

Effects of Fluorocarbons, Chlorinated Solvents, and Inosine on the Cardiopulmonary System

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The effects of fluorocarbons and chlorinated solvents on the cardiopulmonary system are reviewed. The new information, not hitherto reported, relates to the antagonistic action of inosine, a naturally occurring nucleoside formed in the body by deamination of adenosine. The effect of inosine on methylene chloride toxicity was investigated in open chest dogs anesthetized with pentobarbital sodium. Methylene chloride (5% in air or 50,000 ppm) elicited a decrease of ventricular contractility represented by the diminished left ventricular $(dp/dt)_{max}$ and myocardial contractile force measured directly with a Walton-Brodie strain gauge arch. Coronary blood flow decreased slightly after exposure to methylene chloride. Arterial blood pressure and heart rate did not change. The negative inotropic effect of methylene chloride was reversed or prevented to a substantial extent by intravenous infusion of inosine (5 mg/kg-min). The effect of the latter compound was also characterized by significant coronary vasodilation. It was shown by the experiments that the cardiostimulatory action of inosine was associated with improved hypoxic adaptability of the coronary blood vessels. In contrast, the effect of catecholamines (epinephrine and isoproterenol) was not accompanied by such a beneficial coronary vascular effect. On the basis of these results, the conclusion has been arrived at that inosine might be recommended as a useful antidote in methylene chloride poisoning in particular, and of poisoning by chlorinated solvents and fluorocarbons in general.

Introduction

The purpose of this article is to review the cardiopulmonary effects of fluorocarbons and related compounds which have been identified in man and experimental animals. The experimental observations were made at the author's laboratories at the University of Pennsylvania, at the request of the Food and Drug Administration and the Consumer Products Safety Commission, to identify the effects of intentional or accidental use of aerosol products containing fluorocarbon propellants and chlorinated solvents. This article starts with a discussion of fluorocarbons, proceeds with chlorinated solvents, particularly methylene chloride, and then concludes with a description of a nucleoside that can be used to reverse or treat the cardiotoxic properties of the halogenated propellants and solvents under consideration.

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Cardiac Arrhythmia Induced by Fluorocarbons

The three most widely-used propellants in aerosols containing bronchodilator drugs are trichloromonofluoromethane (FC 11), dichlorotetrafluoroethane (FC 114), and dichlorodifluoromethane (FC 12). The potential for these propellants to produce cardiac arrhythmia has been demonstrated in various animal species (1-8), and the concentrations that induce cardiac arrhythmias in the anesthetized dog are as follows: 0.25% for FC 11, 2.5% for FC 114, and 10.0% for FC 12. These concentrations are probably lower in animals without anesthesia and in animals with ischemic hearts (9, 10). In monkeys, ischemia increased the sensitivity of the heart to experimentally-induced cardiac arrhythmia (11).

The mechanisms by which the fluorocarbons induced cardiac arrhythmias are as follows: (a) sensitization of the heart to proarrhythmic effect of epinephrine (5); (b) depression in myocardial con-

tractility (12-14); (c) reduction in cardiac output and coronary blood flow (13, 14); and (d) reflex increase in sympathetic and vagal impulses to the heart by irritation of mucosa in the upper and lower respiratory tract (2). There is no evidence to implicate three other mechanisms: release of epinephrine from the adrenal medulla and from the heart and blockade of conduction by a direct action of the fluorocarbon on the heart muscle. These possible mechanisms can be readily investigated by analysis of catecholamines in the heart and adrenal glands in animals exposed to the fluorocarbons. It should be noted that arrhythmia can be triggered without the fluorocarbon being absorbed from the respiratory tract. Irritation of the upper respiratory tract increases vagal tone, whereas irritation of the lower respiratory tract increases sympathetic activity to the heart (2, 15). It is this neurogenic mechanism which triggers cardiac arrest, especially if the fluorocarbons have been absorbed by the blood in concentrations high enough to influence the heart.

Depression of Myocardial Contractility by Chlorinated Solvents

In the anesthetized dog, the hemodynamic effects of chlorinated solvents have been investigated. The threshold inspired concentrations are 0.05% for trichloroethylene, 0.25% for methyl chloroform, and 2.5% for methylene chloride (16). The most toxic solvent is trichloroethylene and the least toxic is methylene chloride. The primary action of the chlorinated solvents is depression of myocardial contractility, which reduces cardiac output and lowers the systemic arterial blood pressure. By inactivation of baroreceptors in the carotid sinuses and aortic arch, the low blood pressure increases sympathetic discharge to the heart, just as hypoxemia would stimulate chemoreceptors in the carotid and aortic bodies. The end result would be an antagonism against the direct depressant effect of the solvent on the myocardium (16, 17).

There are several mechanisms that have not been elucidated, such as the role of the adrenal medulla in influencing total systemic vascular resistance; the influence of the chlorinated solvent directly on the venous return to the heart, and on the coronary blood vessels. The experiments elaborating on these mechanisms will necessitate the use of total body perfusion and total coronary perfusion (15, 18).

In the subject who inhales the chlorinated solvent, there are primary events that would induce circulatory shock and secondary compensatory mechanisms. It is not possible to assess the importance of circulatory shock relative to cardiac arrest

and respiratory failure (19-21) as a cause of death.

Cardiotonic Properties of Inosine on Methylene Chloride Depressed Heart

In the course of investigating the cardiac effects of the inhalation of chlorinated solvents and fluorocarbon propellants (see above) we thought it worthwhile to test corrective drugs. Since depression of contractility is the most important manifestation of toxic concentrations of methylene chloride, there was a need to find a cardiotonic drug that did not provoke arrhythmias. That methylene chloride sensitizes the heart (17) to cardiac arrhythmia has contraindicated the use of epinephrine and isoproterenol.

Inosine, a cardiotonic drug, does not sensitize the heart to arrhythmia (22, 23). Before inosine can be considered as a clinically useful cardiotonic agent for a heart poisoned with methylene chloride, the antagonism must be established in the laboratory. The experiments reported below fulfill this prerequisite, demonstrating that inosine counteracts the cardiac effect of methylene chloride. It may also be effective with other structurally related chlorinated solvents such as carbon tetrachloride, chloroform, methyl chloroform, and tetrachloroethylene.

Methods

The experiments were carried out on mongrel dogs (12 to 20 kg) of either sex under pentobarbital (30 to 35 mg/kg IV) anesthesia. After insertion of a tracheostomy tube, artificial ventilation was maintained with a Starling Ideal respirator using room air. The chest was opened in the fifth left intercostal space and the pericardium was slit to expose the heart. A short segment of the left anterior descending coronary artery, close to its origin, was dissected free and a Statham electromagnetic flow probe of appropriate size (usually 2 mm) was placed around the vessel. Phasic, as well as mean coronary blood flow, was measured, the latter value being obtained by means of electrical integration. Myocardial contractile force was recorded with a Walton-Brodie strain gauge sewn to the anterior wall of the left ventricle supplied by the anterior descending coronary branch. Usually a second strain gauge was applied to the base of the ventricle supplied by the circumflex coronary artery. A polyethylene catheter was inserted into the left ventricular cavity through the apex; ventricular pressure was measured with the aid of a Statham

transducer (P23AA) connected to the catheter. The maximal rate of rise of the left ventricular pressure, $(dp/dt)_{max}$ was obtained by using a derivative computer (8814 HP). Aortic pressure was recorded with another Statham transducer by cannulating the left carotid artery. All recordings were made on a six-channel Sanborn 7700 recorder. No drugs were injected for at least 30 min after completing the surgery to allow the animals to reach a steady state. Four experimental groups were studied.

Experimental Groups

Group I. Methylene Chloride after Inosine (Five Dogs). Methylene chloride (5% in air) was administered via the inlet of the respirator. The gas mixture was prepared by mixing the appropriate amount of solvent into a known amount of air, as described previously (16). After complete recovery from the control administration of methylene chloride for 5 min, the same procedure was repeated while the dogs had been continuously infused intravenously with a moderate dose (5 mg/kg-min) of inosine (Trophicardyl). The inhalation of methylene chloride started in the fifth minute of inosine infusion which was continued till the end of the inhalation period (5 min duration).

Group II. Inosine after Methylene Chloride (Five Dogs). In this series, after a methylene chloride (5% in air) inhalation period of 5 min duration, the uninterrupted inhalation of the solvent was continued for a further 5 min, but during this second phase, inosine (5 mg/kg-min) was infused simultaneously.

Group III. Inosine, Catecholamines, and General Hypoxia (Six Dogs). In this series, general hypoxia was induced by ventilating the lungs with 5% oxygen in nitrogen for 2 min; a new steady state of all circulatory variables was obtained in every dog at the end of the hypoxic period. After recording the control response to hypoxia, the same maneuver was repeated during the last 120 sec of experimental periods of 6 min duration, when the animals were infused with inosine (10 mg/kg-min), epinephrine (0.5 μ g/kg-min) and isoproterenol (0.5 μ g/kg-min), respectively.

Group IV. Inosine and Adenosine (Three Dogs). In these dogs, the influence of inosine (2.5 mg/kg-min) on the circulatory effect of adenosine was tested. Adenosine was given intravenously in doses of 0.02, 0.10, and 1.0 mg/kg.

Statistical Analysis

Circulatory variables during the last minute of infusion and/or inhalation periods were chosen for

data analysis. All values quoted in the text are mean values \pm S.E. The results were expressed both as absolute and percentage values, 100% being the control level before the administration of drugs or inhalation of methylene chloride. The results were examined statistically by using the Student *t*-test for paired and/or unpaired data. Changes are considered significant if $p < 0.05$.

Measured Experimental Variables

Measured experimental variables were as follows: Mean arterial pressure, in mm Hg, was measured from a catheter inserted through the left carotid.

Heart rate, in beats/min, was computed from the aortic pressure curves, taken at a paper speed of 25 mm/sec.

$(dp/dt)_{max}$, the maximum rate of rise of left ventricular pressure taken in mm Hg/sec was derived from the left ventricular pressure; the latter variable was measured from a catheter in the left ventricular cavity inserted through the apex.

Myocardial contractile force, in percent of control, was measured with a Walton-Brodie strain gauge sutured to the exposed surface of the left ventricle.

Coronary blood flow, mean in ml/min, was measured with a flow probe around the left anterior descending coronary artery and obtained by electrical integration of the phasic flow signal.

Coronary vascular resistance, mean, in dyne-sec/cm⁵, was the ratio of mean arterial pressure in dyne/cm² and the coronary blood flow in cm³/sec.

Coronary blood flow, late diastolic, in ml/min, was measured in the late diastolic phase of the cardiac cycle, when the coronaries are free from extravascular compression.

Coronary vascular resistance, late diastolic, in dyne-sec/cm⁵ is the ratio of late diastolic arterial pressure in dyne/cm² and the late diastolic coronary blood flow in cm³/sec.

Results

The first two groups of experiments consist of administering inosine and methylene chloride in this sequence and in the reversed order. The results are discussed as a group because they indicate antagonism in both cases.

Inosine Versus Methylene Chloride. Inosine administration consistently increased myocardial contractility, whether administered before or after the inhalation of methylene chloride (Groups I and II). The responses characterizing the changes of

Table 1. Effect of inosine (5 mg/kg-min) on cardiac depression induced by methylene chloride (5% v/v) inhalation.

	Group I				Group II			
	Control		Methylene Cl after inosine		Control		Inosine after methylene Cl	
Time of methylene Cl inhalation, min	0	5	0	5	0	5	10	—
Time of inosine infusion, min	—	—	5	10	—	0	5	10
Mean arterial blood pressure, mm Hg	123 ± 4.4	127 ± 3.4	123 ± 4.3	127 ± 6.2	126 ± 9.5	130 ± 6.9	144 ^b ± 11.2	135 ± 7.9
Heart rate, min ⁻¹	172 ± 9.6	171 ± 9.4	182 ^b ± 11.6	181 ^b ± 11.2	154 ± 4.3	151 ± 3.8	147 ± 4.5	153 ± 3.6
(dp/dt) _{max} , mm Hg/sec	3850 ± 528	3225 ^b ± 465	5385 ^b ± 714	4175 ± 691	4200 ± 463	3025 ^b ± 498	3975 ± 655	5925 ^b ± 998
Myocardial contractile tone, %	100 ± 0	70 ^b ± 6.7	136 ^b ± 9.5	87 ± 11.9	100 ± 0	60 ^b ± 7.1	77 ± 9.1	122 ^b ± 7.5
Mean left AD coronary blood flow, ml/min	18.6 ± 2.4	17.6 ± 2.8	22.9 ^b ± 3.3	21.1 ± 3.0	28.5 ± 5.5	28.9 ± 7.2	43.0 ^b ± 10.5	43.5 ^b ± 5.8
Mean coronary vascular resistance × 10 ⁴ , dyne-sec/cm ⁵	60.0 ± 8.3	64.8 ^b ± 11.6	47.8 ^b ± 8.6	51.5 ± 10.3	42.2 ± 9.1	44.0 ± 9.2	33.4 ^b ± 8.2	27.6 ^b ± 3.4
Late diastolic left AD coronary flow, ml/min	25.9 ± 2.7	25.4 ± 3.6	41.4 ^b ± 7.7	32.8 ^b ± 4.6	47.6 ± 7.9	46.9 ± 10.6	67.7 ^b ± 14.4	67.2 ^b ± 7.5
Late diastolic vascular resistance × 10 ⁴ , dyne-sec/cm ⁵	40.0 ± 3.4	40.1 ± 6.9	25.0 ^b ± 5.0	29.3 ^b ± 5.0	21.3 ± 3.1	24.6 ± 4.5	18.3 ± 3.7	16.7 ^b ± 2.1

^a Mean values ± SEM.

^b Significant difference of change (*p* < 0.05) from control values.

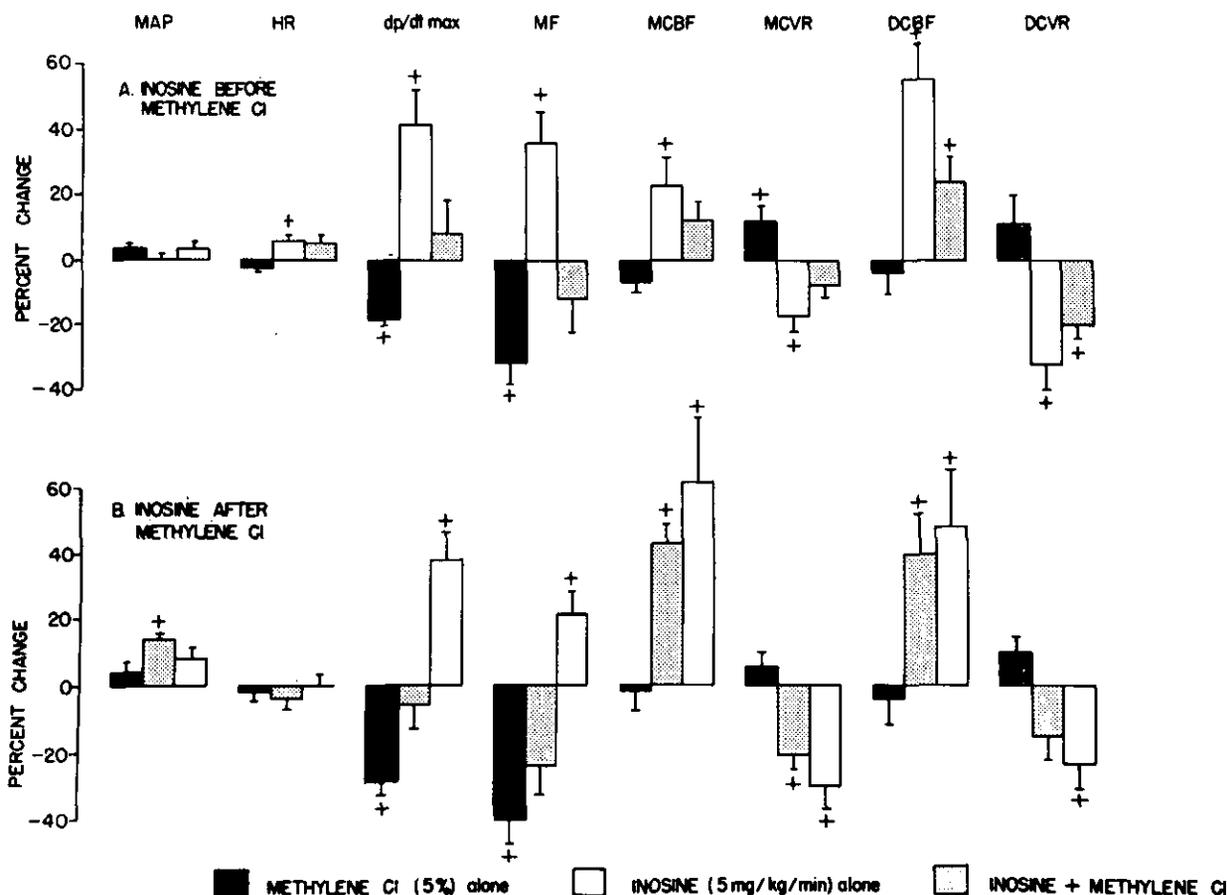


FIGURE 1. Protective effect of inosine against inhalation of methylene chloride; (MAP), mean arterial pressure; (HR) heart rate; (MF) myocardial contractile force; (MCBF) mean coronary blood flow; (MCVR) mean coronary vascular resistance; (DCBF) late-diastolic coronary blood flow; (DCVR) late-diastolic coronary vascular resistance. Mean values ± SE; + denotes significant change from control.

cardiovascular variables are tabulated in Table 1, while the percentage changes are graphically displayed in Figure 1. The predominant feature of the methylene chloride toxicity is the depression of myocardial contractility; this effect is clearly revealed by data in Table 1 (under the "control" headings) and by the black columns of Figure 1. The levels of arterial blood pressure and heart rate did not decrease after the inhalation of the solvent; the former variable even exhibited a statistically non-significant increase. At the same time, the values of the contractility indices $[(dp/dt)_{max}]$ and myocardial contractile force] substantially and significantly diminished after the inhalation of methylene chloride.

Together with the induced cardiac depression, the coronary blood flow decreased slightly (both the mean and the late diastolic values), and the vascular resistance increased slightly. These latter changes, however, were not found to be statistically significant, except in one set of measurements (mean resistance values in Group I).

The action of inosine on the circulatory system is best envisaged by the second (white) columns in Figure 1 and the third row of Table 1, respectively. These effects, as they have been fully described previously (23), consist of cardiostimulating and coronary vasodilator components: the values of $(dp/dt)_{max}$ and myocardial contractile force signifi-

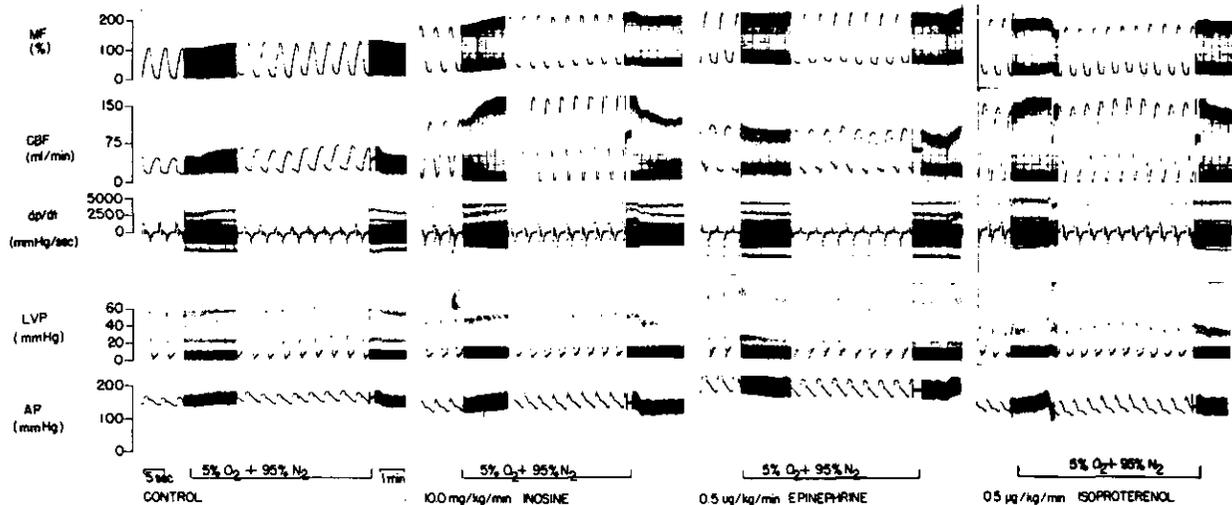


FIGURE 2. Behavior of the hypoxic coronary adaptation expressed in percent vascular conductance: range of coronary adaptation to inhalation of 5% O₂ + 95% N₂. There is a significant increase during inosine infusion.

Table 2. Effect of inhalation of 5% O₂ on the circulation.^a

	Control		Inosine (10 mg/kg-min)		Epinephrine (0.5 μg/kg-min)		Isoproterenol (0.5 μg/kg-min)	
	21% O ₂	5% O ₂	21% O ₂	5% O ₂	21% O ₂	5% O ₂	21% O ₂	5% O ₂
Mean arterial blood pressure, mm Hg	129 ± 6.0	136 ± 1.7	125 ± 5.2	123 ± 9.4	156 ± 12	147 ± 10.0	104 ^b ± 17.2	104 ^b ± 16.0
Heart rate, min ⁻¹	153 ± 7.2	159 ^b ± 6.3	170 ^a ± 5.7	173 ^b ± 6.9	159 ± 7.1	159 ± 7.2	193 ^b ± 7.9	194 ^b ± 8.5
$(dp/dt)_{max}$, mm Hg/sec	3395 ± 457	3938 ^b ± 563	5292 ^b ± 594	6167 ^b ± 805	5875 ^b ± 551	6042 ^b ± 476	5563 ^b ± 819	5564 ^b ± 991
Myocardial contractile force, %	100 ± 0	109 ± 2	140 ^a ± 8	148 ^b ± 8	161 ^b ± 10	156 ^b ± 9	179 ^b ± 18	157 ^b ± 12
Mean left AD blood flow, ml/min	17.9 ± 2.1	22.8 ^b ± 2.8	32.5 ^b ± 5.0	47.5 ^b ± 8.2	31.6 ± 6.1	31.3 ^b ± 5.1	52.0 ^b ± 6.5	58.8 ^b ± 9.1
Mean coronary vascular resistance × 10 ⁴ , dyne-sec/cm ⁵	65.5 ± 6.1	51.5 ^b ± 5.2	36.1 ^b ± 7.6	26.0 ^b ± 6.8	47.6 ± 9.4	43.7 ^b ± 7.9	16.2 ^b ± 2.5	14.9 ^b ± 2.8
Late diastolic left AD flow, ml/min	28.6 ± 3.9	36.3 ^b ± 5.0	60.7 ^b ± 10.8	90.8 ^b ± 19.0	46.5 ± 9.1	47.1 ^b ± 7.9	106.6 ^b ± 13.6	116.2 ^b ± 21.2
Late diastolic vascular resistance × 10 ⁴ , dyne-sec/cm ⁵	35.4 ± 4.0	29.5 ^b ± 4.2	17.9 ^b ± 4.4	13.6 ^b ± 4.6	27.5 ± 6.2	25.2 ^b ± 5.2	6.7 ^b ± 1.1	6.2 ^b ± 1.0

^a Mean values + SEM.

^b Significant changes ($p < 0.05$) from the normoxic control value.

cantly increased together with the enhancement of the coronary flow parameters and the diminution of the vascular resistance in the coronary bed. These effects were accompanied by a moderate, but significant tachycardia.

When the methylene chloride inhalation was repeated during the uninterrupted infusion of inosine, the cardiovascular action of the solvent was found to be substantially different from the control methylene chloride effect, (see Fig. 1 and Table 1). The action of methylene chloride was no longer powerful enough to elicit a significant depression of cardiac contractility, although the positive inotropic effect of inosine became diminished. Similarly, although the inosine-induced coronary vasodilation decreased as a consequence of methylene chloride inhalation, the vasodilatory effect of inosine was still prevalent enough to be statistically significant in the late diastolic phase of the cardiac cycle.

An essentially similar picture emerges from the experiments where the inosine infusion was started during the uninterrupted administration of methylene chloride by inhalation (Group II). Figure

1B as well as Table 1 show that the depressive methylene chloride effect was partially counteracted or even fully reversed by inosine: the values of myocardial contractility were no longer reduced in this period of experimental observations and the slight increase of coronary vascular tone, which was elicited by the inhalation of solvent, had been replaced by a significant coronary vasodilator action, i.e., the effects related to the myocardial blood supply were completely reversed. After discontinuing the methylene chloride inhalation the uninhibited inosine action became obvious.

Hypoxia. In the next series of experiments, performed in six dogs (group III), a mixture of 5% oxygen and 95% nitrogen was administered for 2 min in order to gauge the effect of inosine on the hypoxic dilator capacity of the coronary vessels. The modulator effect of inosine has been compared to that of epinephrine and isoproterenol. Figure 2 depicts a typical response, while the results obtained in six dogs are summarized in Table 2 and Figure 3. Briefly, the vasodilator and inotropic actions of inosine were found to be associated with the

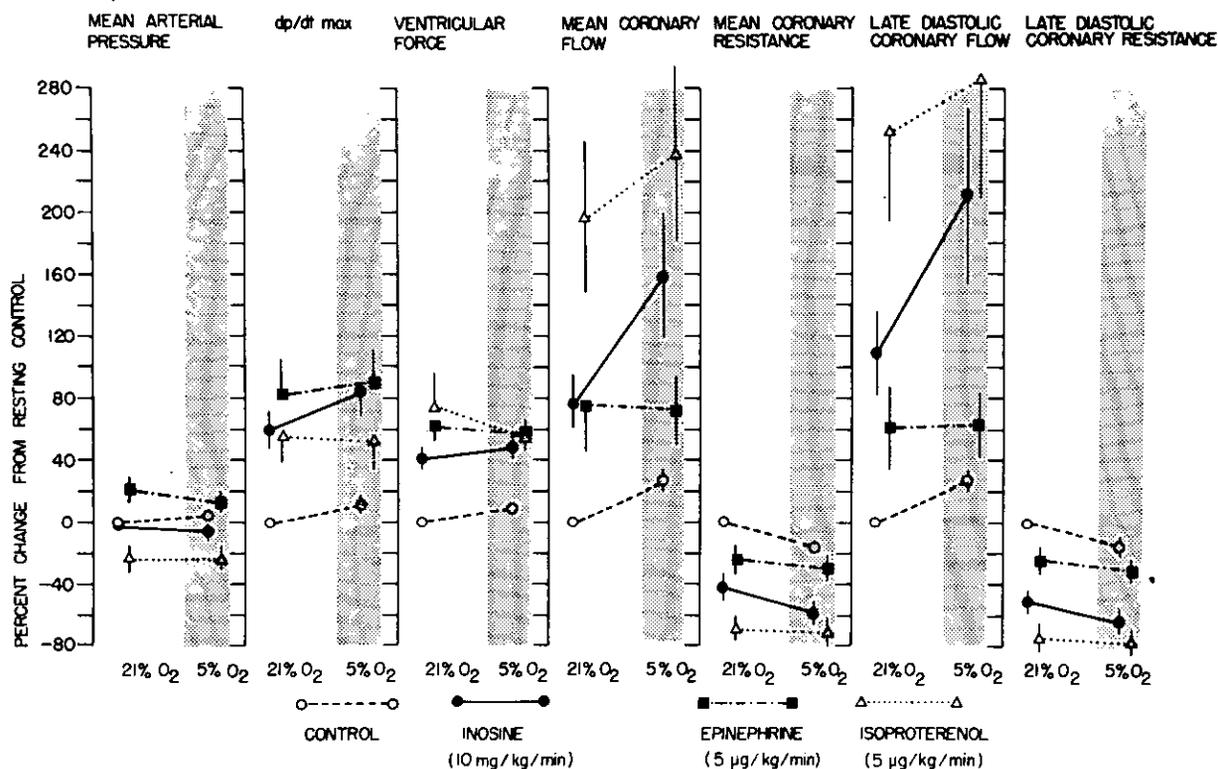


FIGURE 3. Changes of cardiovascular responses to hypoxia during intravenous infusion of inosine, epinephrine and isoproterenol. Abbreviations as in Fig. 1.

increase of hypoxic coronary adaptation (an augmented vascular capacity for further vasodilation), while those of epinephrine or isoproterenol, themselves equally potent augmentors of coronary flow and cardiac activity, were not. Although, in this respect, the large differences between inosine on one hand, and the catecholamines on the other, are evident by the behavior of coronary flow itself, commonly the true relationships of vascular reactivity are somewhat obscured by the fact that during the infusion of the three drugs, the arterial blood pressure was also differently affected (Fig. 3). The inspection of the calculated vascular resistance values is not very helpful in this particular case, since the latter parameter, being the product of the pressure and the reciprocal value of the flow, tends to minimize any vasodilator effect superimposed on an already established one. Therefore, in situations like this, it is more helpful to use the parameter of flow conductance C instead of the flow resistance R ; (where $C = 1/R$). The relations are clarified by Figure 4, where the range of hypoxic coronary responses is expressed in percent of the control (nonhypoxic, preinfusion) vascular conductance, i.e., in the same relative units. The conductance changes indicate a significant modulator effect of inosine on hypoxic coronary adaptability.

Modulating Action of Inosine on the Adenosine Coronary Effect. The results described above revealed the unexpected modulation of hypoxic coronary adaptability during inosine infusion. Since adenosine, a nucleoside chemically re-

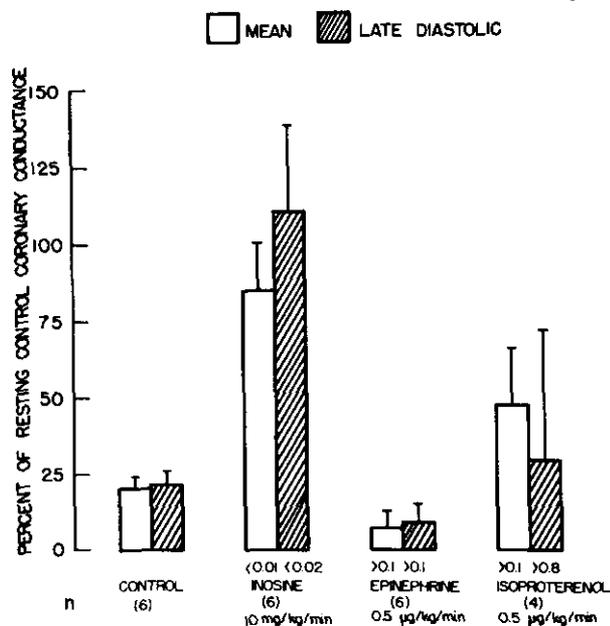


FIGURE 4. Percent changes of mean and late diastolic conductance in six dogs subjected to hypoxia. Mean value \pm SE.

Table 3. Potentiation of adenosine effect on the coronaries by inosine.^a

Dose of adenosine, mg/kg	Mean coronary blood flow, ml/min ^a	
	Control	Inosine (2.5 mg/kg-min)
0.0	17.3 \pm 1.4	20.6 \pm 0.9
0.02	20.0 \pm 2.1	40.4 \pm 4.7 ^b
0.10	26.8 \pm 2.7	44.6 \pm 5.1 ^b
1.0	44.6 \pm 5.5	50.6 \pm 5.9

^a Mean values \pm SEM.

^b Significant differences between inosine and control animals.

lated to inosine, is the suspected key substance in the physiologic mechanism of hypoxic coronary vasodilation, the interaction of these two compounds was tested in the last series of three dogs (Group IV). A significant potentiation of the coronary vasodilator effect of adenosine was observed by inosine infused in a threshold dose which, in itself, scarcely affected the basic level of coronary blood flow (Table 3).

Discussion

In these studies, as in former experiments conducted by Aviado et al. (17) the acute cardiovascular toxicity of methylene chloride was found to be characterized by an almost selective myocardial depressant action. This was indicated by the unequivocal decrease in left ventricular $(dp/dt)_{max}$ and the myocardial contractility measured directly by strain gauges sutured to the ventricular wall. Despite the weakened cardiac inotropism, the arterial blood pressure remained unchanged or even increased slightly. A similar pattern was observed in former experiments (17) with the additional observation of a significantly diminished cardiac output. These observations led Aviado et al. (17) to conclude that methylene chloride action is associated with a general vasoconstrictor effect in the systemic arterial bed. The present studies revealed a similar tendency in the coronary circulation. The average level of the coronary vasomotor tone as reflected by the calculated value of vascular resistance did not exhibit dramatic changes after exposure to methylene chloride. However, it was quite clear that the depressant action of methylene chloride on the cardiac muscle is not accompanied by a parallel depressant effect on the smooth muscle cells of coronary blood vessels and the coronary blood flow was usually slightly decreased during the inhalation of the solvent. Since the level of coronary flow is set primarily by the rate of myocardial metabolic requirement, which, in turn, is considerably influenced by ventricular contractility, the observed

changes in coronary tone could probably be ascribed to a secondary vascular adjustment to the diminished cardiac performance. Although the latter mechanism can be regarded as a natural (physiologic) adaptive phenomenon, its consequences might be detrimental in special cases of human toxicity, when the blood supply to the heart is already in jeopardy due to organic disorders of the coronary vessels. Sudden cardiac depression associated with a relative reduction of the ventricular blood supply might be a major factor in initiation of serious cardiac arrhythmias, such as ventricular fibrillation, infrequently seen in methylene chloride poisoning of human subjects with heart disease. Such possibilities raise the challenging problems of effective prevention and appropriate treatment of the cardiac depression brought about by methylene chloride.

As a first approximation, every drug is a potentially beneficial one if it can prevent the arrhythmogenic action of methylene chloride. However, the efficacy of drugs should be described on a much narrower basis; if the potential hazards involved in the administration of the agent came close to (or even match) those involved in methylene chloride inhalation, the attempted therapy is self-defeating.

Inosine, which was selected in this study to counteract the harmful cardiac effect of methylene chloride, is a drug of apparently low toxicity. The fundamental cardiac stimulatory and coronary vasodilator actions elicited by inosine resemble those induced by catecholamine administration, as it was reported previously by other workers (24, 25) and by Juhasz-Nagy and Aviado (23). At the same time, inosine was reported to be an agent with virtually no acute toxicity, the LD₅₀ of the compound being several grams per kilogram body weight. Contrary to the well-known sensitizing effect of catecholamines toward arrhythmogenic tendencies, no such effect has been reported in connection with the inosine administration. In this study, particular attention was given to the inosine actions exerted on the physiologic adaptive capacity of the coronary vessels. The reason for doing so was that no relevant experiments had been reported until now concerning this aspect of inosine treatment. At the same time, it seemed of the utmost importance to elucidate this aspect considering the critical importance of maintenance of adequate blood supply and adequate coronary reactivity in the diseased human heart.

This problem directed our attention to the possibility of an influence of inosine on hypoxic coronary adaptation. We observed a significant improvement of the adaptive vascular capacity during inosine

administration. The effect was found to be superimposed on the significant, but not excessive, coronary vasodilation elicited by the drug. In contrast, no similar augmentation occurred during infusion of catecholamines (sometimes referred to as "malignant" coronary vasodilators) which elicited a comparable or even greater increase of myocardial flow and contractility. The explanation may be that, unlike most pharmacologic agents, exogenous inosine creates, possibly by its virtue of being a "natural" modulator substance of coronary tone, conditions for better metabolic adaptation in the coronary bed, and thus, for better oxygen supply of cardiac muscle working under hypoxic stress. The unique features of inosine, being both a therapeutic agent and one of the constituents that can be extracted from the heart muscle, seem promising from a clinical standpoint.

It is the opinion of the author that in evaluating the coronary actions of drugs, the effects exerted on physiologic vascular adaptability is of far greater importance than the mere vasodilator effects, the latter being frequently associated with the exhaustion of the physiologic coronary reserve, and in this sense, potentially undesirable. At the same time, since the exact mechanism of physiologic coronary adaptation to cardiac hypoxia and increase of heart metabolism is not known at present, it is not easy to classify cardiovascular therapeutic agents according to the latter point of view. There is every reason to suppose, however, that adenosine release from the myocardial muscle plays an important role in the physiologic mechanism of coronary adaptation (26). Moreover, a close relationship is known to exist between the actions and metabolism of adenosine and inosine, respectively. It was assumed that if an improvement in physiologic coronary adaptation can be achieved by inosine administration, the coronary vasodilator action of adenosine should also be increased by the compound. This supposition was fully confirmed in these experiments. Similar observations that related to the potentiation of adenosine effects by inosine have been reported previously (25, 27). Hence, the close parallel between the potentiation of hypoxic coronary vasodilation and the adenosine-induced coronary vasodilation as elicited by the administration of inosine makes the latter compound a promising candidate for treatment aimed at the improvement of cardiac activity weakened by methylene chloride in particular, and by chlorinated solvents and fluorocarbons in general.

Concluding Remarks

The effect of inosine on methylene chloride tox-

icity was investigated in open chest dogs anesthetized with pentobarbital sodium. Methylene chloride (5% in air or 50,000 ppm) elicited a decrease of ventricular contractility represented by the diminished left ventricular $(dp/dt)_{max}$ and myocardial contractile force measured directly with a Walton-Brodie strain gauge arch. Coronary blood flow decreased slightly after exposure to methylene chloride. Arterial blood pressure and heart rate did not change. The negative inotropic effect of methylene chloride was reversed or prevented to a substantial extent by intravenous infusion of inosine (5 mg/kg-min). The effect of the latter compound was also characterized by significant coronary vasodilation. It was shown by the experiments that the cardiostimulatory action of inosine was associated with improved hypoxic adaptability of the coronary blood vessels. In contrast, the effect of catecholamines (epinephrine and isoproterenol) was not accompanied by such a beneficial coronary vascular effect. On the basis of these results, it is concluded that inosine might be a useful antidote for poisoning from methylene chloride or other chlorinated solvents or fluorocarbons.

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