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Mechanism of the Protective Effect of Angiotensin-Converting Enzyme Inhibition in Hemorrhagic Shock (40617)[1]

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Recent evidence indicates that angiotensin I-converting enzyme inhibitors (CEI) exert beneficial effects in cats (1) and dogs (2, 3) in hemorrhagic shock. The mechanism of the protective effect of CEI could involve actions on either of two major vasoactive peptides: (a) blockade of angiotensin II formation or (b) potentiation of vascular effects of bradykinin (4). In order to differentiate between these two potentially protective mechanisms, the following experiments were performed. Captopril, a CEI, was administered to hemorrhaged cats with and without angiotensin II infusion, thus examining the role of inhibition of angiotensin II formation on the CEI-induced shock antagonism.

Additionally, bradykinin vascular responses were examined after CEI administration in normotensive and hypotensive cats. This experiment tested whether the CEI potentiation of bradykinin was present in hypotensive states. Therefore, the aim of this report was to define the importance of blockade of angiotensin II formation to the protective effect of CEI in hemorrhagic shock, and to examine the influence of CEI on bradykinin vascular responses in hemorrhage.

Materials and methods. Male cats were anesthetized with intravenously injected pentobarbital sodium (30 mg/kg). A carotid artery and a jugular vein were catheterized for the continuous recording of arterial blood pressure and central venous pressure, respectively. A femoral artery was also cannulated to provide a route for blood removal and was attached to an oxygenated, heparinized Lucite reservoir which stored the shed blood during oligemia. A femoral vein was also cannulated for infusion of pharmacological agents. A laparotomy was performed, and a 1.5 mm (i.d.) electromagnetic flow probe was placed around the superior mesenteric artery for blood flow measurement.

In those animals subjected to hemorrhagic shock, cats were bled to 40 mm Hg and maintained at that pressure for 2.5 hr by a servopump connected to the reservoir. All shed blood remaining in the reservoir was then reinfused, and the animals were observed for an additional 2 hr. Two groups of animals were involved in this portion of the study: (i) hemorrhaged cats receiving the CEI, and (ii) hemorrhaged cats receiving the CEI in addition to angiotensin II. Captopril (0.5 mg/kg) was administered immediately after 0 time and was infused at a rate of 0.5 mg/kg/hr for the remainder of the experimental period while angiotensin II was infused at 10 μg/kg/hr. This infusion rate of angiotensin II results in a circulating angiotensin II concentration of 1–2 ng/ml, a concentration that is present in animals in hemorrhagic shock (1, 3).

In the second portion of the study, we utilized normotensive animals (i.e., about 125 mm Hg) and cats bled to a mean arterial pressure of 80 mm Hg. In both groups of cats, angiotensin I (1 μg/kg) and bradykinin (1 μg/kg) were injected before and at hourly intervals after captopril (0.5 mg/kg) injection. A single injection of the CEI was given, thus enabling observation of the rate of recovery from converting enzyme blockade.

Results. Mean postreinfusion survival times of the two groups of hemorrhagic shock cats are presented in Fig. 1. The cats receiving only captopril exhibited a survival time of 110 ± 4 min (mean ± SEM), whereas angiotensin II infusion (10 μg/kg/hr) in conjunction with captopril resulted in a significantly shorter survival time (64 ± 11 min, $P < 0.01$). These results indicate a reversal of the CEI-induced protection in hemorrhagic shock by addition of angiotensin II. Also shown in Fig.

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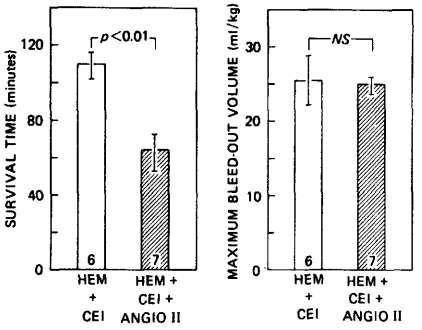

FIG. 1. Survival times and maximum bleedout volumes of cats in hemorrhagic shock. The prolonged survival time in CEI-treated animals was significantly reduced by infusion of angiotensin II. Although mean survival time was reduced, the severity of hemorrhage was equivalent in both groups as indicated by the similar maximum bleedout volumes. Numbers within the bars indicate the number of cats in each group; brackets indicate SEM.

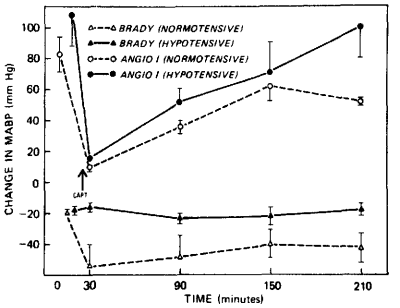

FIG. 2. Mean arterial blood pressure (MABP) responses to angiotensin I (1 μg/kg) and to bradykinin (1 μg/kg) prior to and following CEI administration. Angiotensin I responses were significantly attenuated after injection of CEI in normotensive and hypotensive animals. Bradykinin responses were significantly enhanced in normotensive but not in hypotensive cats. Both groups consisted of five cats. The arrow at 30-min marks the time of captopril (CAPT) (0.5 mg/kg) injection. Values are means ± SEM.

1 are the maximum bleedout volumes of the two groups. Maximum bleedout volumes were virtually identical, indicating that both groups were subjected to an equivalent severity of hemorrhagic shock.

Superior mesenteric artery flows (SMAF) were comparable initially in the two hemorrhaged groups (i.e., 10.6 vs 13.6 ml/kg/min). Both groups of cats experienced similar flow reductions during the oligemic period. At the end of oligemia SMAF were 2.4 ± 1.0 vs 1.9 ± 0.7 ml/kg/min. However, cats given only captopril developed significantly higher blood flows immediately following reinfusion (i.e., 8.9 ± 1.9 vs 2.6 ± 1.0; $P < 0.001$). These data suggest a susceptibility of the splanchnic vasculature to angiotensin II following reinfusion of shed blood. Moreover, the improved survival time of animals given captopril may be related to the improved splanchnic perfusion observed in response to this CEI.

Mean arterial blood pressure (MABP) changes in response to angiotensin I (1 μg/kg) and bradykinin (1 μg/kg) are summarized in Fig. 2. Prior to CEI administration (i.e., at 0 time), angiotensin I increased blood pressure 82 ± 14 and 108 ± 20 mm Hg in normotensive and hypotensive cats. Immediately after CEI injection, these responses were reduced to 10 ± 3 and 16 ± 2 mm Hg, respectively. During the following 3 hr these pressor responses gradually increased to control levels, presumably due to degradation of the CEI. Bradykinin depressor responses, conversely were significantly enhanced by the CEI, from −20 ± 2 to −54 ± 14 mm Hg in normotensive cats. This potentiation of the bradykinin responses diminished slightly with time, but was not totally eliminated at 210 min. In contrast to these results, bradykinin responses in hypotensive cats were not altered by the CEI, indicating a lack of CEI potentiation of the depressor effect of bradykinin at low arterial blood pressures such as those existing in hemorrhagic shock.

Superior mesenteric artery flow (SMAF) responses to angiotensin I and bradykinin are summarized in Fig. 3. SMAF responses to angiotensin I were significantly reduced from −55 to less than −15% in both groups of cats following administration of the converting enzyme inhibitor. These flow responses returned to control values at 210 min. The bradykinin-induced increases in SMAF were only moderately potentiated by the CEI in normotensive animals (+52 vs +84%), but did not occur in the SMAF response in hypotensive cats. This lack of potentiation of the splanchnic artery dilation to bradykinin by captopril in hypotensive cats is consistent with the blood pressure results. Together these data indicate that captopril does not

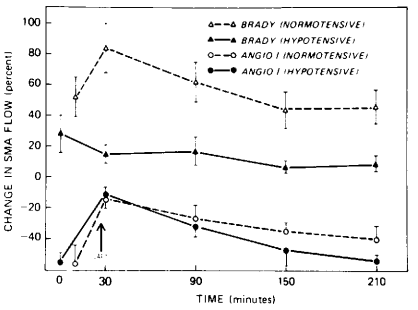

FIG. 3. Superior mesenteric artery flow (SMAF) responses to angiotensin I and bradykinin (1 μg/kg) in five normotensive and five hypotensive cats. Angiotensin I responses were significantly reduced by the CEI, however, bradykinin responses were not significantly increased under either condition. Values are means ± SEM. The arrow at 30 min indicates time of captopril (CAPT) (0.5 mg/kg) administration.

potentiate vascular effects of bradykinin in hypotensive animals. The fact that captopril only modestly potentiated the splanchnic dilator response to bradykinin, while it significantly inhibited the constrictor response to angiotensin I, suggests that inhibition of the conversion to angiotensin II may be a more fundamental action of captopril than is potentiation of bradykinin, particularly in hypotensive states.

Discussion. Angiotensin II, at circulating concentrations approximating those *in vivo* during hemorrhagic shock, prevented the prolongation of survival produced by captopril in hemorrhaged cats. This reduction in survival time may be related to diminished SMAF following the reinfusion of shed blood, since preservation of splanchnic flow has been associated with improved survival after hemorrhage (5). Thus, blockade of angiotensin II formation is probably the major beneficial action of the CEI in shock. In contrast, potentiation of the vascular effects of bradykinin does not appear to be involved in the beneficial effect of CEI in hemorrhagic shock. Since captopril did not increase bradykinin effects in hypotensive animals, this action of the CEI cannot account for the protective effect of CEI in hemorrhagic shock.

Converting enzyme inhibitors, therefore, appear to modulate the severity of hemorrhagic shock by reducing the formation of angiotensin II. Bradykinin-potentiating actions are absent at low pressures, and, therefore, are not essential to the protective mechanism of captopril. The importance of angiotensin II elimination to the beneficial effects of CEI in hemorrhage is in agreement with other studies reporting improved survival in hemorrhagic shock in animals treated with saralasin, an angiotensin II receptor antagonist (6). Also, infusion of angiotensin II has been shown to be associated with cardiac lesions and deterioration of cardiac performance (7, 8). Indeed prolonged elevation of circulating angiotensin II concentrations can induce myocardial infarction (7). Thus, there is a rational basis for preventing elevated angiotensin II concentrations in hemorrhagic shock.

Summary. Anesthetized cats subjected to hemorrhage were treated with captopril, a CEI (0.5 μg/kg/hr) alone or in conjunction with angiotensin II (10 μg/kg/hr). Angiotensin II administration significantly reduced survival time (110 vs 64 min) and lowered superior mesenteric artery flow (SMAF) immediately after reinfusion (8.5 vs 2.2 ml/kg/min). These results suggest that blockade of angiotensin II formation is a prominent aspect of the beneficial actions of captopril in hemorrhage. Furthermore, captopril potentiated the vascular effects of bradykinin at normal blood pressures but not in hemorrhagic hypotension. In the same experiments, captopril blocked the vascular effects of angiotensin I at both pressures. Thus, bradykinin potentiation is not essential for the beneficial actions of captopril in hemorrhagic shock, since hypotension abolishes the bradykinin-potentiating effects of captopril. Reduction of angiotensin II formation appears to be a major mechanism of captopril action in prolonging survival after hemorrhage.

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