Cardiac Cyanide Toxicity Induced by Nitroprusside in the Dog: Potential for Reversal

John H. Tinker, M.D.,* and John D. Michenfelder, M.D.†

Specific sodium nitroprusside (SNP)-induced myocardial cyanide (CN) toxicity was studied in 24 dogs, using a right-heart bypass preparation that enabled calculation of myocardial oxygen consumption (MVox) from direct measurements of coronary blood flow and arterial and coronary venous oxygen contents. Massive doses of SNP (20 mg/kg/hr) were given to obtain rapidly increasing blood CN levels. Isoelectric electroencephalographic (EEG) tracings appeared at a blood CN level of 3.2 µg/ml, whereas MVox did not decrease to significantly below control until blood CN had increased to 5.2 µg/ml (P < .01). In five dogs, the addition of partial left ventricular bypass both decreased left ventricular external work and increased coronary oxygen delivery, but did not appreciably delay the MVox decrease or ventricular fibrillation. In seven dogs, experiments were conducted to determine the blood CN level and extent of systemic acidosis at which CN toxicity could not be reversed with standard anti-CN measures. Animals could be resuscitated when blood CN levels were less than 4 µg/ml and when acidosis had not worsened beyond a base deficit of −11 mEq/l. The authors conclude that: 1) myocardial CN toxicity during SNP administration in dogs occurs at higher blood CN levels than those that result in isoelectric EEG tracings; 2) decreases in myocardial workload and increases in coronary oxygen delivery are not protective; 3) systemic acidosis is a reasonable indicator of SNP-related whole-body CN toxicity; 4) there is no significant decrease in MVox when the SNP-induced systemic CN toxicity has already become irreversible by standard anti-CN treatment. SNP-induced CN toxicity in man, even in the presence of myocardial disease, is likely to be manifested at lower blood CN levels than that which produces myocardial toxicity. (Key words: Anesthetic techniques; hypotension, induced, nitroprusside. Blood pressure: hypotension. Heart: oxygen consumption; myocardial function; cyanide toxicity.)

It has long been known that sodium nitroprusside (SNP) undergoes metabolic breakdown, releasing cyanide (CN).1 Page et al.,2 in 1955, reported low doses to be effective in treating severe hypertension. Deliberate intraoperative hypotension with SNP was reported in 1965.3 Franciosa et al.,4 in 1972, reported that a decrease in afterload produced by SNP resulted in improved left ventricular function in patients with left ventricular failure. Today, SNP is widely employed, often for prolonged periods, following myocardial infarction, in open-heart surgery, and in other patients with myocardial failure.5

Nitroprusside-induced CN toxicity has been found in laboratory studies of dogs6 and baboons,7 and in man both during hypotension induced intraoperatively6,8 and during chronic antihypertensive therapy.9 Some patients (and a larger proportion of laboratory animals) are resistant to SNP-induced vasodilatation. These individuals are at risk of developing CN toxicity, especially when dosage is based solely on titration to a desired blood pressure, because metabolism to CN is dose-related.10,11

We are unaware of any study of SNP-related myocardial cyanide toxicity. Because of its high oxygen consumption, the myocardium might be an early target for CN toxicity. The study is also relevant because patients with existing myocardial dysfunction are being treated for prolonged periods with SNP. Our goals were to determine: 1) the susceptibility of the myocardium to CN toxicity; 2) blood CN levels required for myocardial CN toxicity relative to cerebral CN toxicity; 3) whether increases in myocardial oxygen delivery and decreases in external cardiac work would delay onset of myocardial CN toxicity; 4) the blood CN level and extent of metabolic acidosis beyond which standard anti-cyanide therapy would not reverse myocardial and/or systemic SNP-induced CN toxicity.

Methods

Unpremedicated mongrel dogs weighing approximately 15 kg were used. After induction of anesthesia with halothane and tracheal intubation facilitated by succinylcholine, muscle paralysis was maintained with succinylcholine infusion. Anesthesia was maintained with halothane, 0.4 per cent v/v, nitrous oxide, 60 per cent, and oxygen. After median sternotomy, right-heart bypass was accomplished by diversion of caval flow to a reservoir--roller pump--heat exchanger circuit, as described by Theye et al.12 Blood was reinfused into the proximal pulmonary artery. The azygos vein was ligated. Mechanical ventilation was adjusted to achieve an arterial carbon dioxide partial pressure (Paco2) of 38 ± 4 torr during the control period, and was not changed during the experiment. Direct coronary blood flow measurements were made by timed collection from a right ventricular catheter placed via the right atrium, with the pulmonary artery ligated proximal to the pump inflow.

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Pump flow was assumed to equal left ventricular output (Q). Pump flow was initially adjusted to achieve a mean arterial blood pressure (MAP) of approximately 90 torr, then held constant. Oxygen contents were determined by measurements of oxygen partial pressures (IL electrode) and oxyhemoglobin (IL CO-Oximeter) in arterial, coronary venous, and mixed venous blood samples. Myocardial oxygen consumption (MV<sub>o</sub>) was calculated by the Fick relationship (MV<sub>o</sub> = coronary blood flow × arterial−coronary venous blood oxygen content difference).

The extracorporeal circuit was primed with 1,000 ml of fresh cross-matched donor blood. Pressures were transduced by strain gauge from the left ventricle (for left ventricular end-diastolic pressure—LVEDP), left atrium (left atrial pressure—LAP), and carotid artery (for MAP). Electrocardiogram (leads II and V<sub>4</sub>) and EEG (two channels, bifrontal and biparietal) were continuously recorded. Following surgical preparation, the median sternotomy was approximated with clips. Nasopharyngeal temperature was transduced by thermistor and maintained at 37 ± 0.3°C using the heat exchanger.

In five dogs, an additional roller pump infused blood into the femoral artery. This decreased ventricular external cardiac workload by enabling control MAP of 90 torr to be maintained with lower main pump inflow to the pulmonary artery. A bubble oxygenator was incorporated into the circuit proximal to the two reinfusion pumps to insure uniformity of F<sub>1</sub>O<sub>2</sub>.

Pulmonary arterial inflow (Q) was adjusted to yield a MAP of approximately 90 torr. During the control period, numerous determinations of MV<sub>o</sub> and buffer base were made. Bicarbonate was added as necessary to achieve a control buffer base of 49–50 mEq/l. Control MV<sub>o</sub> was recorded as the mean of three determinations of MV<sub>o</sub>, taken at consecutive 5-min intervals. Additional measurements were: arterial cyanide and thiocyanate by the method of Okawa et al.,<sup>14</sup> arterial lactate and pyruvate by standard enzymatic methods; arterial epinephrine, norepinephrine and total catecholamines by the modified trihydroxyindole method.<sup>15</sup> Following the control period, four separate groups of experiments were conducted.

**Group I: Control**

To determine the effect of time alone on the right-heart bypass preparation, values were obtained in two dogs every 15 min for two hours. An infusion of 5 per cent dextrose in water was given at a rate equal to that of the SNP administration to the other experimental groups.

**Group II: Nitroprusside Infusion**

Seven animals were given a constant infusion of SNP, 20 mg/kg/hr, in 5 per cent dextrose in water (concentration 200 mg/l) by calibrated pump. MV<sub>o</sub>, temperature, and all pressures were determined every 5 min until ventricular fibrillation occurred. Cyanide, thiocyanate, lactate, pyruvate, and buffer base values in arterial blood were determined every 15 min; catecholamine values every 30 min.

**Group III: Nitroprusside Plus Extra Femoral Pump**

Five dogs were studied. The femoral pump was started at approximately a third the pulmonary arterial (main pump) inflow rate. This allowed control MAP to be established similar to Group II at reduced main pump flow (Q), which in turn resulted in a lower control left ventricular stroke work index (LVSWI) in Group III than in Group II. The main pump flow (Q) was held constant throughout the experiment. SNP, 20 mg/kg/hr, was infused, and all measurements taken as described above until ventricular fibrillation occurred. The femoral pump flow (partial left ventricular bypass) was necessarily decreased gradually as acidosis and vasodilation occurred, to maintain an adequate reservoir level. This resulted in a gradual lessening of the difference between Groups II and III with respect to LVSWI. No additional blood or fluid was added to the extracorporeal circuit.

**Group IV: Reversal of CN Toxicity**

Seven dogs were given SNP as in Group II (right-heart bypass without extra femoral pump). Buffer base was determined every 5 min as cyanide toxicity developed. In four animals (Group IVa), treatment was begun at a buffer base value of 40 mEq/l. The other three (Group IVb) were given longer SNP infusions, and treatment was begun at a buffer base value of 33 mEq/l. Treatment consisted of: 1) discontinuance of anesthetic and SNP; 2) addition of sodium nitrite, 5 mg/kg, to the reservoir over 5 min; 3) addition of sodium thiosulfate, 150 mg/kg, as a bolus, to the reservoir after the nitrite, repeated once every 10 min later; 4) adjustment of the buffer base value to control level with sodium bicarbonate.

When fibrillation terminated each experiment, approximately 500-ml biopsy specimens of left ventricular muscle were taken using a specially designed clamp. The clamp, precooled in liquid nitrogen, froze the samples within 1 sec. Specimens for controls were obtained from three dogs anesthetized as above without the right-heart preparation and without SNP. Ventricular muscle was assayed for ATP, phospho-

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<sup>†</sup> Mean ± SEM.
creatinine, lactate, and pyruvate, using methods previously described. 17, 18

Student's t test for paired or unpaired values, as appropriate, was utilized. P < .05 was considered significant.

**Results**

**GROUP I: CONTROL**

No deterioration of the preparation in two hours was evident in any of the measured values, including buffer base, MV\textsubscript{0.5}, MAP, LAP, LVEDP, heart rate, lactate, or pyruvate. ECG and EEG tracings were also unchanged.

**GROUP II: NITROPRUSSIDE INFUSION: TABLE 1**

Ventricular fibrillation occurred before the 90-min values in four dogs, and before 120 min in the remainder. MAP decreased 48 per cent during the first 15 min of SNP infusion, then increased significantly during the next 15 min coincident with peak arterial catecholamine levels, before declining further (fig. 1). Total catecholamine values at the 30-min period were 7.5 times greater than the control values, after which a marked decrease occurred.

Myocardial oxygen consumption also had increased significantly at the 30-min period, then decreased as cyanide toxicity presumably occurred. MV\textsubscript{0.5} did not decrease to significantly lower than control until the 75-min period. Four of the seven dogs died during the next 15 min, and MV\textsubscript{0.5} values for the remaining three continued to decrease during the next two time periods. At the 75-min period, mean MV\textsubscript{0.5} had decreased to 46 per cent of control (fig. 2). The initial increase in MV\textsubscript{0.5} (peak 30 min) was associated with a peak coronary blood flow, increased to three times control. Coronary blood flow then gradually decreased, but was not significantly lower than control until 105 min, whereas MV\textsubscript{0.5} first decreased to significantly below control at 75 min. At the 75-min value, coronary venous P\textsubscript{O2} was 1.9 times control.

Systemic metabolic acidosis rapidly developed. At 30 min, buffer base values had decreased 10 per cent, declining to 62 per cent of control by 75 min. Lactate/pyruvate ratio was 6.2 times greater than control at 75 min; arterial blood pH had decreased from 7.39 to 7.09.

Left atrial pressure increased 15–30 min before fibrillation in every animal. Individual values were widely variable, however, and the group mean dif-
ference from control did not achieve statistical significance until the 105-min values. Group mean LVEDP was significantly increased above control at 75 min.

Arterial whole-blood CN values increased in a nearly linear fashion (fig. 2). At 75 min, the point at which $MV_0$ first decreased to significantly below control, the average CN value was 5.2 $\mu$g/ml.

Electrocardiographic tracings showed numerous arrhythmias, including multifocal premature ventricular beats, from the 30-min period until fibrillation in all animals. Sustained, progressive ST-segment depression was evident after 75 min in all animals. The EEG slowed progressively, with decreasing amplitude. By 45 min, all EEG tracings were isoelectric. Average blood CN level at this point was 3.3 $\mu$g/ml, which was 64 per cent of the CN level at which $MV_0$ first decreased to significantly below control. During the early decrease in MAP caused by the SNP infusion, the EEG remained unchanged. When the EEG tracings were considered isoelectric, at 45 min, group mean arterial pressure was 54 torr.

**GROUP III: SNP INFUSION PLUS EXTRA FEMORAL PUMP**

Addition of oxygenated blood to the femoral artery via a second inflow pump enabled maintenance of arterial blood pressure similar to that in Group II but at a lower left ventricular output (main pump flow). Left ventricular index was $1.84 \pm 0.20$ l/min/m$^2$ in Group II, and decreased to $1.27 \pm 0.16$ l/min/m$^2$ in Group III. Control MAP was 89 $\pm$ 8 torr with the partial left ventricular bypass in Group III, vs. 96 $\pm$ 2 torr in Group II (not significantly different). Control left ventricular stroke work index (LVSWI) was decreased 42 per cent by the partial left ventricular bypass achieved with the femoral pump. Lowering the LVSWI in this manner slightly delayed the first significant decrease in $MV_0$, and all five animals survived.

§ Calculated as follows:

\[
\text{Stroke volume index (SVI)} = \frac{\text{cardiac index}}{\text{HR}}
\]

\[
\text{LVSWI} = \text{SVI} \times \text{MAP}
\]
105 min or more (two survived 120 min). MV$_0$ decreased to significantly below control at 90 min (75 min in Group II), at a slightly higher cyanide level (6.0 vs. 5.2 $\mu$g/ml).

Overall myocardial oxygen delivery was considerably greater in Group III than in Group II to 75 min. This was reflected by significantly greater coronary blood flow values at 15, 45, 60, and 75 min, coupled with significantly higher coronary venous P$_0$ values at 60 and 75 min. Arterial O$_2$ contents in the two groups were similar at all times.

Arterial CN levels increased virtually identically in Groups II and III, as did serum thiocyanate levels. Metabolic acidosis, reflected by pH$_a$, arterial lactate, and lactate/pyruvate ratio increases, and buffer base values, also occurred at approximately equal rates in the two groups. EEG tracings again became isoelectric at 45 min (blood CN 3.1 ± 2 $\mu$g/ml); thus, EEG isoelectricity occurred at 48 per cent of the CN level at which MV$_0$ decreased to significantly below control in Group III.

**GROUP IV: REVERSAL OF CN TOXICITY, TABLE 2**

In these dogs, the intent was to determine the extent of metabolic acidosis at which CN toxicity could no longer be reversed by conventional anti-CN measures. In four dogs (Group IVA) buffer base was 39 mEq/l (decreased 22 per cent from control) when treatment was initiated. In three dogs (Group IVB) buffer base was allowed to decrease further to 33 mEq/l (decreased 33 per cent) before treatment was begun.

Each of the four dogs in Group IVA (base deficit -11 mEq/l) showed evidence of reversal of CN toxicity, whereas reversal could not be achieved in any of the three animals in Group IVB (base deficit -16 mEq/l). Evidence of reversal in Group IVA included sustained reversal of arterial acidosis and mixed venous blood oxygen tension (P$_V$O$_2$) values, and essentially unchanged LAP and LVEDP values. MV$_0$ values in Group IVA (fig. 3) remained unchanged for 30 min, then gradually increased (anesthesia had been discontinued). MAP in Group IVA increased slowly with treatment, returning to 84 torr 90 min after beginning therapy. The EEG, essentially isoelectric at initiation of treatment, had returned to a pattern indistinguishable from control by 60 to 75 min. Total arterial CN at the beginning of treatment in Group IVA, 3.3 $\mu$g/ml, increased to 8.5 $\mu$g/ml within 30 min, remaining near this level over the next 60 min, reflecting CN trapping by nitrite-formed methemoglobin. Fibrillation had not occurred in any of the four dogs when experiments were terminated 90 min after treatment.

By contrast, in Group IVB, SNP was continued longer, allowing acidosis to progress to a base deficit of -16 mEq/l. This resulted in CN toxicity that was not reversed by the same anti-CN measures. Base deficit was corrected to -1 mEq/l at 15 min, but progressively worsened despite additional bicarbonate therapy. MV$_0$ values had decreased to 40 per cent of control 30 min after stopping SNP (fig. 3). All three dogs fibrillated 30 to 45 min after treatment. Total blood CN levels in this subgroup following treatment were the highest seen in the present study, starting at 4.4

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**Table 2. Values for Groups IVA and IVB**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>At Stoppage of SNP</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
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</thead>
<tbody>
<tr>
<td><strong>Group IVA</strong>, Treatment at BB 39 ± 1 (base deficit -11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (torr)</td>
<td>92 ± 3</td>
<td>54 ± 6</td>
<td>41 ± 1</td>
<td>47 ± 1</td>
<td>59 ± 6</td>
<td>84 ± 16</td>
</tr>
<tr>
<td>Left atrial pressure (torr)</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
<td>11 ± 3</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>pH$_a$</td>
<td>7.41 ± .02</td>
<td>7.23 ± .03</td>
<td>7.34 ± .01</td>
<td>7.29 ± .03</td>
<td>7.35 ± .01</td>
<td>7.39 ± .01</td>
</tr>
<tr>
<td>MV$_V$O$_2$ (ng O$_2$/100 g/min)</td>
<td>7.6 ± .04</td>
<td>9.4 ± 1.0</td>
<td>7.2 ± 1.3</td>
<td>8.1 ± 1.2</td>
<td>10.0 ± 1.8</td>
<td>11.5 ± 1.5</td>
</tr>
<tr>
<td>Blood CN (mg/ml)</td>
<td>0.03 ± 0.03</td>
<td>3.3 ± 0.4</td>
<td>6.9 ± 0.8</td>
<td>8.5 ± 2.3</td>
<td>7.1 ± 2.1</td>
<td>7.7 ± 2.8</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio</td>
<td>17 ± 3</td>
<td>67 ± 9</td>
<td>36 ± 6</td>
<td>34 ± 5</td>
<td>30 ± 3</td>
<td>28 ± 4</td>
</tr>
</tbody>
</table>

| **Group IVB**, Treatment at BB 33 ± 1 (base deficit -16) |         |                    |       |       |       |       |
| Mean arterial pressure (torr) | 91 ± 3  | 33 ± 2             | 22 ± 2| 24 ± 0|       |       |
| Left atrial pressure (torr)    | 8 ± 2   | 9 ± 2              | 18 ± 1| 22 ± 0|       |       |
| pH$_a$               | 7.41 ± .01 | 7.13 ± .03      | 7.34 ± .03| 7.30 ± .01| 7.30 ± .01|       |
| MV$_V$O$_2$ (ng O$_2$/100 g/min) | 6.3 ± 1  | 4.6 ± 7           | 2.2 ± 7| 2.5 ± 0|       |       |
| Blood CN (mg/ml)       | 0.04 ± 0.04 | 4.4 ± 0.8        | 10.2 ± 1| 10.4 ± 0|       |       |
| Lactate/pyruvate ratio | 17 ± 1  | 77 ± 10            | 40 ± 0| 36 ± 0|       |       |

* Means ± SEM, n = 4 for Group IVA, n = 3 for Group IVB.
† All three dogs had died by 45 minutes in Group IVB.
Groups IVa and IVb. At the start of anti-CN therapy, M\textsubscript{V\textsubscript{O}}\textsubscript{2} values were not significantly different from control in either group. All animals in group IVb fibrillated by 45 min, whereas none in Group IVb had fibrillated by 90 min. Increases in M\textsubscript{V\textsubscript{O}}\textsubscript{2} values at 90 and 90 min in Group IVa are attributed to reversal of CN toxicity and the fact that anesthetics had been discontinued as part of anti-CN treatment.

Fig. 3. Nitroprusside was given in extreme doses that resulted in ventricular fibrillation with toxic CN levels within two hours. Pilot studies had shown that dosages of 5 and 10 \( \mu \text{g/kg/hr} \) would not result in CN toxicity within this period. Because of the invasive nature of the right-heart bypass preparation, we were concerned that a longer period of study might introduce factors related to time rather than to CN toxicity. No deterioration in any measured value occurred during two hours with this preparation without SNP in two control animals. That SNP, 5 and 10 \( \mu \text{g/kg/hr} \), did not result in toxic CN levels can be explained in part by dilution due to the large extracorporeal priming volume. Previously, we have shown that SNP given to dogs in a dosage of 0.75 or 1 \( \text{mg/kg/hr} \) will result in a roughly linear increase in CN, with death occurring at blood CN levels between 6 and 9 \( \mu \text{g/ml} \).\textsuperscript{10} Time to death is dependent upon rate of increase of blood CN, which in turn is dependent on SNP dosage. At SNP, 0.75 to 1 \( \text{mg/kg/hr} \), given to intact dogs, death occurred at 30–38 hours.\textsuperscript{10} In the present study, SNP, 20 \( \mu \text{g/kg/hr} \), caused death in less than two hours, at essentially the same blood CN levels.

In this study cerebral toxicity was reflected by EEG flattening at approximately 45 min. Blood CN levels were 3.1 to 3.3 \( \mu \text{g/ml} \). In a previous study canine cerebral CN toxicity as indicated by significantly increased sagittal sinus \( \text{P}_{\text{O}}\text{2} \), was found at a blood CN level of 3.4 \( \mu \text{g/ml} \) by Michenfelder.\textsuperscript{6} Defining the point at which myocardial CN toxicity began is more difficult. M\textsubscript{V\textsubscript{O}}\textsubscript{2} values first increased, consonant with the catecholamine peak, presumably related to the initial SNP-induced hypotension. M\textsubscript{V\textsubscript{O}}\textsubscript{2} values then decreased progressively. Assuming myocardial CN toxicity is defined as the point at which M\textsubscript{V\textsubscript{O}}\textsubscript{2} values first decreased to significantly below control, then myocardial toxicity occurred at blood CN levels at least 60 per cent greater than those at which cerebral CN toxicity occurred. Although there was considerable variability, LVEDP values always increased rapidly before fibrillation in Group II. When myocardial CN toxicity is defined as the point at which LVEDP values increased, then myocardial CN toxicity occurred at similar blood CN levels relative to cerebral toxicity. We consider the first significant decrease in M\textsubscript{V\textsubscript{O}}\textsubscript{2} to be a reasonable indicator of myocardial CN toxicity.
Nitroprusside and Myocardial CN Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Group I H</th>
<th>Group II M</th>
<th>Group IVa</th>
<th>Group IVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine triphosphate (μmol/L)</td>
<td>4.36 ± 0.23</td>
<td>3.43 ± 0.18</td>
<td>3.59 ± 0.31</td>
<td>4.13 ± 0.15</td>
</tr>
<tr>
<td>Phosphocreatine (μmol/L)</td>
<td>7.15 ± 0.31</td>
<td>1.12 ± 0.26</td>
<td>2.95 ± 0.64</td>
<td>7.90 ± 0.12</td>
</tr>
<tr>
<td>Lactate (μmol/L)</td>
<td>2.08 ± 0.31</td>
<td>17.77 ± 2.3</td>
<td>13.33 ± 0.71</td>
<td>5.43 ± 0.56</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio</td>
<td>8 ± 2</td>
<td>75 ± 43</td>
<td>43 ± 3</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>Cyanide (μg/g)</td>
<td>0.15 ± 0.01</td>
<td>2.92 ± 0.36</td>
<td>3.42 ± 0.32</td>
<td>0.37 ± 0.04</td>
</tr>
</tbody>
</table>

* Means ± SEM.

It is possible that the myocardial failure documented in this study, (increasing LAP and LVEDP, decreasing MV₀₂) could have been due at least in part to hypotension induced initially by SNP itself, or perhaps to the hypotension plus the systemic cyanide-induced acidosis. Michenfelder et al. have studied dogs made hypotensive for 60 min to mean arterial blood pressure values of 40-50 mmHg with SNP, trimethaphan, deep halothane anesthesia, and hemorrhage. Although MV₀₂ was not measured, their data clearly indicate that this extent of arterial hypotension per se is not irreversibly injurious to the canine myocardium. Ten of the dogs were permitted to awaken. Normotension was re-established without difficulty. We conclude that the steady decline in MV₀₂ observed in the present study, ending in ventricular fibrillation, was probably due to myocardial cyanide toxicity.

Thus, although myocardial oxygen utilization is high, the heart is less sensitive to SNP-induced cyanide toxicity than is the brain. Brain is decidedly non-uniform in its O₂ consumption. Cortical O₂ consumption is probably higher than myocardial, although accurate cortical measurements are difficult to obtain. Still, it seems unlikely that such differences could account for the relatively greater myocardial resistance to CN compared with brain.

It might be hypothesized that the right-heart-bypass preparation decreased total myocardial workload enough to account for the apparent myocardial CN resistance relative to brain. However, left ventricular output was held constant by the pump, whereas otherwise output would probably have decreased with the development of systemic acidosis. Second, the left ventricle accounts for the major part of the myocardial CN resistance. Therefore, we deliberately decreased left ventricular work in Group III, with only a slight delay in onset of myocardial CN toxicity, despite increased oxygen delivery.

Perhaps decreases in afterload due to SNP vasodilation initially protected the heart. Against this postulate is the fact that MV₀₂ values increased greatly during the initial 30-min period, with the catecholamine increase presumably stimulated by the SNP-induced hypotension. In fact, peak MV₀₂ values occurred when blood CN level was already 4.4 μg/ml and rapidly increasing. This extra O₂ consumption, occurring with an already increased CN level, might have been expected, if anything, to hasten the occurrence of myocardial CN toxicity relative to brain.

Addition of the extra femoral pump decreased initial left ventricular stroke work index by 42 per cent, and resulted in greater coronary blood flow and O₂ delivery than in Group II to 75 min. Despite this, myocardial CN toxicity was only slightly delayed. This indicates that CN toxicity was dependent largely upon blood (and tissue) CN levels, and that additional O₂ delivery was not protective.

There is no evidence that there are differences among various tissue cytochrome oxidases with respect to their relative affinities for CN. Such differences, if they exist, would not be likely to be large enough to explain the relative myocardial CN resistance observed.

Perhaps the best explanation for the cerebral cortical vs. myocardial CN resistance difference relates to differences in tissue high-energy phosphate production and stores. Myocardial external work is required to vary as much as sixfold by demands for tissue blood flow during activity ranging from rest to maximal exercise. Myocardial tissue has mitochondria in abundance, and ATP and phosphocreatine levels are higher than those in brain. Resting high-energy phosphate production in myocardium is not likely to be high relative to the potential production capacity of the heart. In the three control dogs (without right-heart bypass), mean ventricular muscle ATP concentration was 4.4 μmol/g, and mean PCr concentration was 7.2 μmol/g. These can be compared with ATP and PCr concentrations of 2.24 and 4.96 μmol/g, respectively, reported for cerebral cortex. Thus, normal canine cerebral cortex, with high-energy phosphate stores half as large as those of the myocardium, seemed to succumb to CN toxicity at approximately 60 per cent of the blood CN level at which myocardial toxicity was first evident. Adequate ventricular function, judged by LAP and LVEDP values, continued somewhat beyond the point at which MV₀₂ values decreased to below control. Even the chronically failing myocardium can maintain relatively normal high-energy phosphate levels. Katz reported that ATP

1 Van Dyke RA, personal communication.
levels 20 per cent below normal would still allow 90 per cent saturation of ATP-binding sites on cardiac contractile proteins. Katz further finds, however, that ion transport may be impaired with smaller ATP decreases. The latter may explain the occurrence of arrhythmias we observed at relatively low CN levels during our experiments. Impairment of membrane ion transport, due to CN-induced impairment of ATP production, leading to arrhythmias, could perhaps be construed as the earliest sign of cardiac CN toxicity in our study, but much higher CN levels were needed before interference with venricular function or oxygen consumption was evident.

As demonstrated in the reversal experiments (Group IV), SNP-induced CN toxicity was reversible only when acidosis had not been permitted to worsen beyond a certain point. The actual lower limit of buffer base may depend on rate of increase of blood CN; this was much more rapid in our study than would be likely clinically. The reversibility was not due to myocardial CN toxicity because MV_{CN} values were not significantly different from control in Group IVb at a buffer base value of 33 mEq/l, a systemic CN toxicity that proved non-responsive to conventional anti-CN measures. Systemic CN toxicity was clearly far advanced by the time myocardial toxicity was evident in the other groups.

It is generally agreed that monitoring acid-base status is the best clinical method for detecting development of CN toxicity during chronic SNP administration.1,3,10,12 This study would suggest that the base deficit should not be permitted to exceed -10 mEq/l. Perhaps slower rates of increase of blood CN would permit reversal at greater acidosis. Still, the limit of acidosis we suggest is in general agreement with findings in human cases of SNP toxicity.8-10

We conclude that myocardial CN toxicity during SNP administration in the dog occurs at blood CN levels of approximately 5.0–5.5 µg/ml. Cerebral cortical CN toxicity occurs at 60 per cent of these levels. Apparent relative myocardial CN resistance seems best explained by the greater capability for myocardial high-energy phosphate production and storage. Irreversible systemic CN toxicity occurs at lower blood CN levels than does myocardial CN toxicity. The extent of metabolic acidosis seems the most useful index of progression of CN toxicity. Finally, although the presence of myocardial disease in man might render the heart somewhat more sensitive to CN toxicity than the normal dog heart studied herein, we doubt that meaningful aggravation would occur. Use of SNP in treatment of myocardial problems is probably not limited by danger of myocardial CN toxicity occurring before whole-body and/or brain injury.

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