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Elevated Blood Pressure in Treated Hypertensives with Low-Level Lead Accumulation

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ABSTRACT. The relationship between blood pressure (BP) and blood lead concentration (PbB) was examined in 51 bus drivers who were treated for hypertension. These drivers were a subset of a representative sample (N = 342) of the driver population (N = ~ 2 000), and were not selected for hypertension or lead exposure. Blood lead concentrations ranged from 2–24 μg/dl (median: 6,9 μg/dl). There were 33 subjects treated primarily with diuretics, and 18 subjects were treated with beta blockers. Adjusted regression coefficients relating systolic BP with PbB were −6,4 ± 11,4 and 4,5 ± 12,9 mmHg/ln(μg/dl) in each group, respectively, but were not statistically significant. The adjusted coefficients for diastolic BP were 1,12 ± 3,89 and 14,3 ± 5,69 mmHg/ln(μg/dl) (p = 0,036), respectively. The latter relationship represents an average increment of 12 mmHg in diastolic BP over the range of observed PbBs (2,0 to 11,4 μg/dl) in subjects treated with beta blockers. Thus, beta blocker therapy may be less effective in reducing diastolic pressure in individuals with higher PbBs and suggests an action of lead at PbBs below current standards.

THE RELATIONSHIP between lead exposure and blood pressure has a long and variegated history.[1] Chronic low-level accumulation as a cause of hypertension in populations exposed via environmental contamination has only recently become a focus of study. Many studies have consistently demonstrated positive relationships between blood pressure (BP) and blood lead concentration (PbB).[2-8]

The biological plausibility of a causal relationship between lead exposure and elevated blood pressure is relatively well established as a result of animal and in vitro experimental research.[1] The most probable mechanisms suggest direct effects at the end-arteriole mediated by perturbations in intracellular calcium metabolism and indirect effects involving subtle renal dysfunction.

Animal studies indicate augmented, but opposite, effects on blood pressure with challenge from alpha agonists and from beta agonists after chronic lead exposure.[1] Thus, we suspected that within a group of sub-

jects treated with beta blockers, those having relatively high blood lead concentrations would have much higher BPs as a result of increased augmentation of a pressor effect related to unoppsed alpha stimulation of the end-arteriole. Within this group the relationship between BP and PbB would be much stronger than that observed in normotensive subjects.

Subjects and methods

Subject selection and data collection. There were approximately 2 000 drivers in the target population, which had an increased prevalence of hypertension.[9] At the time of their mandatory biennial California Department of Motor Vehicles (DMV) medical certification examination, 456 bus drivers were approached. Of these, 342 drivers agreed to participate. Complete data were obtained for 51 subjects who were undergoing treatment for hypertension. Of these, 33 were treated primarily with diuretics only, and 18 were treated with beta blockers and diuretics.

After obtaining Human Subject Committee approval, data collection began in March, 1986, and extended into November, 1986. During the course of the DMV medical examination, three blood pressure measurements were done by nurse practitioners using the standardized procedures of the second National Health and Nutrition Examination Survey (NHANES II).[10]

Data were abstracted from the clinic questionnaire and physical examination record. Participants completed an additional questionnaire either before or after their medical examination.

Blood samples were drawn either before or after the DMV examination, depending on the availability of the driver. A total of 10 ml of blood were drawn for lead analysis into sterile lead-free polypropylene plasma tubes containing Li-heparin-coated plastic beads as the anticoagulant. These tubes were stored for subsequent analysis in a freezer that was maintained at −20 °C.

Blood lead concentration analysis. Blood lead concentrations were determined using graphite furnace atomic absorption spectrophotometry techniques. Because measurement reliability can affect the likelihood of detecting relationships with other variables,[8,11] extreme care was taken to maximize analytic precision.

Each day, whole blood calibration response curves were constructed using CDC bovine blood of a known PbB. Quality control samples (CDC bovine blood standards) were measured after every second to fifth specimen. If a control sample was outside pre-established acceptable limits (i.e., 19 ± 3 μg/dl), then all preceding specimens were reanalyzed after a new calibration curve was constructed. The mean and standard deviation of these quality control samples were 18,7 and 1,28 μg/dl, respectively (N = 122).

Three analytic samples were prepared from each specimen. The third sample was analyzed only if the results of the first two samples differed by more than 10%. The two samples with the closest values comprised the reported measurements. Adjustments in sample results were made for the slight continuous downward trend in control values (within error limits) due to continuous degradation of the graphite furnace during the course of an analytical run.

The mean absolute difference between the two samples reported was 0,51 μg/dl for the entire sample group (N = 342). Five percent of these differences exceeded 1,34 μg/dl.

Twenty-two blind, external, quality controls were incorporated into the specimen collection after every 15th specimen. The mean and standard deviation of these were 4,2 and 0,9 μg/dl, respectively. There was no trend in values of these controls over the course of the analysis.

Statistical analysis. All statistical analyses were done using Statistical Analysis System (SAS) software. Multiple regression was used to analyze relationships. The focus of these analyses was to determine whether the adjusted regression coefficient relating BP and PbB was statistically significantly greater than zero, i.e., did drivers with higher PbBs have higher BPs? Models were constructed based on a priori knowledge of expected relationships of independent variables with the outcome variable—blood pressure.

A two-tailed p value of 0,05 was chosen to determine statistical significance. The logarithmic transformation of the blood lead concentration was used in these models to normalize a skewed distribution. However, the transformation imposes a nonlinear scale transformation, the validity of which has yet to be justified biologically. Results are presented in this manner for consistency with other published studies.[3-5]

Models were constructed using the average of the three BP measurements as dependent variables for both systolic and diastolic pressures. Similar results were noted if each separate measurement was used as the dependent variable. Each model included, in addition to ln(μg Pb/dl), the covariates age, the square of age, body mass index (BMI, kg/m²), sex, the interaction of BMI and sex, race, and three indicator variables reflecting infrequent/none or habitual use of caffeine, alcohol, and tobacco. These covariates represented either potential confounders of the PbB/BP relationship or independent factors related to blood pressure.[12-15]

The subset of 18 drivers who were treated with beta blockers were all males. Thus, the model included the same variables as described above except for the exclusion of those involving sex.

Results

Characterization of all drivers approached for study (N = 456) and the total sample group (N = 342) for various descriptive variables in comparison to the target population has been described previously.[8,16] The sample group appears to be representative of the target population for many variables, including BP, age, body mass index (BMI), and various proportions relating to sex, race, and the diagnosis and treatment of hypertension.

Medians, means, standard deviations, and ranges of selected variables are presented in Table 1 for each group of drivers. The univariate distribution of the average systolic and diastolic pressures, and the PbB are

Table 1.—Medians, Means, Standard Deviations, and Ranges for Selected Variables Measured on Study Subjects

Variable*	Primarily diuretic treatment (N = 33)				Beta-blocker treatment (N = 18)			
	Median	Mean	*SD*	Range	Median	Mean	*SD*	Range
Sys. BP (mmHg)	135	140,0	22,5	110–206	135	136,4	15,9	111–173
Dia. BP (mmHg)	89	90,7	10,2	73–127	85	86,4	9,01	73–109
PbB (μg/dl)	7,3	7,86	4,36	3–24,3	6,0	6,08	2,75	2–11,4
ln(PbB)	1,982	1,944	0,475	1,1–3,2	1,784	1,690	0,517	0,7–2,4
Age (y)	45,9	47,0	7,33	32,7–64,1	47,9	49,4	7,50	40,7–61,6
BMI (kg/m²)	27,9	28,1	3,06	20,9–37,9	28,6	29,6	3,61	24,6–38,6

*Sys. BP = average of the first, second, and third measured systolic blood pressures; Dia. BP = average of the first, second, and third measured diastolic blood pressures; PbB = blood lead concentration; and BMI = body mass index.

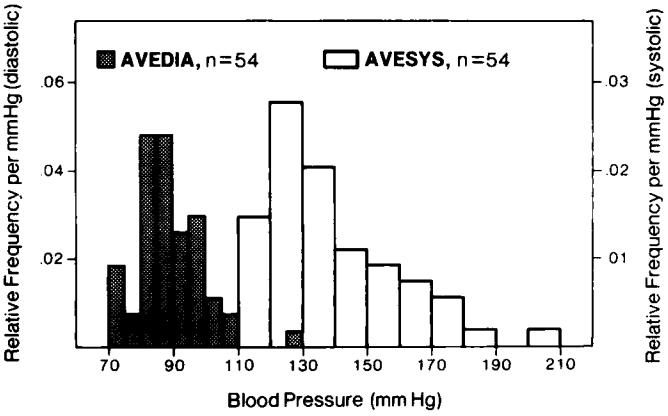

Fig. 1. Distributions of systolic blood pressure (AVESYS) and diastolic blood pressure (AVEDIA) in 54 drivers treated for hypertension with medication.

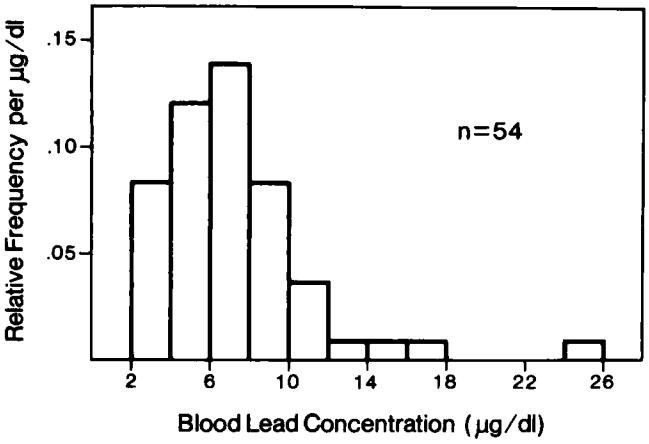

Fig. 2. Distribution of blood lead concentration in 54 drivers treated for hypertension with medication.

presented in Figures 1 and 2 for all subjects with complete data for these variables (N = 54).

Adjusted regression coefficients relating the logarithmic transformation of PbB, and systolic and diastolic BP are presented in Table 2.

The adjusted regression coefficients in subjects treated primarily with diuretics were −6,40 and 1,11 mmHg/ln(μg/dl) for systolic and diastolic pressures, respectively. Neither were statistically significant.

The adjusted regression coefficient between systolic BP and ln(μg Pb/dl) in 18 male drivers treated with beta blockers was 4,5 mmHg/ln(μg/dl) (p = 0,74). However, the coefficient was 14,3 mmHg/ln(μg/dl) (p = 0,036) for diastolic BP. This represents an average increment of 12 mmHg over the range of observed PbBs (i.e., 2,0–11,4 μg/dl). Figure 3 depicts the relationship between adjusted diastolic BP and adjusted ln(μg Pb/dl).

The mean pulse rate in subjects treated with beta blockers was much lower (66,5 ± 1,7) than that of the other group (78,7 ± 2,4). This is consistent with the expected impact of beta blockers on heart rate, and thus acts as an indicator of compliance *for the group as a whole*.

Discussion

The primary purpose of the analysis reported here was to assess the relationship between PbB and BP in bus drivers treated for hypertension. The study sample from which these drivers derive is representative of the larger bus driver population, and was not selected for either the outcome (hypertension) or the predictor (PbB).

The relationships between systolic pressure and ln(μg Pb/dl) in each group are relatively large in magnitude, but not statistically significant. Thus, we cannot be confident that a relationship exists in these groups; however, there may be inadequate statistical power to detect a relationship existing in the target population.

The regression coefficient relating diastolic pressure and PbB in beta blocker-treated subjects was statistically significant and large [14,3 mmHg/ln(μg/dl)] compared to those reported by the NHANES II study, the BRH Study [1,4 to 2,7 mmHg/ln(μg/dl)],[4,5] and our previous report of drivers who were not treated for hypertension [2,5 mmHg/ln(μg/dl)].[8]

Drivers treated with beta blockers. Results of our study of bus drivers treated with beta blockers combined with human clinical[17,18] and animal experimental[19–22] studies are consistent with the following hypothesis: low-level chronic lead exposure, catecholamines, and treatment with beta blockers having beta(2)-blocking properties interact positively with respect to diastolic BP. We propose the following two-component model (with three alternatives for the first component) regarding these interrelationships.

Table 2.—Regression Coefficient* Relating Systolic and Diastolic Blood Pressure to ln(PbB) in Drivers Treated for Hypertension Primarily with Diuretics (*N* = 33) and Beta Blockers (*N* = 18)

Dependent Variable†	Adjusted regression coefficient and SE [mmHg/ln(μg Pb/dl)]	*p* value	Residual *df*
Diuretics			
Sys. BP	−6,40 ± 11,4	0,582	21
Dia. BP	1,12 ± 3,89	0,777	21
Beta blockers			
Sys. BP	4,50 ± 12,9	0.737	8
Dia. BP	14,30 ± 5,69	0,036	8

*Adjusted for age, BMI, sex, race, and frequency of caffeine, alcohol, and tobacco use.
†Sys. BP = average of the first, second, and third measured systolic blood pressures; Dia. BP = average of the first, second, and third measured diastolic blood pressures.

First component: (a) Lead alters the end-arteriole's response to catecholamines, but not the amounts of catecholamines produced; or (b) Lead does not alter the end-arteriole's response to catecholamines, but does alter the amount of catecholamines produced; or (c) Lead alters both the end-arteriole's response to catecholamines and the amount of catecholamines produced.

Second component: Blockage of the beta(2) receptor results in unopposed stimulation of constrictor alpha receptors by endogenous epinephrine and norepinephrine. This process, in combination with one of the alternatives in the first component, acts to magnify the lead/diastolic pressure relationship.

Production of endogenous epinephrine and norepinephrine from "naturally" stressful circumstances (e.g., a mandatory medical examination) must be sufficient to have significant effects on the basal tension level in vascular smooth muscle. The net effect on the tension level depends on the amount of agents delivered to the receptors, the density and relative proportion of alpha and beta(2) receptors[23] and the degree of blockage by beta antagonists.

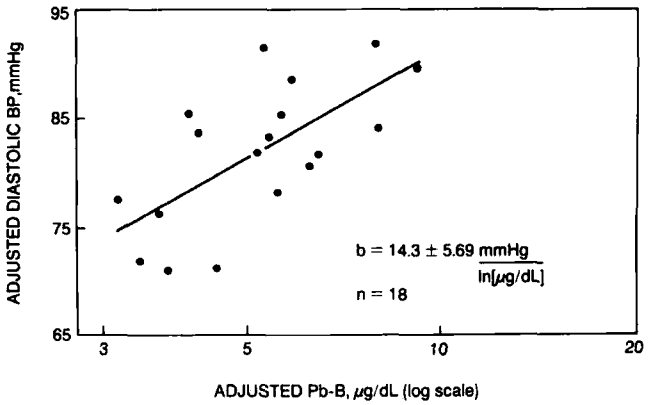

Fig. 3. Plot of adjusted diastolic BP vs. adjusted ln(blood lead concentration) in male bus drivers treated for hypertension with beta blockers. Adjusted for age, age squared, race, BMI, and frequencies of caffeine, alcohol, and tobacco use. Diastolic BP is the average of three measured diastolic blood pressures on each subject. Specific beta blockers taken by the subjects were propanolol,[10] nadolol,[1] atenolol,[5] and metoprolol.[2]

Justification for this model rests on established clinical and animal research examining relationships among BP, treatment with beta blockers, pharmacological challenge with catecholamines, and chronic low-level lead exposure. This evidence derives from two main sources.

First, clinical evidence for exaggerated alpha effects in the presence of beta blockers has been noted in hypertensive subjects treated with non-selective beta blockers.[17,18] Infusions of epinephrine or norepinephrine at various rates of delivery produce mean increases in diastolic BP varying from 5–30 mmHg. The usual response to epinephrine infusion at lower delivery rates without beta blockade is peripheral vasodilation and a drop in diastolic pressure.[18] The lower infusion rates produce plasma epinephrine levels consistent with those measured from subjects under "natural" stress.[17]

Second, animal studies suggest that chronic low-level lead exposure augments the effects of catecholamines on blood pressure. Differences in BP response[19-21] and tension generation in tail artery preparations[22] to infusion of catecholamines and other vasoactive agents between rats chronically exposed to lead and control rats were examined in these studies. Exaggerated reactions in both degree and duration of response are noted in rats chronically exposed to lead compared to controls. These findings suggest that chronic low-level lead exposure increases cardiovascular sensitivity to neurogenic mediators of BP.

Conclusions

The strong relationship between PbB and diastolic BP in male drivers taking beta blockers may have clinical ramifications. Are nonspecific beta blockers effective or indicated in people who may have sustained some type of alteration in cardiovascular function related to blood pressure control from lead accumulation *and* who are subject to continuing stressful life situations? More thorough assessment of this relationship in a clinical setting may help to establish the validity of this suggestion and its clinical implications.

These findings also suggest that beta blockers and catecholamine challenge may be useful as a means to "unmask" or "amplify" the relationship between blood pressure and lead accumulation when trying to better understand the mechanisms by which such a relationship may be mediated. If validated, it would appear that this relationship exists at very low blood lead concentrations.

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