The effects of changes in coronary blood pH on the heart have been studied during CO₂ breathing, hyperventilation and intravenous infusions of HCl, NaHCO₃ and tris hydroxymethyl aminomethane (THAM). Changes in coronary blood flow were variable and, in general, insignificant. From these studies, it is difficult to appraise the direct effects of changes in blood pH on the heart since other segments of the cardiovascular system, as well as its control mechanisms, are influenced by the shift in acid-base balance, thus indirectly affecting the myocardium and the coronary circulation.

Knowledge of the direct effects of acidosis and alkalosis on the heart is derived primarily from studies of isolated, perfused hearts or heart-lung preparations. The majority of these studies dealt with the effects of acidosis. It has been demonstrated repeatedly that acidosis dilates the coronary vessels and weakens contraction of the heart and reduces the heart rate. There are fewer studies of the effects of alkalosis on the heart and the results are not in complete accord. Available evidence indicates coronary dilation, positive or negative inotropic effects and little change in heart rate.

Recently a method was reported from this laboratory for injecting pharmacological agents into the total coronary artery inflow in anesthetized, open-chest dogs. By this method, it is possible to induce a localized acidosis or alkalosis of the heart without changing significantly the pH of systemic arterial blood. The present study was undertaken to investigate the direct effects of acidosis and of alkalosis on the coronary circulation and myocardium, and to determine whether any resulting changes are due to changes in pH or P₇₅₇.

Methods

The experiments were done on 22 mongrel dogs weighing 17 to 27 kg. Each animal was given morphine sulfate, 1 mg/kg, intramuscularly and was anesthetized 30 minutes later with intravenous chloralose (10% solution in polyethylene glycol), 100 mg/kg. Under artificial ventilation, the left chest was opened and the heart suspended in a pericardial cradle. The methods for isolating the total coronary artery inflow and measuring left ventricular output have been described previously. A double-lumen cannula was passed retrograde from the descending thoracic aorta into the left ventricle. The aorta was tied around the cannula proximal to the origin of the brachiocephalic artery. Coronary ostia were located in the segment of the aorta isolated between the ligature and the aortic valve. The coronary arteries were perfused by blood entering the isolated segment around the outside of the cannula during systole. The capacity of this isolated segment, 3 to 7 ml, was more than adequate for perfusion of the coronary arteries during the entire cardiac cycle. The small inner tube of the cannula opened into the isolated segment of aorta and injections through this tube mixed only with the total coronary artery inflow.

The left ventricular output was directed through the large lumen of the cannula, a Hufnagel valve, a Shipley-Wilson rotameter and then returned into the arterial circulation. The coronary sinus was cannulated with a modified Morawitz cannula. Coronary sinus outflow, used as an index of left coronary artery blood flow, was measured with a second Shipley-Wilson rotameter. Arterial blood pressure was measured...
with a Statham transducer. Myocardial contractile force was measured with a Walton strain gauge sutured to the surface of the right ventricle. These four measurements were recorded simultaneously and continuously on a Grass polygraph (model 5B). Heart rate was counted directly from the pressure tracing.

Arterial and coronary sinus blood samples were analyzed for pH, CO₂ content and oxygen content. pH was measured with a Knick pH meter (model 35) with a Sanz micro-glass electrode. Plasma CO₂ content was determined with a Natelson microgasmeter. \( P_{\text{CO}_2} \) and HCO₃⁻ content were calculated from the Henderson-Hasselbalch equation. Oxygen content was determined by a spectrophotometric method.⁹

The following solutions were infused into the coronary circulation: (a) 5,5-dimethyl-2,4-oxazolidinedion (DMO), 0.246 molar; (b) tris hydroxymethyl aminomethane (THAM), 0.3 molar, unbuffered (pH 10.2) and buffered (titrated to pH 7.4); (c) Na₂CO₃, 0.15 molar and (d) NaHCO₃, 0.15 and 0.3 molar. All solutions except the 0.3 molar NaHCO₃ were approximately isotonic. These infusions, which produced changes in coronary sinus blood pH, had no effect on the pH of the systemic arterial blood.

**Results**

1. **DMO Infusion**

Four to five ml of isotonic DMO solution (0.246 molar, pH 3.8) were infused into the total coronary artery inflow in a 40 to 50 second period in ten experiments (9 dogs). A representative tracing is shown in figure 1. In this experiment, 0.98 mmole of DMO solution was infused in 40 seconds. Coronary sinus outflow increased slightly (+6%) for the first 15 seconds, then decreased gradually to 15% below the control level during the next 25 seconds. Myocardial contractile force decreased 15 seconds after the start of infusion. This decrease was concomitant with the fall in coronary sinus outflow and the onset of bradycardia. Left ventricular output and arterial blood pressure did not change significantly. Decreases in myocardial contractile force and heart rate were observed in all ten experiments (table 1). The biphasic change in coronary sinus outflow (an initial increase followed by a decrease) was seen in seven of the ten experiments. The increase in flow preceded the change in myocardial contractile force by 4 to 16 seconds. The late decrease in flow was associated invariably with a decrease in myocardial contractile force. In the three remaining

![Figure 1](image_url)

*Effects of DMO infusion. Records from top to bottom: left ventricular output, coronary sinus outflow, arterial blood pressure, and myocardial contractile force. Between the two arrows, 4 ml of 0.246 molar DMO solution were infused into the coronary artery inflow. Note the biphasic change in coronary sinus outflow (slight increase followed by decrease), the late decrease in myocardial contractile force, and slowing of heart rate. Large swings of output and coronary flow tracings are the results of bradycardia.*
**TABLE 1**

Effects of Intracoronary 5,5-dimethyl-2, 4-oxazolidinedione (DMO), Tris Hydroxymethyl Aminomethane (THAM), Na₂CO₃, and NaHCO₃ on Coronary Sinus Outflow, Coronary Oxygen A-V Difference, Myocardial Contractile Force, and Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>No. exp.</th>
<th>Coronary sinus outflow</th>
<th>Coronary O₂ A-V difference</th>
<th>Myocardial contractile force</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ml/min</td>
<td>Per cent change</td>
<td>vol %</td>
<td>vol %</td>
</tr>
<tr>
<td><strong>DMO, 0.98 to 1.23 mmoles</strong></td>
<td>10</td>
<td>66</td>
<td>+18 [8] *</td>
<td>16.9</td>
<td>-2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>then</td>
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<tr>
<td><strong>THAM, pH 10.2, 0.9 to 1.5 mmoles</strong></td>
<td>14</td>
<td>50</td>
<td>+48</td>
<td>16.1</td>
<td>-3.7</td>
</tr>
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<td></td>
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<tr>
<td><strong>Na₂CO₃, 0.45 to 0.75 mmoles</strong></td>
<td>10</td>
<td>50</td>
<td>+36</td>
<td>16.7</td>
<td>2.0</td>
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<tr>
<td><strong>NaHCO₃, 1.5 to 3.0 mmoles</strong></td>
<td>11</td>
<td>56</td>
<td>+16 [6] *</td>
<td>14.6</td>
<td>+1.4</td>
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</tbody>
</table>

* Numerals in brackets represent number of experiments in which respective response was observed.
† Numerals in parentheses: range of respective responses.
experiments, the initial increase was absent in one, while in the other two, coronary sinus outflow increased initially, then declined gradually but never reached a level below control. Coronary oxygen A-V difference decreased (during decrease in flow) in the majority of experiments (table 1). The infusion of DMO decreased the pH of the coronary sinus blood in all ten experiments. This decrease varied from 0.02 to 0.14 units, averaging 0.08 units. An increase in P_{CO_2} and a slight decrease in HCO_3^- content were also observed (table 2).

2. THAM INFUSION

Three to five ml of isotonic, unbuffered THAM solution (0.3 molar, pH 10.2) were infused into the total coronary artery inflow in 40 to 50 seconds in fourteen experiments (9 dogs). A representative experiment is shown in figure 2. In this experiment, while the left ventricular output and arterial blood pressure remained unchanged, coronary sinus outflow increased markedly. This increase was sustained during the period of infusion, and was associated with a decrease in coronary oxygen A-V difference, a slight increase of myocardial contractile force, and no change of heart rate. Similar changes were noted in all fourteen experiments. The increase of coronary sinus outflow preceded the increase of myocardial contractile force by 2 to 5 seconds. These changes are listed in table 1.

An increase of pH in coronary sinus blood occurred in every experiment (average 0.08 units). There was also a decrease in P_{CO_2}, averaging 6.7 mm Hg. The bicarbonate content did not change appreciably (table 2).

In another five experiments (5 dogs), isotonic THAM solution, titrated to pH 7.4, was similarly infused. Changes of coronary sinus blood pH were minimal and variable (changes from -0.04 to +0.03 units). There was no change in coronary sinus outflow, myocardial contractile force, or heart rate.

3. Na_2CO_3 INFUSION

In ten experiments (8 dogs), 3 to 5 ml
of isotonic Na$_2$CO$_3$ solution (0.15 molar, pH 10.5) were infused into the coronary circulation in 25 to 50 seconds. As shown by the representative tracing in figure 3, the effects of Na$_2$CO$_3$ are similar, both qualitatively and quantitatively, to the effects of THAM infusion. These effects are listed in tables 1 and 2.

![Figure 2](image1)

**FIGURE 2**
Effects of THAM infusion. Records as in figure 1. Four ml of 0.3 molar THAM solution were infused between the two arrows. Note the marked and sustained increase in coronary sinus outflow and slight increase in myocardial contractile force.

![Figure 3](image2)

**FIGURE 3**
Effects of Na$_2$CO$_3$ infusion. Records as in figure 1. Five ml of 0.15 molar solution of Na$_2$CO$_3$ were infused between the two arrows. Note the marked increase in coronary sinus outflow and slight increase in myocardial contractile force similar to the effects of THAM infusion shown in figure 2.
4. NaHCO₃ INFUSION

In five experiments (5 dogs), 5 ml of isotonic NaHCO₃ solution (0.15 molar, pH 8.0) were infused into the coronary artery inflow in 25 to 50 seconds. There were no significant alterations of the coronary sinus blood pH (changes varied from −0.01 to +0.03 units) and no changes in coronary sinus outflow, myocardial contractile force, or heart rate.

In another eleven experiments (10 dogs), 5 to 10 ml of hypertonic NaHCO₃ solution (0.3 molar, pH 8.0) were infused. As shown by a representative tracing in figure 4 and by tables 1 and 2, the most consistent and significant changes were a decrease of myocardial contractile force and an increase in coronary sinus blood pH. Also, a bradycardia was usually present. Changes of coronary sinus outflow were minimal; an increase was seen in six experiments, and a decrease in five experiments. When the coronary sinus outflow increased, it always preceded the decrease in myocardial contractile force. On the other hand, when a decrease of coronary sinus outflow was observed, a concomitant decrease in myocardial contractile force was seen. There was no change in left ventricular output or in arterial blood pressure. Changes in pH, PCO₂ and HCO₃⁻ are listed in table 2.

Discussion

Previous studies of the effects of acidosis and alkalosis on the coronary circulation and myocardium entailed either isolation of the heart from the animal, or changing the pH of the entire animal. The method used in the present study permits determination of the direct effects of acidosis and alkalosis on the coronary blood flow and myocardium in the intact animal. These changes in pH could be detected within 30 seconds after the infusion of DMO, THAM, or Na₂CO₃ into the coronary artery inflow. Acutely induced acidosis or alkalosis was localized to the heart since there was no change in the pH of the systemic arterial blood.

Observed changes in coronary blood flow and myocardial contractile force may be ascribed to the direct effect of acidosis and alkalosis for the following reasons. Changes occurred promptly after the infusion was started, and returned to control just as promptly when the infusion was stopped. Decreasing or increasing the coronary blood pH for less than 60 seconds had surprisingly little effect on cardiac output and arterial blood pressure despite the presence of changes in myocardial contractile force and
Modification of the action of catecholamines by changes in pH cannot account for our results because: the magnitude of pH change is smaller than that required to significantly alter catecholamine action; there were no changes in arterial blood pressure or left ventricular output; the observed changes in coronary blood flow and myocardial contractile force sometimes differed qualitatively from the known effects of catecholamines on these parameters.

The initial effect of DMO infusion was an increase of coronary sinus outflow. This increase, occurring at a time when arterial blood pressure, cardiac output, myocardial contractile force, and heart rate were all unchanged, indicates coronary vasodilation. A direct coronary vasodilating action of acidosis has been observed also in the isolated heart and heart-lung preparation. In the majority of our experiments, coronary sinus outflow decreased after the initial increase. This decrease was associated invariably with a reduction of myocardial contractile force and a reduced heart rate. Although a decrease in myocardial contractile force and heart rate would reduce extravascular support and produce an increase in coronary sinus flow, the observed decrease in coronary sinus flow is probably attributable to a reduction in myocardial metabolic rate secondary to a decrease in myocardial contractile force and heart rate. The delayed appearance of myocardial depression and bradycardia may be attributed to the time required for DMO to enter the myocardial cells and the sinus node. The observed negative inotropic and chronotropic effects of acidosis confirm the results obtained from isolated heart preparations.

It should be pointed out that the vasodilation directly induced by acidosis is of relatively small magnitude and is often overcome by the myocardial depressant effect of acidosis. Hypercapnia has been shown to stimulate the sympathoadrenal system. In the intact animal myocardial depression was not consistently seen with moderate hypercapnic acidosis. It is conceivable that the direct negative ionotropic effect of acidosis can be overcome by the myocardial stimulating action of catecholamines. This myocardial stimulating action must also account indirectly in part for the observed increase of coronary blood flow during hypercapnic acidosis. Thus, the observed responses of coronary blood flow and myocardium to systemic acidosis represent the net results of the direct effects of acidosis and the indirect effects of sympathoadrenal activation.

When alkalosis was induced by intra-coronary infusion of THAM or Na₂CO₃, a marked increase in coronary sinus outflow was seen. This increase is the result of vasodilation since it began before the change in myocardial contractile force occurred, and was associated with a decrease in coronary oxygen A-V difference. The vasodilation is attributed to alkalosis per se, because THAM, titrated to pH 7.4 (only 30% undissociated), produced minimal and inconsistent changes in pH and no change in coronary blood flow. Data regarding the direct effect of alkalosis on coronary circulation in the literature are sparse. Coronary vasodilation following NaHCO₃-induced alkalosis was reported by Elek and Katz and Taylor and Young. In the experiments reported herein, NaHCO₃ was rather ineffective in producing alkalosis or changes in coronary sinus outflow. Larger quantities of hypertonic NaHCO₃ infused into the coronary arteries produced some alkalosis of the coronary sinus blood (average pH increase of 0.03 units). A negative inotropic effect, bradycardia, and a slight increase or decrease of coronary sinus outflow were noted. These changes differ distinctively from those seen with the infusion of THAM or Na₂CO₃, but were qualitatively similar to those seen with the infusion of DMO. These seemingly paradoxical results may be better understood by considering the means by which DMO produces acidosis, and THAM and Na₂CO₃, alkalosis.

DMO is a hydrogen ion donor which in the undissociated form readily penetrates the cell membrane and therefore lowers the intracellular as well as extracellular pH. The increase of blood P₇₅O₂ also contributes to

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the intracellular acidosis since CO\textsubscript{2} diffuses freely into the intracellular compartments.

THAM is a hydrogen ion acceptor, which in the undissociated form readily penetrates the cell membrane and therefore raises the intracellular as well as extracellular pH.\textsuperscript{23, 24} The increase of intracellular pH also results from diffusion of CO\textsubscript{2} out of the cells following the decrease in blood P\textsubscript{co\textsubscript{2}} produced by THAM.

Na\textsubscript{2}CO\textsubscript{3} infusion can also produce an extracellular and intracellular alkalosis but through a mechanism different from that of THAM. Infusion of Na\textsubscript{2}CO\textsubscript{3} can be considered equivalent to the infusion of equimolar amounts of NaOH and NaHCO\textsubscript{3}. The addition of NaOH would result in an increase of pH, and a decrease of P\textsubscript{co\textsubscript{2}}. The addition of NaHCO\textsubscript{3} produces an increase in pH and an increase in P\textsubscript{co\textsubscript{2}}. Since NaOH is a stronger base than NaHCO\textsubscript{3}, the net effect of Na\textsubscript{2}CO\textsubscript{3} infusion is an increase in pH and a decrease in P\textsubscript{co\textsubscript{2}}. The lowering of blood P\textsubscript{co\textsubscript{2}} leads to the diffusion of CO\textsubscript{2} out of the cells, resulting in an intracellular alkalosis.

NaHCO\textsubscript{3} infusion, on the other hand, results in an increase in bicarbonate ion and P\textsubscript{co\textsubscript{2}}. Since the cell membrane is permeable to CO\textsubscript{2} but relatively impermeable to the bicarbonate ion, intracellular acidosis can result when large quantities of NaHCO\textsubscript{3} are infused. An extracellular alkalosis and intracellular acidosis has been reported by Wallace and Hastings\textsuperscript{25} and Robin et al.\textsuperscript{26} following intravenous infusions of NaHCO\textsubscript{3}.

Measurements of intracellular pH were not attempted in the present study. Nevertheless, the effects of THAM, Na\textsubscript{2}CO\textsubscript{3}, DMO, and NaHCO\textsubscript{3} infusions on the coronary circulation and myocardium can best be explained by the postulated changes in intracellular pH. These changes are shown in a schematic diagram in figure 5. The effects of THAM and Na\textsubscript{2}CO\textsubscript{3} are attributed to intracellular alkalosis, and those of DMO and NaHCO\textsubscript{3} to intracellular acidosis.

Summary

The effects of localized acidosis and alkalosis on coronary blood flow, myocardial contractile force, and heart rate were studied in anesthetized, open-chest dogs. Acidosis of the coronary vascular bed was induced by infusion of 5,5-dimethyl-2,4-oxazolidinedione (DMO) into the total coronary artery inflow, and alkalosis by infusion of tris hydroxymethyl aminomethane (THAM), Na\textsubscript{2}CO\textsubscript{3} or NaHCO\textsubscript{3}. DMO infusion caused an initial slight increase of coronary blood flow, followed by a decrease. The decrease was accompanied by and attributed to a moderate to marked decrease of myocardial contractile force and bradycardia. THAM and Na\textsubscript{2}CO\textsubscript{3} infusion caused a marked increase of coronary blood flow, associated with a decrease of coronary oxygen A-V difference, indicating coronary vasodilation. A slight to moderate increase of myocardial contractile force but little or no change in heart rate was noted. NaHCO\textsubscript{3} infusion caused changes similar to those induced by DMO but of smaller magnitude. It was suggested that the direct effects of DMO and NaHCO\textsubscript{3} are attributable to intracellular acidosis, whereas those of THAM and Na\textsubscript{2}CO\textsubscript{3} are attributable to intracellular alkalosis.

Acknowledgment

The authors are grateful to Drs. S. C. Wang, Gabriel G. Nahas, and Marvin R. Blumenthal for their advice and to Miss Mariagnes Verosky and Mrs. Iris Schwartz for their technical assistance.

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Circ Res. 1965;17:114-122
doi: 10.1161/01.RES.17.2.114

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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