(13/16) of animals, whereas the injection of saline caused no animal to die during the 4-h period. Treatment of LPS rats with DA 3 or 10 μg kg^{-1} min^{-1} further reduced survival rates to 57% (8/14) and 50% (8/16), respectively, at 4 h (Fig. 4B).

DISCUSSION

In the present study, the application of DA either by pre-treatment or post-treatment did not ameliorate the circulatory failure elicited by endotoxin injection, but further accelerated the development of hypotension which was accompanied with an enhancement of tachycardia. This was also associated with an increase of mortality in animals with endotoxic shock.

Although DA had been suggested to treat patients in various shock states,[12] the clinical therapeutic significance is not well appreciated in these patients. The beneficial effect of DA on these patients was based on the fact that ,the endotoxin-induced initial fall in blood pressure is primarily due to a decrease in venous return [11] which can be mitigated by DA via increasing cardiac output in patients through a positive inotropic action on the heart and reducing total peripheral resistance.[12] This was confirmed by Lansing and Hinshaw[15] who showed that DA increases cardiac output (by an increase in venous return but with no change in total peripheral resistance), and this increase persists during the post-endotoxin period. However, if we analyze their data of MAP, DA only transiently (within 30 min) attenuated the early fall of MAP. This may explain why the amelioration of blood pressure is transient. Since a longer period of hypotension induced by endotoxin has not been attenuated[14] or even worsened as in this study, one may argue that DA might not be an adequate therapeutic agent in patients with septic shock or, at least, endotoxic shock.

Recently, Broner et al.[16] have demonstrated that the infusion of DA in rabbits with sepsis exerted no beneficial effect on the fall of arterial pressure, but this hypotension was attenuated by diethyldithiocarbamate, an inhibitor of dopamine β-hydroxylase, suggesting that actions of DA itself do not account for the reversal of septic shock. The reversal of hypotension in septic rabbits by diethyldithiocarbamate was a result of its ability to increase the superoxide anion half-life with resulting inactivation of the excess nitric oxide, a potent vasodilator, produced in response to sepsis. The current

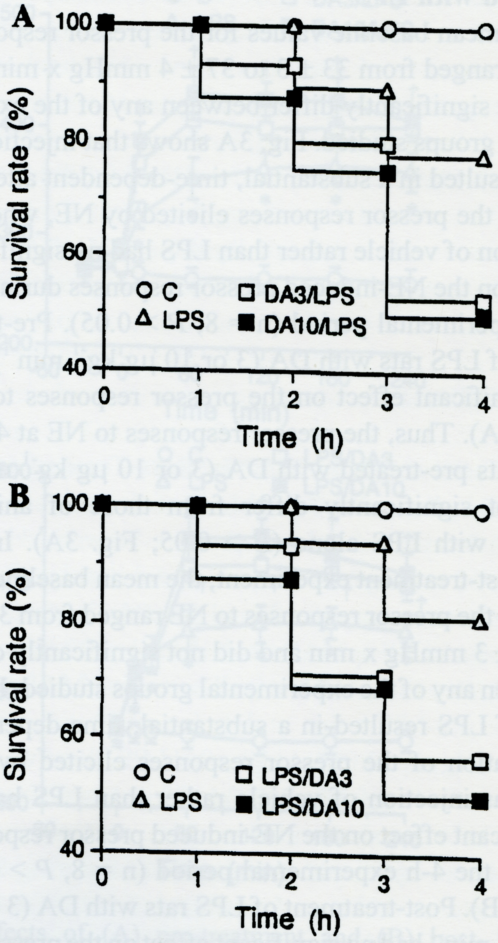

Fig. 4. Effects of (A) pre-treatment and (B) post-treatment of DA on the survival rate of anesthetized rats treated with endotoxin. Depicted are the changes of survival during the experimental period in different groups of rats which received saline (C, n = 8) or *E. coli* LPS (10 mg kg^{-1} i.v.) for 4 h. Groups of LPS-treated animals were pre-treated with vehicle (LPS, n = 16-18) or DA (3 or 10 μg kg^{-1} min^{-1}, at 30 min (A) prior to or (B) after LPS; DA3/LPS, n = 15; DA10/LPS, n = 16; LPS/DA3, n = 14; LPS/DA10, n = 16). LPS was administered at time 0. Data are expressed as the percentage of rats which had survived at the observed time point.