Title page

Changes in $PaCO_2$ induces redistribution of oral tissue blood flow in the rabbit

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Running title: $PaCO_2$ and blood flow redistribution

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Abstract

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Changes in $PaCO_2$ induced redistribution of oral tissue blood flow in the rabbit

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The purpose of this study was to investigate the effect of $PaCO_2$ changes on oral tissue blood flow. Twenty male tracheotomized Japan White rabbits were anesthetized with isoflurane (ISO) or propofol (PROP) under mechanical ventilation. Observed variables included heart rate, blood pressure, common carotid artery blood flow (CBF), tissue blood flow of the mandibular bone marrow (BBF), of the masseter muscle (MBF), and of the mandibular periosteum (PBF). After completion of the experimental preparation, CO_2 was added to inspired gas to change inspired CO_2 tension. Measurements were performed when end-tidal CO_2 tension ($ETCO_2$) was maintained at 4, 5.3, 6.7 and 8 kPa. Heart rate in both groups gradually decreased as $ETCO_2$ increased. In contrast, both systolic and diastolic arterial pressures gradually increased as $ETCO_2$ increased. Both CBF and BBF increased, while MBF decreased as $ETCO_2$ increased. PBF showed no change throughout the experiment. Positive relationship was observed between CBF and BBF. In contrast, negative relationship was observed between CBF and MBF. These results suggested that changes in $PaCO_2$ may induce redistribution of oral tissue blood

flow during both ISO and PROP anesthesia.

Key words: blood flow •oral surgery •$ETCO_2$ •isoflurane •propofol

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Introduction

Blood loss during surgery should be reduced for a good recovery after surgery and to avoid blood transfusion. In oral and maxillofacial surgery, bleeding in the surgical area increases the possibility of not only blood transfusion but also postoperative airway obstruction. Therefore, control of oral tissue blood flow is an important issue in anesthesia care for oral and maxillofacial surgery.

To minimize bleeding, deliberate hypotension using nitroglycerin (NTG), adenosine triphosphate (ATP), sodium nitroprusside (SNP), prostaglandin E_1 (PGE_1) and trimetaphan camsilate (TMP) have been widely used (1-6). Since ATP-induced deliberate hypotension produces stable control of blood pressure and dry surgical field, it is a good candidate for orthognathic surgery. However, deliberate hypotension was sometimes associated with critical complications (7). Therefore deliberate hypotension is not always safe, especially when it is applied to geriatric or medically compromised patients.

Another method to control oral tissue blood flow is to utilize the effects of anesthetic agents on blood vessels (8, 9). Changes in blood flow of the tongue mucosa in rabbits or gingiva in humans during isoflurane (ISO) administration was compared to propofol (PROP) and fentanyl administration (10-12). Blood flow of tongue mucosa or gingiva increased during ISO administration, did not change during PROP administration and decreased during fentanyl administration. These results propose a

new blood control method using pharmacological actions of anesthetic agents without hypotension. However, tissue blood flow in other regions such as bone marrow or muscles is still unknown.

Control of $PaCO_2$ is a possible technique to regulate tissue blood flow. Hypercapnia increased regional myocardial tissue oxygen tension (13, 14), whereas it decreased skeletal muscle tissue oxygen tension (15-17). In our previous study, tissue oxygen tension of the masseter muscle in rabbits decreased during hypercapnia (unpublished data). These results suggest that changes in $PaCO_2$ are associated with blood flow redistribution between vital and non-vital organs. However, those studies have not shown the effects of $PaCO_2$ on blood flow in bone marrows and skeletal muscles. So we investigated the effects of the changes in $PaCO_2$ on tissue blood flow of the masseter muscle (MBF), the mandibular bone marrow (BBF) and the mandibular periosteum (PBF) during isoflurane and propofol anesthesia in a rabbit model.

Material and methods

All animals received humane care in accordance with the Guideline for the treatment of Experimental Animals approved by Tokyo Dental College, Chiba, Japan. Twenty male Japan White rabbits weighing 2.3-2.9 kg were studied. Animals were housed in an air-conditioned room (24 ± 3 ℃ and 65 ± 5 % humidity) regulated by light and dark cycle every 12 h and maintained on commercial laboratory chow and

water *ad libitum* for two weeks before the experiment.

Anesthesia was induced with oxygen and isoflurane with end-tidal concentration at 4 % delivered via a mask and then isoflurane concentration was reduced to 1-2 %. Each experimental preparation was performed with an appropriate dose of lidocaine. A #20 French non-cuffed pediatric endotracheal tube was inserted into the trachea via a tracheotomy. A 22 gauge Teflon catheter was inserted into the left posterior auricular vein for infusion. A 20 gauge Teflon catheter was inserted into the right femoral artery for blood pressure and heart rate (HR) monitoring using a pressure transducer (P23ID, Gould, Oxnard, California). HR was recorded by a tachograph triggered by the blood pressure wave. After muscle relaxation with an intravenous administration of alcuronium chloride, the rabbit was mechanically ventilated with an animal ventilator (Model 613, Harvard, South Natick, Massachusetts). Tidal volume and respiratory rate were kept at 30-50 ml and 30-40 times$\cdot$min^{-1}, respectively, to maintain end-tidal CO_2 tension ($ETCO_2$) at about 4 kPa.

After the skin incision along the left inferior border of the mandible without local anesthesia, the masseter muscle and the periosteum on the mandibular body were exposed. The mandibular periosteum was stripped off at a size of 5 mm in diameter at the front margin of the masseter muscle near the mandibular base. A hole perforating into the bone marrow was drilled with an electrical drilling device. MBF and BBF were monitored using a hydrogen clearance tissue blood flowmeter (MGH-D1, Unique

Medical, Tokyo). Two needle electrodes (UHE-100, Unique Medical, Tokyo) were inserted and fixed into the center of the masseter muscle and the mandiblar medulla through the bone hole. PBF was continuously monitored using a laser Doppler blood flowmeter (ALF21, Unique Medical, Tokyo). A contact-type probe (Type C, Unique Medical, Tokyo) was placed on the mandiblar periosteum at the front margin of the masseter muscle in the mandibular body. Common carotid artery blood flow (CBF) was continuously monitored using an ultrasonic blood flowmeter (T108, Transonic, Ithaca, New York). A flow plobe (Type 3SB, Transonic, Ithaca, New York) was fixed to the left common carotid artery. Arterial blood gas was analyzed using a blood gases analyzer (Stat Profile 5, Nova Biomedical, Masachusetts).

$ETCO_2$ was continuously monitored using a capnograph (Capnomac, Datex, Helsinki). Acetated Ringer's solution was infused at 10 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the experiment. Body temperature was kept at 39.0-39.5 ℃ using a heat lamp.

After completion of the experimental preparation, animals were divided into two groups. Ten rabbits were anesthetized with ISO at 1.0 % of end-tidal concentration (Group I). The other 10 rabbits were anesthetized with continuous infusion of PROP at 12 $ml \cdot kg^{-1} \cdot h^{-1}$ (group P). Sixty minutes were elapsed for hemodynamic stabilization. Then, the control values were recorded (I4 or P4). After that, CO_2 was added to the inspired gas to maintain $ETCO_2$ at about 5.3, 6.7 and 8 kPa. More than 15 min was elapsed for hemodynamic stabilization at each $ETCO_2$ level. Measurements were

repeated at $ETCO_2$ levels of 5.3 kPa (I5.3 or P5.3), 6.7 kPa (I6.7 or P6.7) and 8 kPa (I8 or P8), respectively.

Observed variables included HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MBF, BBF, PBF and CBF. All data except MBF and BBF were continuously recorded on a polygraph (Polygraph series 360, NEC Sanei, Tokyo, Japan).

Data are shown as mean ± standard error of the mean. One-way ANOVA for repeated measurements were used for intragroup comparisons. Student-Newman-Keuls test was used for multiple comparisons. Student t-test was used for intergroup comparisons. Linear regression and Pearson's correlation coefficient were used to analyze the relationship of two variables. A *P* value less than 0.05 was considered to be statistically significant.

Results

$ETCO_2$ in both groups at each observation period was shown in Table 1. There were no differences between respective $ETCO_2$ of the two groups. $PaCO_2$ was almost equal to the respective $ETCO_2$ throughout the experiment.

HR in both groups gradually decreased as $ETCO_2$ increased. In contrast, SAP and DAP gradually increased as $ETCO_2$ increased (Table 1).

1. Changes in CBF

CBF in both groups showed significant increase as $ETCO_2$ increased. In group I, CBF at I4, I5.3, I6.7 and I8 were 32.4 ± 5.8, 36.6 ± 6.2, 40.7 ± 7.1, and 45.9 ± 8.1 $ml \cdot min^{-1}$, respectively. In group P, CBF at P4, P5.3, P6.7 and P8 were 28.4 ± 4.1, 32.9 ± 4.8, 38.0 ± 6.6, and 40.5 ± 6.7 $ml \cdot min^{-1}$, respectively. There were no differences between respective CBF of the two groups, though CBFs in group I were a little higher than those in group P (Fig. 1).

2. Changes in BBF

BBF in both groups showed significant increase as $ETCO_2$ increased. In group I, BBF at I4, I5.3, I6.7 and I8 were 43.9 ± 4.6, 48.0 ± 4.7, 55.0 ± 5.1, and 59.8 ± 5.7 $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively. In group P, BBF at P4, P5.3, P6.7 and P8 were 40.9 ± 6.4, 49.6 ± 5.9, 55.6 ± 5.8, and 59.5 ± 7.3 $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively. There were no differences between respective BBF of the two groups (Fig. 2).

3. Changes in MBF

MBF in group I showed significant decrease as $ETCO_2$ increased. In group I, MBF at I4, I5.3, I6.7 and I8 were 33.3 ± 2.8, 27.4 ± 4.0, 21.9 ± 3.9, and 15.6 ± 2.5 $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively. In group P, MBF at P4, P5.3, P6.7 and P8 were 22.9 ± 3.7, 20.0 ± 3.8, 17.8 ± 4.5, and 19.0 ± 3.7 $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively. MBF at I4 was higher than that at P4 (Fig. 3).

4. Changes in PBF

PBF in both groups did not change throughout the experiment. In group I,

PBF at I4, I5.3, I6.7 and I8 were 19.4 ± 5.0, 18.4 ± 5.2, 20.5 ± 5.6, and 19.1 ± 4.8 ml•min^{-1}•$100g^{-1}$, respectively. In group P, PBF at P4, P5.3, P6.7 and P8 were 11.9 ± 1.5, 11.7 ± 1.4, 12.2 ± 1.6, and 12.3 ± 1.4 ml•min^{-1}•$100g^{-1}$, respectively. There were no differences between respective PBF of the two groups, though PBFs in group I were a little higher than those in group P (Fig. 4).

5. Relationship between CBF and other parameters

Positive correlation (r=0.99 in group I and r=0.99 in group P) was observed between CBF and BBF (Fig. 5). In contrast, negative correlation (r=-0.999 in group I and r=-0.89 in group P) was observed between CBF and MBF (Fig. 6). There was positive relationship between CBF and PBF in group P (r=0.80) (Fig. 7). However, no changes in PBF were observed as $ETCO_2$ increased in both groups.

Discussion

Our results indicate that CBF and BBF increased while MBF decreased and PBF remained unchanged as $ETCO_2$ increased during both ISO and PROP anesthesia. It is therefore suggested that changes in $PaCO_2$ are associated with blood flow redistribution in oral tissues.

In this experiment, anesthesia was maintained with 1% ISO or 12 ml•kg^{-1}•h^{-1} propofol. Minimum alveolar concentration (MAC, anesthetic concentration at which 50% of patients or animals do not respond to surgical stimuli) of ISO in the New

Zealand White rabbit was 2.05 ± 0.18 % (18). Therefore, it was calculated that rabbits were anesthetized at 0.5 MAC level. This level might be well over minimum alveolar concentration for loss of consciousness (MAC-awake, anesthetic concentration at which 50% of patients do not respond to verbal commands) (19-22). Blood concentration of PROP for loss of consciousness ($Cp50_{loss\ of\ consciousness}$, blood concentration at which 50% of patients do not respond to verbal command) was about 3.3-4.4 $\mu g \cdot ml^{-1}$ in humans (23, 24). Infusion rate of PROP to keep this blood concentration was about 9-12 $ml \cdot kg^{-1} \cdot h^{-1}$. Therefore, the depth of anesthesia of the rabbits receiving PROP in the present study was comparable with those receiving 1% ISO.

Hypercapnia increases sympathetic nervous activities which are followed by an increase in cardiac output and peripheral vasodilatation (25-28). Increases in CBF in both groups were proportional to those in $ETCO_2$ in the present study. These results suggest that the change in CBF is attributable to the change in cardiac output. CBF in group I was a little higher than that in group P, though not statistically significant. This might be attributable to stronger vasodilatation of ISO than that of PROP (29, 30).

The increase in CBF may induce an increase in total tissue blood flow in oral and maxillofacial region supplied by the external carotid artery because cerebral blood flow supplied by the internal carotid artery was maintained almost constant by the autoregulation mechanisms. Therefore, it was speculated that BBF, MBF and PBF showed increases propotional to the increase in CBF. However, this hypothesis was

rejected.

It was reported that changes in BBF was dependent on CBF changes which were proportional to cardiac output (31). Results of the present study agree with that study because BBF increases were proportional to CBF increases. Therefore, it is suggested that cardiac output is the main determinant of BBF. In contrast, MBF in both groups decreased as $ETCO_2$ increased. In our previous study, tissue oxygen tension of the masseter muscle showed a decrease during hypercapnia with the $PaCO_2$ level at 8 kPa in rabbits (unpublished data). Since measurement of the tissue oxygen tension was performed during muscle relaxation, muscular oxygen consumption could be minimal. Therefore, decreases in tissue oxygen tension of the masseter muscle might be proportional to those in MBF. Previous studies reported that hypercapnia decreased blood flow of skeletal muscles other than head and neck regions (15-17). These results suggest that changes in $PaCO_2$ inversely affect the blood flow of skeletal muscles. PBF was not affected by hypercapnia under both anesthetic conditions. PBF in group I was a little higher than that in group P, though not statistically significant. This might be attributable to stronger vasodilatation of ISO than that of PROP (29, 30).

Our findings indicate that changes in $PaCO_2$ are associated with blood flow redistribution in oral tissues. Although mechanisms for the redistribution is unclear, it is possible that vascular responses to carbon dioxide itself and secondary sympathetic acceleration or inhibition may be different among various tissues such as bone marrow,

skeletal muscles, periosteum, and mucosal membrane (13, 31-33). It is reported that distributive ratio of adrenergic alpha and beta receptors are different between skeletal muscles and skin / mucosal membrane (34). This diversity of distribution may contribute to redistribution of tissue blood flow.

In the clinical situation, it is suggested that if the mandibular medulla is involved in the surgical field such as orthognathic surgery, bleeding may be reduced under hypocapnic condition. Anesthesia with PROP may be more preferable to that with ISO. In contrast, if the skeletal muscles such as the masseter muscle are involved in the surgical field, bleeding may be reduced under hypercapnic condition. Anesthesia with PROP may be also more preferable to that with ISO. In addition, PROP is better than ISO because PROP has strong anti-emetic effects along with clear emergence (35-37). Therefore, it is suggested that PROP anesthesia with $PaCO_2$ level adjusted by the planned surgery is a good candidate for oral and maxillofacial surgery. Profound hypercapnic and hypocapnia may increase arrythmogenic myocardial sensitivity to epinephrine which will be used along with local anesthetics during surgery (38). Therefore, excessive $PaCO_2$ increase or decrease should be avoided.

In the present study, SAP at I5.3 and I8 were higher than I4. However this difference was only 0.8 kPa and should have minimal effect on tissue blood flows. An elevation of SAP up to 20 kPa did not change oral mucosal blood flow (39). Since fentanyl decreases tongue mucosal blood flow in rabbits (10), studies with a

combination of PROP and fentanyl on tissue blood flow deserve future investigation.

In conclusion, oral tissue blood flow was affected by the change in $PaCO_2$ during both ISO and PROP anesthesia. BBF increase and MBF decrease were both observed during hypercapnia and *vice versa*. Oral tissue blood flow during the PROP anesthesia was relatively less than that during the ISO anesthesia.

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Table and figure legend

Table 1. $ETCO_2$ and hemodynamic variables .

Data are expressed as mean ± standard error of the mean.

$ETCO_2$: End-tidal CO_2 tension, HR: heart rate, SAP: systolic arterial pressure, DAP: diastolic arterial blood pressure.

I4 and P4 show $ETCO_2$ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show $ETCO_2$ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show $ETCO_2$ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show $ETCO_2$ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 1. Changes in CBF. CBF in both groups increased as $ETCO_2$ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show $ETCO_2$ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show $ETCO_2$ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show $ETCO_2$ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show $ETCO_2$ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 2. Changes in BBF. BBF in both group increased as $ETCO_2$ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show $ETCO_2$ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show $ETCO_2$ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show $ETCO_2$ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show $ETCO_2$ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 3. Changes in MBF. MBF in both group decreased as $ETCO_2$ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show $ETCO_2$ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show $ETCO_2$ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show $ETCO_2$ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show $ETCO_2$ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 4. Changes in PBF. PBF in both group did not changed as $ETCO_2$ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show $ETCO_2$ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show $ETCO_2$ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show $ETCO_2$ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show $ETCO_2$ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 5. Relationship between CBF and BBF. Positive correlation (r=0.99 in isoflurane

group and r=0.99 in propofol group) was observed between CBF and BBF.

Fig. 6. Relationship between CBF and MBF. Negative correlation (r=-0.999 in isoflurane group and r=-0.89 in propofol group) was observed between CBF and MBF.

Fig. 7. Relationship between CBF and PBF. No increases (r=0.14 in isoflurane group and r=0.80 in propofol group) in PBF were observed as $ETCO_2$ increased.

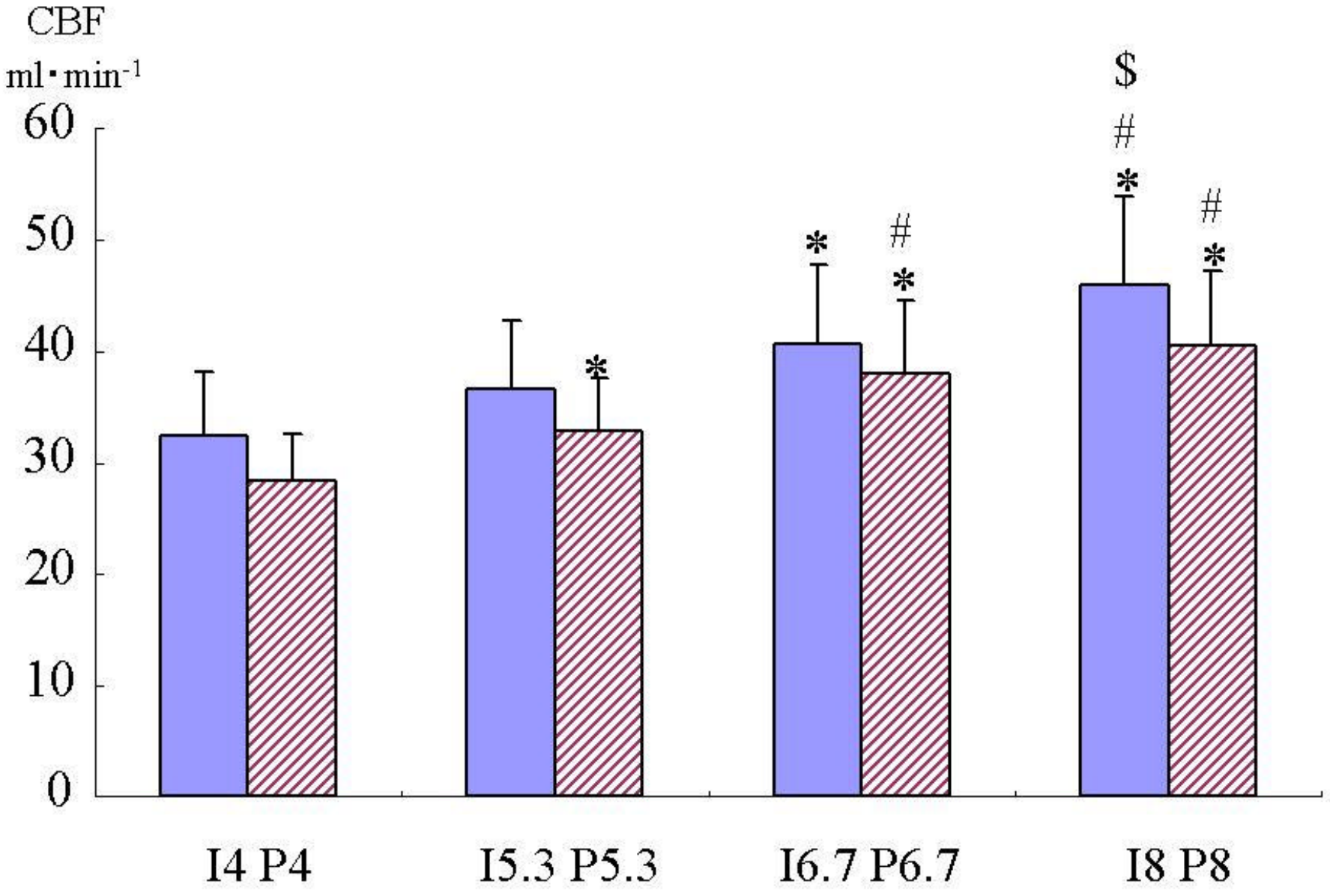

CBF
ml·min-1
60
50
40
30
20
10
0
I4 P4
I5.3 P5.3
I6.7 P6.7
I8 P8
ISO
PROP
* P < 0.05 vs I4 or P4
# P < 0.05 vs I5.3 or P5.3
$ P < 0.05 vs I6.7

Fig. 1

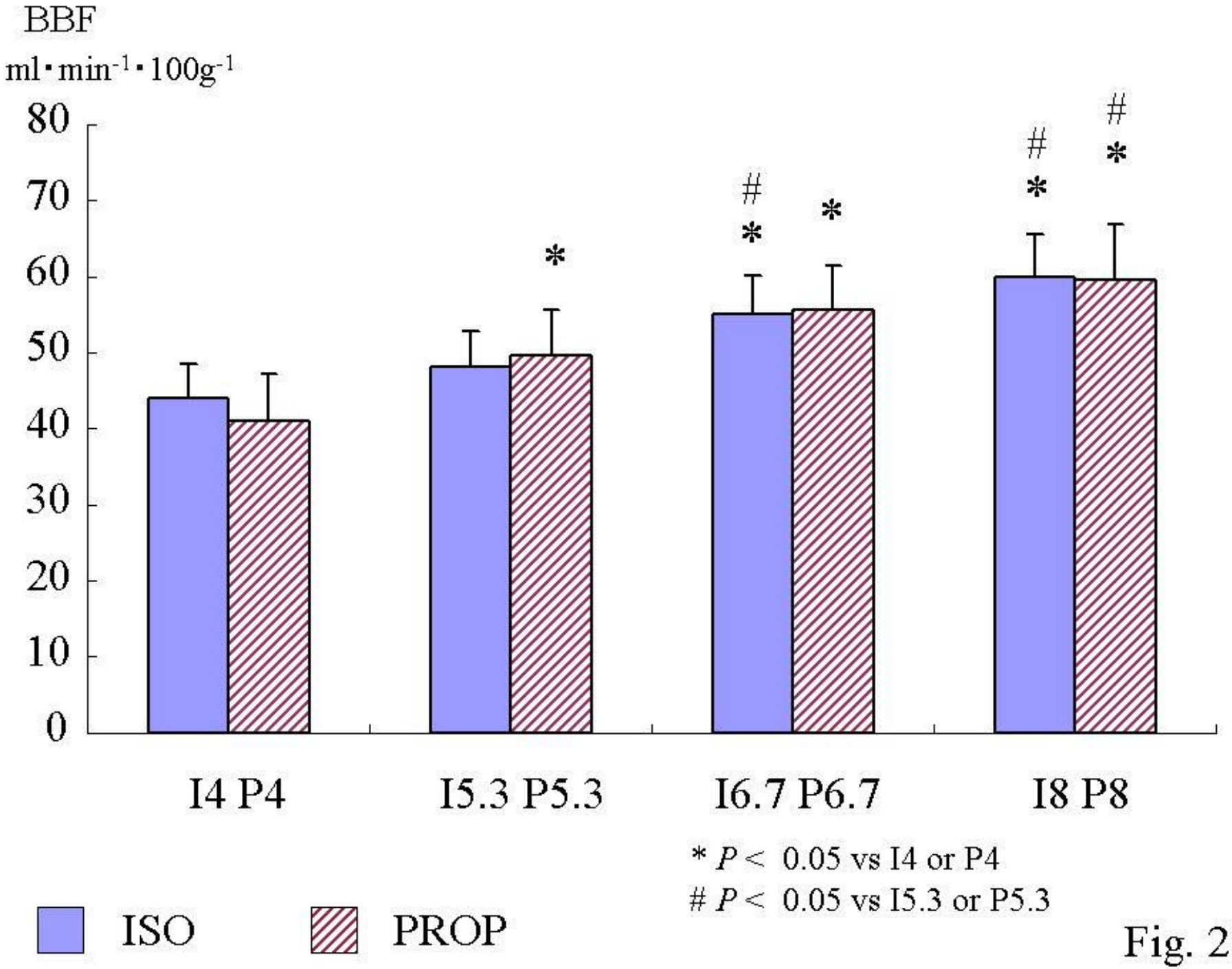
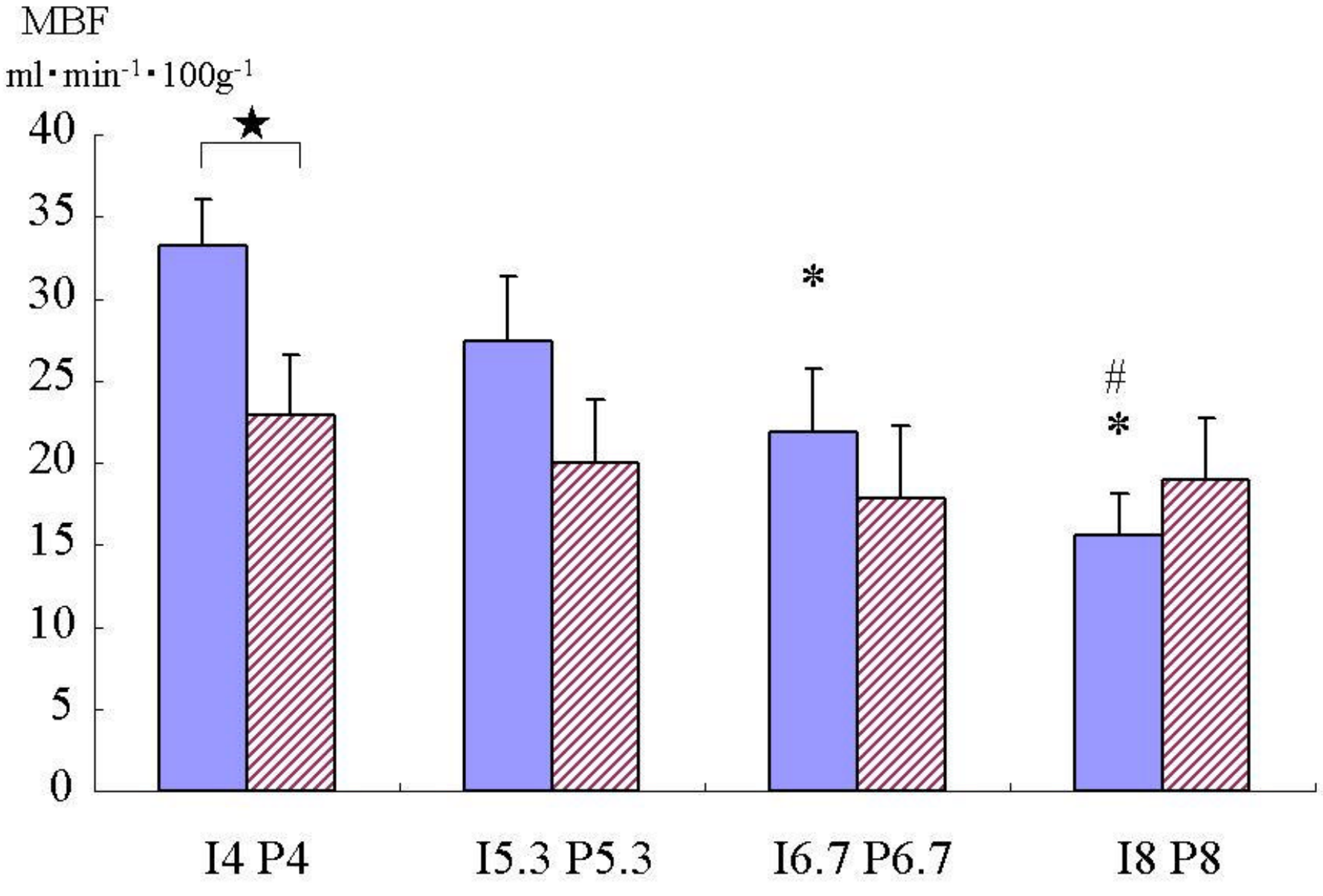

BBF
ml·min-1·100g-1
80
70
60
50
40
30
20
10
0
I4 P4
I5.3 P5.3
I6.7 P6.7
I8 P8
* P < 0.05 vs I4 or P4
# P < 0.05 vs I5.3 or P5.3
ISO
PROP

Fig. 2



* $P <$ 0.05 vs I4
\# $P <$ 0.05 vs I5.3
★ $P <$ 0.05 between 2 groups

Fig. 3

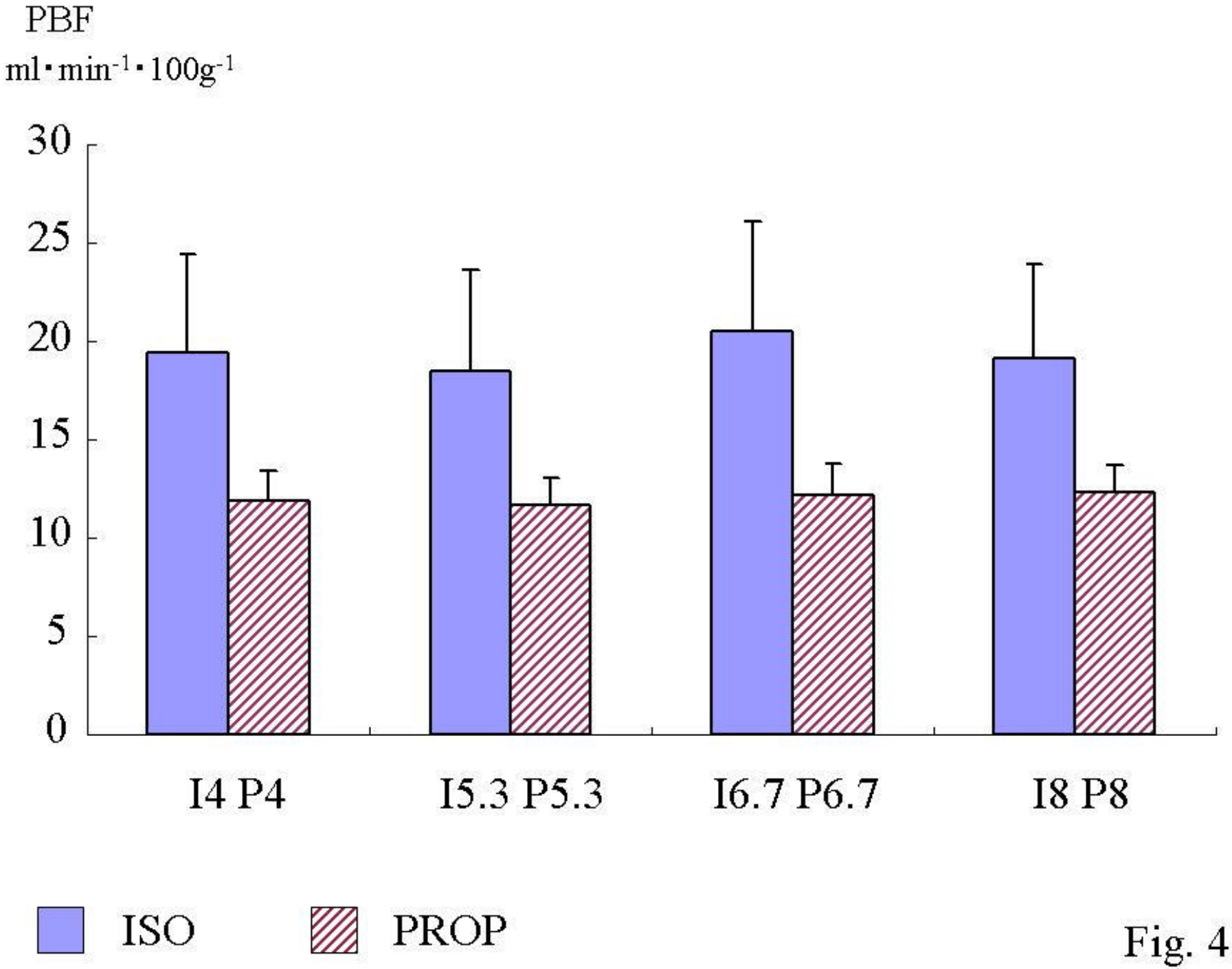

PBF
ml·min-1·100g-1
30
25
20
15
10
5
0
I4 P4
I5.3 P5.3
I6.7 P6.7
I8 P8
ISO
PROP

Fig. 4

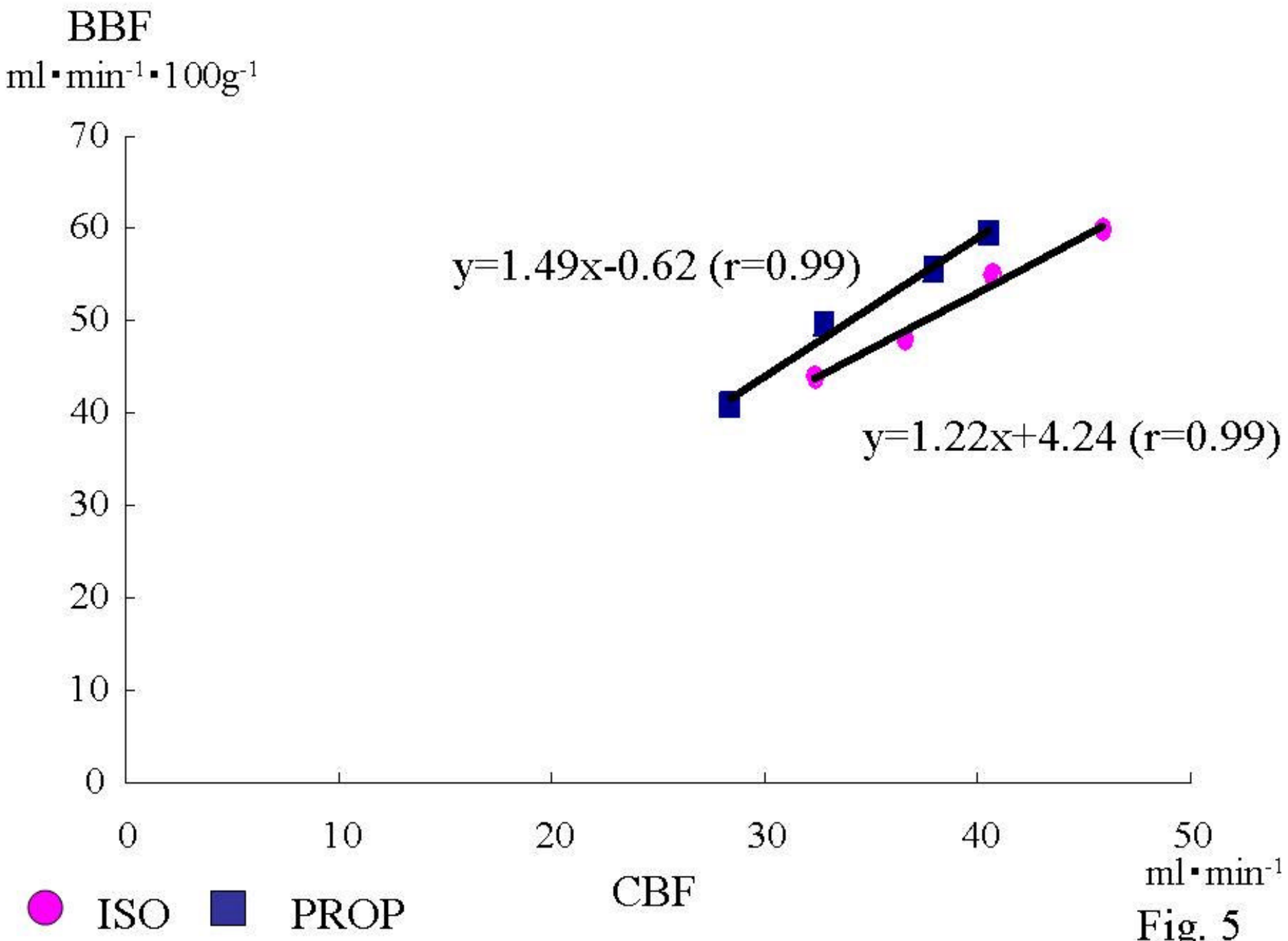

BBF
ml·min-1·100g-1
70
60
50
40
30
20
10
0
y=1.49x-0.62 (r=0.99)
y=1.22x+4.24 (r=0.99)
0
10
20
30
40
50
ml·min-1
CBF
ISO
PROP

Fig. 5

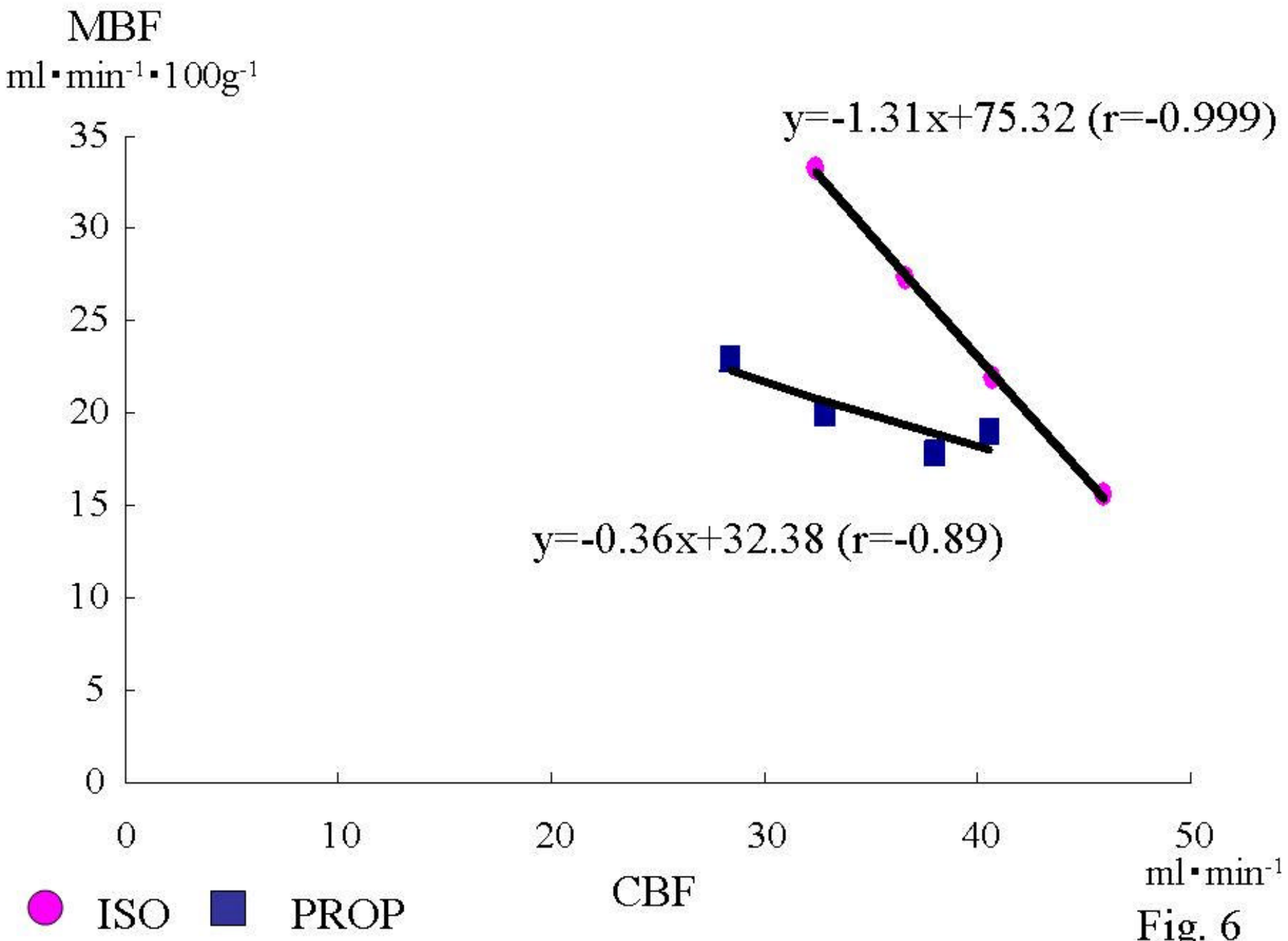

MBF
ml·min-1·100g-1
y=-1.31x+75.32 (r=-0.999)
y=-0.36x+32.38 (r=-0.89)
35
30
25
20
15
10
5
0
0
10
20
30
40
50
ml·min-1
CBF
ISO
PROP

Fig. 6

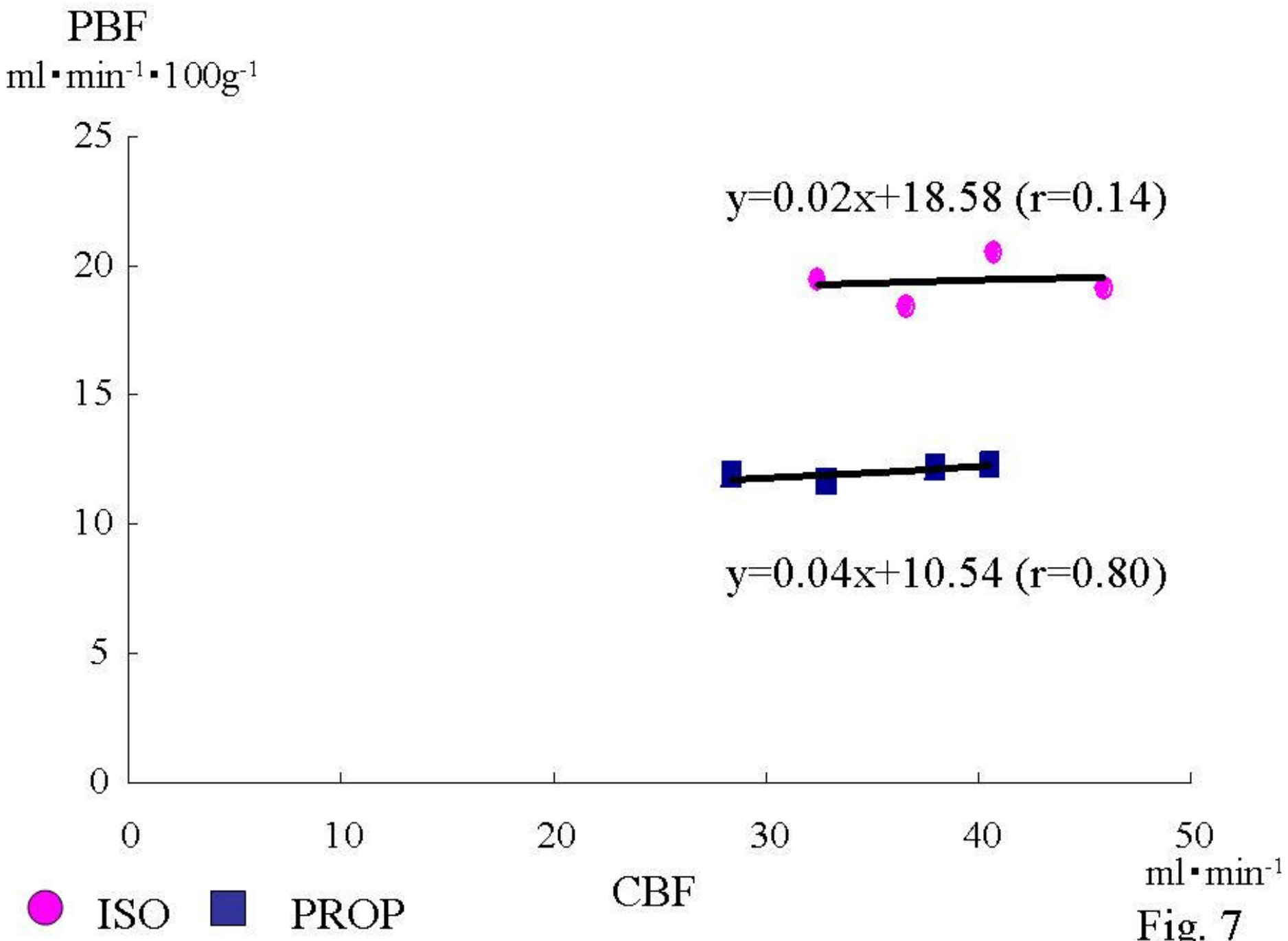

PBF
ml·min-1·100g-1
25
20
15
10
5
0
y=0.02x+18.58 (r=0.14)
y=0.04x+10.54 (r=0.80)
0
10
20
30
40
50
ml·min-1
CBF
ISO
PROP

Fig. 7

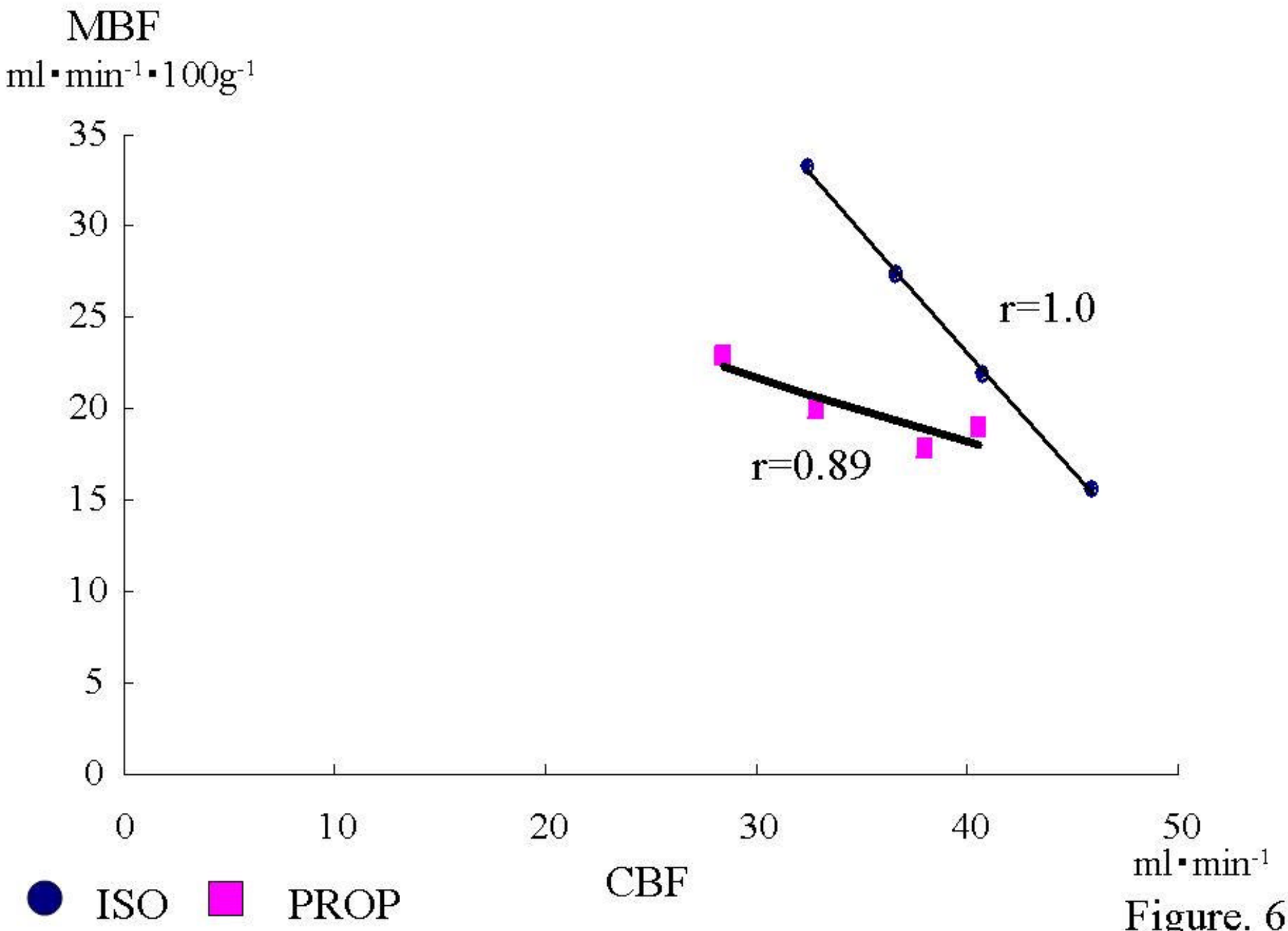

MBF
ml·min-1·100g-1
35
30
25
20
15
10
5
0
0
10
20
30
40
50
ml·min-1
CBF
r=1.0
r=0.89
ISO
PROP

Figure. 6