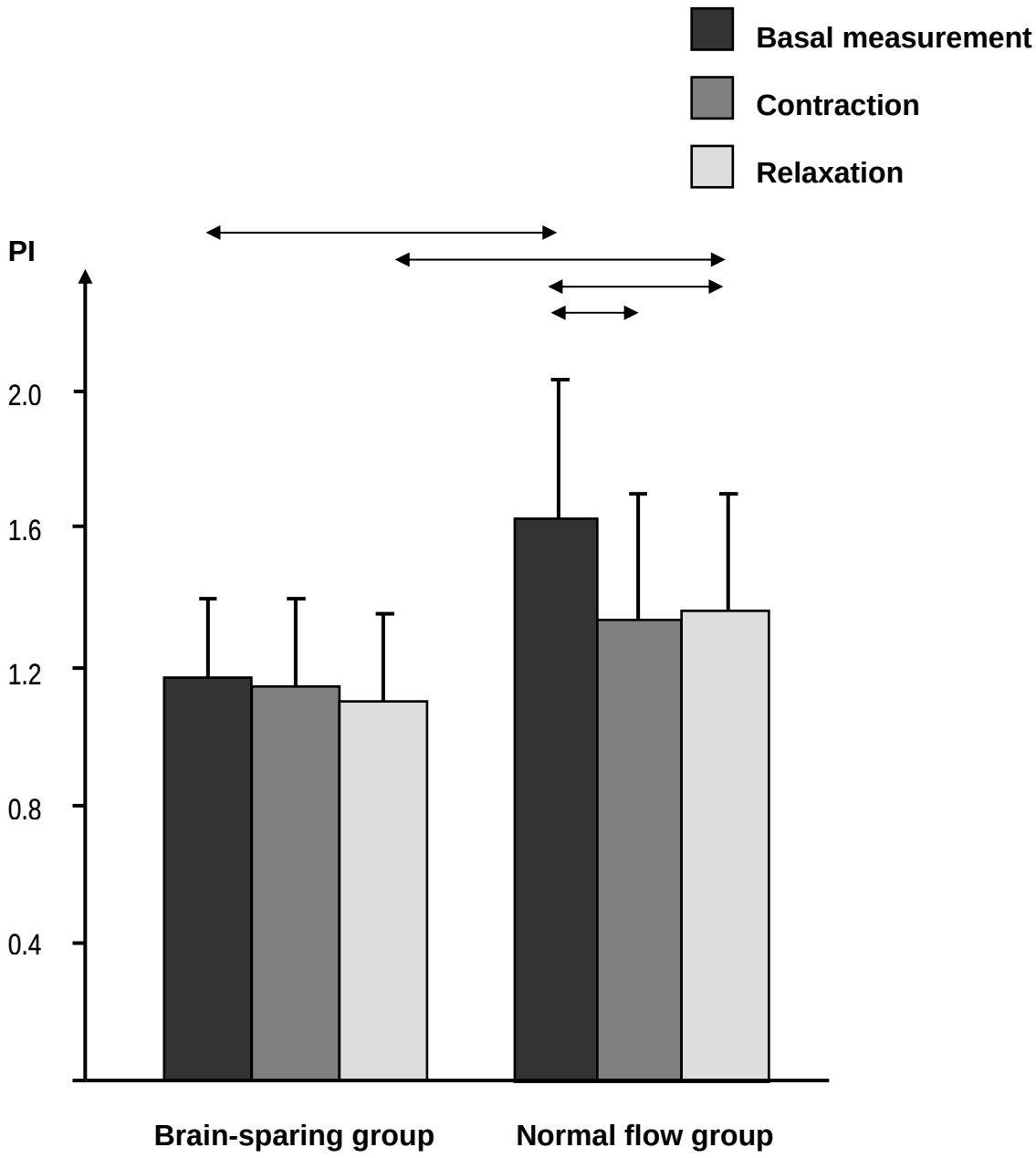
Figure 3

Maximum blood flow velocity in the fetal vein of Galen during an OCT. 6 fetuses with and 32 without brain-sparing flow were investigated.

Figure 4

Fetal transverse sinus pulsatility index for veins (PIV) before and during an OCT. 7 fetuses with and 31 without brain-sparing flow were investigated.


sinus sagittalis superior
sinus rectus
sinus sagittalis inferior
Forehead
v. cerebri magna
Galeni
sinus transversus
sinus sigmoideus


Basal measurement
Contraction
Relaxation
PI
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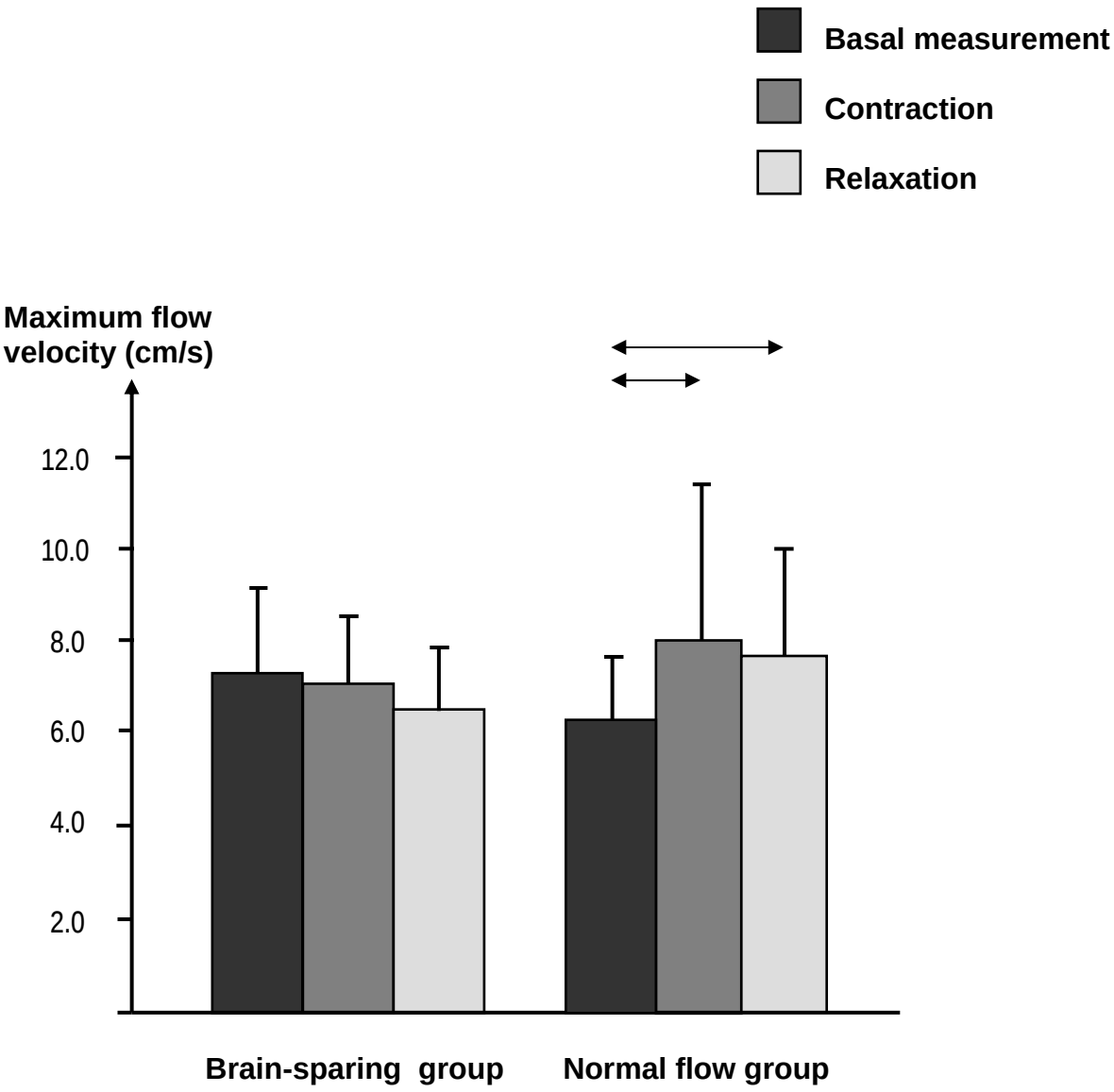
1.6
1.2
0.8
0.4
Brain-sparing group
Normal flow group


Basal measurement
Contraction
Relaxation
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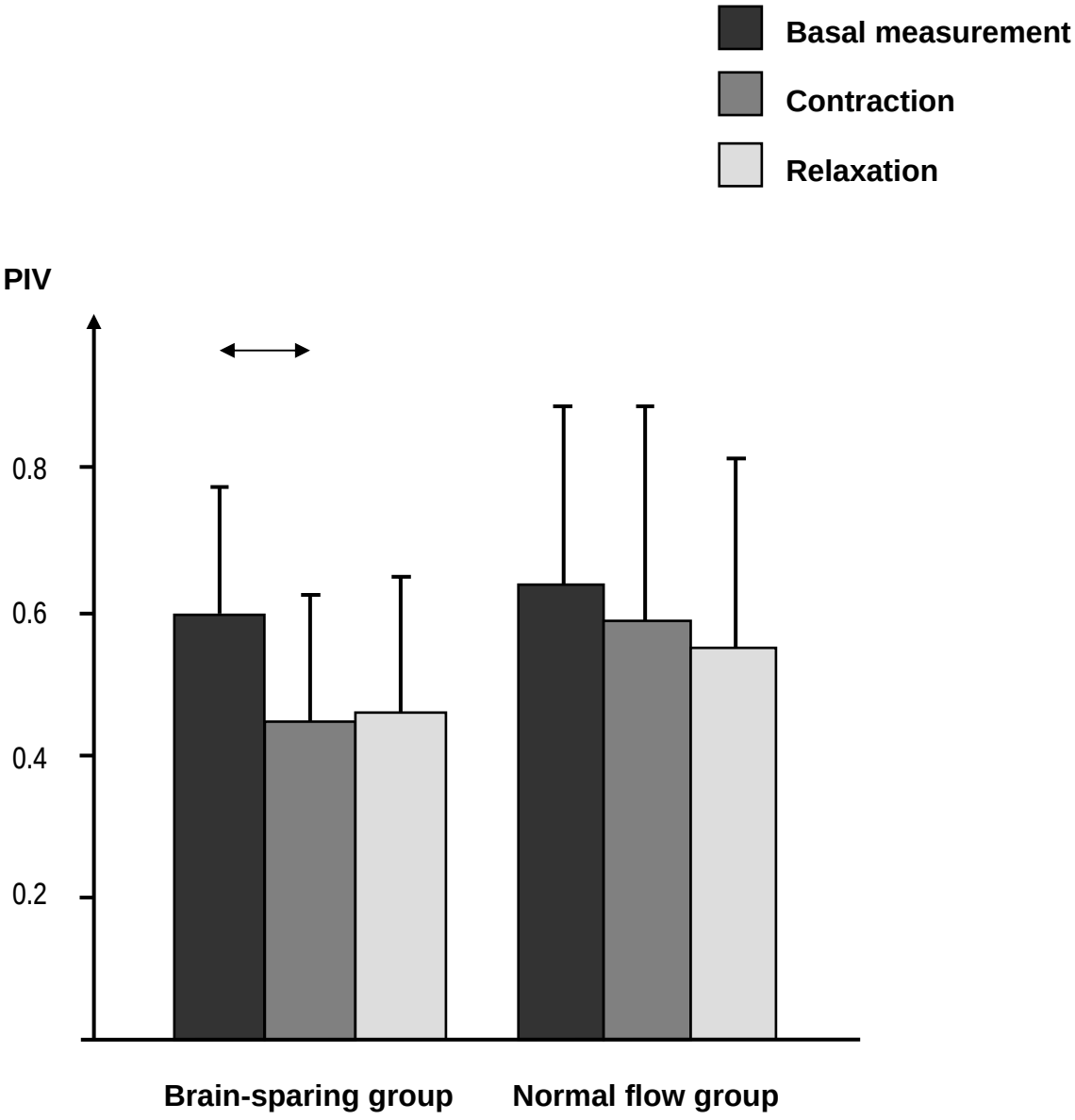
10.0
8.0
6.0
4.0
2.0
Brain-sparing group
Normal flow group


Basal measurement
Contraction
Relaxation
PIV
0.8
0.6
0.4
0.2
Brain-sparing group
Normal flow group