

Chapter 30

Cardiovascular Adaptation in Response to Chronic Hypoxia in Awake Rats

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Abstract To examine how cardiovascular adaptation to chronic hypoxia might evolve, the responses to blood pressure (Pt) and hematocrit (Ht) during long-term systemic exposure to hypoxia were observed in awake rats. Furthermore, the total peripheral vascular resistance (TPR) was estimated using direct measurements of systemic blood pressure (Ps) and blood flow (Qs) in carotid artery based on Darcy's law ($TPR = Ps/Qs$) to evaluate the remodeling procedure in the microcirculation. BP and Ht under normoxic conditions were kept almost constant, while hypoxic exposure immediately increased Ht to 58 % and, thereafter, it remained stable. The TPR values showed no significant differences between hypoxic and normoxic conditions. These results suggest that effects of high viscosity caused by increasing Ht on peripheral vascular resistance can be compensated by inducing microvascular remodeling with the arteriolar dilation and capillary angiogenesis.

Keywords Hypoxia • Total peripheral vascular resistance • Microvascular remodelling • Awake rats

1 Introduction

Whether the long-term exposure of hypoxia results in significant harmful effects to the cardiovascular system or induces protective properties that mediate vascular remodeling remains unclear [1]. In studies of the pathophysiological effects, hypoxic exposure has been used to develop an animal model for pulmonary hypertension [2], while hypoxic training is believed to be capable of potentiating greater performance improvements [3]. In addition, the morbidity rates of hypertension and coronary heart disease are reportedly lower in populations residing at high altitudes [4]. The purpose of the present study was to examine how cardiovascular adaptation to chronic hypoxia might develop. For this purpose, the blood pressure (Pt) and hematocrit (Ht) responses during long-term systemic exposure to hypoxia were observed in awake rats. Furthermore, the total peripheral vascular resistance (TPR)

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2 Material and Methods

2.1 Experimental Protocols

All animal procedures were approved by the Shibaura Institute of Technology Animal Care and Use Committee. A total of 29 male Wister rats weighing 130–220 g (5–8 weeks old) were used in this study. Fourteen rats were used to measure the Pt and Ht responses to chronic exposure of hypoxia for 2 weeks. After Pt and Ht measurements during chronic exposure of hypoxia, these rats were provided to determine the TPR value. The TPR values under normoxic conditions were obtained by the remaining 15 rats. The chronic exposure to hypoxia of rats was carried out by housing the animals in a hypoxic chamber (ProOx110, USA) for 2 weeks, in which this chamber was kept at an oxygen concentration of 10 % by injecting nitrogen. The oxygen concentration of 10 % is equivalent to oxygen concentration at an altitude of 5500 m. The breeding room including the animal chamber and, the Pt and Ht measuring area were maintained a temperature of 20 °C.

2.2 Blood Pressure (Pt) and Hematocrit (Ht) Measurements

Pt and Ht were measured every 3 days during 2 weeks exposure to hypoxia. Pt was measured non-invasively using the tail-cuff oscillometric method (Softron, Japan) and the obtained Pt value was represented as the mean blood pressure. The Ht value was obtained with the conventional method by blood sampling from a tail vein. Only during a measuring period the rats were anesthetized by inhalation of ether and kept on the heated mat to prevent the reduction of body temperature.

2.3 Determination of Total Peripheral Resistance (TPR)

The changes in total peripheral vascular resistance (TPR) under hypoxic and normoxic conditions were determined to measure the Ps and Qs in carotid artery under anesthesia with urethane. First, Qs measurement was performed using a transit time blood flowmeter for small arteries (Transonic Systems, USA). The flow probe was attached to a carotid artery and obtained the flow signal continuously with mean value. On the other hand, to measure the Ps, the catheter was

cannulated to carotid artery and connected to the pressure transducer (Ohmeda, USA). In this measurement, Ps value was also represented by the mean blood pressure. On the other hand, based on these measured Ps and Qs values, Darcy's law was applied to determine a total peripheral vascular resistance as $TPR = Ps/Qs$. All animals in which the Ps or Qs value fell to <60 mmHg or <3 mL/min during experiment were excluded.

2.4 Data Analysis

All data are reported as means \pm SD. Data within each group were analyzed by analysis of variance for repeated measurements (ANOVA). Differences between groups were determined using a t-test with the Bonferroni correction. Differences with a p-value of <0.05 were considered statistically significant.

3 Results

3.1 Changes in Blood Pressure and Hematocrit to Hypoxia

Figure 30.1 shows the changes in mean Pt and Ht under hypoxic conditions in awake rats. Mean Pt and Ht under normoxic conditions before exposure of hypoxia remained almost constant (Pt: 78 ± 8.0 mmHg, Ht: 45 ± 3.5 %), while hypoxic exposure immediately increased Ht to 58 % and, thereafter, it remained stable. The mean Pt during hypoxic exposure showed no significant changes: from 81 ± 8.6 mmHg at the beginning to 84 ± 8.4 mmHg at the end.

3.2 Comparison of Peripheral Vascular Resistance (TPR)

To compare the peripheral vascular resistance under normoxic and hypoxic conditions, the blood flow (Qs) and mean blood pressure (Ps) in carotid artery were measured directly in anesthetized rats. The measured Qs and Ps values with carotid artery during 2 weeks hypoxic exposure are shown in Fig. 30.2. Although the blood flow after 2 weeks hypoxic exposure has a tendency to decrease, there were no significant differences compared with those of normoxic conditions (hypoxia: Qs and Ps: 5.2 ± 2.3 mL/min and 96 ± 22 mmHg, normoxia: 6.8 ± 1.9 mL/min and 89 ± 14 mmHg). The total peripheral resistance (TPR) values obtained by Qs and Ps are shown in Fig. 30.3. Again, there are no significant differences between TPR values under hypoxic and normoxic conditions (21 ± 10 and 15 ± 5 mmHg min mL⁻¹).

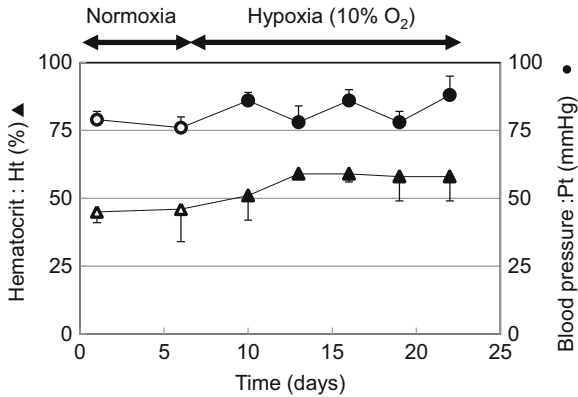


Fig. 30.1 Changes in mean blood pressure (Pt) measured by the tail-cuff method and hematocrit under normoxic and hypoxic conditions. All measurements were carried out under anesthesia by inhalation of ether

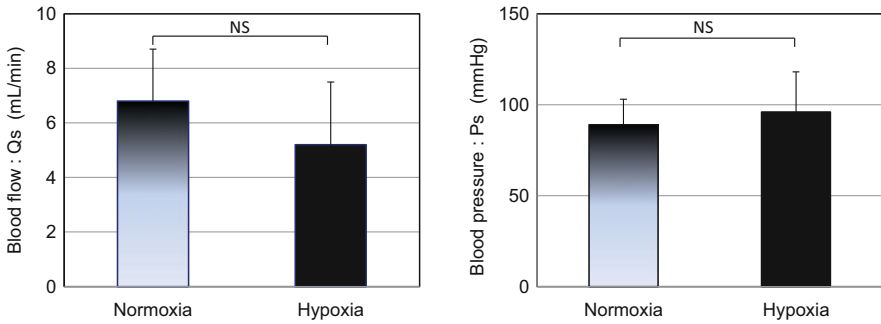


Fig. 30.2 The direct measured blood flow (Qs) and mean blood pressure (Ps) in carotid artery under normoxic conditions and after 2 weeks hypoxic exposure. There were no significant differences between normoxic and hypoxic values

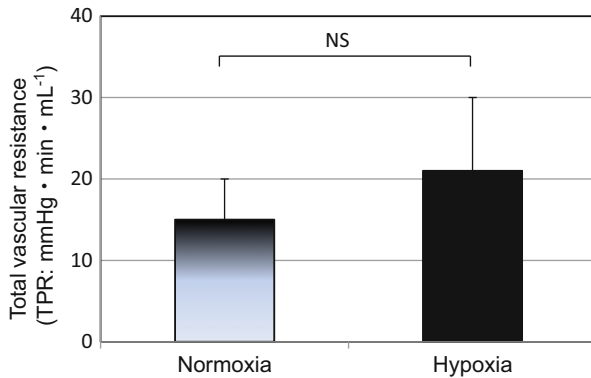
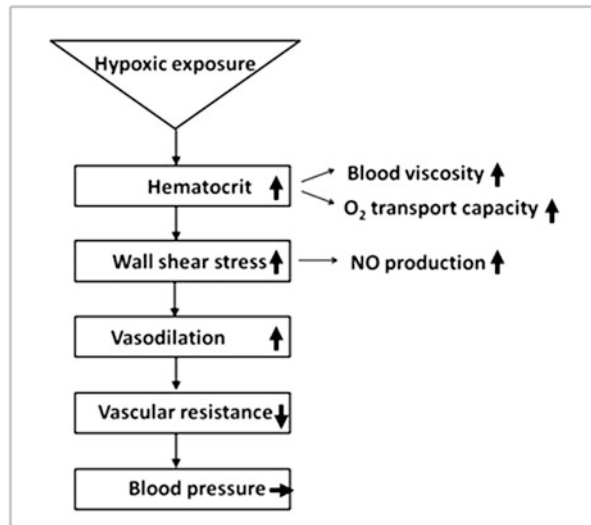


Fig. 30.3 The total peripheral resistance (TPR) values under normoxic conditions and after 2 weeks hypoxic exposure obtained by Qs and Ps. There are no significant differences between the values under hypoxic and normoxic conditions

4 Discussion

In the present study, we aimed to clarify how cardiovascular adaptation to chronic hypoxia would evolve. For this purpose, the responses to blood pressure and hematocrit during 2 weeks systemic exposure to hypoxia were observed in awake rats. The total peripheral vascular resistances under hypoxic and normoxic conditions were compared to evaluate the remodeling procedure in the microcirculation. The Ht values under hypoxic exposure immediately increased to 58 % and, thereafter, remained stable. These changes in Ht are well-known responses to hypoxia or hypobaric conditions [5, 6]. On the other hand, the blood pressure was kept almost constant during 2 weeks exposure to hypoxia in this study. This constancy of blood pressure implies successful adaptation to chronic hypoxia through protective mechanisms that mediate vascular remodeling. There are many reports that the hypoxia induced microvascular angiogenesis [7, 8] and vasodilation [9], in which one of the major factors is the high vascular wall shear stress induced by increased blood viscosity. Increased shear stress increases the endothelial nitric oxide production. The successful process of cardiovascular adaptation to chronic hypoxia considered from the present study is shown in Fig. 30.4.

Fig. 30.4 The successful process of cardiovascular adaptation to chronic hypoxia



5 Conclusion

These results suggest that the effects of high viscosity caused by increasing Ht on peripheral vascular resistance can be compensated by inducing microvascular remodeling with arteriolar dilation and capillary angiogenesis.

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