HAEMATOLOGICAL, BLOOD GAS AND ACID-BASE EFFECTS OF CENTRAL HISTAMINE-INDUCED REVERSAL OF CRITICAL HAEMORRHAGIC HYPOTENSION IN RATS

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In a rat model of volume-controlled irreversible haemorrhagic shock, which results in a severe metabolic acidosis and the death of all control animals within 30 min., intracerebroventricular injection of histamine (100 nmol) produces a prompt and long-lasting increase in mean arterial pressure and heart rate, with a 100% survival of 2 h after treatment. Histamine action is accompanied by a decrease in haematocrit value, haemoglobin concentration, erythrocyte and platelet count, and an increase in residual blood volume at the end of the experiment (2 h). Cardiovascular effects are also associated with a long-lasting rise in respiratory rate and biphasic blood acid-base changes — initial increase of metabolic acidosis with the decrease in arterial and venous pH, bicarbonate concentration and base excess, followed by almost a complete recovery of blood gas and acid-base parameters to the pre-bleeding values, with normalisation of arterial and venous pH, P_{CO_2} bicarbonate concentration and base excess at the end of experiment. It can be concluded that in the late phase of central histamine-induced reversal of haemorrhagic hypotension there is almost a complete restoration of blood gas and acid-base status due to circulatory and respiratory compensations, while accompanying haematological changes are the result of the haemodilution and the increase in residual blood volume.

Keywords: histamine, haemorrhagic hypotension, haematological parameters, blood gases, acid-base status, rat.

INTRODUCTION

Histamine influences the cardiovascular centre function in normovolaemic animals as well as in animals subjected to critical haemorrhagic hypotension (1, 2). In normotensive anaesthetised rats, histamine given intracerebroventricularly (icv) evokes a short-lasting rise in mean arterial pressure (MAP) accompanied by tachycardia, as a result of the increase in the sympathetic activity and the secretion of arginine vasopressin (AVP) (1, 3). In contrast,
according to the author’s previous study, in experimental haemorrhagic shock produced by withdrawal of approximately 50% of total blood volume and resulting in the death of all control rats within 30 min., histamine produces a prompt dose-dependent (0.1—100 nmol) and long-lasting (10—100 nmol) increase in MAP, pulse pressure (PP) and heart rate (HR), up to the pre-haemorrhage values (2). The effects are associated with a 100% survival of 2 h after histamine (100 nmol) treatment. Moreover, the increase in MAP and HR after histamine administration in bled rats in comparison to normovolaemic animals is 2.7—3.3- and 1.3—3.6-fold higher, respectively (2). The previous study revealed that histamine action in haemorrhagic hypotension is due to stimulation of $H_1$ histamine receptors, since chlorpheniramine, $H_1$ receptor antagonist, inhibits histamine effect on MAP, PP, HR and decreases the survival rate. In contrast, pre-treatment with both $H_2$ histamine receptor blocker ranitidine and $H_3$ receptor antagonist thiopemamide fails to influence cardiovascular changes evoked by histamine. Surprisingly, both antagonists given alone produce pressor effect and improvement in survival rate, however, to a lesser degree compared to histamine action (2).

It is postulated that differences in histamine action between normotensive and hypotensive animals are due to its antagonistic properties to endogenous opioid system (2) which becomes activated in pre-terminal conditions of haemorrhagic shock and which inhibits cardiovascular centre function (4). Similarly, other anti-analgesic (non-opioid) neurotransmitters, including ACTH and many ACTH-fragments, CCK peptides, and thyrotropin-releasing hormone (TRH), at doses which show little or no activity in normotensive animals, reveal the resuscitating effects during haemorrhagic shock (5).

The study was undertaken to ascertain to what degree improvement of haemodynamic function after histamine icv administration in critical hypovolaemia influences haematological and blood gases parameters as well as the acid-base balance in anaesthetised rats. The experimental haemorrhagic shock model by Guarini et al. (6) was chosen, as in the previous study (2), to examine histamine action at constant initial values of both the critical MAP and the volume of blood in the critical hypovolaemia.

MATERIAL AND METHODS

Animals

Male Wistar rats weighing 230—250 g (5—6 months old) were used in all experiments. The animals were housed five per cage, under controlled conditions of temperature (22 ± 2°C), humidity (60—70%), lighting (12 h light/dark cycle) and provided with food and water ad libitum. All procedures were reviewed by the Ethical Committee of Silesian Medical University (Notification No. 6/00) and carried out according to EU directives.
Surgical procedure

After induction of general anaesthesia with ethylurethane (1.25 g/kg intraperitoneally), heparinization (Heparinum, 600 IU/kg iv) and clean dissection, rats were implanted with catheters in the right femoral artery and vein. Arterial catheter was used for measurement of MAP and PP by the pressure transducer RMN-201 (Temed, Poland), and sampling of arterial blood. Similarly, a sterile polyethylene catheter (PE-50) was placed in the right atrium via the right jugular vein for sampling of mixed venous blood for determination of haematological parameters as well as blood gas tensions and acid-base balance. HR and respiratory rate (RR) were recorded by means of three electrodes implanted subcutaneously on the chest and connected to the electrocardiograph Diascope 2 (Unitra Biazet, Poland) and transducer RMN-201 (Temed, Poland), respectively. Body temperature was monitored by a rectal thermometer and maintained at 37 ± 0.5°C using the heating lamp throughout the experiment. All the experiments were performed between 12.00 and 16.00.

For icv treatment rats were prepared 5—7 days before the experiment by stereotaxic implantation, under ethylurethane anaesthesia, of polyethylene cannula into the right brain lateral ventricle as previously described (2). All icv injections were made in 5.0 µl of saline vehicle using a Hamilton microsyringe. Correction of icv administration was verified at the end of each experiment, as described earlier (2).

Drugs

The following drugs were used: histamine dihydrochloride (Research Biochemicals Incorporated, USA), ethylurethane (Riedel-de Haen, Germany), heparinum (Polfa, Poland). All drug solutions were prepared fresh on the day of the experiment.

Experimental protocol

Irreversible haemorrhagic shock, according to the modified method of Guarini et al. (6), was produced by intermittent blood withdrawal from the catheter inserted into femoral vein over a period of 15—25 min., until MAP decreased to and stabilised at 20 to 25 mmHg. Five minutes after termination of bleeding, haemorrhage-shocked rats were injected icv with histamine (100 nmol) or saline. The 100 nmol dose of histamine was chosen since in an earlier study by the author, in the same experimental model, it produced a complete reversal of haemorrhagic hypotension and long-lasting survival (2). The animals were monitored continuously for 2 h after treatment, or until death, if it occurred earlier. Blood samples were taken before and after bleeding, and 5, 20 and 120 min. after icv treatment, if animals were still alive. Arterial and mixed venous blood gas tensions, acid-base status, and venous haematological parameters were measured immediately after blood withdrawal using a blood gas analyser (AVL OMNI 3, AVL LIST GmbH Medizintechnik, Austria) and a haematological analyser (Coulter Micro Diff II, Coulter Electronics Ltd., USA), respectively.

In separate groups (n = 6), plasma volume was measured 20 min. after saline injection, and 20 min. and 120 min. after histamine treatment using the Evans blue dye dilution technique (7). Blood volume was calculated based on haematocrit value (HCT).

To compare the respiratory central histamine-induced effects in critical hypovolaemia and normovolaemia, histamine (100 nmol) was injected icv to normotensive rats (n = 5).
Statistical analysis

All data are given as means±SD with p < 0.05 considered as the level of significance. Differences between control and histamine groups were analysed using a one-way analysis of variance (ANOVA) and Dunnett's test. Significance of differences within groups over time was tested with a paired Student's t-test.

RESULTS

The pre-bleeding baseline values of MAP, PP, HR and RR in both groups did not reveal significant differences (Table 1). Similarly, there were no differences with respect to blood cell counts, HCT, haemoglobin concentration (HGB) (Table 2) as well as blood gas and acid-base parameters (Fig. 1–2). Total bleeding volume for induction of critical hypotension was 2.24±0.18 ml/100 g body weight, which is approximately 50% of the total blood volume (8). Bleeding from MAP 94±6 mmHg to 20–25 mmHg was associated with the decrease in PP from 19±4 mmHg before haemorrhage to 6±4 mmHg after shock induction and the decrease in HR from 357±21 beats/min to 266±26 beats/min in the control group. Moreover, the decrease in RR from initial 68±5 breaths/min to 48±4 breaths/min at the end of haemorrhage was noted (Table 1).

Table 1. Effects of icv administered saline (S) and histamine (H) on MAP, PP, HR and RR in rats subjected to haemorrhagic shock; six animals per group; *p < 0.05 vs. pre-bleeding value, "p < 0.05 vs. corresponding value in the control group.

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<th>Before bleeding</th>
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<td>5 min</td>
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<tr>
<td>MAP (mmHg)</td>
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<tr>
<td>S</td>
<td>94±6</td>
<td>22±2*</td>
<td>23±3*</td>
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<tr>
<td>H</td>
<td>92±7</td>
<td>23±3*</td>
<td>48±5**</td>
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<td>PP (mmHg)</td>
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<tr>
<td>S</td>
<td>19±4</td>
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<td>H</td>
<td>20±5</td>
<td>5±3*</td>
<td>12±5**</td>
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<td>HR (beats/min)</td>
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<td>S</td>
<td>357±21</td>
<td>266±26*</td>
<td>237±19*</td>
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<td>H</td>
<td>364±17</td>
<td>251±17*</td>
<td>324±16**</td>
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<td>RR (breaths/min)</td>
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<tr>
<td>S</td>
<td>68±5</td>
<td>48±4*</td>
<td>47±5*</td>
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<tr>
<td>H</td>
<td>64±3</td>
<td>45±5*</td>
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Haemorrhage produced a significant decrease in HCT, HGB, erythrocyte (RBC) and leukocyte (WBC) counts, and no changes in platelet (PLT) count in comparison to pre-bleeding values, with no differences between groups (Table 2). Acid-base parameters showed at the end of haemorrhage a severe metabolic acidosis with a fall in arterial pH to 7.13 ± 0.04, \( P_{\text{co}_2} \) to 37.9 ± 3.4 mmHg, base excess (BE) to \(-9.7 ± 1.3\) mmol/l, bicarbonate concentration to 15.1 ± 2.1 mmol/l, and the increase in arterial \( P_{\text{O}_2} \) to 115.8 ± 7.4 mmHg, without significant changes in haemoglobin saturation (\( S_{\text{O}_2} \)) in the control group (Fig. 1). Induction of critical hypotension was associated with the decrease in venous pH to 7.11 ± 0.04, BE to \(-10.1 ± 1.74\) mmol/l, bicarbonate concentration to 18.8 ± 1.2 mmol/l, \( P_{\text{O}_2} \) to 21.3 ± 3.3 mmHg and \( S_{\text{O}_2} \) to 28.4 ± 3.1%, and the increase in venous \( P_{\text{co}_2} \) to 59.1 ± 4.9 mmHg (Fig. 2).

Table 2. Haematological effects of icv administered saline (S) and histamine (H) in rats subjected to haemorrhagic shock; six animals per group; *p < 0.05 vs. pre-bleeding value, *p < 0.05 vs. corresponding value in the control group.

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<td>20 min</td>
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<td><strong>HCT (%)</strong></td>
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<tr>
<td>S</td>
<td>43.41 ± 1.91</td>
<td>36.92 ± 1.31*</td>
<td>32.93 ± 0.9*</td>
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<td>H</td>
<td>46.13 ± 2.14</td>
<td>38.44 ± 1.62*</td>
<td>33.82 ± 1.11*</td>
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<td><strong>HGB (g/dl)</strong></td>
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<tr>
<td>S</td>
<td>15.91 ± 0.72</td>
<td>14.37 ± 0.63*</td>
<td>12.1 ± 0.11*</td>
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<tr>
<td>H</td>
<td>15.4 ± 0.85</td>
<td>14.22 ± 0.54*</td>
<td>11.8 ± 0.2*</td>
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<tr>
<td><strong>RBC (× 10⁶)</strong></td>
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<tr>
<td>S</td>
<td>8.16 ± 0.19</td>
<td>7.23 ± 0.33*</td>
<td>6.15 ± 0.14*</td>
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<tr>
<td>H</td>
<td>7.81 ± 0.22</td>
<td>7.02 ± 0.26*</td>
<td>6.02 ± 0.17*</td>
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<td><strong>WBC (× 10³)</strong></td>
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<tr>
<td>S</td>
<td>8.73 ± 0.93</td>
<td>6.9 ± 0.55*</td>
<td>6.54 ± 0.46*</td>
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<tr>
<td>H</td>
<td>8.92 ± 0.89</td>
<td>7.21 ± 0.45*</td>
<td>8.2 ± 0.93*</td>
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<td><strong>PLT (× 10³)</strong></td>
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<tr>
<td>S</td>
<td>924 ± 58</td>
<td>913 ± 44</td>
<td>845 ± 38*</td>
</tr>
<tr>
<td>H</td>
<td>912 ± 38</td>
<td>885 ± 35</td>
<td>835 ± 41*</td>
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**Effects of icv administered histamine on MAP, PP, HR, RR and survival rate in haemorrhagic hypotension**

Histamine produced a rapid long-lasting increase in MAP, PP and HR which began within 1 min. of drug administration, reached the pre-bleeding values within 5—20 min. and persisted to the end of the experiment (Table 1). The effects were associated with 100% survival of 2 h, while in the control saline-treated group no significant changes in MAP, PP and HR were noted (Table 1), and the mean survival time was 25.2 ± 3.1 min. Histamine also
Fig. 1. Arterial blood gas and acid-base parameters before bleeding (-5 min.), after bleeding (0 min.) and 5, 20 and 120 min. after icv histamine (black columns) and saline (white columns) treatment; six animals per group; * p < 0.05 vs. pre-bleeding value, # p < 0.05 vs. corresponding value in the control group.
Fig. 2. Mixed venous blood gas and acid-base parameters before bleeding (−5 min.), after bleeding (0 min.) and 5, 20 and 120 min. after icv histamine (black columns) and saline (white columns) treatment; six animals per group; * p < 0.05 vs. pre-bleeding value, # p < 0.05 vs. corresponding value in the control group.
evoked a significant long-lasting increase in RR which started within 1 min. of icv treatment (Table 1). In normotensive rats initial RR was 67 ± 5 breaths/min, and histamine did not produce any significant effect.

**Haematological and residual blood volume changes associated with icv histamine-induced reversal of haemorrhagic hypotension**

Data on haematological parameters are shown in Table 2. In both groups the decrease in all haematological parameters was observed at 20 min. after icv treatment, except for WBC in histamine-treated group where the rise in leukocyte count was noted. Moreover, in the histamine group further decrease in HCT, HGB, RBC and PLT was observed at 120 min. of the study.

In histamine-treated and control groups 20 min. after icv treatment there were no differences in residual blood volumes, the values being 2.84 ± 0.15 and 2.93 ± 0.18 ml/100 g b.w., respectively. However, a significant increase in residual blood volume to 3.97 ± 0.33 ml/100 g b.w. (p < 0.001, paired Student's t-test; n = 6) was noted 2 h after histamine administration.

**Blood gas and acid-base changes associated with icv histamine-induced reversal of haemorrhagic hypotension**

Histamine produced biphasic changes in arterial and venous gas and acid-base parameters. Initially, 5 min. after treatment there was a further decrease in arterial and venous pH, BE and bicarbonate concentration, with an increase in venous P<sub>O<sub>2</sub></sub> and P<sub>CO<sub>2</sub></sub>, and no significant changes in arterial P<sub>O<sub>2</sub></sub>, P<sub>CO<sub>2</sub></sub> and S<sub>O<sub>2</sub></sub> and venous S<sub>O<sub>2</sub></sub>, compared to the control group (Fig. 1—2). At 20 min. significantly higher values of arterial pH, P<sub>O<sub>2</sub></sub>, BE and bicarbonate concentration, venous pH, P<sub>O<sub>2</sub></sub>, BE, bicarbonate concentration and S<sub>O<sub>2</sub></sub>, and lower values of arterial and venous P<sub>CO<sub>2</sub></sub> were observed in comparison to the control group (Fig. 1—2). Two hours after histamine treatment there was a complete recovery to the pre-bleeding values of arterial and venous pH, P<sub>CO<sub>2</sub></sub>, BE and bicarbonate concentration, whereas arterial P<sub>O<sub>2</sub></sub> was still elevated and venous P<sub>O<sub>2</sub></sub> and S<sub>O<sub>2</sub></sub> were decreased (Fig. 1—2).

**DISCUSSION**

The present results confirm previous findings by the author that histamine given icv in the early phase of critical haemorrhagic hypotension restores the cardiovascular functions and improves the survival rate in anaesthetised rats (2). The study presents for the first time changes in residual blood volume and haematological parameters, as well as central histamine-induced restoration of
respiratory function in rats subjected to haemorrhagic shock. Moreover, it shows the association between haemodynamic and respiratory improvement and blood gases and acid-base correction.

Mechanisms of histamine action in critical hypovolaemia, similarly to normovolaemic animals, may include activation of the sympathetic nervous system and secretion of AVP (1, 9), since both are essential in the maintenance of blood pressure in haemorrhagic shock, causing increased vascular resistance as well as mobilisation of blood from venous reservoirs, and leading to centralisation of the circulation (10). In addition, the action can be involved with central histamine-induced secretion of CRH (11—12). CRH and AVP are activators of the pituitary-adrenal system and stimulate synergistically the release of ACTH (9, 11), which belongs to the anti-opioid neurotransmitters participating in modulation of information from nociceptors and also demonstrating anti-shock properties (5, 13). Moreover, AVP, via a histaminergic mechanism located in hypothalamus and hippocampus, is involved in stimulation of the ACTH secretion (12).

Histamine (100 nmol) administered at 5 min. of the experimental volume-controlled haemorrhagic shock evokes prompt long-lasting increase in MAP and PP, up to the complete reversal to the pre-haemorrhage values and 100% survival of 2 h. Furthermore, central histamine reverses reflex-induced bradycardia elicited from left ventricular unmyelinated nerve fibres associated with critical hypovolaemia. Improvement in cardiovascular functions is accompanied by the increase in residual blood volume 2 h after treatment. The mechanism of the effect is probably the transfer of water from the extravascular to the intravascular compartment, and thus an increase in circulating blood volume leading to haemodilution. Indeed, present results show that massive haemorrhage in rats is associated with the decrease in HCT, HGB, RBC and PLT, and similar effects were earlier obtained by Guarini et al. in the same haemorrhagic shock model (13, 14). Moreover, in both studied groups further decrease in haematological parameters was noted 20 min. after icv injection, and in the histamine group the tendency continued to the end of experiment, except for leukocyte count which was significantly higher in histamine-treated group compared to the control. Similarly, in ACTH-(1—24)-induced reversal of experimental haemorrhagic shock the rise in WBC was observed, probably as a result of leukocyte mobilisation from the spleen (13).

Induction of critical haemorrhagic hypovolaemia is associated with the decrease in RR, as described previously (15). Present results reveal for the first time that histamine given icv under these conditions evokes a prompt long-lasting increase in RR. There are two possible mechanisms of the effect: direct stimulation of respiratory complex neurones by histamine or the increase in P O₂ in central nervous system due to the pressor effect and reperfusion.
Although histamine given icv does not influence RR in normovolaemic animals, both mechanisms may be involved, since the amine belongs to anti-opioid neurotransmitters demonstrating resuscitating effects (5). On the other hand, the same RR changes in haemorrhagic shock were observed by Guarini et al. (15) after ACTH-(1—24) intravenous administration, probably as a result of the increase in MAP and higher oxygenation of the respiratory centre.

Similarly to earlier studies based on the same shock model, an increase in arterial $P_{O_2}$ during shock was observed, which was explained by Bazzani et al. by the decrease in HGB and a subsequent increase in free $O_2$ (16). Furthermore, the study revealed that arterial high $P_{O_2}$ values remained unchanged after haemorrhage and during histamine-induced pressor effect, which may lead to better oxygenation of the peripheral tissues. In comparison to pre-bleeding values in both groups $S_{O_2}$ was not altered in arterial blood but was decreased in mixed venous blood, probably due to higher peripheral $O_2$ utilisation (17).

It has already been shown that in critical hypovolaemia metabolic acidosis develops due to decreased tissue perfusion and hypoxia (16, 18—21). Also in the present study, in both groups, post-bleeding period of critical hypotension was associated with the decrease in arterial and venous pH, bicarbonate concentration and BE indicating metabolic origin of acidosis. Since restoration of respiratory and cardiovascular function is of essential importance in compensation of acid-base parameters in haemorrhagic shock (16, 19), central histamine-induced increase in RR produces the decrease in arterial and venous $P_{CO_2}$ lasting to the end of experiment. Interestingly, during the early phase (5 min.) after histamine treatment arterial and venous pH continue to decrease, possibly as a result of diffusion of intracellular products of anaerobic glycolytic metabolism to interstitium and into blood. Similar effects occurred also in rats after resuscitation with ACTH-(1—24) (16) and TRH (19). A possible explanation is that a rapid rise in circulating blood volume, due to mobilisation of blood from venous reservoirs, produces beneficial effect on tissue flow, and subsequently, reperfusion. On the other hand, lower values of $P_{CO_2}$ in histamine-treated group indicate significantly more severe compensatory hyperventilation compared to the control animals. Finally, the recovery of arterial and venous pH, bicarbonate concentration and BE at 2 h of experiment in the histamine group suggests a metabolic improvement with normalisation of tissue perfusion and reoxygenation, despite the persistence of hypovolaemia.

In conclusion, this study demonstrates that central histamine-induced reversal of haemorrhagic hypotension in rats is associated with the decrease in HCT, HGB, RBC and PLT as a result of the haemodilution and the increase in residual blood volume. Moreover, haemodynamic effects are accompanied by the biphasic changes in blood gas and acid-base parameters, initially, the
increase of metabolic acidosis conditions, followed by almost a complete
restoration of blood gas and acid-base parameters due to improvement in
cardiovascular and respiratory function.

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