Br. J. clin. Pharmac. (1982), **13**, 279S–283S

HAEMODYNAMIC DIFFERENCES IN UNTREATED HYPERTENSION AND HYPERTENSION TREATED WITH VARIOUS β-ADRENOCEPTOR ANTAGONISTS

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1 As a rule, hypertension progresses from an early stage with a high cardiac output (CO) and an inappropriately normal total peripheral resistance (TPR) to later stages with a normal or decreased CO and a high TPR.

2 Low CO and high TPR can be considered detrimental to the blood perfusion in the tissues and organs and thus to their functional and structural integrity.

3 Among β-adrenoceptor antagonists, some lower blood pressure by reducing CO, thus bringing about a reactive increase in TPR. The result is that, even though blood pressure is reduced, the haemodynamic conditions commanding regional blood flow are qualitatively similar to those in untreated hypertension. To what extent these circumstances may curtail the benefit expected from blood-pressure reduction deserves careful investigation.

4 Pindolol, a β-adrenoceptor antagonist with an appropriate degree of intrinsic sympathomimetic activity (ISA), lowers blood pressure while lowering TPR and not unduly reducing cardiac performance. These features should on theoretical grounds lead to a greater improvement in the prognosis of hypertension.

Introduction

Arterial blood pressure is sustained at both ends of the arterial limb of the cardiovascular system, namely by cardiac output (CO) at the one end and total peripheral resistance (TPR) at the other. Besides, CO and TPR are the direct determinants of blood flow to the various tissues and organs. Whereas CO can be measured directly, TPR must be calculated from mean arterial blood pressure (MAP) and cardiac output (TPR = MAP : CO). Although knowing the values of CO and TPR enables only an overall estimate of blood flow through the organism and gives no clue to the differences in blood flow between the various tissues and organs, CO and TPR provide valuable information on the nature of the haemodynamic disturbances involved in conditions such as arterial hypertension.

Little attention has been paid up to now to the possible differences in the long-term prognosis of untreated and treated hypertension as a function of the changes that occur in CO and TPR and thus in regional blood flow, in contrast to the blood pressure values.

Untreated hypertension

In spite of an elevated CO in the initial stage, the main haemodynamic abnormality present in essential hypertension appears to involve TPR. The high CO of early hypertension (Widimský *et al.*, 1958; Eich *et al.*, 1962) is attended with a TPR that is numerically normal, i.e. no higher than in a population of healthy subjects, yet inappropriately normal, i.e. abnormally high in view of the elevated CO: TPR is indeed higher than in non-hypertensive subjects with an identically elevated CO (Julius & Conway, 1968; Lund-Johansen, 1977). In other words, any increase in CO should normally trigger a corresponding decrease in TPR.

As the condition progresses from the early to the late stage, i.e. from labile to established hypertension, TPR gradually increases while CO decreases to normal, until eventually the elevated blood pressure is maintained solely through high TPR (Widimský *et al.*, 1958; Eich *et al.*, 1966; Frohlich *et al.*, 1970). With increased severity of the disease, CO falls below normal while TPR increases further (Lund-Johansen, 1977).

0306–5251/82/130 279–05 $01.00

How a state with high CO and mildly elevated TPR evolves in time into one with low CO and high TPR has been a matter of controversy. A reactive vasoconstriction aimed at protecting the tissues against excessive perfusion has been postulated (Ledingham & Cohen, 1963; Ledingham & Pelling, 1967). However, no such autoregulatory mechanism appears necessary, since the high CO seen in early hypertension represents a response to increased oxygen consumption in the organism and there is no luxury perfusion (Julius & Conway, 1968; Lund-Johansen, 1967). The agreement between increased CO and increased tissue oxygen requirements is evidenced by the fact that the arteriovenous oxygen difference is not decreased in high-CO hypertension (Sannerstedt, 1966). The increased pressure load could bring about structural changes, probably fostered by some genetic predisposition, in the resistance vessels. Thus, medial hypertrophy would, by increasing the wall-to-lumen ratio, lead not only to a steeper increase in vascular resistance for any degree of vascular smooth muscle shortening, but also to a state of increased flow resistance even at maximum vasodilation (Folkow *et al.*, 1958; Conway, 1963; Folkow *et al.*, 1973).

Clearly there is in essential hypertension an abnormality, present from the very beginning, in the control of TPR that with time impedes cardiac function. The resulting high TPR with a normal or low CO necessarily implies reduced blood flow in most tissues and organs. What part this inadequate perfusion plays in the prognosis of hypertension does not appear to have been given much attention. It has been put forward that those hypertensives who retain a high CO (i.e. who do not develop high-TPR hypertension) over the years probably have the longer life expectancy (Widimský *et al.*, 1958).

The choice of therapy in hypertension

Even though it is known that the therapeutic lowering of blood pressure improves the prognosis of hypertension, little has been done to find out how blood pressure is most suitably lowered in order to provide the best possible prognosis. An occasional remark can be found on the illogicality of further reducing CO and blood flow to vital organs in late hypertension (Meyer *et al.*, 1968), but the subject of what therapy-induced haemodynamic pattern yields the best outlook will yet have to be explored (Lund-Johansen, 1980). However, since the prognosis of hypertension is dominated by the organ damage resulting from the disease and low perfusion can logically be expected to play a major role in the pathogeny of such damage, it is probably better in late hypertension to lower blood pressure by lowering TPR and thus improving local blood flow than by further lowering CO and thus worsening local blood flow. In other words, any therapy of hypertension that reverses the haemodynamic changes that occur and gradually worsen during the spontaneous evolution of hypertension should be given preference over any therapy that allows these changes to proceed unchecked or even fosters them.

β-adrenoceptor antagonists

After an initial phase of distrust, β-adrenoceptor antagonists have gained increasing acceptance for the treatment of hypertension, owing to their effectiveness and the relative paucity of severe or otherwise unacceptable side-effects. Their haemodynamic mode of action during long-term administration is far from being as uniform as would be expected of members of the same drug class; Figure 1 shows the haemodynamic findings in well-known long-term therapeutic trials with three different β-adrenoceptor blockers. Propranolol was shown mainly to decrease resting cardiac index (CI); although a small recovery was seen after 19.6 months of treatment, CI remained significantly below the pretreatment level. On the other hand, resting total peripheral resistance index (TPRI), initially raised by propranolol, fell after 19.6 months of treatment, but not significantly below the pretreatment value (Tarazi & Dustan,

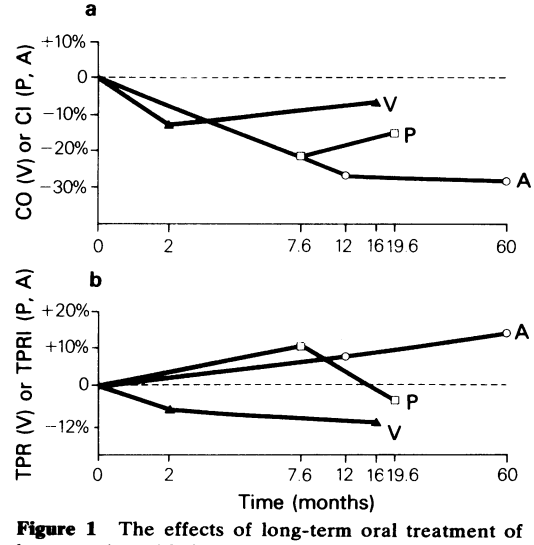

Figure 1 The effects of long-term oral treatment of hypertension with three different β-adrenoceptor blockers on resting cardiac output (CO) or cardiac index (CI), a, and resting total peripheral resistance (TPR) or total peripheral resistance index (TPRI), b; (▲) pindolol (V), data from Atterhög *et al.* (1977), $n = 10$; (□) propranolol (P), data from Tarazi & Dustan (1972), $n = 10$; and (○) atenolol (A), data from Lund-Johansen (1979), $n = 10$.

Table 1 Changes in resting cardiac output (CO) or cardiac index (CI) and total peripheral resistance (TPR) or total peripheral resistance index (TPRI) in hypertensive patients treated with pindolol

Authors	*Daily dose (mg)*	*Duration of trial*	*Number of patients*	*Change in CO or CI*		*Change in TPR or TPRI*	
Savenkov *et al.* (1977)	15–20	2 weeks	18	CI	−2.9%	TPR	−5.8%
Lang & Holtmann (1974)[1]	7.5	2 weeks	6	CO	+6.6%	TPR	−13.2%
Tsukiyama *et al.* (1976)[2]	15–60 (mean = 30)	5 weeks	12	CI	+8.7%	TPRI	−16.1%
			9[3]	CI	+12.5%	TPRI	−22.9%
Kuramoto *et al.* (1974)	15	8 weeks	9	CI	+9.9%	TPRI	−17.6%
Klein *et al.* (1976)	10–15	8 weeks	10	CI	ca.+10%	TPR	ca.−10%
Velasco *et al.* (1980)	15	2 months	8	CO	+3.0%	TPR	−17.3%
Torres Zamora *et al.* (1975)	15–45	3 months	6[4]	CI	+21.7%	TPR	−30.6%
Atterhög *et al.* (1977)[5]	20–40 (mean = 34)	16 months	10	CO	−7.3%	TPR	−11.1%

[1] with propranolol, 80 mg daily for 2 weeks in the same six patients, CO −23.5%; TPR +23.5%.
[2] with propranolol, 60–120 mg daily (mean 75 mg) in ten patients, CI −15.9% (−25.8% in four responders); TPRI +22.1% (+28.6% in four responders).
[3] responders only (nine out of the twelve patients).
[4] responders only (six out of seven patients).
[5] after only 2 months, CO −12.7%; TPR −7.4%.

1972). With atenolol, there was a continuous fall in resting CI and a continuous increase in resting TPRI over 5 years; in spite of the continuing fall in CI, there was no further reduction in blood pressure after 1 year of treatment. Interestingly, there was no decrease over the 5 years in the oxygen consumption at rest or during exercise, an observation which, in view of the constantly decreasing CI, suggests that the arteriovenous oxygen difference must have increased: in the presence of a CI reduced by up to 28% at rest and 22% during exercise, the organism resorts to increased oxygen extraction from the blood (Lund-Johansen, 1979). Pindolol (Visken®) acted mainly by reducing TPR; the reduction in CO by 7% after 16 months was not significant (Atterhög *et al.*, 1977). The results with pindolol just mentioned are shown again in Table 1, together with those of 7 other trials of a duration ranging from 2 weeks to 3 months. In all instances TPR or TPRI was reduced by 6 to 18% (31% for responders only). CO or CI was increased in all trials (by 3 to 10% [22% for responders only]) except the first one, in which the 2 weeks of pindolol treatment were separated by 1 week on placebo, and the last one, previously discussed. Footnotes 1 and 2 to Table 1 also give results with propranolol, either in the patients also treated with pindolol in a cross-over design (Lang & Holtmann, 1974) or in a parallel group of patients (Tsukiyama *et al.*, 1976).

In hypertension pindolol thus has actions on the immediate determinants of blood pressure and blood flow quite different from those of propranolol and atenolol, even granting that there is a delayed circulatory readjustment with propranolol. Pindolol is a β-adrenoceptor blocker with clinically relevant intrinsic sympathomimetic activity (ISA), whereas propranolol and atenolol are devoid of ISA. Pindolol's ISA not only precludes undue interference with cardiac performance and the ensuing compensatory rise in TPR, but also can act directly on the vascular β-receptors to induce vasodilation, as shown in animal experiments (Sybertz *et al.*, 1981; Clark, 1982), and thus contributes to the drug's antihypertensive activity. Relative β_1-adrenoceptor selectivity (atenolol) is seen to confer no particular advantage over nonselectivity (propranolol, pindolol) with respect to haemodynamics.

Discussion

The changes in resting CO and TPR occurring in hypertensive patients given propranolol or atenolol did not differ qualitatively from those observed in hypertension left to its own course, which is to say that, even though blood pressure was lowered, no improvement was seen in haemodynamics that could have benefited regional blood flow. There is evidence that a drug-induced situation of low CO can induce rapid deterioration in organ function, e.g. in an already impaired renal function (Warren *et al.*, 1974); gradual deterioration would be more difficult to detect and to ascribe to a definite cause. In view of the similarity of flow conditions in untreated late hypertension and in hypertension palliated merely with a reduction in CO, one would be tempted to characterize the latter conjuncture by coining the term 'ahypertensive hypertension' (on the analogy of 'aleukaemic leukaemia') or the term 'masked hypertension'. Such a term would convey the notion that any unfavourable prognostic tendency related to reduced regional blood flow in untreated hypertension

could also be present in hypertension treated in such a way as not to improve regional blood flow; the problem certainly deserves careful investigation by means of longitudinal studies. The reduction in blood pressure achieved could at first sight be considered at least to diminish the workload on the heart, but this inference is obviously spurious, since it is the reduction in heart performance itself that causes the blood pressure to decrease; in addition, the reduction effected in the pump function of the heart is only partly translated into a blood-pressure reduction, since the reactive increase in TPR counterbalances it to a large extent.

Pindolol, although a β-adrenoceptor blocker, in effect behaves in hypertensive patients much as would a vasodilator; this is due to pindolol's ISA. Unlike a vasodilator, however, pindolol causes no reactive tachycardia, since it controls any cardiac activity in excess of normal; this is due to pindolol being basically a β-adrenoceptor blocker.

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