Key messages

- Smoking habit during pregnancy is associated with lower birth weight
- The issue of weight growth in babies born to smoking mothers remains controversial
- Data obtained in this study confirm the association of smoking during pregnancy with lower birth weight
- The reduction of weight at birth, however, may be completely overcome by 6 months of age

published data^{1,2} in our sample birth weights of girls and boys born to light or heavy smokers were, respectively, 88 g, 107 g, 168 g, and 247 g lower than those of infants born to non-smoking mothers.

The deficit of weight at six months of age was reduced to +9 g for girls and -64 g for boys in children born to light smokers and to -28 g and -24 g in children born to heavy smokers. These data indicate that the deficits of weight at birth in children born to smoking mothers are overcome by 6 months of age. This trend was consistent in almost all subgroups evaluated.

The same findings have been obtained by multiple analysis of variance model. The analysis with parity and gestation considered as covariates showed that birth weight is related to mother's smoking habit; rate of growth from 0 to 6 months is higher in babies born to smoking mothers; weight differences between children born to smoking or non-smoking mothers are no longer measurable at 6 months. Weight recovery was faster in girls. Mother's age and social class were not associated with the weight of the baby.

Our data suggest that the well known effects of smoking during pregnancy on birth weight are not

permanent and that smoking in pregnancy does not affect the growth in childhood when smoking habit during pregnancy is not associated with other unfavourable variables. Future investigations on this issue should evaluate carefully the role of other factors, such as exposure to environmental smoke after birth¹⁵ and socioeconomic class.

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Pressor reactions to psychological stress and prediction of future blood pressure: data from the Whitehall II study

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Abstract

Objective—To examine whether reactions of blood pressure to psychological stress predict future blood pressure.

Design—Blood pressure was recorded at a medical screening examination after which pressor reactions to a psychological stress task were determined. Follow up measurement of blood pressure was undertaken, on average, 4.9 years later.

Setting—20 civil service departments in London.

Subjects—1003 male civil servants aged between 35 and 55 years at entry to the study.

Main outcome measure—Blood pressure at follow up screening.

Results—Reactions of systolic blood pressure to stress correlated positively with systolic blood pressure at follow up screening ($r=0.22$, $P<0.01$). The dominant correlate of follow up blood pressure was blood pressure at initial screening ($r=0.60$; $P<0.01$ between initial and follow up systolic blood pressure; $r=0.59$, $P<0.01$ between initial and follow up diastolic blood pressure). Stepwise multiple regression analysis indicated that reactions to the stressor provided minimal prediction of follow up blood pressure over and above that afforded by

blood pressure at initial screening. In the case of follow up systolic blood pressure, systolic reactions to stress accounted for only 1% of follow up variance; systolic blood pressure at initial screening accounted for 34%. With regard to diastolic blood pressure at follow up, the independent contribution from diastolic reactions to stress was less than 1%.

Conclusion—Pressor reactions to psychological stress provide minimal independent prediction of blood pressure at follow up. Measurement of reactivity is not a useful clinical index of the course of future blood pressure.

Introduction

What has come to be called the "reactivity hypothesis" considers that cardiovascular reactions to episodic psychological stress are involved in the aetiology of essential hypertension.¹⁻³ Large magnitude increases in blood pressure, heart rate, or cardiac output provoked by stress may lead, over time, to sustained increases in resting blood pressure. Some authorities remain sceptical⁴ and the precise character of the risk conferred by cardiovascular hyperreactivity

remains a matter of speculation,³ but the reactivity hypothesis continues to receive much attention.⁵

People vary distinctly in the magnitude of their cardiovascular reactions to psychological stress, and individual reactivity profiles are typically stable over time.^{6,7} Furthermore, people known to be at increased risk for hypertension, as a result of parental blood pressure or increased, although subhypertensive, resting blood pressures, show greater cardiovascular reactions to psychological stress than people at lower risk.⁸⁻¹¹ Of the relatively few prospective studies which have been completed, most have measured cardiovascular reactivity to a cold pressor procedure, which conventionally entails immersion of the hand in 4°C water for one minute. These studies have yielded contradictory findings. A positive relation between reactions of blood pressure to a cold pressor test and subsequent hypertensive state has been found and has been observed to persist even when resting blood pressure at study entry is considered,^{12,13} but several other prospective studies have failed to find such an association.¹⁴⁻¹⁷ Studies exploring the relation between reactions to the cold pressor test and subsequent incidence of coronary heart disease yield a similarly contradictory picture.^{18,19}

Several commentators have argued that cold pressor procedures are far from optimal in this context.^{3,11} Firstly, as originally conceived and propagated,^{1,2} the reactivity hypothesis has as its focus cardiovascular reactions to active mental stressors rather than passive physical ones like the cold pressor. Secondly, the cold pressor test would seem to be a poor analogue of everyday stress.²⁰ This indicates a need for prospective studies entailing active mental stressors. To date, five such studies have been published, but all suffer from low power.²¹⁻²⁵ We report here the first large scale prospective study of the relation between reactions of blood pressure to an active mental stressor and subsequent blood pressure.

Methods

SUBJECTS

The parent population for this investigation was 10 308 London based civil servants (6895 men, 3413 women) aged 35 to 55 years who attended a medical screening as part of the Whitehall II study. This represented 73% of all eligible civil servants. Full methodological details have been reported elsewhere.²⁶ At the screening, blood pressure was measured twice in the sitting position after five minutes' rest by using a Hawksley random zero sphygmomanometer. After the first 20% had been screened, every fourth man at screening was selected to participate in a stress testing session. Of those selected, 1389 agreed to participate.

Summary of study design, indicating timing and derivation of key blood pressure measures

Women were excluded because of the possibility that fluctuations in the menstrual cycle would affect cardiovascular reactions during stress testing.²⁷

Equipment failure and other technical problems resulted in the loss of data on 79 subjects. A further 80 who registered blood pressures in the hypertensive range ($\geq 160/100$ mm Hg) at initial screening or were taking antihypertensive drugs or drugs that lower blood pressure were eliminated from the study. This left an effective sample size of 1230. Follow up screening was conducted 3.9 to 7.2 years after the initial stress test; 1003 subjects in the effective sample were available for rescreening, and blood pressure was determined in the same manner as at the initial examination. The mean (SD) length of follow up was 4.9 (0.45) years.

APPARATUS

Blood pressure during the stress testing was recorded by using a Copal (UA251) automatic digital sphygmomanometer. Previous research has shown the Copal to be an accurate and reliable monitor.^{28,29}

Raven's matrices served as the mental stress task. This challenge provokes sizeable increases in cardiovascular activity while requiring little in the way of physical energy expenditure.³⁰ Problems were selected from sets A, B, C, D, and E.³¹ The matrices were reproduced as slides and presented by a carousel projector. Timing was controlled by means of a BBC microcomputer and a locally fabricated interface. Individual problems were presented for 10 seconds, within which time the subject had to select the correct solution from the alternatives displayed; choice of solution was signified by pressing the appropriate numerical key on the microcomputer keyboard. Slide change took one second. In all, 34 matrix problems were presented. Finally, all subjects received through standard headphones four blasts of 3 seconds of white noise; these were synchronised to immediately precede four of the more difficult matrix problems; timing of the white noise was identical for all subjects and independent of their response.

PROCEDURE FOR STRESS REACTIVITY TESTING

On arrival at the laboratory, subjects were seated in a comfortable chair. The blood pressure cuff was attached and a first reading taken; this was not used in the analysis reported here. Subjects were then asked a series of routine questions about recent consumption of food, alcohol, and tobacco and given five minutes in which to relax; a further blood pressure reading was taken at the end of this period. Another three minutes of relaxation followed, at the end of which time another blood pressure reading was taken; the average of these last two readings served as the laboratory baseline. The nature of the task and the response requirements were then explained to subjects and an example of a matrix problem projected by way of illustration. Subjects were also instructed that the computer would keep a running count of their performance; if it fell below an unspecified criterion, a short burst of white noise would be delivered through headphones. As indicated, in reality noise delivery was preprogrammed and independent of performance. Four evenly spaced measurements of blood pressure were taken during the 3rd, 11th, 19th, and 27th slides.

DATA REDUCTION AND ANALYSIS

Analysis focused on initial screening blood pressures (taken as the average of the two initial screening measures); laboratory baseline blood pressure; blood pressure reactivity (average blood pressure during stress tasks minus laboratory baseline pressure); and follow up screening blood pressure (again, the average of the two follow up screening readings). The figure

illustrates the schedule of these measurements and their derivation. Analysis was by correlation and stepwise multiple regression. Initial concern lay with whether blood pressure at initial screening and laboratory baseline blood pressure predicted blood pressure reactivity. After this, focus shifted to the issue of whether blood pressure reactivity predicted follow up screening blood pressure and, most critically, whether it did so independently of blood pressure at initial screening.

As indicated, the main representation of reaction of blood pressure to stress was the simple arithmetic difference between average blood pressure during the stress task and laboratory baseline blood pressure. This index of reactivity has been utilised in most studies on reactivity of blood pressure to date.^{32,33} This index may be susceptible, however, to the well known problems involved in relating change in a variable to initial values.^{34,35} Therefore, we used three additional methods of representing reactivity to test the robustness of the findings determined by the standard method. Firstly, we used absolute blood pressure during the stress task. Secondly, analyses were performed by using the residuals from a regression of blood pressure during the stress task on laboratory baseline blood pressure. This indexes the degree to which blood pressure during the task is above or below that which would be predicted on the basis of knowledge of baseline blood pressure. By definition, the residuals so computed are uncorrelated with laboratory baseline blood pressure. Thirdly, we represented change in blood pressure as the residual obtained from the regression of change score on the mean of the laboratory baseline and stress task values.

Results

DEMOGRAPHIC CHARACTERISTICS

The mean (SD) age of the subjects at entry was 44.1 (5.92) years. The distribution of participants among the various occupational grades within the civil service closely reflected that of men in the parent sample.²⁶ Subjects were allocated to one of six categories of

employment; category 1 comprised the highest status jobs, category 6 the lowest. Table I gives the proportion in each of the six categories, along with the corresponding percentage distribution for men in the parent sample.

INITIAL SCREENING BLOOD PRESSURE AND LABORATORY BLOOD PRESSURE REACTIVITY

Table II lists the average systolic and diastolic blood pressures at the initial screening and the average laboratory baseline blood pressures. Table II also shows that the active psychological stressor provoked substantial reactions in blood pressure. Table III summarises the associations between initial screening blood pressure and laboratory baseline blood pressure, and reactions to the stressor. Reactions of systolic blood pressure to stress correlated positively with both initial screening and laboratory baseline blood pressure, and the relation held for both systolic and diastolic pressure. In contrast, reactions of diastolic blood pressure to stress showed no such association; indeed the only reliable correlation was between reactivity and laboratory baseline diastolic blood pressure, and that was negative.

PREDICTORS OF BLOOD PRESSURE AT FOLLOW UP

Table II also presents the average systolic and diastolic blood pressure at follow up. Matched pairs *t* tests, computed to compare initial and follow up measurements, showed that whereas diastolic blood pressure was reliably higher at follow up ($P < 0.01$), systolic blood pressure had not changed significantly ($P = 0.16$). Table III summarises the outcomes of the bivariate correlation analysis to illuminate predictors of follow up measurements, inspection of which indicates substantial associations between blood pressure at initial screening and laboratory baseline blood pressure on the one hand and blood pressure at follow up on the other. Reactivity of systolic blood pressure predicted blood pressure at follow up, although more modestly; the coefficients for reactivity of diastolic blood pressure were close to zero.

Stepwise multiple regression techniques were then applied to these data to determine the independent contribution of reactions to stress to the prediction of follow up blood pressure. Age at entry to the study was entered at step one in these analyses as bivariate correlation indicated that age at entry was positively associated with follow up blood pressure ($r = 0.16$, $P < 0.01$ for follow up systolic blood pressure $r = 0.14$, $P < 0.01$ for follow up diastolic blood pressure). Age was also significantly correlated with reactivity of systolic blood pressure ($r = 0.15$, $P < 0.01$) and, to a lesser extent, with reactivity of diastolic blood pressure ($r = 0.06$, $P < 0.05$). Length of follow up, however, was not associated with either systolic or diastolic blood pressures at follow up ($r = 0.05$, $P = 0.10$ in both instances), and its inclusion did not materially alter the outcome of the analyses. Accordingly, the analyses reported here do not include length of follow up.

With regard to systolic blood pressure at follow up,

TABLE I—Percentage of participants in each employment category for study sample and parent sample

Sample	Category of employment						Total
	1	2	3	4	5	6	
Parent sample	14.9	23.6	17.8	21.7	12.8	9.3	6895
Study sample	13.9	24.3	17.4	23.8	12.2	8.4	1003

($\chi^2 = 4.87$, $P = 0.43$)

TABLE II—Mean (SD) of key blood pressure variables (in mm Hg)

Variable	Systolic blood pressure	Diastolic blood pressure
Initial screening	122.8 (12.74)	77.3 (9.23)
Laboratory baseline	120.4 (13.54)	77.6 (10.72)
Reactivity	20.4 (9.82)	8.0 (5.87)
Follow up screening	122.3 (13.01)	81.8 (9.20)

TABLE III—Correlations among key blood pressure measures

Measure	Initial screening		Laboratory baseline		Reactivity		Follow up screening systolic blood pressure
	Systolic blood pressure	Diastolic blood pressure	Systolic blood pressure	Diastolic blood pressure	Systolic blood pressure	Diastolic blood pressure	
Initial screening diastolic blood pressure	0.64**						
Laboratory baseline:							
Systolic blood pressure	0.70**	0.53**					
Diastolic blood pressure	0.43**	0.66**					
Reactivity:			0.64**				
Systolic blood pressure	0.25**	0.17**	0.12**	0.11**			
Diastolic blood pressure	0.01	0.05	-0.05	-0.14**	0.31**		
Follow up systolic blood pressure	0.60**	0.47**	-0.58**	-0.39**	0.22**	0.04	
Diastolic blood pressure	0.43**	0.59**	0.41**	0.51**	0.13**	0.05	0.72**

the following variables, in addition to age, entered the equation: systolic blood pressure at initial screening, laboratory baseline systolic blood pressure, reactivity of systolic blood pressure, and diastolic blood pressure at initial screening. Table IV shows that age and systolic blood pressure at initial screening together accounted for 36% of the variation in systolic blood pressure at follow up. Laboratory baseline systolic blood pressure contributed an additional 5%. While reactivity of systolic blood pressure entered the equation, it accounted for only an additional 1% of the variance not explained by the two resting measures. In a model which did not include laboratory baseline systolic blood pressure, reactivity of systolic blood pressure still accounted for less than 1% of additional explained variance ($R^2 < 0.01$; $\beta = 0.77$; 95% confidence interval 0.10 to 1.44; $P < 0.05$).

Table V gives the outcome of a similar regression analysis of diastolic blood pressure at follow up. Again, it was diastolic blood pressure at initial screening which, after age, entered the equation first, accounting for an additional 32% of the variance in diastolic blood pressure at follow up. Reactivity of diastolic blood pressure entered the regression equation but accounted for only an additional 0.4% of additional variance. With laboratory baseline diastolic blood pressure excluded from the model, diastolic reactivity was no longer significantly associated with diastolic blood pressure at follow up ($R^2 < 0.01$; $\beta = 0.44$; 95% confidence interval -0.07 to 0.95; $P = 0.09$).

USE OF ALTERNATIVE INDICES OF REACTIVITY OF BLOOD PRESSURE

As described in the methods, we analysed the data by using three other indices of reactivity of blood pressure. The outcomes of these analyses did not change the conclusion that reactivity contributes little to the prediction of future blood pressure. Full details and results of these analyses can be obtained from the first author.

Discussion

In line with previous research³⁰ the Raven's matrices stressor used in our study provoked increases in cardiovascular activity. In addition, our findings that blood pressure at screening and laboratory baseline blood pressure correlated positively with reactions of systolic blood pressure to mental stress complements previous studies that showed larger systolic blood pressure reactions to stress in subjects with hypertension or borderline hypertension relative to unambiguously normotensive controls.¹¹

This association, however, was particular to reactivity of systolic blood pressure. Diastolic reactivity was either unrelated to resting blood pressure or, in the case of laboratory baseline diastolic blood pressure, negatively related. The relative insensitivity of diastolic reactivity in this regard may reflect the somewhat modest reactions provoked by our stress task. Others have found that reactions of diastolic blood pressure to active mental stressors fail to discriminate between normotensive subjects and subjects with high resting blood pressures.^{10,36} The negative correlation between laboratory baseline blood pressure and diastolic reactivity may indicate that subjects whose diastolic blood pressure had decreased most during a relatively prolonged laboratory baseline rest period had more scope for increase during stress. This interpretation receives support from the observation that the correlation between systolic reactivity and laboratory baseline systolic pressure was lower than that between systolic reactivity and systolic blood pressure at initial screening.

With regard to blood pressure five years on, re-

TABLE IV—Predictors of follow up screening systolic blood pressure

Variable	Contribution to R^2	β (95% confidence interval)	P value
Age	0.02	0.97 (0.34 to 1.60)	< 0.01
Initial screening systolic blood pressure	0.34	3.86 (2.88 to 4.84)	< 0.01
Laboratory baseline systolic blood pressure	0.05	3.99 (3.07 to 4.91)	< 0.01
Reactivity of systolic blood pressure	0.01	1.09 (0.44 to 1.74)	< 0.01
Initial screening diastolic blood pressure	< 0.01	1.20 (0.40 to 2.00)	< 0.01

R^2 = Proportion of variance in systolic blood pressure at follow up accounted for.

β = Change in systolic blood pressure at follow up associated with 1 SD difference in variable.

TABLE V—Predictors of follow up screening diastolic blood pressure

Variable	Contribution to R^2	β (95% confidence interval)	P value
Age	0.02	0.14 (-0.33 to 0.61)	0.56
Initial screening diastolic blood pressure	0.32	3.41 (2.70 to 4.12)	< 0.01
Laboratory baseline diastolic blood pressure	0.02	2.12 (1.49 to 2.75)	< 0.01
Initial screening systolic blood pressure	< 0.01	0.87 (0.28 to 1.46)	< 0.01
Reactivity of diastolic blood pressure	< 0.01	0.55 (0.08 to 1.02)	< 0.05

R^2 = Proportion of variance in diastolic blood pressure at follow up accounted for.

β = Change in follow up screening diastolic blood pressure associated with 1 SD difference in variable.

activity of systolic blood pressure emerged from the bivariate correlation analysis as a positive predictor of both systolic pressure and diastolic pressure at follow up; diastolic reactivity was unrelated to either. The best predictors of blood pressure, both systolic and diastolic at follow up, were the initial screening values. Reactivity of systolic blood pressure accounted for only 1% of the variance of systolic blood pressure at follow up in a multiple regression model that included initial screening and baseline laboratory systolic blood pressure. For diastolic blood pressure at follow up, reactivity accounted for even less of the variance.

REACTIVITY AND PREDICTION

Our findings seem to be at odds with those reported from the other smaller scale prospective studies that used active mental stressors. In two of these, however, the authors did not attempt to establish the independent predictive contribution for reactivity.^{21,22} In our study systolic blood pressure at initial screening was associated with reactivity of systolic blood pressure, and, importantly, reactivity of systolic blood pressure considered in isolation provided reasonable prediction of systolic blood pressure at follow up. As indicated, though, when resting blood pressure measurements were entered into the regression analysis, systolic reactivity afforded only minimal additional prediction. Accordingly, the positive conclusions drawn by previous researchers could simply reflect the failure of their analyses to take account of initial blood pressure. This criticism, however, cannot be levelled at the three other studies.²³⁻²⁵

In one study blood pressure was recorded 10-15 years after initial exposure to a stressor in a sample of initially normotensive young men.²³ Baseline systolic blood pressure at outset was the best predictor of subsequent resting systolic blood pressure. Nevertheless, a model which included reactivity of systolic blood pressure to the stressor added to the prediction of final resting systolic blood pressure. The most successful predictive model of final diastolic pressure was a combination of initial baseline diastolic blood pressure and reactivity of heart rate and diastolic blood pressure. The small sample size, however, limits the confidence which can be placed in the outcome of

speculative regression analyses of the sort undertaken. It is also important to note that across the 10-15 years' follow up the average resting systolic blood pressure remained unchanged. In this respect these data parallel those reported here and accordingly make it difficult to attribute the fragility of our systolic reactivity effects to the absence of overall change in systolic blood pressure between screenings. We observed that diastolic blood pressure, unlike systolic blood pressure, was reliably higher at follow up, a result that also accords with their data. As indicated, however, in our study diastolic reactivity possessed even less predictive significance than systolic reactivity.

In another pertinent study,²⁴ blood pressure was measured at rest and during the playing of a video game in an effective sample of 477 children aged 9.²⁴ Follow up assessment of blood pressure was at one year, by which time resting systolic and diastolic pressure had unexpectedly increased by 8 mm Hg and 4 mm Hg, respectively. In addition, reactivity emerged from multiple regression as a predictor when represented as blood pressure during the stress but not when depicted, in the conventional fashion, as change in blood pressure—that is, the difference between the blood pressure during stress and laboratory baseline blood pressure. Blood pressure during stress is obviously confounded by laboratory baseline blood pressure.

In the most recent published prospective study, blood pressure was measured 6.5 years after testing of mental stress in an effective sample of 182 middle aged adults and their 143 school age children.²⁵ Though the authors conclude that “mental stress-induced blood pressure changes provide a unique marker of future risk of hypertension,” their analyses show that, when corrected for age, body mass index, and, importantly, initial blood pressure, the amount of variance in follow up blood pressure predicted by reactivity was modest; in adults the contribution ranged from 2% to 6%, depending on the blood pressure measurement and the mental stress task.

STUDIES USING COLD PRESSOR TEST

Our results also contrast with the positive findings reported from two large scale prospective studies that used cold pressor procedures.^{12,13} Although several other cold pressor studies have failed to find effects,¹⁴⁻¹⁷ these two are of sufficient size to merit serious consideration. Both report that reactions of systolic but not diastolic blood pressure to the stressor predict eventual hypertensive state independently of initial resting blood pressure. In one of these studies,¹³

however, a follow up recovery rate of less than 50% and the lack of a uniform criterion for characterising the reactivity of subjects are recognised weaknesses.³⁷ These criticisms do not apply to the other study.¹² Nevertheless, the independent relation obtained between reactivity of systolic blood pressure and the self reported hypertensive state of physician subjects was dependent on age and length of follow up. Unless age and length of follow up were taken into account no independent association emerged. Essentially, the relation between incidence of hypertension and cold pressor reactivity was more distinct for those who reported hypertension before the age of 45 years. In addition, subjects were initially stress tested at an average age of 23 years, and at least 20 years of follow up would seem to be required before stress reactivity emerges as an independent predictor. Accordingly, it is possible that in our study stress testing was undertaken at too late an age or subjects were followed up for too little time to yield predictive dividends. Longer follow up will allow us to study the second of these two issues. At present, however, measurement of reactivity of blood pressure cannot be advocated as a useful clinical index of the course of future blood pressure. Our findings seriously question an important role for reactivity in the aetiology of hypertension.

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Key messages

- Resting laboratory blood pressure offers no advantage over casual blood pressure with regard to predicting blood pressure five years later
- Reactions of blood pressure to psychological stress are less predictive of future blood pressure than either resting laboratory or casual blood pressure
- Reactions of blood pressure to psychological stress afford minimal prediction of future blood pressure independently of initial blood pressure
- Reactions of blood pressure to stress cannot be advocated as a useful clinical index of the course of future blood pressure
- Reactions of blood pressure to psychological stress may have little or no role in the aetiology of hypertension

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Surgical bleeding: unexpected effect of a calcium antagonist

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Calcium antagonists are among the most commonly used cardiovascular drugs. They have received regulatory approval for their antianginal and anti-hypertensive actions. While these agents provide appreciable improvement in symptoms in patients with angina pectoris, they have not yet been shown to prevent fatal and non-fatal cardiovascular events. Indeed, evidence suggests an adverse effect in survivors of myocardial infarction and in patients with angina.¹

Speculation about a neuroprotective effect of calcium antagonists is based on the observation of an excessive influx of calcium at the time of neuronal death. This postulated mechanism, together with vasodilation, formed the theoretical basis for a clinical trial in patients undergoing replacement of a cardiac valve. It has been documented that patients placed on cardiopulmonary bypass are subject to arterial microemboli.² The recognised clinical consequences of this phenomenon are neurological, neuro-ophthalmological, and neuropsychological deficits ranging from transient psychomotor deficits to stroke.

Methods and results

We performed a randomised, placebo controlled, double blind clinical trial of patients undergoing replacement of a cardiac valve to test whether nimodipine, a dihydropyridine, in a dose of 30 mg started 12 hours before surgery and given for five days four times a day would reduce the combined incidence of neurological, neuroophthalmological, and neuropsychological deficits over six months compared with placebo. Anticipating that at least half of the patients would experience one or more of these deficits, we estimated the sample size of this single centre trial at 400, with 90% power for detecting a 17% difference ($\alpha=0.05$) in deficit rates. Randomisation was balanced within surgeon.

From an interim analysis of 149 enrolled patients, an independent monitoring committee recommended suspension of recruitment due to an excess mortality in the patients receiving nimodipine compared with those receiving placebo (8/75 (11%) *v* 1/74 (1%) (small sample odds ratio: 8.6; 95% confidence interval 1.1 to 392)). Comparison of over 50 preoperative variables (demographics, functional state, medical history, and

haemodynamics) showed only minor imbalances between the two groups. Major bleeding seemed to occur often so we undertook a detailed review. Bleeding was defined as major if the patient (a) needed more than 10 units of blood products during the operation or (b) had a postoperative chest tube drainage exceeding 2400 ml in the first 24 hours.³ Twelve patients met this criterion (two (3%) in the group receiving placebo, 10 (13%) in the group receiving nimodipine (Fisher's exact test, $P=0.03$)). Six of the nine deaths (five in patients receiving nimodipine and one in a patient receiving placebo) occurred among the patients with major bleeding. Four of the six deaths were a direct result of blood loss despite transfusion: one patient receiving placebo died from surgical trauma during repeat sternotomy, and two of the remaining three patients who died (who were all receiving nimodipine) had pre-existing blood disorders (chronic lymphocytic leukaemia, thrombocytopenia). The remaining two deaths among the six patients with major bleeding occurred in patients receiving nimodipine at 31 and 162 days due to multiple organ failure associated with appreciable blood loss. In two of the remaining three deaths (all due to multiple organ failure) that did not meet the criterion for major bleeding, bleeding was a possible contributing cause of death.

Comment

This observation of major surgical bleeding associated with a calcium antagonist has not been reported previously. Calcium antagonists have been linked, however, with increased frequency of intracerebral haemorrhage among survivors of myocardial infarction given thrombolysis ($P=0.009$)⁴ and with increased blood loss from ear incisions in a rabbit model ($P=0.003$).⁵ The bleeding may be the result of vasodilation promoted by the calcium antagonists or by the drugs' known antiplatelet action.⁶ This unexpected finding, observed in a post hoc analysis, requires further exploration. Until definitive data are available it seems prudent to evaluate carefully the use of dihydropyridines in the perioperative period.

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