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Hypoxia-induced cardiac hypertrophy in rabbits treated with verapamil and nifedipine

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1 Young rabbits were exposed, eight at a time, to 310 h of hypoxia (O_2 at 70–80 torr), at atmospheric pressure. The animals were injected with 1 mg kg^{-1} nifedipine (F) or 5 mg kg^{-1} verapamil (V) or an equivalent volume of the vehicle (H) (Cremophor EL), i.p. twice a day. A fourth group (N), also injected with vehicle, was not made hypoxic.

2 The animals were from 6 litters, 6 rabbits in each litter, and were distributed so that every group had litter mates in the other groups.

3 Right ventricular hypertrophy was induced in all the hypoxic groups (H, + 39%; V, + 46%; F, + 44%). Differences between groups were not statistically significant, but all were significantly hypertrophied relative to their normoxic litter mates (N). The right atria were less hypertrophied (H, + 3.6%; V, + 20%; F, + 21.6%), but there was no left ventricular or left atrial hypertrophy.

4 There was also a small increase in haematocrit in the hypoxic groups (H, + 20.6%; V, + 17.5%; F, + 28.8%).

5 The doses administered were equivalent to the highest used clinically producing blood levels of verapamil and nifedipine within or above the clinical range and had no effect on the development of cardiac hypertrophy.

Introduction

Cardiac muscle hypertrophies as an adaptive response to a number of stimuli. Although the hypertrophy is usually accompanied by an increase in DNA, it has long been recognised (Alpert, 1971) that, at least in adult hearts, hyperplasia is confined to connective tissue, and that the hypertrophy represents an increase in the mass, but not in the number, of contractile myocardial cells. After a myocardial infarction there is evidence that the uninvolved ventricular muscle can hypertrophy to compensate for the loss of the dead region (Gould, Lipscomb, Hamilton & Kennedy, 1973). Several trials have demonstrated that prolonged treatment of post-infarction patients with β-blocking drugs can provide some protection against reinfarction and sudden death. Indeed the evidence is now so convincing that further blind trials could be regarded as unethical, because patients on placebo would be deprived of the benefits of therapy (Chamberlain, 1983).

However, there is evidence that prolonged treatment of young animals with β-blockers retards cardiac growth in relation to body weight (Vaughan Williams, Raine, Cabrera & Whyte, 1975), and that in human infants with hypertrophic cardiomyopathy prolonged β-blockade may arrest the hypertrophy (Shand, Sell & Oates, 1971). It is probable that many causative and permissive factors are concerned in stimulating cardiac hypertrophy but in recent years it has been suggested that release of adrenaline and/or some other trophic factor from sympathetic nerves provides the final link in the chain (Östman-Smith, 1981). If this were so, treatment of post-infarction patients with β-blockers could inhibit compensatory hypertrophy of the surviving myocardium, but in a previous paper (Dennis & Vaughan Williams, 1982) it was shown that much larger than clinical doses of the β-blockers atenolol (cardio-selective) and propranolol (non-selective) did not inhibit the right ventricular hypertrophy induced by hypoxia. The hypertrophy could, of course, have been triggered by some non-adrenergic influence released from sympathetic nerve endings and this possibility could only be tested by destruction of the nerves themselves. Chemical sympathectomy with guanethidine or 6-hydroxydopamine, however, had no effect on hypoxically induced ventricular hypertrophy (Vaughan Williams & Dukes, 1983).

It is clearly important that drugs used to treat

patients should not inhibit compensatory cardiac hypertrophy and so far as antisympathetic compounds are concerned, the evidence suggests that there is no reason to believe they would be deleterious. Verapamil, nifedipine and other drugs loosely termed 'calcium antagonists' are used for the treatment of angina pectoris and hypertension, sometimes in association with ischaemic heart disease. It seemed worthwhile, therefore, to investigate whether verapamil or nifedipine could inhibit hypoxically-induced hypertrophy, employing the methods already developed to study the effects of antisympathetic agents (Dennis & Vaughan Williams, 1982; Vaughan Williams & Dukes, 1983).

Methods

Hypoxia

Four cages were enclosed in a box supplied with streams of air and nitrogen, the method being as previously described. Temperature was maintained between 19 and 23°C. Air from the box was sampled continuously, and its O_2 content monitored by a Radiometer O_2 meter. The door was opened twice daily, for injection of the rabbits. Weighing the animals and their food, and cleaning the cages, took less than an hour, so that, overall, it was possible to maintain for about 22 h per day, at atmospheric pressure, hypoxia (70–80 torr) equivalent to an altitude of approximately 6000 m (73 torr at 6096 m).

Six litters containing six rabbits were used. Three groups of rabbits, each group containing animals from two litters, were exposed eight at a time to prolonged periods of hypoxia. There were two animals per cage, one from each litter, disposed as follows: (1) hypoxic controls, treated with cremophor-saline; (2) verapamil-treated; (3) nifedipine-treated; (4) one verapamil and one nifedipine treated. One verapamil-treated rabbit jammed its head under the food container, causing injury, and was destroyed. The hypoxic totals were thus: controls (H) 6, verapamil (V) 8, and nifedipine (F) treated 9. The remaining 12 animals, the heaviest and lightest from each litter, served as normoxic controls.

Verapamil and nifedipine were dissolved in a mixture of cremophor EL at 70°C diluted with saline to a final concentration of 25% (v/v). The nifedipine solutions were made up in the darkroom. Injections of 5 mg kg^{-1} verapamil, 1 mg kg^{-1} nifedipine, or an equivalent volume of vehicle to hypoxic and normoxic controls were given i.p. while the solution was still warm, every morning and evening for 14 days. The hypoxic animals were exposed to their hypoxic envi-

Table 1 Food consumption and growth of hypoxic rabbits treated with verapamil or nifedipine compared with those of normoxic and hypoxic controls

Day:	n	3	5	7	9	11	13	*Mean total weight gained*
A *Food consumption*								
Normoxic controls (N)	12	103 (7.4)	102 (14.8)	114 (10.8)	86 (12.2)	90 (14.3)	105 (5.9)	+573
Hypoxic controls (H)	6	100 (2.6)	85 (10.5)	84 (8.2)	60 (28.0)	106 (14.2)	75 (10.1)	+348
Verapamil -treated (V)	8	79 (7.1)	80 (9.9)	85 (1.3)	81 (6.4)	67 (18.0)	73 (5.6)	+254
Nifedipine -treated (F)	9	78 (9.2)	58 (20.5)	52 (2.3)	98 (11.4)	76 (20.9)	85 (11.7)	+290
B *Growth* (Daily weight gain)								*Final weights*
(N)		57 (10.3)	33 (4.8)	43 (2.2)	30 (2.6)	38 (4.3)	43 (5.1)	1455 (62)
(H)		37 (4.3)	23 (13.0)	19 (8.0)	23 (5.3)	19 (16.2)	23 (7.1)	1172 (74)
(V)		32 (4.3)	13 (6.3)	22 (10.0)	24 (4.4)	−1 (10.5)	25 (7.2)	1166 (58)
(F)		17 (5.8)	18 (7.5)	16 (6.5)	22 (6.5)	12 (15.2)	18 (5.9)	1208 (34)

Values are mean ± s.e.mean; given as g day^{-1} per rabbit.

ronment for a total of 310 h.

At the termination of the experiment the animals were given 100 units heparin-saline i.v., and were stunned. Their hearts were rapidly removed after 2 ml of blood had been withdrawn by cardiac puncture. The four chambers were dissected, and weighed wet and dry as previously described. Blood was also taken from another group of control animals of similar age at various times after i.p. injections of verapamil and nifedipine. After centrifugation the plasma was kept in the deep freeze in tubes wrapped in aluminium foil, and was eventually sent for analysis of plasma levels of verapamil and nifedipine.

The statistical significance of differences was calculated from the raw data by Student's *t* test. Drugs used: verapamil HCl was a gift from Abbott laboratories, and nifedipine was a gift from Bayer.

Results

Food consumption and growth

The mean initial weights (± s.e.mean) in g of the two control groups were: normoxic 882 (42), hypoxic (H) 824 (23); and of the hypoxic treated groups, verapamil (V) 912 (41) and nifedipine (F) 918 (22). The mean daily food consumption and growth rates are presented in Table 1. As previously observed, the hypoxic animals ate rather less than their normoxic litter mates, the cumulative effects resulting in the final weights of the hypoxic animals being significantly reduced ($P < 0.001$). Nifedipine also seemed to have a small additional depressant effect on food consumption initially, but this was made up for during the second week, and the mean final weights of the three hypoxic groups were virtually identical. Thus neither verapamil nor nifedipine had any significant effect on appetite or growth.

Ventricular hypertrophy

Since every treated animal had an untreated litter mate in the same box breathing the same air for the same length of time, the effect of treatment could be estimated by dividing the weight of the ventricles of each treated animal by the weight of the corresponding chamber of its own vehicle-only treated litter mate. The results are presented in Table 2A, uncorrected figures on the left, values corrected for body weight on the right. The ratios are all so close to 1.0 that it is clear that the treatment had no effect on ventricular growth.

In spite of the greater size of the normoxic controls, even the uncorrected ventricular dry weight ratios (Table 2B) show that all three hypoxic groups had right ventricles significantly heavier than those of their normoxic litter mates, and the weight corrected values on the right indicate right ventricular hypertrophy of 39% (H), 46% (V) and 44% (F), in the absence of any left ventricular hypertrophy, all differences being statistically significant ($P < 0.025$, $P < 0.02$ and $P < 0.001$, respectively).

The mean total ventricular dry weight in the normoxic controls ($n = 12$) was 584.2 mg with s.e.mean 29.2 mg (5.0%). The corresponding figures for the

Table 2 Ventricular hypertrophy of hypoxic rabbits treated with verapamil or nifedipine compared with those of normoxic and hypoxic controls

A *Hypoxic animals only*

	Uncorrected values		*Values corrected for body weight* (g dry wt. (kg body wt)$^{-1}$)	
Group	*Left* Treated/ untreated	*Right* Treated/ untreated	*Left* Treated/ untreated	*Right* Treated/ untreated
Verapamil-treated	1.021	0.996	1.021	1.036
Nifedipine-treated	1.017	1.041	0.985	1.049

B *Hypoxic ventricular weights divided by those of normoxic litter mates*

	Hypoxic/normoxic		Hypoxic/normoxic	
Hypoxic controls (H)	0.793	1.167	0.990	1.389
Verapamil-treated (V)	0.810	1.161	0.975	1.457
Nifedipine-treated (H)	0.807	1.214	1.011	1.439

C *Left ventricular dry weights divided by right ventricular dry weights*

Normoxic controls	2.748
Hypoxic controls	1.870
Verapamil-treated	1.918
Nifedipine-treated	1.827

Table 3 Atrial hypertrophy in hypoxic rabbits treated with verapamil or nifedipine

Group	*Uncorrected values*		*Values corrected for body weight* (g dry wt. (kg body wt)$^{-1}$)	
	Left Treated/ untreated	*Right* Treated/ untreated	*Left* Treated/ untreated	*Right* Treated/ untreated
A *Hypoxic animals only*				
Verapamil	1.11	1.15	1.12	1.15
Nifedipine	1.1	1.21	1.07	1.18
B *Hypoxic atrial weights divided by normoxic atrial weights*				
Hypoxic controls	0.758	0.834	0.941	1.036
Verapamil	0.845	0.960	1.004	1.199
Nifedipine	0.831	1.009	1.055	1.216

left and right ventricles individually were 428.3 ± 22.5 mg and 155.9 ± 7.6 mg respectively. Since these standard errors represent only 5.25 and 4.9% of the left and right means, it was clear that virtually the whole of the variation was due to real differences in total ventricular weight, and that splitting the ventricles into left and right had introduced negligible additional variation. Calculations in the other groups yielded similar results. It seemed permissible, therefore, to use the left ventricle of each animal as a 'control', so that any right ventricular hypertrophy would become apparent without the need for corrections for body weight. The left ventricular weight of each animal has been divided by its own right ventricular weight, and the mean ratios have been presented in Table 2C, illustrating the large and uniform degree of right ventricular hypertrophy in the hypoxic groups, in spite of the absolute variations in body weight and total ventricular weight. It is apparent that the treatments had no effect on the hypertrophy.

Atrial Hypertrophy

In Table 3 the results for the atria have been presented in the same way as those for the ventricles in Table 2. As in the ventricles, there was no hypertrophy on the left side, and on the right the hypertrophy was not as great, only 3.6% in the controls and 20% and 21.6% in the verapamil and nifedipine treated rabbits respectively, only the last being statistically significant ($P < 0.025$).

Haematological data

The measurements made have been presented in Table 4. There was a rise in haematocrit, haemoglobin and red cell count in all three hypoxic groups. The variation was greater and the increases were marginally smaller in the verapamil-treated rabbits, and did not reach statistical significance in comparison with normoxic controls in this group, but were significant in the others. Otherwise, apart from small increases in white cell counts in the treated animals, there were no significant changes.

The plasma levels of verapamil following an intraperitoneal injection of 5 mg kg^{-1} were 588 and 540 ng ml^{-1} after 30 min, and the norverapamil concentrations were 24 and 20 ng ml^{-1} respectively. After 2 h the verapamil concentrations were 288 and 710 ng ml^{-1}, and the norverapamil concentrations were 17 and 37 ng ml^{-1}. These values may be compared with mean peak levels of 424 ng ml^{-1} in man (Storstein, Midtbø, Hals & Myhre, 1981) after oral doses of 160 mg three times per day (about 2.5 mg kg^{-1}). Much lower concentrations, however, have been quoted for human therapeutic levels, 15–100 ng ml^{-1} (Henry, 1980). In blood samples taken from 2 rabbits 30 min after injections of 1 mg kg^{-1} i.p. the nifedipine concentrations were 65.9 and 79.3 ng ml^{-1}.

Raw data on weights and water contents

The actual dry weights of the individual cardiac chambers are presented in Table 5, together with the water contents in g H_2O. (g dry wt)$^{-1}$. Wet weight is, therefore, dry weight + (dry weight × water content). The mean final weights have already been given in Table 1, in conjunction with which Table 5 enables any statistics to be derived, e.g. whole heart wet weights, absolute and relative to body weight, etc. It is apparent that neither hypoxia nor treatment had any significant effect on the water content of any cardiac chamber, implying absence of changes in capillarity or extracellular space.

Table 4 Haematological data for hypoxic rabbits treated with verapamil or nifedipine compared with those of normoxic and hypoxic controls

Group	n	*Hct* %	*Hb* ($g\,dl^{-1}$)	*RBC* ($\times 10^{12} l^{-1}$)	*WBC* ($\times 10^{9} l^{-1}$)	*MCV* (fl)	*MCHC* ($g\,dl^{-1}$)	*MCH* (pg)
N	12	32.79 (1.72)	10.46 (0.583)	4.85 (0.237)	3.07 (0.279)	67.36 (0.945)	31.9 (0.304)	21.5 (0.36)
H	6	39.55* (1.97)	12.37* (0.558)	5.68* (0.188)	3.78 (0.935)	69.4 (1.62)	31.33 (0.401)	21.78 (0.49)
V	8	38.53 (2.39)	12.16 (0.733)	5.49 (0.308)	5.04* (0.842)	69.97 (0.987)	31.6 (0.258)	22.10 (0.246)
F	9	42.24*** (1.52)	13.01*** (0.44)	6.05*** (0.204)	4.88* (0.842)	69.88 (0.987)	30.8 (0.315)	21.54 (0.44)

Statistical significance of differences: * = $P<0.05$; *** = $P<0.001$

Discussion

Since hard-working hearts hypertrophy, and since calcium ions traversing the membrane from outside to inside are involved in excitation coupling, the possibility that drugs restricting calcium entry might reduce cardiac hypertrophy deserved consideration. Such drugs have been used in the treatment of hypertrophic obstructive cardiomyopathy (HOCM), but although the haemodynamic effects may improve symptoms, there is no evidence that the hypertrophy regresses. Goodwin (1982), in a recent review, concluded: 'In some patients verapamil certainly improves symptoms, haemodynamics, and exercise capacity, but others do badly, as we have noted'. The doses of verapamil recommended for clinical use are 40–120 mg three times daily orally (6 mg kg^{-1} per day) and up to 100 mg i.v. (1.5 mg kg^{-1}). We administered 5 mg kg^{-1} i.p. twice daily, which represents the equivalent of a high human dosage regime. For nifedipine up to 20 mg three times daily is recommended for human use (1 mg kg^{-1}) (Data Sheet Compendium, 1982), so that our regime of 1 mg kg^{-1} twice daily is equivalent to high human dosage. Although we do not know accurately for how many hours per day therapeutic concentrations were present in the blood, we did find that higher than therapeutic concentrations were present after the injections. If the human beta phase half life of 4.2 h for verapamil (Storstein et al., 1981) and 14 h for nifedipine (Horster, 1975) are applicable to rabbits, therapeutic concentrations would have been present for most of the time. In any case it is certain that the hearts were exposed to substantial amounts of both drugs for many hours per day, and if they had been inhibiting the hypertrophy at least some reduction of right ventricular weight should have been observed.

Verapamil and nifedipine relax vascular smooth muscle in the coronary and peripheral arteries, nifedipine being the more potent (Editorial, 1980). It

Table 5 Raw data for dry weights and water contents of individual heart chambers of all groups

	Ventricles				*Atria*			
	Left		*Right*		*Left*		*Right*	
	Dry wt mg	Water content	Dry wt mg	Water content	Dry wt mg	Water content	Dry wt mg	Water content
N	428.3 (22.51)	4.093 (0.024)	155.9 (7.62)	4.043 (0.041)	48.8 (2.92)	4.803 (0.062)	35.63 (2.68)	4.493 (0.151)
H	339.9 (23.01)	4.073 (0.061)	181.7 (22.0)	4.087 (0.051)	37.0 (2.84)	4.845 (0.155)	29.73 (2.69)	4.457 (0.168)
V	347.1 (23.33)	3.956 (0.040)	180.9 (16.7)	3.966 (0.047)	41.2 (2.76)	4.750 (0.112)	34.21 (3.06)	4.292 (0.166)
F	345.5 (16.47)	4.079 (0.058)	189.1 (10.81)	4.077 (0.066)	40.59 (2.10)	4.771 (0.069)	35.96 (1.19)	4.350 (0.133)

Mean dry weights (± s.e.mean), and water contents in g H_2O. (g dry wt)$^{-1}$ [= (wet wt − dry wt)/dry wt].

had been thought initially that if hypertrophy had been inhibited by nifedipine, but not by verapamil, this would have implied that the inhibition was due to relaxation of pulmonary arterial smooth muscle. In the event neither drug had any effect at all.

In a previous study (Vaughan Williams & Dukes, 1983), in which animals were exposed to hypoxia for 23 h per day continuously for totals of 283 and 298 h, the right ventricles hypertrophied by a mean of 98% in untreated rabbits. In the present series, because injections needed to be administered twice daily, the hypoxia had to be interrupted more often. The animals were accordingly exposed for totals of 310 h, the longer period more than compensating for the additional time the door was open each day. Nevertheless, in the present series the right ventricular (45%) and right atrial hypertrophy (3.6%), and the increase in haematocrit (21%) were smaller than in hypoxic controls exposed to hypoxia for more than 23 h daily, the corresponding figures being RV 98%, RA 103%, Hct 46%. In the latter group there was also a significant *left* ventricular hypertrophy. A possible explanation for these results is that exposure to normoxia, even for a brief period, inhibits erythropoietin production for several hours. Blood viscosity rises logarithmically as a function of haematocrit (discussed in detail by Vaughan Williams & Dukes, 1983), and the 46% increase in Hct may have greatly increased the work load causing the left ventricular hypertrophy, and a right-sided hypertrophy disproportionate to the total duration of hypoxia. It is of interest that in another study (Dennis & Vaughan Williams, 1982) in which rabbits were exposed to hypoxia with two intermittent periods of normoxia daily, as in the present series, there was no left-sided hypertrophy, and the right ventricular and atrial hypertrophies were 57% and 32% respectively.

Both verapamil (Storstein *et al.*, 1981) and nifedipine (Tauchert, Behrenbeck, Niehues & Hilger, 1980), especially the latter, increase heart rate in conscious humans, an effect commonly attributed to reflex sympathetic activity in response to hypotension, although other explanations are possible (Chah, Lang, Lakhal, Bouzouitta, Bertrix & Faucon, 1983). It was of interest, therefore, that a small degree of right atrial hypertrophy was observed of 20% (NS) in the hypoxic verapamil-treated group, and of 21.6% ($P = 0.025$) in the nifedipine group. In our previous studies (Vaughan Williams & Dukes, 1983) right atrial hypertrophy in the untreated group was 103%, but was less in animals treated with guanethidine (34%) or 6-hydroxydopamine (39%). These findings suggest that right atrial hypertrophy was partly due to increased sympathetic activity, which is not unreasonable in view of the dense distribution of sympathetic nerves to the right atrium.

Our results imply that neither nifedipine nor verapamil was able to inhibit right ventricular hypertrophy by a direct myocardial action or indirectly by relaxing pulmonary arteries. In contrast, Davidson, McMurtry & Reeves (1978) found that injections of 12 mg kg^{-1} of verapamil twice daily i.p. (2.5 times the dosage used by us) reduced right ventricular hypertrophy by 19% in rats kept at 5500 m in a hypobaric chamber for 20 days, but Sheldon & Cameron (1982) failed to confirm these results. The latter authors used even higher doses of verapamil (2 doses of 20 mg kg^{-1} spaced 3 h apart) and observed that the right ventricles of treated rats were 17% less heavy than those of untreated rats. The animals were exposed to hypoxia for 6 h only per day for 4 weeks, and since no comparisons were made with normoxic rats, there was no evidence that right ventricular hypertrophy had been achieved. On balance, there is no justification for extrapolating from animals to man any suggestion that verapamil could reduce myocardial hypertrophy at doses used clinically.

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