Effects of OKY-046, a Selective Thromboxane A₂ Synthetase Inhibitor, on Ventricular Arrhythmias and Prostaglandins during Coronary Artery Ligation and Reperfusion in Anesthetized Dogs

Toshitsugu OGURA, Ichiro WATANABE, Tomoaki SAITO, Satoshi SAITO, Yukio OZAWA and Michinobu HATANO
2nd Department of Internal Medicine, Nihon University School of Medicine, 30-1, Oyaguchi-Kamimachi, Itabashi-ku, Tokyo, Japan

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Abstract—Effects of OKY-046, a selective thromboxane synthetase inhibitor, on ischemia-induced ventricular arrhythmias were investigated in anesthetized dogs. OKY-046 (30 mg/kg, intravenously) decreased ventricular arrhythmias significantly both during 30 min of coronary artery ligation and subsequent reperfusion, which corresponded with a significant reduction of thromboxane concentration, suggesting that thromboxane released during ligation is an important factor in the development of ventricular arrhythmias. Inhibition of thromboxane synthesis with OKY-046 might be useful for the prevention of ischemia-induced ventricular arrhythmias.

Since the release of thromboxane A₂ (TXA₂), which contracts the coronary artery and induces platelet aggregation, is thought to exert a deleterious influence on the regulation of the coronary circulation, inhibition of TXA₂ synthesis might therefore have a beneficial effect on myocardial ischemia (1, 2). However, there is little information concerning the possible effects of TXA₂ inhibition on cardiac arrhythmias in the ischemic setting. The present study was performed to assess the effects of a specific TXA₂ synthetase inhibitor, OKY-046 (3), on ventricular arrhythmias both during 30 min of coronary artery ligation and subsequent reperfusion and on coronary sinus prostaglandins in anesthetized dogs.

Nineteen mongrel dogs weighing from 15 to 20 kg were anesthetized with sodium pentobarbital (30 mg/kg, intravenously) under artificial ventilation with a Harvard ventilator. Catheters were placed in the aorta, the coronary sinus and the external jugular vein. Both aortic blood pressure and surface ECG were continuously monitored. Following a midthoracic thoracotomy, the heart was suspended in a pericardial cradle and a ligature placed around the left anterior descending artery just proximal to the first diagonal branch. K⁺-sensitive electrodes made from a valinomycin-polyvinyl chloride matrix membrane were inserted to the center of the expected ischemic myocardium, and the interstitial K⁺ concentrations ([K⁺]) were monitored (4, 5). In nine dogs (OKY group), a bolus of 5.0 mg/kg of OKY-046 (Ono Pharmaceutical Co., Ltd., Osaka, Japan) was dissolved in saline and injected intravenously followed by intravenous drip infusion at 2.0 mg/kg/hr 30 min prior to the coronary ligation. Ten control dogs (control group) received appropriate volumes of saline. The coronary artery was ligated and released 30 min later, resulting in reperfusion of the formerly ischemic myocardium. Blood samples were taken from the coronary sinus before ligation, just before reperfusion and immediately after reperfusion. Thromboxane B₂ (TXB₂) and 6-keto prostaglandin F₁α (6-keto PGF₁α), i.e., stable degradation products of TXA₂ and prostaglandin I₂ (PGI₂), respectively, were measured by a specific radioimmunoassay. All data were expressed as the mean±S.E.M. Statistical significance between the control and the OKY group was determined using the unpaired Student’s t-test. Differences were considered significant when P<0.05.

The number of ventricular premature con-
tractions (VPC) during coronary ligation and the incidence of ventricular fibrillation (VF) within 30 min after reperfusion in the control and the OKY group are shown in Fig. 1. In the control group, the mean number of VPC during ligation was 266±91, and the incidence of VF after reperfusion was 70%, while both the mean number of VPC during ligation (30±21) and the incidence of VF after reperfusion (22%) in the OKY group were significantly lower than those in the control group (P<0.05). The changes in coronary sinus TXB2 and 6-keto-PGF1α concentrations before and during coronary ligation and after reperfusion in the both groups are shown in Fig. 2. Before ligation, TXB2 concentration (631±252 pg/ml) and 6-keto PGF1α concentration (731±135 pg/ml) in the OKY group were lower than those in the control group (860±222 pg/ml and 733±149 pg/ml, respectively), but they were not statistically significant. OKY significantly reduced TXB2 concentrations both during ligation (1040±232 pg/ml vs. 317±64 pg/ml, P<0.01) and after reperfusion (953±242 pg/ml vs. 389±77 pg/ml, P<0.05) as compared to the control group, while there were no significant differences in 6-keto-PGF1α concentrations between the control and the OKY group both during ligation (1051±298 pg/ml vs. 666±121 pg/ml) and after reperfusion (1183±408 pg/ml vs. 814±158 pg/ml). Furthermore, the TXB2/6-keto-PGF1α ratio, which indicates the balance between these two substances, was lower in the OKY group (<1.0) than that in the control group (>1.0) both during ligation and after reperfusion. [K+] measured by K+-sensitive electrodes before ligation was 3.8±0.2 mM in the control group and 3.6±0.2 mM in the OKY group, this being not statistically significant. [K+] was rapidly elevated just after coronary ligation in both groups. However, the maximal concentration in the OKY group (8.6±0.5 mM) was significantly lower than that in the control group (13.6±1.3 mM, P<0.01). Prior to the administration of OKY-046, there were no significant differences in mean blood pressure and heart rate between the control (98±9 mmHg and 166±7/min, respectively) and the OKY group (96±7 mmHg and 156±19/min). Mean blood pressure was slightly decreased after the administration of OKY-046 (81±6 mmHg), but it was not statistically significant. After the administration of OKY-046, there were no changes in PQ, QRS and QT intervals.

The present study showed that inhibition of TXA2 synthesis with OKY-046 effectively prevents ventricular arrhythmias both during coronary artery ligation and after reperfusion.

![Fig. 1. The effects of OKY-046 on the number of ventricular premature contraction during 30 min of coronary artery ligation (A) and the incidence of ventricular fibrillation after coronary reperfusion (B). *P<0.05 compared to the control group.](image-url)
The most likely explanation of the antiarrhythmic effects of OKY-046 involves its effects on the coronary microcirculation. With inhibition of TXA₂ synthesis, arachidonic acid metabolism may be shunted toward PGI₂ synthesis. Since TXA₂ contracts the coronary artery and induces platelet aggregation, whereas PGI₂ has opposite effects, either reduction of TXA₂ concentration or increase of PGI₂ concentration in the coronary circulation is thought to protect the ischemic myocardium. In the OKY group, since TXB₂ concentration in the coronary sinus was significantly reduced, the TXB₂/6-keto-PGF₁α ratio was lower than 1.0, in contrast to the control group. It is possible that inhibition of TXA₂ synthesis and the improvement of the TXA₂/PGI₂ balance with OKY-046 reduce the severity of myocardial ischemia, resulting in a prevention of ventricular arrhythmias during coronary ligation. This protective effect, which is also shown by the fact that OKY-046 significantly reduced the increased [K⁺] after coronary ligation, a reliable parameter of the ischemic state, corresponds to the reports that OKY-046 significantly reduced lactate production during myocardial ischemia and the infarct volume after five hours of coronary artery ligation. With sudden reperfusion, the rapid onset of the electrical instability seen within seconds strongly suggests a process dependent on a washout or redistribution of metabolites stored in the ischemic myocardium. Therefore, the antiarrhythmic effects of OKY-046 seen after reperfusion might reflect a reduction of the metabolites such as TXA₂ or K⁺: Washout of TXA₂ might exacerbate ischemic changes by platelet aggregation and vasoconstriction in the perfused myocardium, and washout of K⁺ might cause the electrical gradients resulting in the electrical inhomogeneity across the ischemic myocardium.

Whether the antiarrhythmic effects of OKY-046 simply reflect a reduction of the severity of the myocardial ischemia remains to be elucidated: There might be a direct electrophysiological effect of TXA₂ inhibition. Ac-
cording to the recent report that a stable TXA₂ analog does not directly influence either action potential parameters or activation patterns both in the infarcted and non-infarcted myocardium in dogs (9), the expected electrophysiological effect of TXA₂ inhibition might be caused by a relative increase in PGI₂ concentration and resulting improvement of the TXA₂/PGI₂ balance. Further studies are needed to delineate the electrophysiological effects of prostaglandins and its synthetase inhibitors in the ischemic setting.

References
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