

**TITLE:** CONVERSION OF SODIUM NITROPRUSSIDE TO ITS ACTIVE VASODILATOR, NITRIC OXIDE, REQUIRES CHEMICAL REDUCTION AND RELEASE OF CYANIDE.

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Sodium nitroprusside (SNP) is believed to cause vasodilation by releasing nitric oxide (NO) which activates guanylate cyclase in vascular smooth muscle<sup>1</sup>. The mechanism of NO release from SNP is not known. Current theories assume that SNP releases NO spontaneously. It is also known that in clinical use SNP also releases cyanide in large amounts<sup>2</sup>. The mechanism of cyanide release and its relationship to the normal pharmacology of SNP are also unknown. In an *in vitro* study the release of NO from SNP was studied by continuously purging solutions of SNP with argon and measuring NO in the argon with a chemiluminescent NO analyser.

Solutions of SNP between 0.05-10 mM and pH 3-9 did not spontaneously release any NO. SNP is known to be photochemically unstable. When solutions of SNP were irradiated with visible light NO was released at rates linearly proportional to SNP concentration and light intensity. SNP is also known to be readily reduced. When solutions of SNP were reduced by any of several reducing agents,

including glutathione, cysteine, N-acetylcysteine, penicillamine, N-acetylpenicillamine, ascorbic acid, sodium dithionite, sodium borohydride, ferrous chloride, hemoglobin, myoglobin, or cytochrome P450 with an NADPH regenerating system, NO was produced. Excess reducing agent and prolonged reaction times resulted in depressed rates of NO release that could be transiently restored by exposure to oxygen. Potassium cyanide caused no release of NO from SNP and blocked NO release by reducing agents. Solutions containing reduced SNP released almost no NO at pH 9. NO release increased markedly as pH was incrementally lowered to 3. In some experiments a sodium hydroxide trap was placed in line between the SNP reaction vessel and the NO analyser. HCN removed from the reaction vessel was trapped and was measured continuously with a cyanide electrode. The kinetics of HCN production showed that HCN release preceded NO release. Four major conclusions can be drawn from these results:

- 1: SNP does not spontaneously release NO or cyanide.
- 2: SNP releases NO by photolysis (which plays no role in the normal pharmacology of SNP).
- 3: SNP releases NO after it has undergone a 1-electron reduction and subsequently lost part or all of its cyanide ligands.
- 4: The generation of cyanide by SNP appears to be an essential step in the mechanism of action of SNP.

**References**

1. Pharmacol. Rev. 39:163-196, 1987.
2. Anesthesiology 45:340-354, 1976.

**Title:** EFFECTS OF ISOFLURANE ON CORONARY FLOW AND DEVELOPMENT OF DYSRHYTHMIAS DURING ISCHEMIA AND REPERFUSION

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Temporary ischemia resulting from tissue hypoperfusion (HP) can cause impairment of cardiac function. With reperfusion (RP) the heart may or may not regain full function. Volatile anesthetics may reduce myocardial damage and dysrhythmias during ischemia and RP. The purpose of this study was to examine the direct effects of ISO on isolated heart during HP and RP.

Guinea pig hearts (n=38) were perfused at perfusion pressure (PP) of 55 torr with modified Krebs-Ringer solution (pH 7.38, PO<sub>2</sub> 561 torr) at 36.8°C. Heart rate (HR), atrio-ventricular conduction time (AVCT), left ventricular systolic pressure (SLVP), O<sub>2</sub> consumption, coronary flow (CF), and incidence and duration of dysrhythmias during HP and RP were measured. Hearts were divided into four groups: Groups 1 and 2 (n=9 for each group) were perfused at 0% and groups 3 and 4 (n=10 for each group) at 25% of the initial PP for 30 min: Groups 2 and 4 were exposed to 1.25% ISO 10 min prior to, during, and 10 min following HP. ISO was delivered by vaporizer and measured in the perfusate by gas chromatography (300±30 µM). HP was followed by 40 min RP at 55 torr. Statistical differences were determined by ANOVA and Chi-square tests. Data are means ± SEM.

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ISO decreased duration of ventricular fibrillation (VF) and premature ventricular contractions (PVC's) during RP following HP at 0% PP (Figure 1). During HP major dysrhythmias were 2° and 3° AV block and atrial and/or ventricular arrest during 0% PP. Incidence of VF and PVC's was lower after 25 than after 0% PP but was not significantly changed by ISO. In ISO group at 0% PP CF was higher before HP and during early RP. The same group had a significantly higher response following adenosine (A) administration (Figure 2). There was no significant difference in CF between control and ISO group during RP at 25% PP. Although ISO significantly decreased SLVP and oxygen extraction before HP and early during RP, ISO did not improve recovery of SLVP during reperfusion.

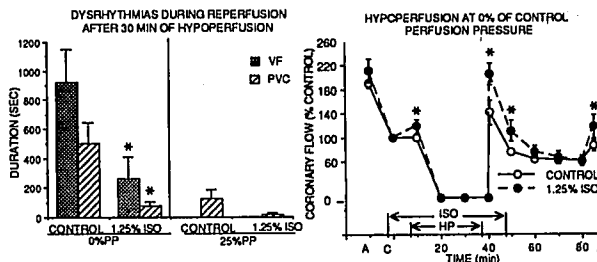


Figure 1 \* p < 0.05 vs. Control Figure 2

Results of our study show that ISO has antiarrhythmic effects following global HP after 0% PP and improves coronary flow response to vasodilatation to A after 0% PP.