Permissive range of hypercapnia for improved peripheral microcirculation and cardiac output in rabbits*

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Objectives: **Permissive hypercapnia improves outcomes in patients with respiratory failure, most likely because of a reduction in ventilator-induced lung injury. Because hypercapnia is a potent vasoactive stimulus, adequate tissue perfusion and oxygen delivery to dilated microvessels may be restored. We examined how $Paco_2$ affects microvascular changes, hemodynamics, and cardiac output in rabbits. We evaluated the permissive range of $Paco_2$ required for maintenance of the peripheral circulation.**

Design: **Prospective experimental animal study.**

Setting: **Animal research laboratory.**

Subjects: **A total of 31 Japanese domestic white rabbits.**

Interventions: **The animals were anesthetized with pentobarbital. An ear chamber was prepared to examine blood vessels by intravital microscopy. The rabbits were mechanically ventilated with air, oxygen, and CO_2. The values of $Paco_2$ were adjusted to about 20 (hypocapnia), 40 (normocapnia), 60, 80, 100, 125, 150, and >250 mm Hg (hypercapnia). After stabilization at each $Paco_2$ level, microvascular changes were recorded with a microscope-closed video camera to permit analysis of arteriolar diameter and blood flow.**

Measurements and Main Results: **The pH and heart rate decreased and mean blood pressure increased progressively as the $Paco_2$ was increased. When $Paco_2$ was increased from 20 to 80 mm Hg, vessel diameter, blood-flow velocity, and blood-flow rate increased markedly. Cardiac output increased slightly. When $Paco_2$ exceeded 100 mm Hg, all of these variables decreased. When $Paco_2$ exceeded 150 mm Hg, all variables were significantly lower than the control values ($p < .01$).**

Conclusion: **Intravital microscopic visualization of the rabbit ear microcirculation showed that 150 mm Hg is the permissive upper limit of acute hypercapnia with respect to maintenance of the peripheral microcirculation. (Crit Care Med 2007; 35:2171–2175)**

KEY WORDS: permissive hypercapnia; respiratory acidosis; microcirculation; cardiac output; hemodynamics

Recent clinical studies have suggested that ventilatory strategies designed to limit ventilator-induced lung injury may improve outcomes in acute respiratory distress syndrome (1, 2). These strategies limit tidal volume and inflation pressure, potentially causing hypercapnic acidosis. Until recently, hypercapnic acidosis was considered acceptable if it reduced the risk of other side effects (3) and improved outcomes in patients with respiratory failure (permissive hypercapnia). In addition to reducing ventilator-induced lung injury, hypercapnia is a potent vasoactive stimulus that may restore adequate tissue perfusion and promote oxygen delivery to dilated microvessels (4).

How to maintain the microcirculation during tolerated hypercapnia is a very important issue. The microcirculation has an important role in regulating substance exchange, metabolism, and hemodynamics. Microcirculatory disorders can impair the supply of nutrients and oxygen to tissues, causing organ failure. Conversely, maintenance of the microcirculation can prevent the onset of organ failure. Therefore, investigation of the microcirculation during hypercapnia may help to establish acceptable limits of CO_2 that permit maintenance of adequate blood flow to tissues. However, most previous investigations have focused on cerebrovascular responses to hypercapnia (5), and studies of peripheral vessels during hypercapnia are scant. We therefore evaluated whether the microcirculation was maintained during hypercapnia in rabbits. The microcirculation was assessed by means of the rabbit ear chamber (REC) method (6).

The REC method developed at our laboratory allows a single blood vessel to be observed by intravital microscopy, both directly and noninvasively, on a real-time basis. This method has been confirmed to be useful for observing the effects of various interventions on peripheral hemodynamics (6). Vasomotor activity, neural control, and responses of vessels to drugs in an REC are similar to those of *in situ* vessels 6 wks after attachment to a clear window (6). We have used this model to study the peripheral microcirculation during wound healing (7), systemic agglutination anaphylaxis (8), acute severe hemorrhage during colloid resuscitation (9), and the effects of inspired oxygen concentrations (10).

In the present study, we examined how $Paco_2$ affects microvascular changes, hemodynamics, and cardiac output in rabbits. We evaluated the permissive range of $Paco_2$ required for maintenance of the peripheral circulation.

MATERIALS AND METHODS

Animal Preparation. All experiments were in accordance with the National Institutes of Health guidelines on the use of experimental

***See also p. 2229.**

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The authors have not disclosed any potential conflicts of interest.

Supported, in part, by grant-in-aid 18591727 from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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DOI: 10.1097/01.ccm.0000281445.77223.31

animals. Approval from the Animal Use Committee of Tokyo Women's Medical University was obtained before initiating the experiments.

A total of 20 randomly selected Japanese domestic white rabbits (body weight, 2.5–3.0 kg) were studied. Transparent round chambers made of acrylic resin were inserted in the earlobes as described previously (6). New microvessels arose from the blood vessels of the dermis and covered the entire cavity within 6 wks. More than 6 wks after insertion of the ear chamber, the RECs were observed microscopically at a magnification of ×100. Microcirculatory changes were recorded using a microscope-closed video camera (DXC 750, SONY, Tokyo, Japan) with a shutter speed of 1/10,000 of a second.

After intravenous injection of pentobarbital, 30 mg/kg, the trachea of the rabbit was intubated, and 1 mg/kg pancuronium was administered intravenously. Anesthesia was maintained by the intravenous injection of 30 $mg \cdot kg^{-1} \cdot hr^{-1}$ pentobarbital. Respiration was controlled with the use of a ventilator (ART-100, ACOMA, Tokyo, Japan). Arterial blood gases were monitored with a continuous intraarterial blood-gas monitoring system (Paratrend 7TM, Ciba-Corning, Tokyo, Japan) and measured with a blood-gas analyzer (ABL330, Radiometer, Tokyo, Japan) throughout the study. The accuracies of $Paco_2$ and pH were ±1.0 mm Hg and ±0.005 (±SD), respectively. The Pao_2 was maintained at >100 mm Hg during the study to eliminate potential effects of systemic hypoxemia on the results. $Paco_2$ of >250 mm Hg or pH <6.75 could not be measured by the blood-gas analyzer. Oral temperature was continuously monitored, and body temperature was kept constant with the use of a heating pad.

Heart rate was monitored with an electrocardiograph. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure were monitored with a high-fidelity transducer-tipped catheter (Millar Microtip catheter pressure transducer, 6F SPC-360, Millar Instruments, Houston, TX) placed in the right femoral artery. A similar catheter was placed in the left femoral artery to insert a sensor probe for continuous intraarterial blood-gas monitoring. A 20-gauge, 3.2-cm catheter (Terumo, Tokyo, Japan) was placed in the left auricular vein for administration of lactated Ringer solution at a rate of 10 $mL \cdot kg^{-1} \cdot hr^{-1}$ throughout the experiment in all rabbits. All signals were monitored continuously with a multichannel polygraph (360, NEC San-ei, Tokyo, Japan). All variables were recorded continuously throughout the experiments.

Study Design and Experimental Protocol. The rabbits were first mechanically ventilated with air and oxygen to maintain Pao_2 at 100–150 mm Hg and $Paco_2$ at around 20 mm Hg (hypocapnia). The tidal volume was 15 mL/kg. The respiratory rate was 35 breaths/min. The respiratory flow was 6 L/min. About 20 mins was required for stabilization of arteriolar hemodynamics. The stabilized arteriolar hemodynamics were then observed during hypocapnia. The ventilation conditions remained constant, and 0.5 L/min CO_2 was added to inspired gas; $Paco_2$ rose to around 40 mm Hg (normocapnia). About 20 mins was required to stabilize arteriolar hemodynamics, and then the stabilized arteriolar hemodynamics and the microcirculation were observed. The ventilation conditions were unchanged, and 1 to 3 L/min CO_2 was added to inspired gas to achieve $Paco_2$ values of around 60, 80, 100, 125, 150, and >250 mm Hg (hypercapnia). About 20 mins was required to stabilize arteriolar hemodynamics for each of these conditions, and then the stabilized arteriolar hemodynamics were observed. About 30 mins was required for each observation.

During the hypocapnia stabilization period after surgical preparation, we selected arterioles with diameters of 20 to 100 μm, displayed on a video television screen. Blood-vessel diameter, blood-flow velocity, and blood-flow rate after adding CO_2 were compared with the normocapnia values. To analyze blood-flow velocity, the play speed of the video recorder was set at 1/60 of a second. The distances between two erythrocytes at the center of the blood vessel were measured ten times, and the values were averaged. Blood-flow rate was calculated by multiplying the blood-flow velocity by the blood vessel cross-sectional area.

Cardiac output was measured in another group of 11 rabbits. The rabbits underwent thoracotomy, and an electromagnetic flowmeter probe (MVF-3200, Nihonkoden, Tokyo, Japan) was placed at the origin of the aorta. Similar to the procedure described above, the rabbits were exposed to inhaled CO_2, and the change in cardiac output was determined relative to the change in $Paco_2$. Because the microcirculation may be influenced by thoracotomy, which was required to measure cardiac output, different groups of rabbits were used to measure cardiac output and to observe the microcirculation. Stroke volume was calculated on the basis of cardiac output and heart rate.

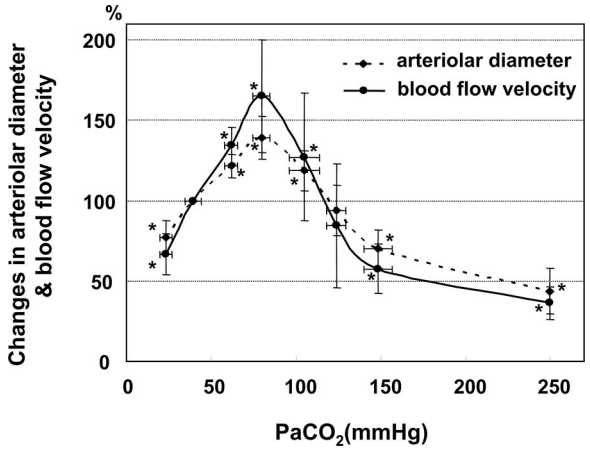

Figure 1. Changes in arteriolar diameter and blood-flow velocity. *Dotted lines*, arteriolar diameter; *solid line*, blood-flow velocity. Data are expressed as mean ± SD; *$p < .01$ vs. the normocapnia value.

Statistical Analysis. All data are expressed as mean ± SD. Statistical comparisons were performed using repeated-measures analysis of variance followed by Fisher's protected least-significant difference test. A value of $p < .01$ was considered to indicate statistical significance.

RESULTS

Figure 1 shows the changes in arteriolar diameter and blood-flow velocity as a function of $Paco_2$. The arteriolar diameter during normocapnia (a $Paco_2$ of around 40 mm Hg) served as control (100%). As compared with control, the arteriolar diameter significantly decreased when the $Paco_2$ was around 20 mm Hg (77.2% ± 10.6%, $p < .01$) and significantly increased when the $Paco_2$ was around 60 mm Hg (121.6% ± 7.1%) or around 80 mm Hg (139.1% ± 13.2%, $p < .01$). When the $Paco_2$ exceeded 100 mm Hg, arteriolar diameter began to decrease. At a $Paco_2$ of around 150 mm Hg, arteriolar diameter significantly decreased (69.9% ± 11.8%), as compared with control ($p < .01$). The blood-flow velocity showed a similar trend. As compared with control, the blood-flow velocity significantly decreased at a $Paco_2$ of around 20 mm Hg (66.8% ± 12.9%, $p < .01$) and significantly increased at a $Paco_2$ of around 60 mm Hg (134.5% ± 11.3%) or 80 mm Hg (165.3% ± 35.1%, $p < .01$). The blood-flow velocity began to decrease when the $Paco_2$ exceeded 100 mm Hg. The blood-flow velocity significantly decreased at a $Paco_2$ of about 150 mm Hg (57.7% ± 15.3%), as compared with control ($p < .01$).

Figure 2 shows the changes in blood-flow rate, cardiac output, and stroke volume as a function of $Paco_2$. Blood-flow rate showed a trend similar to the

changes in arteriolar diameter. As compared with control, the blood-flow rate significantly decreased at a $Paco_2$ of 20 mm Hg (39.7% ± 10.7%, $p < .01$) and significantly increased at a $Paco_2$ of 60 mm Hg (199.3% ± 28.6%) and 80 mm Hg (320.9% ± 84.1%, $p < .01$). When the $Paco_2$ was ≥100 mm Hg, the blood-flow rate started to decline and was significantly lower than the control value at a $Paco_2$ of around 150 mm Hg.

Cardiac output increased when $Paco_2$ increased from 20 to 80 mm Hg and decreased when $Paco_2$ exceeded 100 mm Hg. As compared with control, the cardiac output significantly decreased at a $Paco_2$ of around 20 mm Hg (93.9% ± 9.6%, $p < .01$) and significantly increased at a $Paco_2$ of around 80 mm Hg (108.3% ± 7.5%, $p < .01$). The cardiac output significantly decreased at a $Paco_2$ of around 150 mm Hg (66.3% ± 14.4%), as compared with control ($p < .01$). Changes in cardiac output were smaller than those in blood-flow rate.

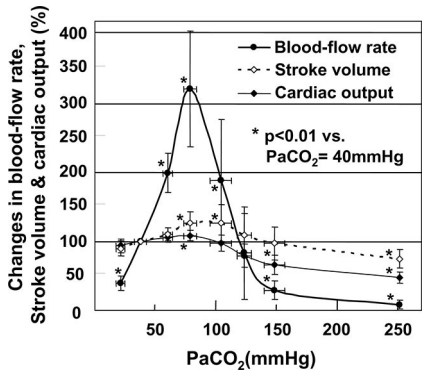

Figure 2. Changes in blood-flow rate, cardiac output, and stroke volume. *Heavy line*, blood-flow rate; *thin line*, cardiac output; *dotted line*, stroke volume. Data are expressed as mean ± SD; *$s < .01$ vs. the normocapnia value.

Stroke volume increased when $Paco_2$ increased from 20 to 100 mm Hg and decreased when the $Paco_2$ exceeded 125 mm Hg. As compared with control, the stroke volume significantly increased at a $Paco_2$ of around 100 mm Hg (126.6% ± 26.6%, $p < .01$) and significantly decreased at a $Paco_2$ of around 250 mm Hg (74.8% ± 13.5%, $p < .01$). The percentage increases and decreases in stroke volume were greater than those in cardiac output.

Microscopic views of microvessels observed with the REC method are shown in Figure 3. Arterioles became dilated with an increase in the $Paco_2$ from 20 to 80 mm Hg and became constricted when the $Paco_2$ exceeded 100 mm Hg.

Table 1 shows the measured values of $Paco_2$ and summarizes pH, mean blood pressure, heart rate, and Pao_2. The pH decreased with an increase in $Paco_2$. As compared with the control value during normocapnia, the pH significantly increased during hypocapnia (a $Paco_2$ of around 20 mm Hg, $p < .05$) and significantly decreased at a $Paco_2$ of ≥60 mm Hg ($p < .05$). The mean blood pressure increased with elevation of $Paco_2$. As compared with the control value during normocapnia, the mean blood pressure significantly decreased during hypocapnia (a $Paco_2$ of around 20 mm Hg, $p < .05$) and significantly increased at a $Paco_2$ of ≥60 mm Hg ($p < .05$). Heart rate was significantly lower than the control value when $Paco_2$ exceeded 80 mm Hg ($p < .05$). There were no significant differences in Pao_2.

DISCUSSION

CO_2 is an important factor contributing to the tension of vascular smooth muscle. Previous studies have demonstrated that dilation and contraction of cerebral (11) and coronary blood vessels are caused by changes in $Paco_2$ in response to CO_2 inhalation or hyperpnea (12, 13), thereby altering blood flow. The microcirculation of the brain has been studied extensively (5, 14–16), but studies assessing the effects of $Paco_2$ on the microcirculation of other organs are scant (17–19). The microcirculation responds to changes in $Paco_2$ in an organ-dependent manner. In previous studies, laser Doppler (14, 15, 17, 19) and microsphere techniques (18) were used to as-

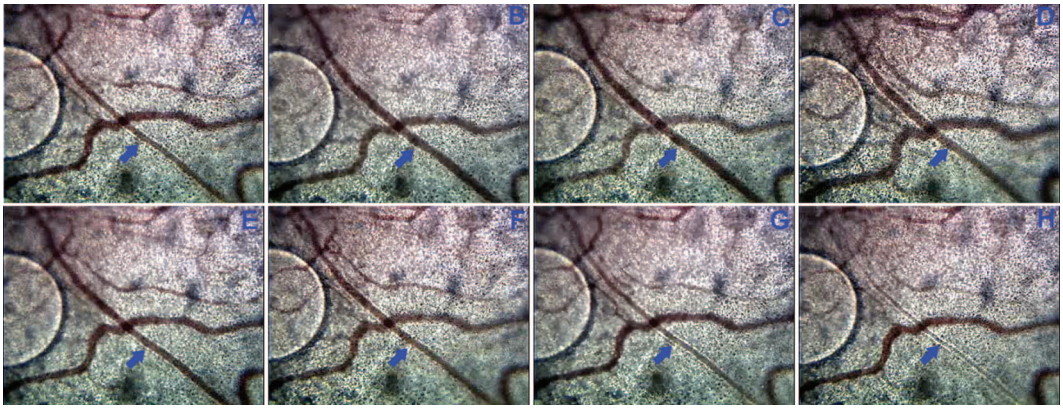

Figure 3. Photographs of microvessels. *A*, $Paco_2$ of ~20 mm Hg; *B*, $Paco_2$ of ~40 mm Hg; *C*, $Paco_2$ of ~60 mm Hg; *D*, $Paco_2$ of ~80 mm Hg; *E*, $Paco_2$ of ~100 mm Hg; *F*, $Paco_2$ of ~125 mm Hg; *G*, $Paco_2$ of ~150 mm Hg; *H*, $Paco_2$ of ~250 mm Hg. The *arrow* in each figure indicates an arteriole.

Table 1. Blood gas analysis and hemodynamics

$Paco_2$, mm Hg	23.0 ± 3.6	39.4 ± 4.9	61.8 ± 3.9	80.0 ± 5.2	104.7 ± 8.9	123.7 ± 5.9	148.4 ± 3.9	>250
Pao_2, mm Hg	121.1 ± 13.1	117.7 ± 9.0	119.1 ± 11.1	111.1 ± 14.1	108.7 ± 11.3	115.0 ± 14.7	115.1 ± 9.7	116.8 ± 14.8
pH[a]	7.58 ± 0.04[a]	7.41 ± 0.08	7.28 ± 0.03[a]	7.18 ± 0.05[c]	7.07 ± 0.06[a]	6.99 ± 0.06[a]	6.90 ± 0.09[a]	>6.75
MAP, mm Hg	106.9 ± 13.0[a]	117.4 ± 10.5	126.0 ± 11.8[a]	127.7 ± 12.2[c]	129.5 ± 11.3[a]	132.1 ± 12.7[a]	133.9 ± 11.6[a]	137.5 ± 10.6[a]
HR, mm Hg	240.0 ± 25.8	228.8 ± 27.5	220.3 ± 28.3	199.5 ± 31.2[c]	180.0 ± 19.5[a]	172.5 ± 26.4[a]	156.8 ± 22.6[a]	144.0 ± 20.9[a]

MAP, mean arterial blood pressure; HR, heart rate.
[a]$p < .05$ compared with corresponding normocapnic value. Values are mean ± SD.

sess overall blood flow to organs, such as by measuring blood flow in the main trunk of supply arteries.

In our study, the REC method was used to observe the peripheral microcirculation. With this method, the microcirculation is observed after the wound has healed, 6 wks after surgery. REC is therefore noninvasive and permits real-time observations of the hemodynamics of the same peripheral blood vessels under direct vision. In addition, the REC method allows the same animals to be observed repeatedly (20). Long-term survival can be confirmed after hypercapnia is returned to normocapnia. In the microcirculation, arterioles act as resistance vessels, controlling blood flow. Arteriolar resistance is considered to control up to 60% of systemic vascular resistance (21). Therefore, the effects of changes in $Paco_2$ on the peripheral microcirculation can be determined by using the REC method to assess arterioles, which act as resistance vessels.

The range of $Paco_2$ was up to a little higher than 250 mm Hg, which was the maximum measurable value. Although severe hypercapnia associated with a $Paco_2$ of ≥150 mm Hg is sometimes encountered clinically, such reports are uncommon (22–24). Previous studies reported that severe hypercapnia occurs in patients with respiratory disorders, such as severe asthma (22) and acute respiratory distress syndrome (23). In our study, a high $Paco_2$ of up to 250 mm Hg was maintained and then returned to normocapnia. We found that all animals survived.

In the peripheral microcirculation, arteriolar dilation occurred and blood flow increased with an increase in the $Paco_2$ up to 80 mm Hg. When the $Paco_2$ exceeded 80 mm Hg, the peripheral microcirculation decreased and the blood pressure increased. At a $Paco_2$ of ≥150 mm Hg, arteriolar blood flow significantly decreased as compared with the control value. These findings are quite in contrast to the response of cerebral blood flow to $Paco_2$ (25). The cerebral blood flow increases linearly at $Paco_2$ values ranging from 20 to 80 mm Hg and then reaches a plateau level.

The decrease in the peripheral arteriolar blood flow at a $Paco_2$ of ≥150 mm Hg is attributed to a drop in the pH to ≤6.9, leading to marked respiratory acidosis. Although the peripheral microcirculation was not maintained at this time, the decrement in the cardiac output was mild, consistent with the results of previous studies (26) Therefore, even when the $Paco_2$ increases to ≥150 mm Hg and the peripheral circulation is compromised, blood flow to the brain (25) and other major organs may be maintained to a certain degree. However, peripheral circulatory disorders may cause lethal complications such as sepsis induced by necrosis of the extremities, culminating in multiple organ failure. It is therefore important to maintain the peripheral circulation.

In the microcirculation, arteriolar dilation in response to CO_2 results from a chemical control mechanism dependent on changes in pH in vascular smooth muscle (27). Diffusion of CO_2 to tissues may alter intracellular or extracellular hydrogen-ion concentrations, influencing calcium channels (28). This phenomenon has been sporadically reported to involve adenosine triphosphate–sensitive potassium channels (16) or to be endothelial dependent (14, 15).

CO_2 indirectly influences the sympathetic nervous and adrenal systems, in addition to directly acting on arterioles. Direct actions include vasodilatation mediated by chemical control. An indirect action of CO_2 is activation of the sympathetic nervous and adrenal systems. Sympathetic nerve activity varies, depending on $Paco_2$ (29). In our study, blood pressure and cardiac output varied slightly, as compared with the changes in arterioles. These disparate effects are attributed to the balance between the direct and indirect actions of CO_2. The elevation of blood pressure accompanying the rise in $Paco_2$ was ascribed to activation of the sympathetic nervous and adrenal systems. The arteriolar dilation seen up to a $Paco_2$ of 100 mm Hg was most likely a direct effect of CO_2. The peripheral blood flow was substantially altered by changes in $Paco_2$, whereas cardiac output was minimally affected. These disparate responses are attributed to organ-specific differences in blood-flow distribution and the responsiveness to changes in blood flow.

In our study, arteriolar diameter, blood-flow velocity, and blood-flow rate during hypocapnia decreased significantly, as compared with the respective values during normocapnia. A reduction in $Paco_2$ has been associated with decreased blood flow in the brain (11), coronary arteries (13), liver (30), and gastrointestinal tract (31) and no change in blood flow in the kidney (32) or skeletal muscle (33). The microcirculation is associated with phenomena that are common to each organ and species and with those that are organ specific. Observation of the microcirculation by means of the REC method enabled us to confirm the influence of hypocapnic alkalosis on peripheral circulation. The microcirculation should be borne in mind in patients receiving ventilation.

A critical limitation of our study is that healthy animals were used. Extrapolation of our results on the effects of changes in $Paco_2$ in healthy animals, not in a model of lung injury, to patients with lung disease might therefore be of limited value. However, we believe that our experimental model was a valuable tool for examining the effects of changes in $Paco_2$ on the peripheral circulation.

CONCLUSION

Effects of changes in $Paco_2$ on peripheral arteriolar hemodynamics were examined under direct vision by the REC method. Arteriolar dilation occurred at $Paco_2$ values up to 80 mm Hg. When the $Paco_2$ was increased to ≥150 mm Hg, arteriolar diameter, blood-flow velocity, and blood-flow volume significantly decreased, as compared with rabbits with normocapnia. In acute hypercapnia, the acceptable upper limit of $Paco_2$ required to maintain the microcirculation is considered to be 150 mm Hg.

ACKNOWLEDGMENTS

We thank Professor Emeritus Makishige Asano, Professor Emeritus Chiyoji Ohkubo, and Dr. Akira Ushiyama (National Institute of Public Health, Japan), and the Japanese Heart Pressure Research Laboratory and Japanese Heart Pressure Research Promotion Society for supplying the facilities and equipment for the present study.

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