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Vasoconstriction to Platelet Lysis induced by Menadione and Menadione-induced Impairment of Vasorelaxation

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Our previous studies have shown that menadione is cytotoxic to platelets, leading to substantial release of vasoactive substances. To test whether platelet lysis induced by menadione could cause vasoconstriction, we investigated the effect of platelet lysate induced by menadione on rat aorta in organ bath system. We showed that menadione-induced platelet lysate caused vasoconstriction in a dose- and time-dependent manner. These effects were seen in aortic rings both with and without endothelium, but it was much greater in rings without intact endothelium. Time course of vasoconstriction was well correlated with the time courses of platelet lysis (assessed by LDH release) as well as serotonin release. The vasoconstriction by platelet lysate was not blocked by thromboxane A_2 receptor antagonist, SQ29,548, but by serotonin antagonists, ketanserin and LY53,857, suggesting that vasoconstriction mainly occurred via the release of serotonin in our *in vitro* system. These results suggest that chemically-induced platelet cytotoxicity can provoke alteration in vasomotor tone by release of serotonin.

To determine direct effect of menadione on vascular function, menadione itself was added to the aortic rings with or without intact endothelium. Treatment of menadione directly resulted in contraction of aortic rings with endothelium, but did not cause any effect on aortic rings without endothelium. Menadione inhibited relaxation of aortic rings with endothelium induced by acetylcholine and histamine in a dose- and time-dependent manner which were irreversible events. Menadione increased superoxide generation in aortic rings in a dose-dependent manner. Menadione also inhibited relaxation induced by NO donor, sodium nitroprusside in a dose-dependent manner. Menadione resulted in a dose-dependent reduction of cGMP levels both in basal state and stimulated by acetylcholine. Consistent with these *in vitro* results, when menadione was administrated intravenously to rats, blood pressure increased significantly in a dose-dependent manner. Furthermore menadione infusion suppressed the blood pressure reduction induced by acetylcholine. These results suggest that menadione can cause vascular dysfunction by inhibition of nitric oxide pathway via superoxide generation in blood vessel.

Collectively, quinones like menadione can induce cardiovascular diseases through vasomotor tone alteration mediated by platelet cytotoxicity and direct endothelial dysfunction.