Cardiovascular Effects of 1,1,1-Trichloroethane

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Acute exposure of anesthetized dogs to 1,1,1-trichloroethane (TCE) results in a dose-dependent, biphasic decline in arterial pressure similar to that observed following exposure to a commercial solvent containing TCE. The initial phase of pressure decline is associated with peripheral vasodilation whose magnitude exceeds concomitant, reflex, positive chronotropic and inotropic effects on myocardial function. The peripheral dilation could be reversed by injection of the α-agonist, phenylephrine hydrochloride. The second phase of pressure decline is primarily associated with a depression of myocardial function; heart rate, stroke output, and myocardial contractility declined. Injection of Ca^{++} ameliorated the TCE-induced alteration of myocardial contractility and blood pressure was protected. The data suggest that comprehension of the mechanism(s) by which TCE induces cardiovascular depression may lead to more effective clinical management of the toxic effects of this compound.

A halogenated hydrocarbon that was introduced in 1954 as an industrial solvent,[1] 1,1,1-trichloroethane (TCE) is sold on the retail market in various spot remover preparations and so on. Its potentially toxic effects have been recognized for several years.[2,3] However, since TCE is less toxic than several other halogenated compounds of comparable function (it is reported to be replacing carbon tetrachloride under numerous circumstances[1,2,4]), its commercial use is increasing greatly. In 1971, 169.6 million kilograms of TCE were produced, an increase of 50% over the previous five years.[4]

At least 30 deaths have been directly attributed to intoxication by TCE[5-8] and, further, this compound has been shown to have arrhythmigenic properties.[9-11] The resultant cardiac malfunction is thought to be due to spontaneous[10] adrenergic-mediated arrhythmias[9-11] or both during exposure to TCE, and possibly subsequent to exposure, during an adrenergic crisis.[9,10] Compounds containing TCE and sold on the retail market, eg, spot removers and, more recently, nasal decongestants,[5] have proved dangerous and fatal in the hands of "glue sniffing" youngsters.[8] Particularly alarming in this regard has been a recent report from the Food and Drug Administration that at least 18 deaths have occurred due to the use (one death) and abuse (17 deaths) of an over-the-counter nasal decongestant spray which contained TCE as a carrier solvent.[5]

During development of a clinical procedure for detection of organic solvents in the breath,[12] profound cardiovascular depression was noted after acute exposure of anesthetized dogs to TCE. Although central nervous system depression is described as the usual mechanism for TCE-induced toxicity,[1,2] the above experimental observation, as well as the fact that TCE sensitized the heart to the development of arrhythmias,[9,10] suggested that TCE may exert additional direct effects on the cardiovascular system. In view of the growing commercial importance of this compound and the increased frequency of reported intoxication,[8] the cardiovascular effects of TCE were explored. Evidence is presented that a sequence of specific cardiovascular events is associated with inhalation of TCE in the anesthetized dog and, in addition, that the toxic properties of this compound, particularly during acute inhalation, cannot be adequately explained as a manifestation of generalized CNS depression.

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Methods

Dog Experiments.—Nine mongrel dogs (25 to 35 kg) were anesthetized with pentobarbital sodium (35 mg/kg), or chloralose (50 mg/kg) and 10% pentobarbital sodium. Arterial pressure was measured by a transducer connected to a femoral arterial cannula, and left ventricular pressure (LVP) was obtained from a manometer catheter inserted (fluroscopically) into the left ventricle. Cardiac stroke output was measured with an electromagnetic flowmeter chronically implanted at the base of the aorta, and blood flow was integrated electronically and defined by arbitrary units, as noted in "Results" (Fig 1). These various monitors, as well as electrocardiogram leads, were connected to an eight-channel recorder.

In order to measure myocardial contractility (in vivo), ie, the force-generating capacity of the heart, the first derivative of the LVP trace, dP/dt, derived electronically, was used during our initial experiments.[13,14] However, these values are reported to be suspect because of their sensitivity to alterations in cardiac afterload.[13,14] Subsequently, in order to obviate this potential difficulty, (see "Results" and Fig 3 for comparison) the maximum contractile element, velocity (V_{max}), was calculated according to the method described by Grossman et al.[14] These values are purported to be less susceptible to alterations in cardiovascular loading than dP/dt.

A positive pressure ventilation apparatus was connected in parallel with a bubble-type vaporizer. Each animal received mechanical ventilation for a 30-minute control period, and then a designated fraction of the inspired air was bubbled through a solution of TCE at 20 C. Following exposure (lasting no more than five minutes), the animals were allowed to recover. The criteria for recovery were the return to initial values of both blood pressure and heart rate, approximately 10 to 45 minutes, respectively, for most doses of TCE tested.

A second dose of TCE was then administered, approximately one hour after the first exposure, and this procedure was carried out during the course of each experimental day. In experiments in which drug effects were studied (Table, Fig 5 through 7), care was taken to insure that subsequent exposures to TCE were independent of possible long-term effects of these compounds. In addition to the monitoring of cardiovascular dynamics, control (ie, with-

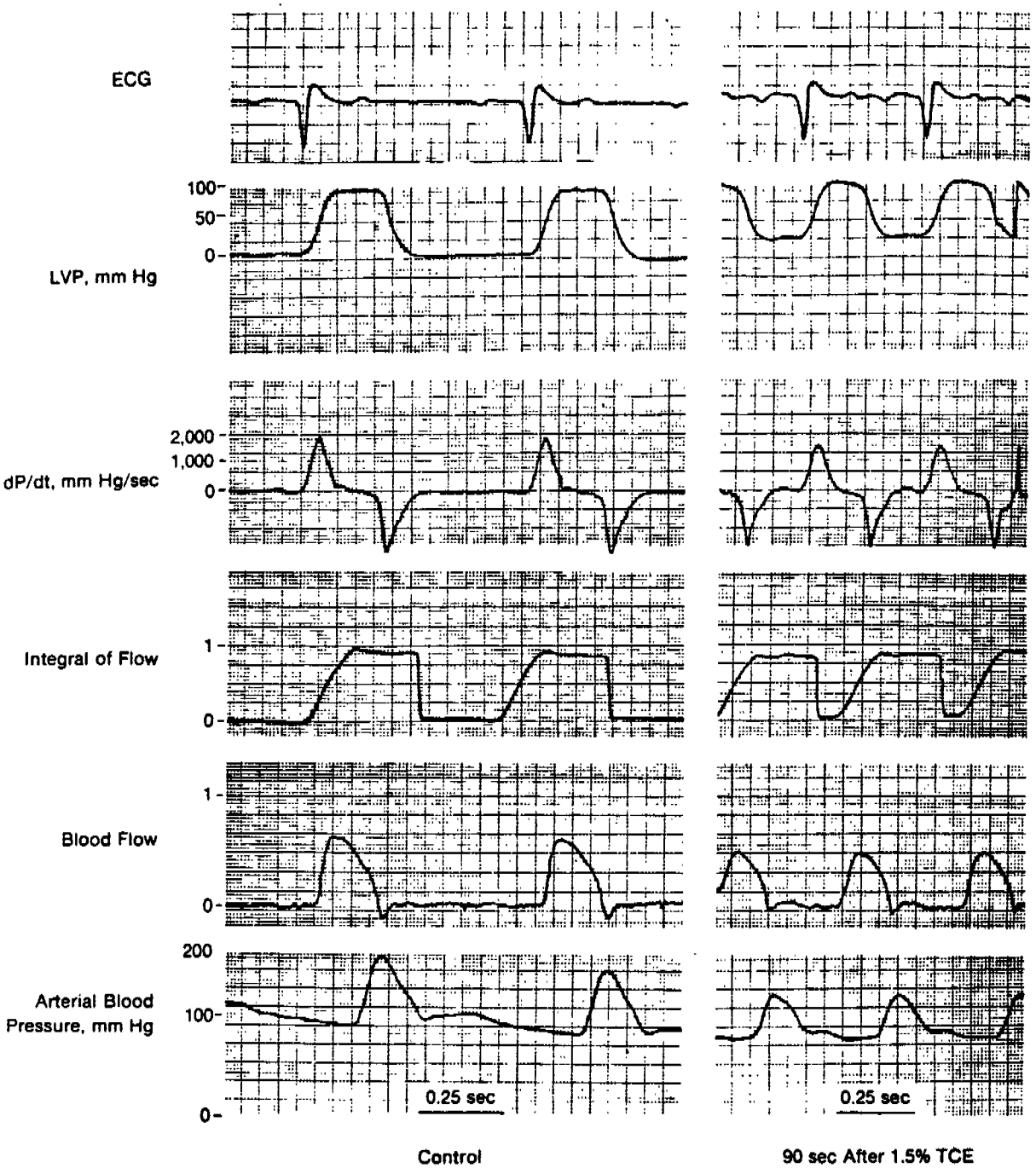

Fig 1.—Cardiovascular response to TCE. Typical data obtained from 24-kg dog anesthetized with chloralose pentobarbital and exposed to 1.5% TCE.

out added drug) exposures of TCE were generally interspersed between drug interventions to insure the reproducibility of the data.

In several experiments pH and arterial blood gas levels were measured throughout the course of a day's experiment. Only during severe exposure to TCE, ie, greater than 2.5%, were these hematological measurements altered (specifically, pH declined from 7.42 to 7.30 during an exposure to 2.8% TCE), and these data are not reported here. Under our experimental conditions, blood pH remained between pH 7.44 to 7.38 and blood gas levels were unaltered from initial conditions.

Data.—The data presented in this report represent typical experiments which were repeated at least three times on at least two different animals (see "Results" for additional experimental details and number, N, of experiments).

Papillary Muscle Experiments.—Papillary muscles (weighing 2 to 3 mg) obtained from 200 to 250-gm female albino rats were prepared and isometric contractions were studied according to the technique of Henderson et al.[13] The muscles were stimulated at 12 beats per minute (at 5 to 10 v, 0.5 msec in duration). After an initial equilibration period of two hours in Krebs-Ringer solution (pH 7.4) supplemented with 0.5% bovine serum albumin, during

CORRECTION

Base Line Erroneously Elevated.—In the article "Cardiovascular Effects of 1,1,1-Trichloroethane," published in the April ARCHIVES (28:227-233, 1974), the base line in Figure 1, page 228, for the left ventricular pressure (LVP, mm Hg) was elevated erroneously. Compared with that for the control (column 1), the left ventricular end diastolic pressure (base line) was unchanged after exposure to TCE (column 2). Coincidentally, the left ventricular end systolic pressure declined when compared with that for the control. Figure 1 has been corrected and is published below.

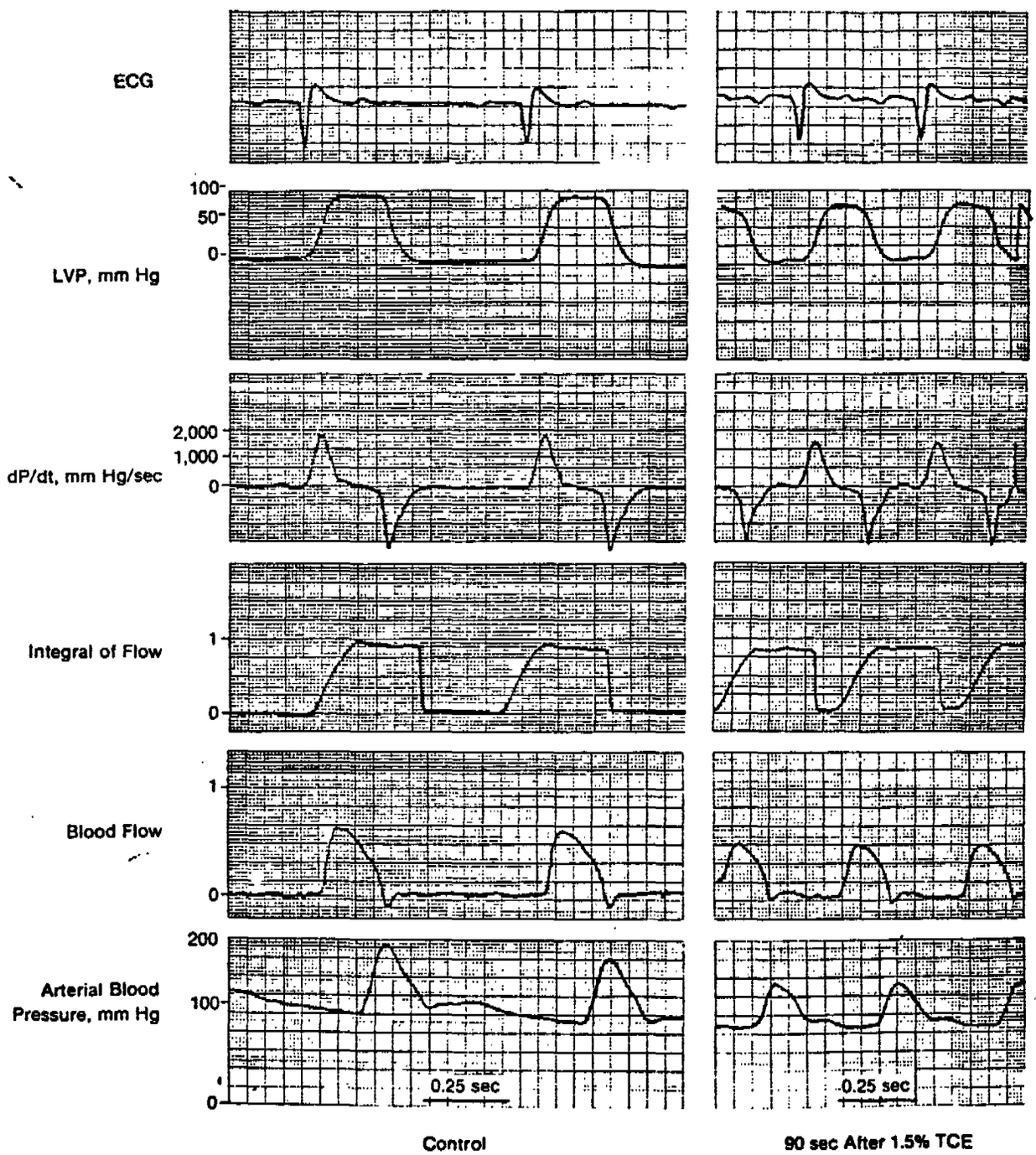

Fig 1.—Cardiovascular response to TCE. Typical data obtained from 24-kg dog anesthetized with chloralose pentobarbital and exposed to 1.5% TCE.

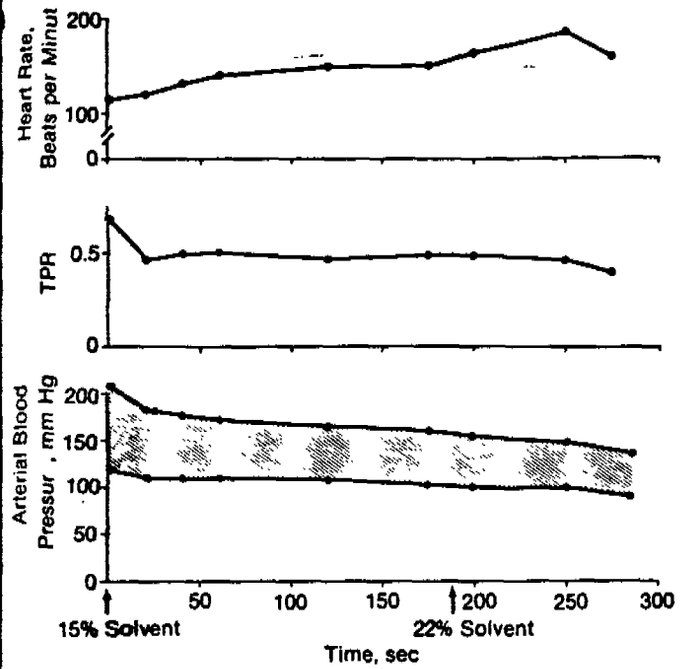

Fig 2.—Effects of commercial spot remover on blood pressure, heart rate, and TPR on 24-kg dog anesthetized with chloraiose/pentobarbital. Various fractions of inspired air (designated as solvent) bubbled (at 20 C) through chamber containing commercial spot remover reported to contain 10% TCE.

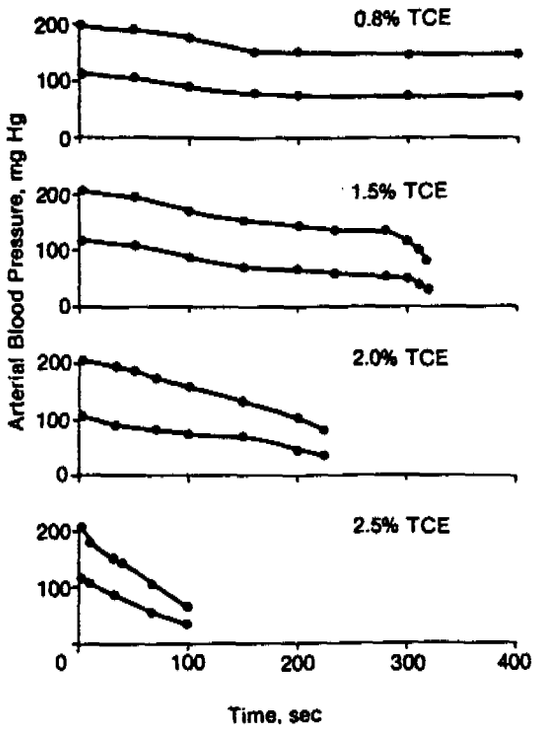

Fig 3.—Effects of varying doses of TCE on blood pressure of 25-kg dog anesthetized with pentobarbital and sequentially exposed to increasing doses of TCE.

which maximal resting tension was obtained, the muscles were divided into groups (usually two per group) and were administered TCE by saturating the aeration mixture (95% oxygen/5% carbon dioxide) with the drug (at 20 C). In addition to developed tension and the rate of tension generation (dT/dt), the total tension time interval, the time to peak developed tension, and the time to peak rate of tension generation were measured.[16]

Reagents.—Preliminary evaluation of 1,1,1-trichloroethane indicated approximately 3 to 3.5 vol% contamination as seen by vapor phase chromatography. The primary contaminant (2 to 2.5 vol%) had a retention time identical with that of dioxane, and it was extracted with water, hydrogen sulfate, and then additional water to remove acid. This procedure resulted in preparations of TCE yielding a minimum of 99.5 vol% purity by vapor phase chromatography, and this reagent was used throughout the course of the investigation.

Results

Exposure of anesthetized dogs to a commercial spot remover containing TCE results in a dose-dependent decline in blood pressure (Fig 2). Initially, total peripheral resistance (TPR) declines and then stabilizes. The heart rate increases following exposure to the spot remover and increases further with increased dose of solvent, but then begins to decline. Stroke output (not shown in Fig 2) began to fall slowly approximately 50 seconds after exposure to the solvent, and the rate of fall increased with increasing dose of solvent. Essentially identical data were obtained in two additional experiments in which the fraction of inspired solvent was varied.

The decline in blood pressure seen during exposure to a commercial spot remover (Fig 2) is similar to that observed when anesthetized dogs ($N = 9$) are exposed to TCE (Fig 1 and 3). The decline in blood pressure begins within 10 to 15 seconds after introduction of TCE into the ventilator, and the magnitude and pattern of pressure decline were found to be dependent on the dose of TCE inspired (Fig 3). Under these conditions, two distinct phases of pressure decline were observed (Fig 2). The initial phase (Fig 3, 0.8% and 1.5% TCE, and Fig 4) is characterized by a parallel decline in systolic and diastolic pressures, while both myocardial contractility and cardiac output (both heart rate and, to a lesser extent, stroke volume) increase. Thus, the decline in blood pressure during this initial phase results from a marked decrease in TPR (Fig 4).

The positive chronotropic (and inotropic) response seen during the initial phase of pressure decline (Fig 3) could be abolished by pretreatment with the β-receptor antagonist, propranolol hydrochloride (Inderal), as seen in the Table. These data suggest a neurohumoral-mediated stimulation of myocardial function during this phase.

The second phase of blood pressure decline is characterized by a reduction in cardiac output, marked by decreases in both stroke volume and heart rate (Fig 4). In addition, myocardial contractility also declines, as evidenced by the decline in V_{max} as well as dP/dt. The TPR is not markedly altered during this second phase of blood pressure decline, an indication that maximum peripheral vasodilation is obtained during the initial phase and that peripheral vas-

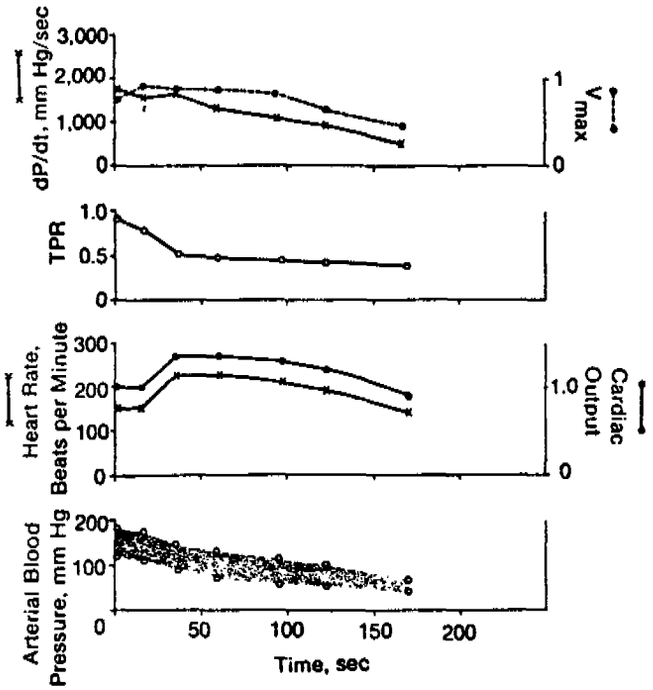

Fig 4.—Alterations in cardiovascular measurements following exposure to TCE. Typical data (N = 9) obtained from 30-kg dog anesthetized with chloralose/pentobarbital and exposed to 1.5% TCE.

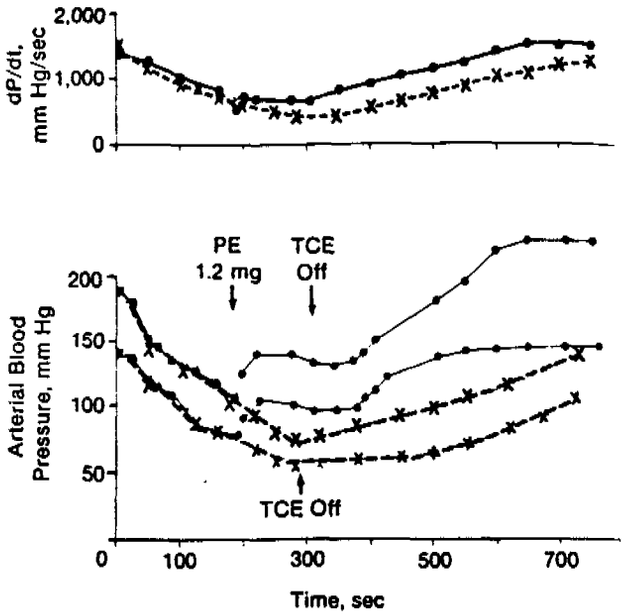

Fig 5.—Effect of phenylephrine (PE) on TCE-induced alteration in blood pressure and dP/dt in 28-kg dog anesthetized with chloralose/pentobarbital and exposed to control exposure (x) of TCE, followed by second exposure in which phenylephrine was injected intravenously (solid circles).

culature plays a minor role in the subsequent cardiovascular depression.

The decline in arterial pressure could be terminated by removal of TCE from the inspired air. However, at pressures below 50 mm Hg (systolic), most animals died. At autopsy, no unusual changes were noted in the lungs, liver, brain, and so on upon either gross or histologic examination (H. Martin, PhD, unpublished data). These results agree with earlier reports.[6,7]

During the course of these experiments (a total of 60 exposures obtained during 12 trials on nine dogs), we did not observe the development of spontaneous, TCE-dependent arrhythmias.

It is also noteworthy that the type of anesthetic used in the experiments contributed in part to the cardiovascular response to TCE. Pentobarbital sodium, as one of its central effects, inhibits myocardial parasympathetic tone,[17] and, thus, sympathetic tone is enhanced. In general, these animals (N = 3) had higher initial heart rates (and V_{max}) than the chloralose anesthetized dogs, and there was little or no attendant positive chronotropic (or inotropic) response immediately following exposure to TCE. However the TCE-induced alterations in TPR and myocardial function were unaltered.

Effect of Phenylephrine Hydrochloride.—In lieu of epinephrine or norepinephrine administration to counteract TCE-induced cardiovascular depression with associated risk of induction of arrhythmias,[9-11] most clinical methods for resuscitation suggest supportive, rather than active, treatment following exposure.[1,2] The pure α-agonist, phenylephrine, is reported to have minimal direct effects on the myocardium.[18] It appears to act primarily on the peripheral vasculature to produce vasoconstriction. Injection of phenylephrine, 1.2 mg, as demonstrated in Fig 5, reverses the course of blood pressure decline in anesthetized dogs exposed to TCE, although no marked alterations were noted in dP/dt. Heart rate fell transiently, but returned to preinjection levels within 20 seconds after injection of the drug and was unaltered, with respect to the control, during subsequent alterations in blood pressure.

Effect of Propranolol Hydrochloride on Positive Chronotropic Response Following Inhalation of 2.0% TCE

Time After Exposure, sec	Heart Rate* Beats/Min TCE	Heart Rate* Beats/Min TCE and Propranolol Hydrochloride
0	150	130
20	150	140
40	180	145
60	190	140
80	200	130
100	192	118
120	190	110

* Data obtained from single dog anesthetized with chloralose and pentobarbital. Control (TCE) repeated twice and animal then given propranolol hydrochloride (250μg/kg) and exposed to TCE five minutes later. Similar results were obtained in second animal, similarly prepared.

The slight alteration in dP/dt that was observed may be ascribed to the increase in arterial pressure[11,14] rather than to a direct effect on myocardial contractility. No alteration in left ventricular end diastolic pressure was observed, and the rate of return of dP/dt to initial values was similar

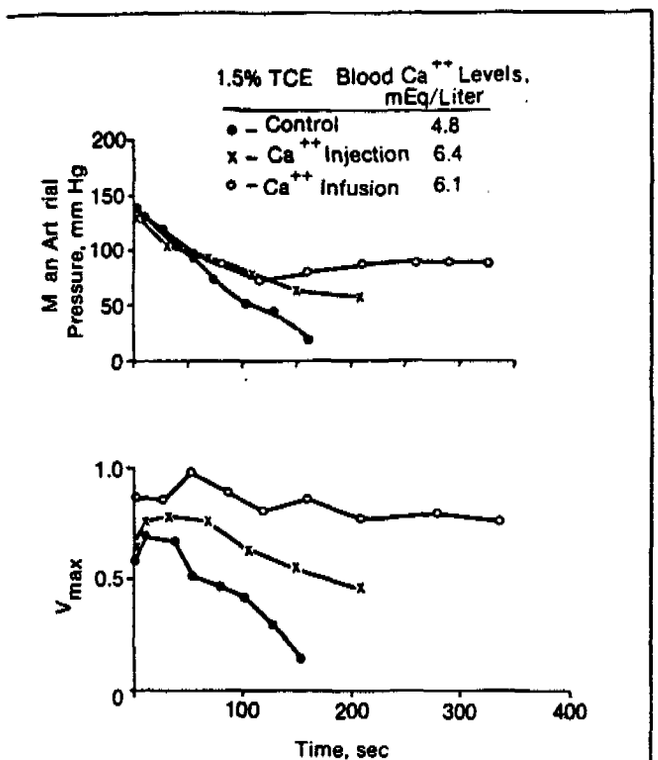

Fig 6.—Effect of exogenous Ca^{++} injection (x) and infusion (open circles) on mean blood pressure and myocardial contractility during exposure to 2.0% TCE in 35-kg dog (N = 4) anesthetized with chloralose/pentobarbital. Data similar to those obtained from four additional experiments in which levels of Ca^{++} injected were varied. Following return of blood Ca^{++} levels to control values (4.8 mEq/liter), fourth exposure to TCE resulted in essentially identical cardiovascular alterations as seen in initial control (solid circles).

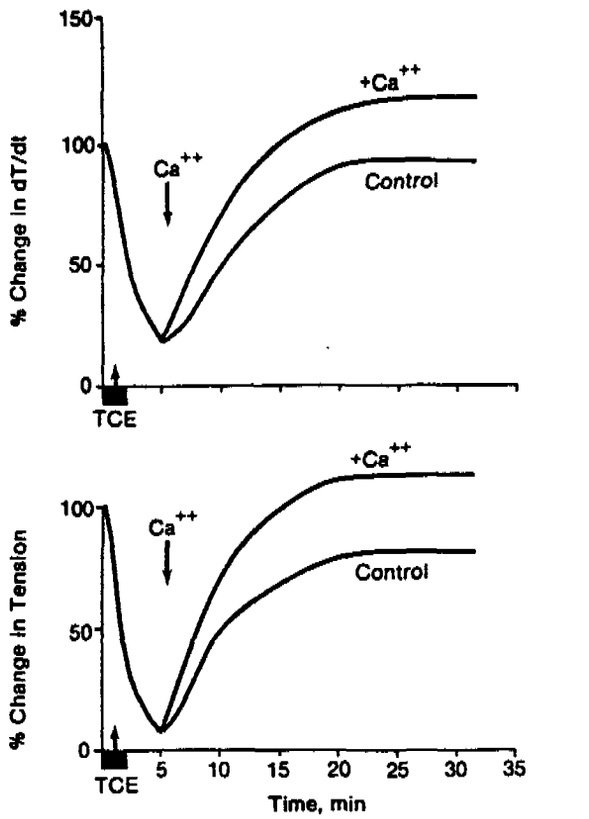

Fig 7.—Effect of raising exogenous Ca (2.54 mM to 5.08 mM) on recovery of isolated rat papillary muscles from exposure to TCE.

in both cases. Upon cessation of exposure to TCE, the phenylephrine-injected preparation returned to or, as seen in this case (Fig 5), exceeded the initial blood pressure values at a much faster pace than in the preparation without phenylephrine.

Ninety minutes after exposure to TCE and phenylephrine, the dog was again exposed to TCE, and blood pressure declined in a manner identical to that seen in the initial control experiment (Fig 5).

Essentially similar results were obtained in eight additional exposures on three animals. The response to phenylephrine appeared to be dependent on the dose used and the initial level of mean blood pressure. It is also noteworthy that, in the presence of phenylephrine (injection or preinfusion), no evidence of arrhythmigenic activity was observed that could be ascribed to an interaction between phenylephrine and the TCE-altered myocardium.

Myocardial Effects.—In addition to peripheral vascular effects, our data (Fig 1 through 3) indicate that significant alterations in myocardial function also occur during exposure to TCE. During the course of these experiments it was noted that blood pressure returned to initial values within 15 minutes after cessation of exposure to TCE, but that the myocardial factors, eg, heart rate, stroke volume, and V_{max}, recovered much more slowly, requiring at least 45 minutes to return to initial values. Since extracellular Ca^{++} levels are known to affect myocardial contractility dramatically,[19-21] alteration of exogenous Ca^{++} was studied to determine its effect on the TCE-dependent decline in myocardial function.

In Fig 4, the effects of Ca^{++} injection (9.4 mEq gluconate calcium) and Ca^{++} infusion (9.4 mEq gluconate calcium followed by infusion of 0.48 mEq Ca^{++}/min) on the TCE-dependent alteration of myocardial contractility and mean blood pressure are presented. The initial phase of blood pressure decline is similar in each case and was associated with a similar decrease in TPR (not shown). However, myocardial contractility differed in the calcium-injected preparation: contractility increased to a much greater extent than in the initial control, and in the Ca^{++}-infused preparation the initial level of myocardial contractility was markedly greater than that of the control and did not change appreciably during exposure to TCE. With continued exposure to TCE, mean blood pressure falls precipitously in the control preparation, but not in the Ca^{++}-treated preparations, and this maintenance of mean pressure was paralleled by

higher levels of V_{max}.

That exogenous Ca^{++} is acting directly on the contractile mechanism and thereby enhancing the force-generating capacity, ie, contractility, of the myocardium is also seen in Fig 7. Pairs of rat heart papillary muscles ($N = 4$) were simultaneously exposed to TCE. After exposure, the Ca^{++} concentration was raised in one muscle group and the return of developed tension and the rate of tension generation (dT/dt) were followed. The TCE had no effect on the time taken to develop peak tension or on the duration of a contraction cycle. However, in agreement with similar results obtained with halothane,[22] the time taken to develop peak dT/dt decreased approximately 10% during the exposure period, independent of dosage of TCE used in these experiments. Addition of Ca^{++} following exposure to TCE produced a marked enhancement of the rate of return of developed tension and dT/dt toward initial values. The final values for developed tension and dT/dt were generally slightly greater (at least 10%, four experiments) than those obtained in control experiments, ie, when Ca^{++} was added in the absence of TCE (not shown).

Comment

The demonstration of a dose-dependent, biphasic depression of blood pressure associated with the inhalation of TCE (Fig 3 and 4) is consistent with the suggestion of Bass[3] that an adequate explanation for the toxicological effects of acutely inhaled organic solvents cannot be ascribed solely to generalized CNS depression. Thus, during the initial phase of pressure decline, positive chronotropic and inotropic effects were observed (Fig 3 and 5); since these effects were abolished by β-blockade (Table), the findings suggest reflex stimulation of the heart.

The decline in TPR associated with this initial phase of inhalation (Fig 3) is analogous to the reflex, peripheral vasodilation which occurs following chemical irritation of the respiratory stretch receptors[23]; alternatively, passive vasodilation resulting from ganglionic blockade[24] may also serve to explain this observation. In preliminary studies designed to identify which mechanism is responsible for the peripheral vasodilation, the effects of vagotomy and α-receptor blockade were studied. Although preliminary evidence suggested that vagotomy abolished the TCE-induced peripheral vasodilation, the data were complicated by concomitant reflex alterations in sympathetic tone which prevented a clear-cut analysis of the results (P. Herd, PhD, M. Lipsky, unpublished data). Further clarification must await additional studies, such as cross-perfusion experiments (eg, that of Van Stee and Back[24]), in order to elucidate the actual mechanisms involved in the TCE-induced peripheral vasodilation.

With respect to the myocardial effects of TCE, our data suggest that the drug acts by inhibiting myocardial contractility. The active state of muscle contraction has been divided into extensive and intensive components.[21] The extensive component, ie, the duration of the active state, is defined as the time required for peak tension development and is a function of two events: intracellular Ca^{++} release and its sequestration.[20,21] This time interal was unaffected by TCE in the papillary muscle experiments, as reported above. In contrast, the intensive component, ie, the rate of force generation defined by V_{max} (Fig 4 and 6) and dT/dt (Fig 7), is markedly affected by TCE.

The extracellular Ca^{++} concentration has been shown to control the rate of force generation because it, in part, determines the level of bound intracellular Ca^{++} which is available for contractile function, thereby controlling the magnitude and rate at which Ca^{++} binds the troponin-actinomycin complex[21,25] Ca^{++}-troponin formation releases actinomycin for adenosine triphosphate (ATP)-dependent cross-linkage formation, ie, myocardial contractility, as seen in Fig 6. In addition, increase is extracellular Ca^{++} concentration protected against the TCE-induced decrease in myocardial contractility (Fig 6) and enhanced the rate of return of myocardial function to preexposure levels (Fig 7).

At the present time, the precise site(s) at which TCE affects myocardial contractility remain(s) to be determined. Perhaps, because it is highly lipophilic, TCE affects membrane-dependent functions. In this regard, Krantz and co-workers[26] have shown that TCE inhibits the respiration of tissue slices obtained from the rat heart, and we have recently observed that TCE depresses mitochondrial respiration associated with ATP synthesis as well as low-level Ca^{++} uptake.[27] Whether these findings reflect the in vivo situation remains to be determined. However these data[26,27] are consistent with a possible explanation that TCE-induced depression of myocardial contractility results from a decrease in the capacity of the cardiac mitochondria to supply sufficient ATP to mediate the contractile process. Elevation of the extracellular Ca^{++} concentration (Fig 6 and 7) would then increase the contractile efficiency of the available supply of ATP by increasing the intracellular Ca^{++} concentration available for contraction.[20,21,25]

Thus, in acute intoxication with TCE, eg, during exposure in confined spaces[28] or as a result of "glue sniffing," one may expect profound alterations in cardiovascular function to occur independent of, but perhaps in addition to, CNS depression.[1] It is suggested that the extent to which these cardiovascular effects may be altered by exogenous Ca^{++}, or phenylephrine, or both may, following more detailed study, provide a basis for more active and safe resuscitation of exposed individuals.

Previous studies[9,11,29-31] of the toxic effects of TCE have, in general, used exposure levels lower than those in the present study, especially in human toxicity experiments.[29-31] Stewart and Andrews have pointed out that the effective dose of TCE is a function of several variables of which not only the inspired concentration and duration of exposure are important, but also the lipophilicity of the exposed areas contribute significantly to the net effective accumulation of this compound in the body. Indeed, in human trials,[30,31] TCE can be detected in the breath more than 24

hours after a single, low-dose exposure and is detectable for longer periods after chronic, low-dose exposures. Routine blood, urine, and hepatic function studies are generally carried out during these trials,[29-31] but studies of dynamic alterations in cardiovascular function have not been pursued. Under these circumstances, it is not known whether slight alterations in myocardial function occur during low-level exposure which may lend themselves to more dramatic sequelae on subsequent insult to the cardiovascular system, eg, during adrenergic crisis.[8,10] Unfortunately, epidemiological evidence such as the incidence of cardiovascular accidents in industrial workers who are exposed to TCE vapors, are not available at the present time (G. Hickey, MS, oral communication, February 1973). However, we believe that our data suggest a need for further investigation of the myocardial effects of low-level (ie, close to the threshold limit value) and cumulative exposures to TCE, such as those that may occur under normal working conditions.

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MYTHOLOGY FOR ECOLOGY

Herakles' Reducing Salon

A girdle was no easy thing to find
In the ancient Attic time,
And when Eurystes' chubby daughter
Heard about Omphale's, she thought she'd orter
Have one, too. It's no proper labor for a hero
To find a girdle labeled forty—zero.
So Herakles most gaily
Brought his problem to Omphale,
Who with fast and exercise reductive
Contrived to make herself seductive
Without the use of belt or stay.
She promptly gave away
Her girdle, on condition
That Herakles would stay
And help in her attrition.

—Rusticatus.