Cardiovascular Actions of Lead and Relationship to Hypertension: A Review

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Chronic and acute lead poisoning cause overt, clinical symptoms of cardiac and vascular damage with potentially lethal consequences. Morphological, biochemical, and functional derangements of the heart have all been described in patients following exposure to excessive lead levels. Disturbances in cardiac electrical and mechanical activity and postmortem evidence of morphological and biochemical derangements of the myocardium have all been reported following excessive exposure to lead in humans. In addition, signs of vascular degeneration, abnormal vascular smooth muscle function, and altered vessel compliance have been described in humans chronically and acutely exposed to toxic lead levels. Similar cardiovascular complications have been detected following excessive lead exposure in experimental animals. Myocarditis, electrocardiographic disturbances, heightened catecholamine arrhythmogenicity, altered myocardial contractile responsiveness to inotropic stimulation, degenerative structural and biochemical changes affecting the musculature of the heart and vasculature, hypertension, hypercholesterolemia, atherosclerosis, and increased vascular reactivity to α-adrenergic agonists have been among the reported cardiovascular disturbances linked to lead poisoning. Less certain are the cardiovascular effects of subclinical lead poisoning. Although controversial, chronic low-level lead exposure has been linked to hypertension and other cardiovascular disturbances in both clinical and experimental studies. In general, it can be concluded that lead over a wide range of exposure intensities can induce significant changes in the function of the cardiovascular system. Evidence points to the involvement of multiple sites of action. Cardiac and vascular sites, as well as sites within the central nervous system, have all been implicated in the sequelae of cardiovascular effects. The exact pathogenic mechanisms that underlie the actions of lead in the cardiovascular system, however, have yet to be elucidated definitively.

Overview

Intense lead exposure has been linked since antiquity to serious, sometimes lethal disturbances in cardiac rhythmicity and contractile function. More subtle effects have been reported following lead exposure at lower levels; in some instances effects have been reported at levels approaching those encountered passively in the general environment (1–6). These observations suggest that acute and chronic lead exposure over a relatively broad dose range may be associated with significant changes in the function of the cardiovascular system. The severity of the reported effects and the extent to which the cardiovascular system is affected by lead appears to be influenced most directly by the dose of lead and the duration of lead exposure. Other factors, such as route of exposure, age of the individual, temperature, and dietary calcium intake level, also appear to influence the expression and severity of the cardiovascular symptoms manifested in

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response to both acute and chronic forms of lead exposure (7).

For the most part, the interactive relationships among these various factors have not been well-delineated. The experimental findings that have been reported suggest that lead acts at multiple sites within the cardiovascular system. These findings include direct effects on the excitability and contractility of the heart (8–10), vascular sites of action affecting the compliance and contractility of vascular smooth muscle (11–15), and possibly sites of action within the central nervous system affecting blood pressure regulation (16–18). Although somewhat controversial, there are also indications that chronic lead exposure may affect systemic lipid metabolism. Elevated vascular lipid levels, vascular lipid infiltration, and increased plaque deposition on arterial walls have all been reported following chronic lead exposure (16,19,20).

Cardiac Effects of Lead in Humans

Case-based reports that have appeared in the clinical literature during the last three decades have presented rather compelling evidence attesting to the nature and

extent of the cardiac complications that develop in humans in response to chronic and acute lead poisoning (21–26). Myocarditis (21,22), electrocardiographic abnormalities (16,23,24), altered heart rate activity (16,24), slowed ventricular systole (16,25), hypertension (16,26–29), and vascular degeneration (16,22) have all been among the reported cardiovascular aberrations detected in humans chronically and acutely exposed to toxic lead levels (Table 1). Although the threshold blood lead level that triggers cardiac involvement and symptoms of cardiotoxicity has not been determined conclusively, it is apparent that environmental and occupational lead exposures that raise blood lead levels above 100 µg% and 60 µg% in adults and children, respectively, are frequently associated with transient as well as permanent cardiac and vascular lesions and functional disturbances (21–29). At lower blood levels the effects of lead on the heart and vasculature have not been firmly established. The possibility exists, based on recent epidemiologic findings, that lead may induce adverse cardiovascular effects (i.e., hypertension) at blood levels commonly found in the general, nonoccupationally exposed population (1–3,29,30). The postulated causal association between lead and hypertension remains a subject of considerable debate and controversy (1–3,16,27–34).

Clinical evidence suggesting that lead poisoning may induce cardiac disturbances symptomatic of myocarditis was first reported by Read and Williams (21). Shortly thereafter, Kline (22) presented histological findings that unequivocally characterized the degenerative and inflammatory changes in the myocardium that occurred in conjunction with chronic lead poisoning. This latter study involved five children ages 12 to 26 months who died of complications of acute lead poisoning. Three of these deaths were attributed to heart failure secondary to chronic myocarditis. Lead poisoning has also been shown in these and other studies to cause significant disturbances in the electrical activity of the heart (16,23,24). Electrocardiographic abnormalities, including sinus bradycardia (21,23–25), multifocal ventricular escape beats (21), T-wave inversion (24), left bundle branch block (LBBB) (21), first degree heart block (16,23), and ectopic atrial rhythms (24) have all been reported in conjunction with chronic lead poisoning. Chelation therapy generally has been shown to reverse these disturbances; however, instances of permanent damage have also been reported (Table 1) (24).

Other cardiac and vascular complications linked to excessive lead exposure in occupationally exposed workers have also been reported. These effects, which have been summarized in reviews by Stöfen (16), include abnormally low voltage waves (P and T waves) in the ECG, S-T interval changes, arteriosclerotic changes characterized by vascular degeneration, intimal fatty infiltration and proliferation of perivascular connective tissue, and reduced physical work endurance and abnormal cardiovascular responses to exercise. These latter effects are remarkably similar to

Table 1. Cardiotoxic manifestations of environmental lead in humans.

Group; Blood lead, µg%	Reported disturbances	Reference
Lead worker NR[a]	Bradycardia, LBBB, multifocal ventricular escape beats, myocarditis	(21)
Children died from complications of acute lead poisoning: 3/5 cause of death attributed to heart failure secondary to chronic myocarditis, NR	Autopsy findings: Myocarditis—muscle fiber degeneration, interstitial edema; connective tissue infiltration, compression and replacement of adjacent muscle fibers	(22)
Lead workers, > 100	A-V conduction disturbances; 1° HB; ectopic atrial rhythms	(23)
Children, > 60	Atrial arrhythmias (5/30; rev 4/5) Abnormal PR interval (6/30; rev 5/6) QT_c interval prolonged (15/30; rev 15/15) Inverted T wave (5/30; rev 4/5)	(24)
Lead workers, NR	Bradycardia, shorter ventricular ejection time, prolonged ventricular contraction time	(25)
Adult, > 250	Impaired β-receptor-mediated cardiovascular function: ↑Heart rate at maximum physical work capacity ↓Chronotropic responsiveness to isoproternol (12-fold dose) ↑Heart rate by 25 beats ↓Plasma renin activity (1/10 of control)	(26)

[a]NR, not reported.

those described by Bertel and co-workers (26).

According to the findings reported by Bertel et al. (26), the abnormal cardiovascular responses to exercise may emanate from a lead-induced defect in systemic β-adrenergic receptor function. Severe lead intoxication was associated in the Bertel study with a suppression of plasma renin activity, an exaggerated blood pressure but truncated heart rate response to exercise, an increase in plasma norepinephrine levels, and a marked attenuation of the positive chronotropic response to catecholamine (isoproterenol) stimulation. Collectively, these results were interpreted by these authors to indicate that excessive blood lead levels may have caused a generalized desensitization of β-adrenergic receptors, which depressed the normal circulatory

adjustments to exercise (e.g., decreased peripheral vascular resistance, tachycardia). As a consequence, blood pressure regulation was altered in the case studied, leading to hypertensive episodes under basal and exercise-stress conditions. This observation is noteworthy in that it suggests a possible mechanism for the transient hypertension reported in cases of lead intoxication(16,26), and it may also play a role in the blood pressure effects of lead following lower dose exposures commonly encountered by the general population (1-3, 28-30).

Although the heart and vasculature are generally not regarded as primary target sites for lead in mammalian systems, it is readily apparent from the foregoing summary that human lead poisoning can lead to overt, clinical symptoms of heart disease. Myocardial contractile function, excitability, and responsiveness to β-adrenergic receptor stimulation have all been reported to be affected by lead in these cases. Depending on the dose and the duration of the lead exposure, the cardiac and vascular complications and the damage that results are potentially life threatening. Less certain are the cardiovascular effects of lead at lower exposure levels. Until recently, the pluricausal nature of heart and vascular diseases combined with their generally slow progression before clinical symptoms develop have confounded attempts to identify what, if any, effect low-level lead exposure may have on the human cardiovascular system. Recent epidemiological findings, however, have provided strong support for the hypothesis that lead may be a contributing pathogenic factor in human essential hypertension (1-3). Although still controversial, positive correlations between blood lead levels and systemic arterial pressure have been repeatedly reported in these epidemiologic studies. The relationship reported indicates that blood pressure varies as a direct function of the blood lead concentration at levels commonly encountered in the average population. Thus, it is conceivable that lead may induce adverse cardiovascular effects in humans at levels well below those previously reported to induce overt, toxic manifestations. Further studies, particularly ones that provide a more sensitive indication of lead exposure than that provided by blood lead levels, are needed before this and other issues relating to the human health effects of lead can be resolved.

Cardiac Effects of Lead in Experimental Animals

Generally, chronic administration of lead to experimental animals has been shown to cause adverse cardiovascular changes similar to those reported in humans (4,6,14,17-20,35-44). As illustrated in Figure 1, diverse cardiovascular effects have been detected over a wide range of oral lead doses of varying duration. Unfortunately, as noted in Figure 1, blood lead levels were reported in relatively few of these studies. As a consequence, the only basis for comparing the results

obtained in these different studies appears to be in terms of the dose of lead administered. Not surprisingly, the extent of the cardiac and vascular involvement appears to escalate as a direct function of the oral lead dose. In general, administration of lead, most commonly as the acetate salt, to experimental animals has been shown to induce myocarditis (42), degenerative structural and biochemical changes affecting the musculature of the heart and vasculature (35,37,42,43), hypertension (4,6,14,38-40), hypercholesterolemia (6,16,19,20), increased arterial plaque deposition (19,20), electrocardiographic disturbances (38,39), accentuated catecholamine-arrhythmogenicity (5,17,41), altered contractile responsiveness of the myocardium to inotropic stimulation (44), and increased vascular reactivity to α-adrenergic agonists (5,17,41,44). Although incomplete, recent evidence suggests a role for calcium in the chronic and acute toxicity of lead in the cardiovascular system (6). Perhaps the most noteworthy association between these metals is that involving the direct cardiotoxic actions of lead (10).

Contractile and Metabolic Actions

The most severe myocardial damage attributed to chronic lead exposure has been reported in studies that have used lead doses that are overtly toxic (37,42,43). Diffuse, degenerative structural changes in the myocardium suggestive of myocarditis have been reported by Asokan following acute, oral lead administration (approximately, 6.5 mg/mL drinking fluid) for 6 weeks (42). Similar morphologic abnormalities, however, have been described by Moore and co-workers (43) in rats receiving a 60-fold lower dose than that used by Asokan for 25 weeks. These investigators also reported a significant decline in enzyme (heme synthetase and aminolaevulinic dehydratase) activities in conjunction with this level and duration of lead exposure.

Administration of lead to isolated heart preparations at effective doses appears to induce cardiotoxic manifestations similar to those reported in conjunction with lead poisoning in vivo. As such, this experimental approach has been used to more thoroughly characterize the cardiotoxic actions of lead. In these latter studies, lead has been consistently shown to induce a profound depression of myocardial contractile function, electromechanical dissociation, and marked disturbances in myocardial energy metabolism (10,44). The magnitude of these effects has been shown to depend on the extracellular calcium levels; below 3.5 mM, calcium antagonizes the cardiotoxic effects of lead; 5.0 mM calcium exacerbates the lead effects. This latter observation suggests that the increased metabolic demand placed on the heart by elevated extracellular calcium levels may increase the vulnerability of the heart to lead.

Subsequent studies focusing on the mechanistic basis for the contractile dysfunction induced by lead in
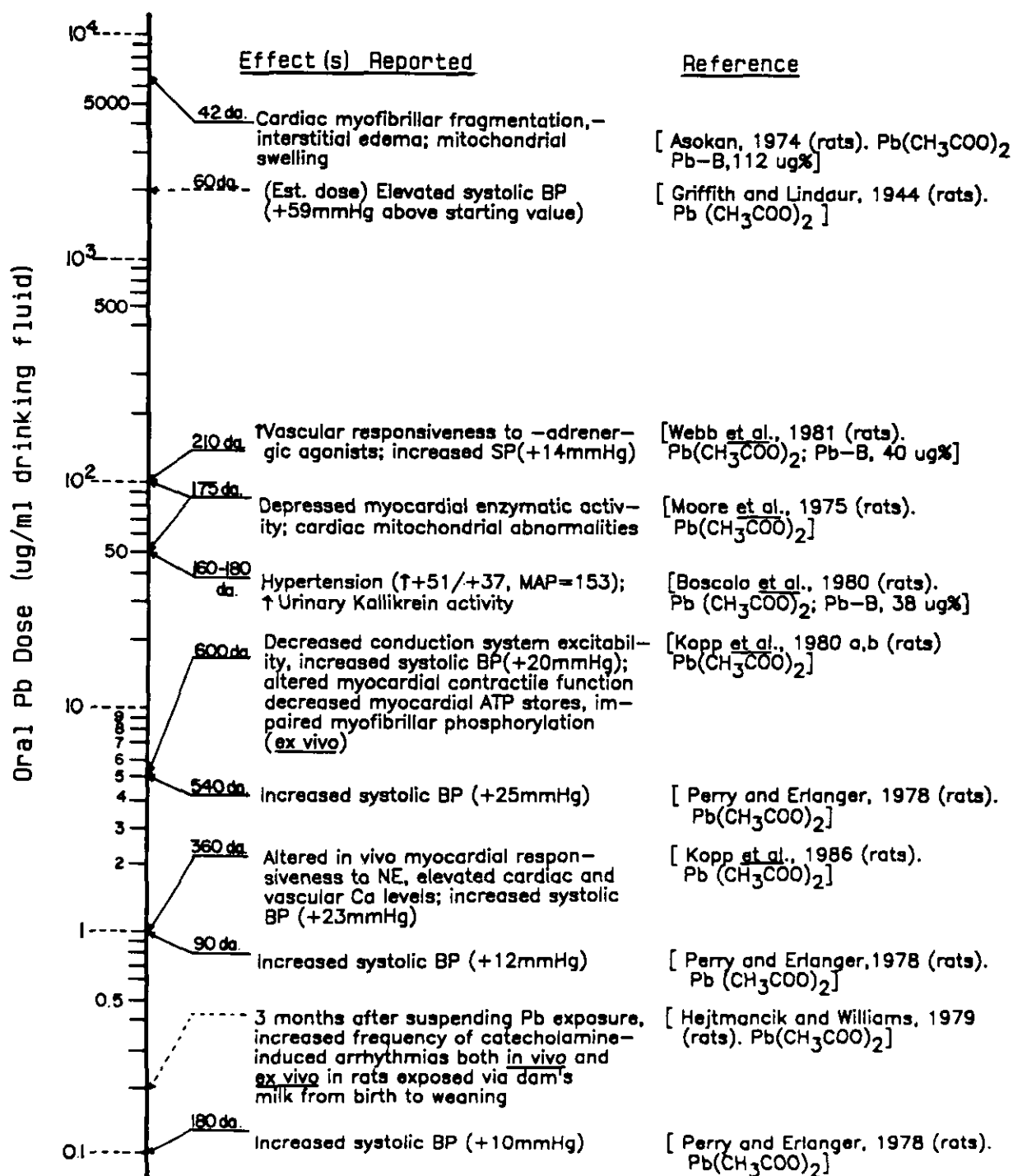
FIGURE 1. Representative spectrum of reported cardiovascular effects of lead in experimental animals as a function of oral lead dose. As noted in the left-hand column, the duration of lead administration, which varied considerably among the different studies, is noted for each study in days (da.) in the left-hand column. The lead salt administered and the reported blood lead level (µg%) are listed in the reference column.

the heart and the corresponding disturbances in myocardial energy metabolism support this interpretation. In these studies it has been possible to determine that the negative inotropic actions of lead are linked to disturbances in mitochondrial and sarcoplasmic proton gradients (Fig. 2). These effects, which were most pronounced in hearts perfused with lead (30 µM) in combination with 5 mM calcium, were followed by a time-dependent decline in cellular high-energy phosphate (primarily ATP) stores and contractile performance. These findings have been interpreted as a lead-induced inhibition of mitochondrial
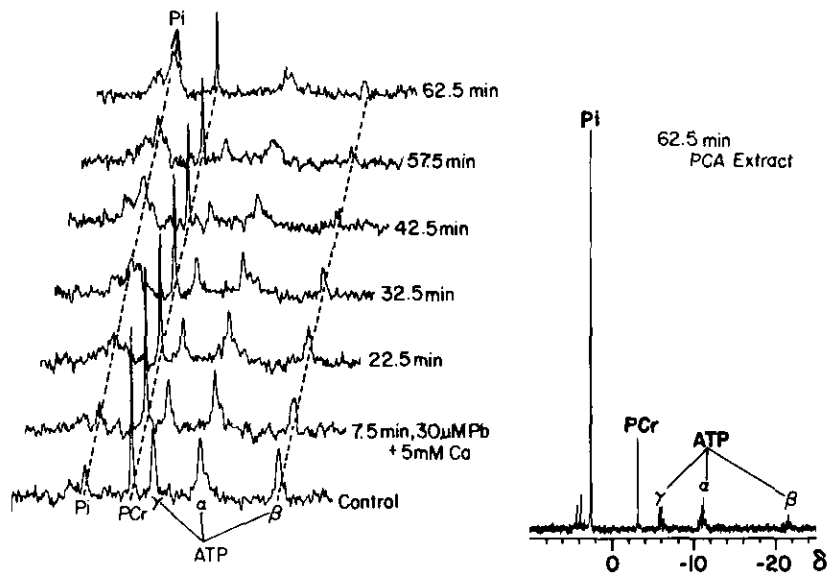
FIGURE 2. Left panel: selected, sequential intact heart 31P NMR spectra of a 30 μM Pb-perfused rat heart illustrating the emergence of multiple, intracellular acidic pools of inorganic phosphate (P$_i$) and the progressive decline in cellular high energy phosphate stores, principally ATP. The dashed lines are a visual aid to follow the plot-offshift of the sequentially plotted spectra. Right panel: 31P NMR spectrum of the tissue perchloric acid extract prepared from the heart shown in the left panel. Heart was immediately frozen by compression in liquid N2-chilled Wollenberger clamps at the conclusion of the experiment and subsequently acid-extracted under cryogenic conditions. PCr, phosphocreatine; ATP, adenosine triphosphate with respective g, a, and b phosphorus resonance signals.

respiration, which perturbs intracellular proton gradients and leads to impaired energy metabolism (44,45). The depressed contractile function of lead-treated hearts thus appears to emanate initially from the effects of lead on intracellular proton gradients, which is then aggravated by the progressive loss of cellular ATP stores. There was no evidence obtained by the ³¹P NMR spectroscopic procedures used in this study (45) that indicated that lead altered the availability of ATP by forming a lead-ATP complex. This interpretation suggesting a mitochondrial site of action of lead in the intact heart is consistent with the reported actions of lead on isolated heart mitochondria (46).

Significant cardiac effects have also been detected following administration of lower, oral doses of lead (4,5,9,14,18–20,38–41). Certain of these effects are similar to those observed in the isolated heart studies, while other effects are not. Myocardial contractile performance measured under ex vivo conditions in hearts from rats administered lead (5 μg/mL drinking water) for 20 months was shown to be depressed significantly (38,39). This effect of lead was linked to disturbances in myocardial energy metabolism and defective phosphorylation of putative regulatory phosphoproteins suspected of being involved in the regulation of chemicomechanical energy transduction in heart muscle (38,47,48).

In contrast, in vivo measures of myocardial contractile activity (44) performed in rats following 12 months of oral exposure to lead (1 μg/mL drinking water) have revealed a heightened contractile response of the myocardium to norepinephrine (6 × 10⁻¹¹

mole/kg body weight) without evidence of depressed function under basal conditions. This relationship is illustrated in Figure 3, which depicts the dose-dependent effects of norepinephrine on the maximal rate of change in left ventricular pressure development (+dP/dt). This effect appeared to be a compensatory response for the effect of lead on myocardial outflow resistance, as evidenced by the increased aortic afterload detected in these animals (Fig. 4).

Intraventricular pulse pressure and heart rate responses were not affected by lead treatment. The duration of the positive inotropic response to norepinephrine was prolonged significantly at the two highest norepinephrine concentrations, suggesting an increased norepinephrine half-life in the lead-treated rats relative to the control group. The paradoxical findings obtained in these studies suggest that prior lead treatment significantly alters the capacity of the heart to function under experimentally imposed conditions (i.e., ex vivo perfusion versus in vivo conditions). It is conceivable that the cardiodepressive effects of lead following relatively low prior exposure are unmasked under ex vivo conditions due to the elimination of neural and hormonal influences on the heart.

Effects on Cardiac Excitability

As described earlier, clinical evidence exists suggesting that lead may also affect the electrical stability and excitability of the heart (16,23,24). It has been postulated that these disturbances result from effects of lead on the parasympathetic and sympathetic nerves in-
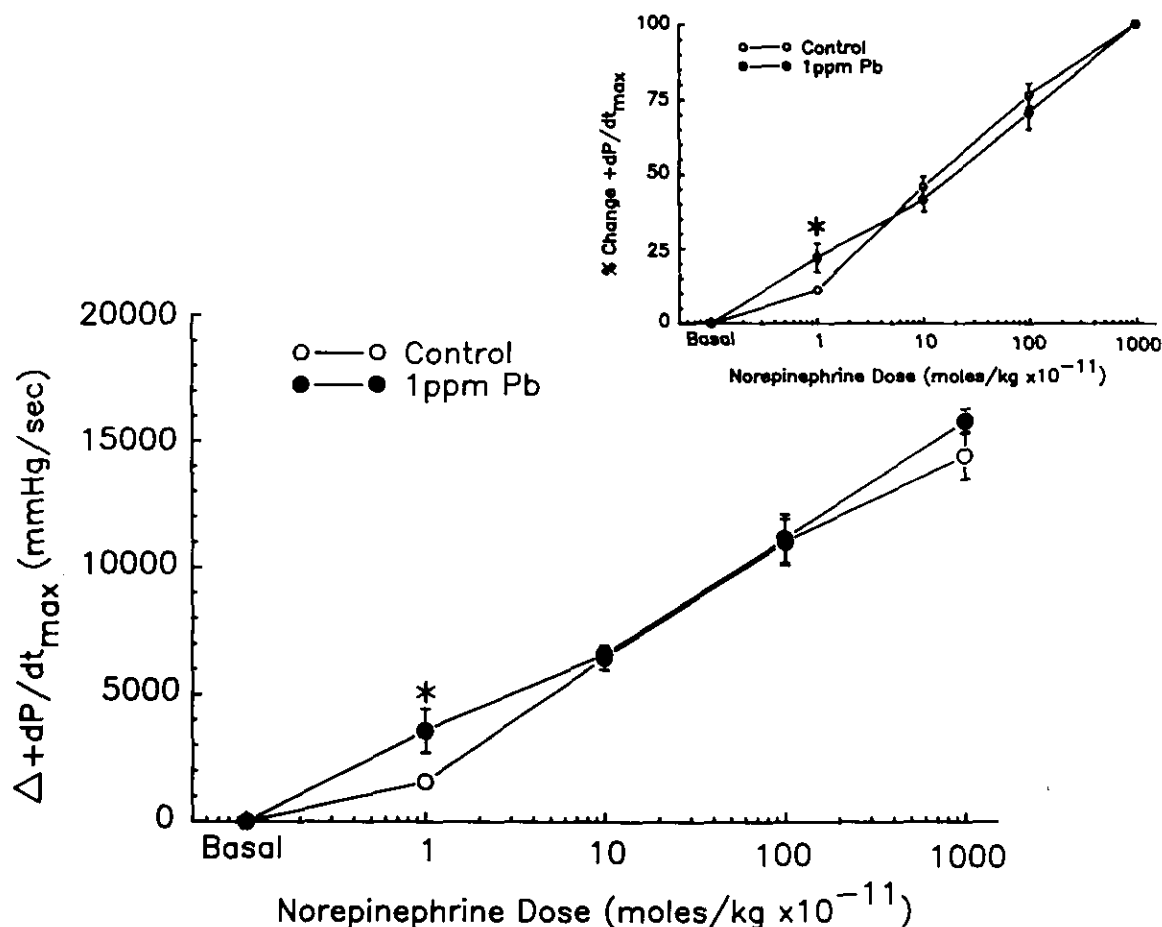
FIGURE 3. *In vivo* myocardial contractile performance as measured by the rate of change in left ventricular pressure development (+dP/dt), shown as a function of IV norepinephrine (NE) dose in rats that received either control or lead-containing (1 µg Pb/mL) drinking water for 12 months. The graph illustrates the increased responsiveness of hearts in lead-treated rats that occurred in response to the lowest, and perhaps the most physiologically relevant dose of norepinephrine administered. The inset graph presents essentially the same relationship in relative terms as percent change in contractile performance. Values represent mean ± SE for 10 rats per group; asterisk (*) $p < 0.05$.
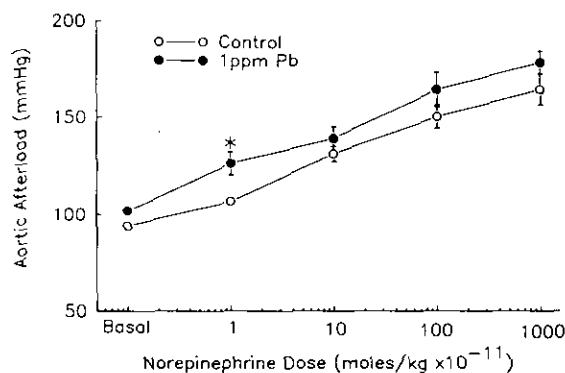

FIGURE 4. *In vivo* aortic afterload as a function of IV norepinephrine dose in the same groups of rats described in Fig. 3. In this figure aortic afterload corresponds to aortic diastolic pressure just prior to the onset of ventricular ejection. Although not shown, ventricular pulse pressure during ventricular ejection was significantly higher at the lower norepinephrine doses in the lead-treated rats as compared to the control group. Values correspond to mean ± SE for 10 rats per group; asterisk (*) $p < 0.05$.

nervating the heart. The reported electrocardiographic findings (e.g., bradycardia, heart block, slowed sinus rate with ventricular escape beats) are consistent with the interpretation that vagal tone on the heart is increased (49). This action of lead has been studied, though not extensively, at the level of the intact animal and in the isolated heart. Oral administration of lead (5 µg/mL drinking water) for 15 and 20 months has been reported to be associated with a significant slowing of atrioventricular conduction, as evidenced by prolongation of the P-R interval in the ECG (39). This effect was localized in these studies to the His-Purkinje system by His bundle electrocardiographic analysis. Atrioventricular node excitability (A-H interval), Q-S interval, and heart rate were not affected significantly by lead treatment. These *in vivo* effects of lead generally parallel those reported in isolated perfused rat heart studies (8,10). The ability of lead to depress atrioventricular conduction in the intact, denervated rat heart suggests that the reported effects of lead on cardiac excitability may involve direct actions in addition to the postulated neurally mediated mechanisms. The

susceptibility of the heart to ischemia- and catecholamine-induced arrhythmias (ectopic ventricular extrasystoles) has also been shown to be affected by chronic lead exposure (5,17,41). These effects have been demonstrated both in adult rats exposed to lead as neonates (5) and in adult rats exposed to lead (5 or 25 µg/mL drinking water) since weaning for 12 to 16 months (41). Overall, the reported actions of lead on myocardial excitability are indicative of possible lead-induced disturbances in cell membrane function and ion conductance. Further studies are needed to identify the membrane sites affected by the action of lead.

Vascular Actions

As illustrated in Figure 1, the most pervasive, and perhaps most controversial, effect of lead is its apparent effect on systemic blood pressure following chronic oral administration. The pressor effect of lead has been demonstrated over a wide range of lead doses (4,18,20, 36,39,40). The mechanistic basis for this effect has eluded discovery. It is apparent from the foregoing summary that the pressor effect of lead is not likely cardiac in origin. Instead, Webb (14) and others (11–13,15,18) have provided evidence implicating vascular sites of action. Increased in vivo vascular reactivity to α-adrenergic agonists has been reported in lead-treated rats following 7 months of exposure (14).

In addition, lead has been shown to directly induce arterial smooth muscle contraction in potassium-depolarized vascular preparations incubated with and without calcium (12,13,15). Recent studies performed in our laboratories have demonstrated lead administration to helical carotid artery strips causes an increase in basal contractile tone of vascular smooth muscle but does not significantly alter the maximal tension elicited by norepinephrine (Fig. 5). Vessels were mounted in a constant temperature (37°C) muscle chamber and equilibrated for 2 hr prior to Pb treatment in a standard physiological salt solution (PSS) aerated with 95% O_2 and 5% CO_2 (pH 7.4). Passive tension sufficient to simulate 100 mm Hg mean arterial pressure was applied to each preparation. Following equilibration, the functional integrity of each vessel
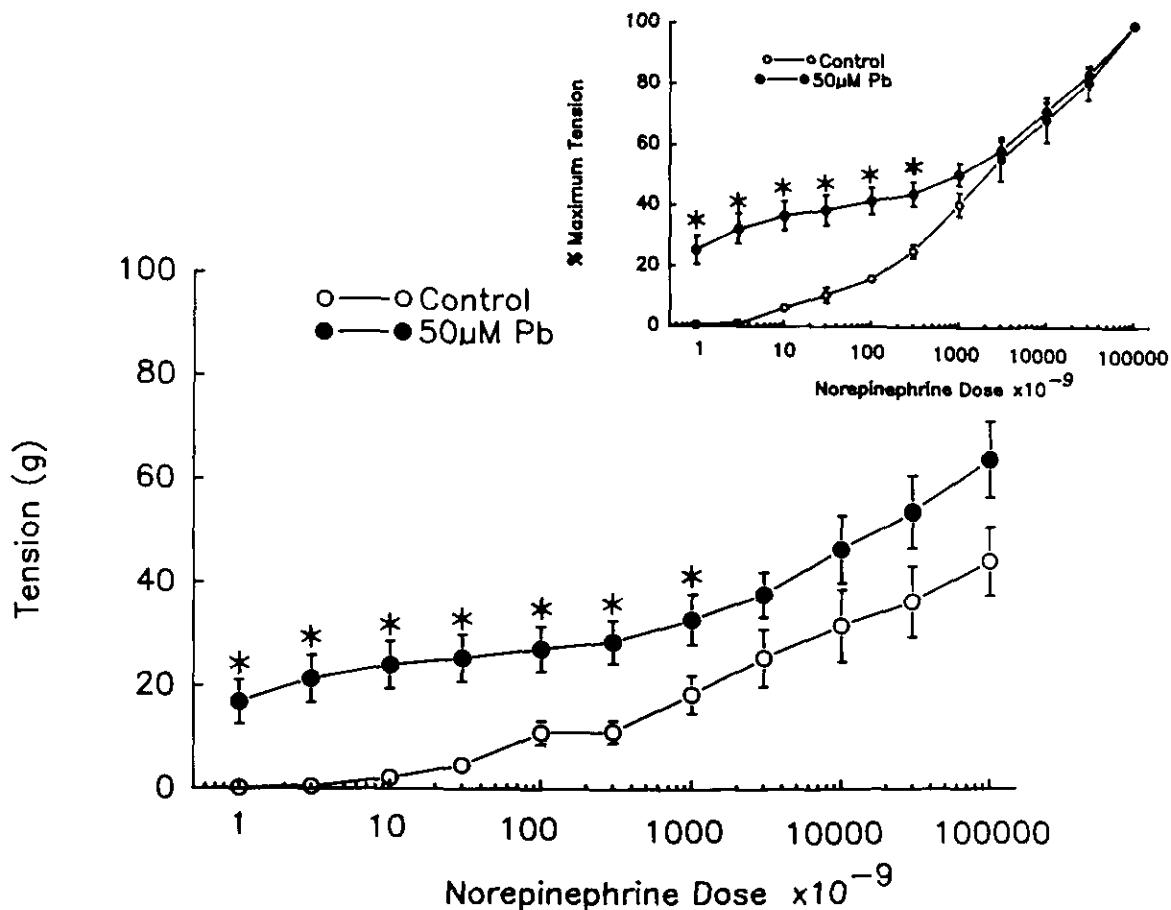

FIGURE 5. The effect of lead on the contractile function [tension and percent maximum tension (inset)] produced by isolated vascular smooth muscle strips (helically cut porcine carotid artery) in response to various norepinephrine doses. This experiment was conducted according to standard procedures (50). Values presented represent means ± SE of a minimum of six different vessels; asterisk (*) $p < 0.01$.

was assessed: tension capacity, response to 5×10^{-6} M norepinephrine; endothelial integrity, response to 1×10^{-5} M acetylcholine. Abnormally responding vessels were discarded; the remainder were incubated in either control or Pb-containing PSS for 1.5 hr and subsequently treated with norepinephrine at the doses indicated. Collectively, these *in vitro* observations support the mechanism proposed by Piccinini and co-workers (*13*), which asserts that lead inhibits cellular calcium extrusion, thereby increasing the intracellular concentration of calcium available to support contraction-coupling processes. It is conceivable that similar effects of lead *in vivo* may contribute to the reported pressor effects and enhanced vascular reactivity observed in rats subjected to chronic lead administration.

Concluding Remarks

Lead poisoning unequivocally results in significant derangements in cardiovascular function in humans and experimental animals. The cardiotoxic manifestations include depression of myocardial contractile activity, electrical disturbances, and tissue metabolic damage. The degree of cardiac involvement during episodes of lead intoxication appears to depend on the level and duration of exposure. Less certain are the effects of subclinical lead exposures on the cardiovascular system. As summarized, chronic low-level lead exposure has been shown to affect the electrical and mechanical activity of the heart and to alter vascular smooth muscle function in experimental animals. Whether lead produces similar effects in humans is unknown; however, recent findings suggest that lead may play a role in human essential hypertension. Further studies are needed that will more completely characterize the cardiovascular effects of low lead exposure, identify the factors that predispose the heart and vasculature to the actions of lead, and define the cellular and subcellular mechanisms through which lead acts to disturb the normal function and regulation of the cardiovascular system.

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