Adenosine for Reversal of Hemorrhagic Shock in Rabbits

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ABSTRACT—The potential use of adenosine in the treatment of hemorrhagic shock was evaluated in rabbits. Hemorrhagic shock was induced by bleeding the animals to a mean arterial blood pressure of 30–35 mmHg that was maintained for 2 hr. The intravenous infusion of 300 μg/kg/min adenosine for 1 hr, after reinfusion of the shed blood, was found to be capable of increasing the survival rate of rabbits subjected to hemorrhagic shock. In shocked rabbits, adenosine profoundly improved the postreinfusion depressed contractility of the heart, but it produced a decrease in the mean arterial blood pressure and heart rate. In the same animals, the plasma concentrations of glucose, lactate and inorganic phosphate, which were markedly elevated during shock, were returned back toward normal levels by the intravenous infusion of adenosine. Similarly the alteration that occurred in the plasma sodium, potassium and calcium levels during shock was corrected by adenosine. It is consequently concluded that the use of adenosine after shock improves tissue perfusion and enhances the functional recovery of cells by restoring their metabolic machinery and thereby improves the survival rate.

Keywords: Hemorrhagic shock, Reinfusion of the shed blood, Adenosine, Survival rate, Shocked rabbit

Hemorrhagic shock can be defined as depletion of intravascular volume to a point where the body can no longer compensate and the blood can not adequately perfuse organs. At a cellular level, this means that cells and organelles are not receiving adequate oxygen and fuel substrates because of inadequate capillary perfusion (1). With the onset of shock, various vasoactive constrictor mediators are released into the blood stream to compensate for the blood loss by decreasing the size of the vascular compartment. The continued elaboration of these constrictor substances will also eventually lead to microcirculatory failure, resulting in tissue ischemia and hypoxia (2, 3).

As a result of prolonged reduction in tissue perfusion, various alterations in tissue metabolism, function and structure occur at the systemic, cellular and subcellular levels (4, 5). The cellular transmembrane potential difference and energy production within the cell are depressed. With the fall in energy available to the cells, one would expect its vital functions to deteriorate (4, 6).

The biological nucleoside adenosine participates in a wide variety of physiological processes in virtually every cell of the body (7). A wide range of effects occurs in response to local adenosine, and many of these effects are hemostatic and protective in nature (8). The production of adenosine is therefore found to increase in response to ischemia and hypoxia and functions to restore a physiologic oxygen supply-demand ratio (9) and to enhance energy production (10).

Hemorrhage was found to evoke endogenous adenosine release. However, the released adenosine, due to its rapid elimination from plasma, is not able to serve a hormonal role by attaining sufficiently high circulating levels to cause systemic effects at sites distant from the site of production (11).

The objective of this study, therefore, was to determine whether exogenously infused adenosine is effective in reversal of hemorrhagic shock and also to evaluate the effects of adenosine on the hemodynamic and metabolic responses to shock.

MATERIALS AND METHODS

Induction of hemorrhagic shock

Adult male rabbits weighing 1.5 to 2.5 kg were fasted overnight before the experiment but allowed water ad libitum. The rabbits were lightly anesthetized with diethylether. All animals were subjected to the same sur-
Hemorrhagic shock was induced, according to Wigger's fixed-pressure model (12), by withdrawing blood from the femoral artery in equal amounts at equal intervals over 20 to 30 min to a mean arterial blood pressure of 30–35 mmHg. This blood pressure was then maintained at that level for 2 hr by blood movement to or from the reservoir. The shed blood was stored at room temperature at that level for 2 hr by blood movement to or from the reservoir. The shed blood was stored at room temperature in a heparinized sterilized plastic syringe. At the end of the shock period, the blood in the reservoir was infused intra-arterially over 20 to 30 min. Adenosine or saline was then infused intravenously for 1 hr.

The arterial blood pressure was recorded via the femoral artery, which was connected to a PT400 Blood Pressure Transducer and an amplifier of a 2-channel oscillograph MD2 (Bioscience, Kent, UK). The transducer was then calibrated. The electrocardiographic changes were simultaneously recorded using standard lead II.

Data were collected before hemorrhage and every 0.5 hr for 5 hr after starting hemorrhage. The cannulas were then removed from the animals after ligation of the artery and vein and the incisions were closed. The animals were placed in a cage with food and water and observed for survival for 24 hr.

In another set of experiments, rabbits were anesthetized with intraperitoneal injection of urethane solution (25%) in a dose of 6.4 ml/kg, and their tracheae were cannulated for artificial respiration. In each rabbit, after completion of the right femoral artery and right femoral vein cannulation, the thorax was opened rapidly and the pericardium was carefully removed. The isometric contraction of the heart was monitored by means of a photoelectric force transducer (E & M Physiograph Myograph, Houston, TX, USA) connected to a heart clips at the apex of the ventricle and displayed on an amplifier of a 6-channel physiograph (Narco Biosystem, Houston, TX, USA). After a 20-min stabilization period, hemorrhagic shock was induced as previously described and then the shed blood was reinfused into the hemorrhaged rabbits. Adenosine or a saline solution was thereafter infused intravenously for 1 hr. By adding saline (or Locke-Ringer) solution to the well formed by the body cavity, the heart can be kept moist and in good condition. The sham shock rabbits were subjected to all surgical procedures and treatments experienced by the hemorrhaged animals, but were not bled. The percentage change in the amplitude of the myocardial contractility was determined. Data were collected before hemorrhage and every 0.5 hr for 5 hr after starting hemorrhage.

**Metabolic measurements**

Blood samples were collected into dry clean heparinized tubes and were replaced by intravenous administration of an equal volume of saline to rabbits. These samples were collected from rabbits before hemorrhage, during hemorrhagic shock, after reinfusion of the shed blood and 1 and 2 hr after starting the adenosine or saline infusion.

After centrifugation, the plasma samples were taken for determination of the plasma glucose, lactate, inorganic phosphate and electrolyte levels. The samples could be used directly or stored at −20°C until assay.

The plasma glucose level was assayed by an enzymatic colorimetric method using a commercially available Glucoxy-Kit (bioMérieux, Marcy L’Etoile, France). The plasma lactate level was measured enzymatically using a commercially available Lactate-Kit UV (bioMérieux). The plasma inorganic phosphate was estimated by a colorimetric method using a commercially available kit (Sigma, St. Louis, MO, USA).

The plasma sodium, potassium and calcium levels were determined by flame photometry using a corningel flame photometer. Standard calibration curves for sodium, potassium and calcium ions were constructed by preparing known but different concentrations of sodium chloride, potassium chloride and calcium chloride using Analar sources of these salts. The ion concentration of these solutions was determined flame photometrically. From these standard curves, the ionic content of the samples could be determined by interpolation.
Statistical analyses of results

The variability of results is expressed as the mean ± S.E. The significance of differences between mean values was determined by Student's t-test.

RESULTS

The model of hemorrhagic shock used in this study is quite severe, and untreated animals exhibited postreinfusion high mortality rates (i.e., 80%). Animals that died during the experiment (5 hr after starting hemorrhage) were excluded from the tabulation of results.

The intravenous infusion of adenosine for 1 hr after reinfusion of the shed blood markedly increased the survival rate of hemorrhaged rabbits (Table 1).

The mean arterial blood pressure and heart rate of sham-operated rabbits did not change significantly over the time course of the experiment, indicating that the surgical procedure itself does not contribute to the severity of the shock state. Intravenous infusion of 300

Table 1. Twenty-four-hour survival rates of rabbits subjected to hemorrhagic shock and treated with intravenous infusion of adenosine or an equal volume of the vehicle (saline) after reinfusion of the shed blood

| Treatment                          | No. tested | Survivors/Total rabbits | % Survivors |
|------------------------------------|------------|-------------------------|-------------|
| Saline                             | 10         | 2/10                    | 20          |
| Adenosine, 150 µg/kg/min for 1 hr  | 10         | 5/10                    | 50**        |
| Adenosine, 300 µg/kg/min for 1 hr  | 10         | 9/10                    | 90**        |

**Significant difference from the control (saline) at P < 0.01.

Fig. 1. Time course of changes in the mean arterial blood pressure (MABP) of the sham shock (Sh) and hemorrhaged (H) rabbits receiving either 300 µg/kg/min adenosine (A) or an equal volume of normal saline (S) for 1 hr. R = reinfusion of the shed blood. Values presented are the means ± S.E. (n=10). *P<0.05, **P<0.01 vs pretreatment values. Sh+S (△), Sh+A (●), H+S (□), H-A (○).
Fig. 2. Time course of changes in the heart rate of the sham shock (Sh) and hemorrhaged (H) rabbits receiving either 300 μg/kg/min adenosine (A) or an equal volume of normal saline (S) for 1 hr. R=reinfusion of the shed blood. Values presented are the means±S.E. (n=10). **P<0.01 vs pretreatment values. Sh+S (△), Sh+A (○), H+S (□), H+A (●).

Fig. 3. Time course of changes in the cardiac contractility of the sham shock (Sh) and hemorrhaged (H) rabbits receiving either 300 μg/kg/min adenosine (A) or an equal volume of normal saline (S) for 1 hr. R=reinfusion of the shed blood. Values presented are the means±S.E. (n=10). **P<0.01 vs pretreatment values. Sh+S (△), Sh+A (○), H+S (□), H+A (●).
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Table 2. Plasma glucose, lactate, inorganic phosphate and electrolyte levels of rabbits subjected to hemorrhagic shock and treated with intravenous infusion of 300 μg/kg/min adenosine or an equal volume of the vehicle (saline) for 1 hr after reinfusion of the shed blood

|                          | Glucose (mg/dl) | Lactate (mg/dl) | Inorganic phosphate (mg/dl) | Na⁺ (mEq/l) | K⁺ (mEq/l) | Ca²⁺ (mEq/l) |
|--------------------------|-----------------|-----------------|-------------------------------|-------------|------------|-------------|
| Control                  | 108.60±3.2      | 11.92±1.19      | 3.83±0.28                     | 143.88±2.62 | 4.98±0.46  | 6.56±0.32   |
| During shock             | 152.61±7.32     | 25.40±2.22      | 6.81±0.38                     | 106.12±2.02 | 11.43±1.01 | 2.96±0.26   |
| After reinfusion of the shed blood | 128.72±6.81**  | 16.52±1.21**    | 4.92±0.41**                   | 123.61±3.56** | 7.96±0.76** | 4.16±0.32** |
| After 1 hr of saline infusion | 126.96±8.11    | 15.91±1.12      | 4.76±0.32                     | 125.11±4.52 | 7.12±0.69  | 4.26±0.38   |
| After 2 hr of saline infusion | 125.92±9.20    | 15.26±1.20      | 4.61±0.39                     | 125.92±6.56 | 7.01±0.62  | 4.41±0.39   |
| After 1 hr of adenosine infusion | 110.60±6.32**  | 12.01±1.16**    | 3.91±0.21**                   | 141.98±5.20** | 5.02±0.49** | 6.18±0.41** |
| After 2 hr of adenosine infusion | 109.21±7.32**  | 12.02±1.21**    | 3.86±0.31**                   | 142.72±6.32** | 5.04±0.50** | 6.48±0.52** |

Each figure represents the mean±S.E. (n=6), **P<0.01 vs corresponding values during shock; #P<0.01 vs corresponding after reinfusion values.

μg/kg/min adenosine for 1 hr resulted in a marked reduction in the mean arterial blood pressure and heart rate in this group of rabbits. All adenosine effects were rapidly terminated when the infusion was discontinued. Intravenous infusion of an equal volume of the vehicle (saline) at the same rate produced no change in the mean arterial blood pressure and heart rate of the sham-operated rabbits (Figs. 1 and 2).

During the course of the hemorrhagic shock, the mean arterial blood pressure of rabbits was maintained at 30–35 mmHg. The heart rate of hemorrhaged rabbits was markedly increased above the basic (prehemorrhage) level. Reinfusion of the shed blood into these animals resulted in elevation of the mean arterial blood pressure and decrease in the heart rate to values that were not significantly different from the prehemorrhage values. The intravenous infusion of 300 μg/kg/min adenosine for 1 hr, after reinfusion of the shed blood, into shocked rabbits resulted in a decrease in the mean arterial blood pressure and heart rate in these animals. The intravenous infusion of an equal volume of saline at the same rate, after reinfusion of the shed blood, into shocked rabbits did not alter significantly these parameters (Figs. 1 and 2).

The results presented in Fig. 3 show that the cardiac contractility of the sham-operated rabbits did not change significantly over the course of the experiments. Also, the intravenous infusion of 300 μg/kg/min adenosine for 1 hr or an equal volume of saline at the same rate into these animals produced no change in the myocardial contractile force. In hemorrhaged rabbits, the cardiac contractility was depressed after completion of hemorrhage. During the course of hemorrhagic shock, the contractility was markedly depressed. Reinfusion of the shed blood into these rabbits resulted in an improvement in the contractility, but to values still lower than the prehemorrhage values. The intravenous infusion of 300 μg/kg/min adenosine for 1 hr, after reinfusion of the shed blood, into shocked rabbits restored the cardiac contractility to the prehemorrhage level. On the other hand, the intravenous infusion of an equal volume of saline at the same rate, after reinfusion of the shed blood, into these rabbits did not improve the cardiac contractility, but there was a progressive decline in contractility with time.

It can be seen in Table 2 that the plasma glucose, lactate and inorganic phosphate levels were markedly increased during hemorrhagic shock. Reinfusion of the shed blood into these rabbits significantly decreased the plasma concentration of these substrates. The intravenous infusion of saline for 1 hr, after reinfusion of the shed blood, produced no further improvement in the plasma glucose, lactate and inorganic phosphate levels. The concentration of these substrates in plasma returned toward normal values by intravenous infusion of 300 μg/kg/min adenosine for 1 hr, after reinfusion of the shed blood, into hemorrhaged rabbits.

It is also evident from Table 2 that the plasma potassium level was markedly increased, while the plasma sodium and calcium levels were profoundly decreased during hemorrhagic shock. Reinfusion of the shed blood into shocked rabbits produced an improvement in the disturbed plasma concentration of these electrolytes. The intravenous infusion of saline for 1 hr, after reinfusion of the shed blood, into these animals produced no additional effects. The concentration of these electrolytes in plasma returned toward normal values after the intravenous infusion of 300 μg/kg/min adenosine for 1 hr, after reinfusion of the shed blood, into shocked rabbits.

It is of interest that, in preliminary experiments, the intravenous infusion of 300 μg/kg/min adenosine or an equal volume of saline for 1 hr into sham-operated rabbits produced insignificant changes in the plasma concentration of these substrates and ions.
DISCUSSION

The foregoing results clearly demonstrate that the intravenous infusion of adenosine, after reinfusion of the shed blood, effectively increased survival in experimental hemorrhagic shock in rabbits. Reinfusion of the shed blood followed by saline was much less effective. Hemorrhagic shock is characterized by hypotension, tachycardia, increased systemic vascular resistance, decreased venous return and decreased cardiac output. This results in poor tissue perfusion with concomitant alterations in tissue metabolism (4, 5). Rabbits in this study responded to hemorrhage in a similar manner. They developed hypotension, tachycardia, a marked decrease in cardiac contractility and various metabolic alterations. Although reinfusion of the shed blood into these shocked rabbits increased the reduced mean arterial blood pressure, decreased the elevated heart rate to values near to the prehemorrhage values and improved the depressed cardiac contractility to some extent, the mortality rate was still very high.

Since the inadequate circulation with a diminution of blood flow to tissues and alterations in cellular function and metabolism are common features of the shock syndrome (4, 13), pharmacological interventions that improve blood flow, the microcirculation and cell function after shock are necessary when volume restoration has failed.

It has been found that extreme metabolic stresses such as ischemia and hemorrhage evoke endogenous adenosine release. The released adenosine exerts protective effects (14, 15), but due to its rapid elimination from the plasma, endogenous adenosine produces few systemic effects even under conditions of extreme metabolic stress (11).

Adenosine is a potent endogenous coronary arteriolar vasodilator involved in the regulation of myocardial blood flow (16–18). It was found to dilate the isolated coronary arteries of various species (19–21) and to increase the coronary blood flow several fold (22). A number of studies have also shown that the continuous intravenous infusion of adenosine markedly reduced the systemic vascular resistance and mean arterial blood pressure in experimental animals (23, 24) and in humans (25, 26). Furthermore, adenosine has been shown to cause vasodilatation in canine (27), porcine (28), bovine (29) and human (30) isolated vascular smooth muscle strips. In addition, there is almost a general agreement that adenosine produces inhibitory effects on the sinoatrial node and atrioventricular conduction in the mammalian heart (17, 30). With regard to the cardiac contractility, the effect of adenosine has been variously described. It has been found that adenosine reduces the force of contraction of isolated rabbit heart (31) and isolated guinea pig atrium (32). In intact animals, adenosine infusion was also found to decrease the cardiac contractility and cardiac output (23) and to decrease left ventricular systolic pressure (24). In contrast to these observations, it has been found that adenosine increases contractility of the isolated rabbit heart (33) and ventricular preparations from the guinea pig heart (32). Adenosine infusion was also found to increase the cardiac output in normal subjects and in patients with coronary disease (25, 26, 34).

On the other hand, it has been shown that adenosine produced no inotropic effect in isolated guinea pig ventricles (35).

The data obtained in this study indicate that the intravenous infusion of adenosine decreased the mean arterial blood pressure and heart rate in sham-operated rabbits, but the cardiac contractility did not change significantly. On the other hand, the intravenous infusion of adenosine, after reinfusion of the shed blood, into shocked rabbits decreased the mean arterial blood pressure and heart rate, restored the myocardial contractile force of these animals to the prehemorrhage level and markedly increased the survival rate. The mechanism of this beneficial effect of adenosine on the cardiac contractility in shocked rabbits is postulated as follows: adenosine, through producing vasodilatation and reducing heart rate in both sham-operated and shocked rabbits, led to a great enhancement in the coronary blood flow (22). This supranormal coronary blood flow was not associated with an increase in contractile function above the baseline level in sham-operated animals. In shocked rabbits, however, the situation may be different due to the presence of a significant decrease in the coronary blood flow (13), which is responsible for a decrease in the myocardial contractile force (10). Therefore, the function of the postischemic myocardium could be selectively enhanced by augmentation of coronary blood flow to the level greater than normal in rabbits with shock.

In the presence of tissue hypoxia, the production of ATP is impaired and glucose is converted mainly to lactate that accumulates within cells and then enters the blood (4). When oxygen is insufficient to aerobically convert ADP to ATP, the tissue becomes saturated with inorganic phosphate, which also diffuses into the blood (4, 36). Moreover, the sodium pump that is responsible for maintaining the concentration gradient of ions and cellular transmembrane potential difference is inhibited during tissue ischemia (4, 37).

The data obtained in the present study demonstrate that the concentrations of glucose, lactate and inorganic phosphate were markedly elevated in the blood of shocked rabbits. Also, the plasma potassium level was elevated, while the plasma sodium and calcium levels were markedly decreased in these animals. Similarly, hyperglyc-
mnia has been reported in the experimental hemorrhagic shock (5, 38), which may be attributed to increased adrenal gland secretion, and deficient and delayed glucose use due to inadequate perfusion of tissues. An increase in the concentration of blood lactate has also been reported in hemorrhagic shock (5, 38), and acidosis becomes progressively more severe during shock (4). In addition, it has been reported that liberation of inorganic phosphate by active tissues is a good indication of tissue ischemia (36). The information available indicates that hemorrhagic shock is characterized by a great increase in cellular sodium and calcium and by a decrease in cellular potassium (4).

In this study, reinfusion of the shed blood into shocked rabbits reduced the elevated blood concentrations of glucose, lactate and inorganic phosphate and produced an improvement in the disturbed plasma concentrations of sodium, potassium and calcium. The intravenous infusion of adenosine, after reinfusion of the shed blood, restored the blood level of these substrates to the preshock level and corrected the disturbance in plasma electrolyte levels.

It is generally accepted that an insufficient energy supply is a critical factor for determining survival in hemorrhagic shock. Failure to regenerate tissue ATP was found to correlate with cell death (6). Also, high lactic acid levels were found to correlate with reduced survival (39). In addition, the sodium-potassium transport mechanism across plasma membrane was found to be important not only in the transmembrane distribution of ions but also in the regulation of cell volume and cell metabolism (37).

Some investigators have demonstrated a beneficial effect of ATP during hemorrhagic shock in experimental animals (4, 40). However, it has been found that the administered ATP was extensively and rapidly degraded in blood (41), and the actions of ATP were dependent on its rapid breakdown to adenosine (23).

In view of these considerations, the results of this study are in favor of the possibility that the intravenous infusion of adenosine, after reinfusion of the shed blood and circulatory blood volume expansion, provided an improvement of the cardiovascular performance, which resulted in maintenance of microvascular patency and improved tissue perfusion. This might have relieved tissue ischemia and hypoxia restored the metabolic machinery of cells and, in turn, increased the likelihood of survival.

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