β-ADRENOCEPTOR-BLOCKING AGENTS AND THE KIDNEY: EFFECT OF NADOLOL AND PROPRANOLOL ON THE RENAL CIRCULATION

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1 Nadolol was administered intravenously to five hypertensive patients and three healthy volunteers in balance on a 10 mEq sodium intake.

2 Nadolol (0.3-10.0 μg/kg) induced a significant, dose-related increase in renal blood flow, measured with radioxenon, with a maximum increase of 72 ± 4 ml/100g/min (26%) at 3.0 μg/kg.

3 Heart rate and plasma renin activity decreased significantly over the same dose range.

4 The renal vascular response to nadolol contrasts sharply with those found with other β-adrenoceptor-blocking agents.

5 The magnitude of the increase in renal blood flow, its time-course and the parallel fall in plasma renin activity raise the possibility that the renal vasodilatation reflects the reversal of angiotensin's influence on the renal arterial bed.

Introduction

A NUMBER of investigators have demonstrated a propranolol-induced reduction in renal blood flow and, where measured, in glomerular filtration rate (Schirmeister *et al.*, 1966; Nayler *et al.*, 1967; Carriere, 1969; Fenyvesi & Kallay, 1970; Nies *et al.*, 1971; Krauss *et al.*, 1972; Ibsen & Sederberg-Olsen, 1973; Sullivan *et al.*, 1976). Because a reduction in renal blood flow and glomerular filtration rate are common with agents that reduce cardiac output (Sannerstedt & Conway, 1970), as does propranolol, the renal response was widely attributed to the systemic effects of the agent. On that basis a reduction in renal blood flow would be anticipated in response to other β-adrenoceptor-blocking agents, as has been indeed demonstrated for dichloroisoproterenol, oxprenolol, and pindolol (Cooper *et al.*, 1967; Bufano & Piacentini, 1969; Abdel-Razzak, 1977; Heierli *et al.*, 1977).

On the other hand, several investigators have presented evidence which suggests that the response to propranolol might reflect a local intrarenal effect rather than a systemic one; the effect might, therefore be specific for the agent. Carriere (1969) has demonstrated that the renal vasculature in the dog responds to propranolol when infused into the renal artery in doses too small to have a systemic effect, and that the local effects of propranolol are reversed with phenoxybenzamine, an observation that was quickly confirmed by Fenyvesi & Kallay (1970). Nies *et al.* (1971), in a widely cited study, did not report a preferential action of propranolol infused into the renal artery, and therefore concluded that the renal action must be secondary to systemic effects. Unfortunately, Nies *et al.* used the same dose infused into the renal artery as was shown earlier to have a systemic effect, so that an influence on the contralateral kidney during intra-arterial infusion should not have been surprising. Other investigators employed a subthreshold dose of propranolol for intra-arterial infusion and thus were unable to document a local preferential action (Carrier, 1969; Fenyvesi & Kallay, 1970). Similarly, we have demonstrated in man that propranolol induces renal vasoconstriction in doses too small to reduce heart rate or measured cardiac output (Sullivan *et al.*, 1976).

These observations suggest that all β-adrenoceptor-blocking agents might not result in renal vasoconstriction. Because of evidence that angiotensin plays a role in the control of renal perfusion in man (Hollenberg *et al.*, 1977; Hollenberg, 1978) and because β-adrenoceptor blocking agents suppress renin release, it became important to examine other β-adrenoceptor-blocking agents in an attempt to identify an agent which was free of intrinsic activity, or ideally dilated the renal vasculature.

Methods

Studies were carried out in eight subjects ranging in age from 36-62 years. Three were normal potential

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kidney donors, studied at the time of selective renal arterial catheterization for arteriography. The other five had essential hypertension, diagnosed on the basis of criteria described earlier (Sullivan *et al.*, 1976), and came to arteriography to rule out renal artery stenosis. None of the patients with essential hypertension had received previous antihypertensive therapy. The study protocol was approved by the Human Experimentation Committee of the Peter Bent Brigham Hospital, and all subjects were informed of the experimental nature of the protocol and gave their written consent.

Each patient received careful evaluation with special emphasis on cardiovascular, renal and adrenal status (Sullivan *et al.*, 1976; Hollenberg *et al.*, 1977). They were admitted to a metabolic ward and placed on a diet which provided a daily intake of 10 mEq sodium and 100 mEq potassium for at least 5 d before study. Balance was assessed by measurements of sodium excretion in 24-h urine collections, by a detailed assessment of daily dietetic intake and by serial weight measurements. All subjects were in metabolic balance at the time of the haemodynamic study.

Percutaneous selective renal arterial catheterization, the determination of renal blood flow with radioactive xenon (^{133}Xe) and external probe counting, and cardiovascular monitoring during the administration of vasoactive agents have been described in detail (Hollenberg *et al.*, 1977). The catheter was used for the continuous monitoring of BP and heart rate, for injecting ^{133}Xe and for drawing arterial blood samples for measurements of electrolytes and hormones. Blood pressure was measured with a transducer (Statham P23 Db) and recorded continuously along with the instantaneous pulse rate (cardiotachometer) and the ECG.

The study was initiated at least 30 min after BP stability had been achieved after aortography. A control blood flow determination was obtained and a control arterial blood sample was drawn for the measurement of plasma renin activity. Then, nadolol was administered intravenously according to one of two protocols. The first four subjects received a single dose of 0.3, 1, 3 or 10 μg/kg and the cardiovascular response was monitored for 40 minutes and the fall in heart rate was achieved within 2 min and was stable thereafter for at least 20 minutes. Because the renal vascular response was stable after 10 min, a second protocol was adopted to obtain a dose–response curve. In four subjects graded doses, from 0.3-10 μg/kg nadolol, were administered intravenously and the responses to each dose monitored for 10 minutes. In this way, a cumulative dose–response curve was constructed. Arterial blood samples were drawn at 20 min after nadolol administration to assess the hormonal response, as in previous studies (Hollenberg *et. al.*, 1977).

Plasma renin activity was measured by radioimmunoassay of angiotensin I generated during a 30-min incubation with endogenous substrate at 37°C (Emanuel *et al.*, 1973). Creatinine concentration, and sodium and potassium concentrations in urine and serum were measured using the auto-analyzer method. Mean renal blood flow was measured from the initial slope of ^{133}Xe disappearance from the kidney, with a haematocrit-corrected partition coefficient; compartmental analysis was carried out using the Maximum Likelihood method with a PDP 11/70 computer (Hollenberg *et al.*, 1973). The statistical package in the same computer was used to calculate group means ± s.e.m. as the index of dispersion, and to carry out multiple linear regression analyses. The evaluation of statistical probability (*P*) was carried out, where appropriate, using Student's *t* test or paired data *t* tests, the Wilcoxon Rank Sum test for non-parametric data, and analysis of variance. The null hypothesis was rejected when the *P* value was less than 0.05.

Results

In the dose range used, nadolol reduced heart rate and increased renal blood flow in every patient studied (Figures 1, 2 and 3). Mean renal blood flow increased from 270 ± 19 ml/100 g/min in the control state by a mean of 46.9 ± 9 ml/100 g/min at 1.0 μg/kg, by 72 ± 4 ml/100 g/min at 3 μg/kg, and 70 ± 5 ml/100 g/min at 10 μg/kg, an increase of 26%. There was a strong correlation between the logarithm of the

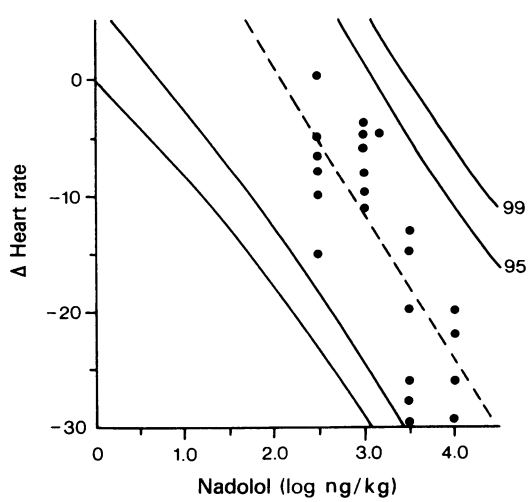

Figure 1 Relationship between nadolol dose and change in heart rate. $r = 0.76$; $F = 31.4$.

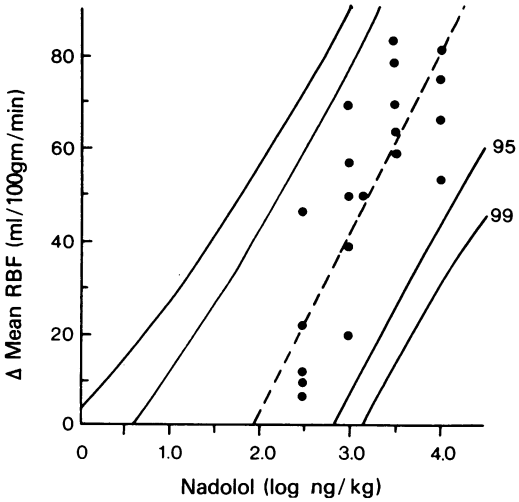

Figure 2 Relationship between nadolol dose and change in mean renal blood flow. Δ, Mean renal blood flow.

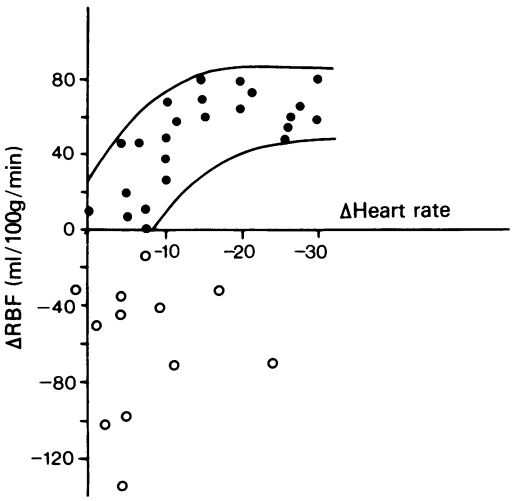

Figure 3 Comparison of relative influence of two β-adrenoceptor-blocking agents, nadolol (●) and propranolol (O), on heart rate and change in renal blood flow. Δ, Mean renal blood flow.

nadolol dose and the change in renal blood flow ($r = 0.79$; $P < 0.001$).

Heart rate also fell in every patient from a mean control of 79.8 ± 4.6 beats/min, with a threshold dose of 0.3 μg/kg and by —23.6 ± 1.9 at a nadolol dose of 10 μg/kg ($P < 0.01$). Again, the relationship between the dose of nadolol and the fall in heart rate was significant ($r = -0.76$; $P < 0.01$).

The relationship between change in heart rate and change in blood flow in the subjects ($r = 0.60$; $P < 0.01$) is evident in Figure 3. For comparison the change in renal blood flow is plotted with the change in heart rate in earlier studies we carried out using a similar patient population with identical techniques, in which propranolol was administered (Sullivan *et al.*, 1976). Propranolol resulted in a fall in renal blood flow over the entire range of doses and heart rate responses. Nadolol, conversely, resulted in an increase in renal blood flow at the threshold dose which reduced heart rate. When a maximal increase in renal blood flow of about 70 ml/100 g/min had been achieved with nadolol, however, incremental doses further reduced heart rate without any additional influence on the renal blood supply.

Changes in plasma renin activity following nadolol were determined in part by the control plasma renin activity (Figure 4; $r = 0.85$; $P < 0.01$). When multiple linear regression was carried out, in which the logarithm of the nadolol dose and the control plasma renin activity were the independent variables, and the change in plasma renin activity was the dependent variable, the correlation increased to 0.97 ($P < 0.001$). Thus both the control plasma renin activity and nadolol dose contributed to the fall in plasma renin activity.

An excellent correlation was also demonstrable when nadolol dose and change in plasma renin activity were defined as the independent variables, and change in mean blood flow was the dependent variable ($r = 0.89$): nadolol dose and the fall in plasma renin activity therefore accounted for about 80% of the variation in renal blood flow after nadolol administration.

Discussion

Because any agent that reduces cardiac output is expected to reduce renal perfusion, the observation that many β-adrenoceptor-blocking agents reduced renal perfusion came as no surprise. The notion that a fall in renal blood flow reflected a systemic effect of propranolol was supported by the experiments of Nies *et al.* (1971), reviewed earlier. Their demonstration that propranolol, when infused into the canine renal artery, did not induce a potentiated local effect led to the inescapable conclusion that the fall in renal blood flow was secondary to the reduced cardiac output or some other systemic effect. If that were the entire explanation, of course, all β-adrenoceptor-blocking agents would be expected to reduce renal blood flow. On the other hand, the observations of Carriere (1969), Fenyvesi & Kallay (1970) and Sullivan *et al.* (1976) using propranolol doses too low to have a systemic effect, suggested a specific local action of propranolol in the renal

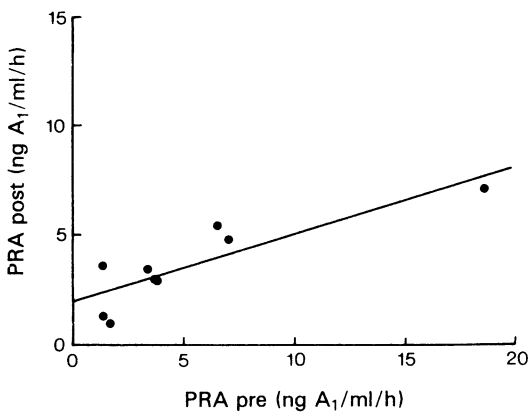

Figure 4 Relationship between plasma renin activity (PRA) before and after nadolol administration. Note that the higher the control value, the larger the fall in plasma renin activity. $y = 0.30x + 2.0$; $r = 0.85$.

vascular tree. This study, too, suggests that β-adrenoceptor-blocking agents need not reduce renal blood flow. Nadolol, in doses that produced a substantial reduction in heart rate, induced a consistent increase in renal blood flow over this same dose range.

Propranolol not only reduces renal plasma flow; glomerular filtration rate has also been shown to be reduced in a number of reports (Schirmeister *et al.*, 1966; Nies *et al.*, 1971; Ibsen & Sederberg-Olsen, 1973), presumably by way of mechanisms similar to those responsible for the reduction in renal blood flow. Under most circumstances, the reduction in glomerular filtration rate does not seem to have clinical significance, although it may contribute to the reduced capacity of patients receiving propranolol to handle a sodium load (Epstein & Braunwald, 1966; Krauss *et al.*, 1972) and to the sodium retention that occurs occasionally; this latter may limit the antihypertensive effect (Wilkinson *et al.*, 1974). Warren *et al.* (1974) have described three patients with moderately severe chronic renal failure in whom a rapid deterioration of renal function followed therapy with propranolol or oxprenolol. They attributed the renal response to the β-adrenoceptor-blocking agents because of the close temporal association and the absence of any other precipitating factors for the azotemia. On the other hand, substantial experience, including patients with moderate renal insufficiency, has failed to reveal a consistent deleterious effect of propranolol on renal function. Stephen (1966) has reported a moderate increase in blood urea in only 7 out of 137 patients treated with propranolol. Greenblatt & Koch-Weser (1973) have noted a substantial increase in adverse reactions to propranolol in patients in whom the blood urea nitrogen exceeded 25 mg/dl, but progressive azotemia was not mentioned. Thompson & Joekes (1974) have reported no systematic effect of propranolol on creatinine clearance, including many patients who were already azotemic, an observation that was surprising in view of the already well-documented effects of propranolol on glomerular filtration rate.

Other β-adrenoceptor-blocking agents including pindolol (Heierli *et al.*, 1977), acebutolol and atenolol (Zech *et al.*, 1977) also reduce glomerular filtration rate and sodium excretion. That these are not inevitable concomitants of β-adrenoceptor blockade is evident from the demonstration by Gibson (1972) that practolol induces an increase in sodium excretion, urine output and renal free water clearance. Moreover neither alprenolol (Pedersen & Mogensen, 1976) nor tolamolol (Bianchi *et al.*, 1976) in doses which achieved unequivocal β-adrenoceptor blockade influenced either renal perfusion or filtration rates. Thus it is impossible to define a single theme which accounts for all of the renal responses to β-adrenoceptor-blocking agents. Until the studies on nadolol, however, no agent has induced a consistent, dose-related increase in renal perfusion. In this regard nadolol is unique.

The β-adrenergic blocking agents have a number of actions that could account for their impact on renal perfusion and function. Their action on myocardial β-adrenoceptors and the resultant reduction in cardiac output has already been alluded to (Nies *et al.*, 1971). On the other hand increasing evidence suggests that angiotensin plays a role in the control of renal perfusion (Hollenberg, 1978) and thus, to the extent that these agents suppress renin release, an increase in renal perfusion might be anticipated in a setting in which the renin–angiotensin system is activated. Each agent, in addition, may well have actions that are unrelated to their activity as β-adrenoceptor-blocking agents.

The mechanism by which nadolol increased renal perfusion in this study remains to be determined. One distinct possibility is that this agent is a direct renal vasodilator and that the blood flow increase does not reflect modification of an intrinsic renal system. Experience with non-specific vasodilators such as acetylcholine and dopamine has generally revealed a much larger increase in renal blood flow than was induced by nadolol. Acetylcholine, for example, doubles renal blood flow in normal subjects and patients with essential hypertension, in contrast to the modest 26% increase induced by nadolol (Hollenberg *et al.*, 1975). Secondly, the time course of the response to non-specific vasodilators is typically different, in that a new steady-state occurs within 3 minutes. A longer period was required for the renal vascular response to nadolol to reach a plateau, consistent with an indirect influence.

Because the magnitude of the renal blood flow increase induced by nadolol is strikingly similar to that induced by angiotensin antagonists and converting enzyme inhibitors in man studied under similar circumstances, that is, with activation of the renin–angiotensin system by reduced sodium intake (Hollenberg *et al.*, 1977) it is tempting to implicate the fall in plasma renin activity as a responsible mechanism. Certainly the time-course of the renal vascular response is similar to that seen with SO20881, a parenteral inhibitor of angiotensin converting enzyme. Multiple linear regression, furthermore, revealed a statistically significant interaction between nadolol dose and fall in plasma renin activity in the renal vascular response. It is reasonable to ask if the fall in plasma renin is only a marker of β-adrenoceptor blockade and why other β-adrenoceptor-blocking agents which reduce plasma renin activity do not also lead to renal vasodilatation. Perhaps, by analogy with propranolol which clearly has a direct action on the renal vasculature, their net influence on the renal blood supply is the resultant of a number of actions, often opposite in direction and the fall in output and block of renal β-adrenergic vasodilatation may outweigh the local vasodilator effect of suppression of renin release. Further studies are required both to define the mechanism by which nadolol induces renal vasodilatation and to ascertain whether this vasodilator response will promote a better-sustained level of glomerular filtration and capacity to handle a sodium load during chronic use despite β-adrenoceptor blockade.

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Discussion

DR KNILL (Princeton): You mention there were obvious clinical implications of the increased renal blood flow associated with nadolol. I have some ideas of what those clinical implications would be, but I would like to hear your opinion.

DR HOLLENBERG (Boston): It is not yet clear to me that the increase in renal blood flow will be paralleled by an increase in glomerular filtration rate (GFR) and an enhanced ability of the kidney to handle a sodium load. The rest of the answer is predicated on the assumption that those will follow. A drop in GFR has been well established with most β-adrenoceptor-blocking agents. The clinical implications of that vary. For one, it means that the handling of all other drugs which have an important renal excretion will be modified — for example, amino glycosides and digoxin. Secondly, it probably contributes to the reduced ability of patients on β-blockers to handle a sodium load, I think originally shown by Epstein & Braunwald (1966) and subsequently by others. As Dr Finnerty pointed out earlier, this may limit the antihypertensive effect of other drugs. The evidence that clinically important reductions in GFR occur in patients who start off with some renal insufficiency, I think is marginal. The report by Warren *et. al.* (1974) on oxprenolol and propranolol has not been widely reproduced. There was a strong temporal association which we, for instance, have not seen, but presumably there would be a reduced probability of such a response with an agent which was a renal vasodilator rather than an agent with reduced renal blood flow. That's the general area, I think, of potential clinical application.

DR HOROVITZ (Princeton): We recently completed studies looking at renal dynamics in the dog. These studies were carried out by Dr Kenneth Duchin at our laboratories at the Squibb Institute in anaesthetized dogs who are sodium replete not deplete. Following intravenous infusion of nadolol at doses of 0.1 and 1.0 mg/kg, very little effect on BP was observed at low β-blocking doses. Although we did find a small decrease in heart rate, it was not significantly different from the control reading, but we did definitely see renal blood flow increases at a dose of nadolol 1 mg/kg but essentially no change in GFR measured by inulin clearance (Table 1). Table 2 reflects on what you were asking. At least in the sodium replete dog, we did see a marked effect on urinary sodium output which was clearly dose-dependent and significant. We also saw a slight effect on potassium output and early data did indicate that there probably is some increase in plasma potassium which is, I think, overflowing at this dose (Table 3).

Table 1 Effect of nadolol on systemic and renal haemodynamics

	Control	*Nadolol 0.1 mg/kg*	*Nadolol 1.0 mg/kg*
Mean arterial BP (mm Hg)	139± 3	141± 6	138± 6
Heart rate (beats/min)	174±12	162± 7	163±10
Renal blood flow (ml/min)	190±26	205±28	217±24*
GFR (ml/min)	40± 3	40± 3	38± 3

Values are mean ±s.e.m. ($n = 5$).
*$P < 0.05$, compared with control (two-way analysis of variance).