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ANTIADRENERGIC ANTIHYPERTENSIVE DRUGS: THEIR EFFECT ON RENAL FUNCTION

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INTRODUCTION

Since Richard Bright's first intimation of the link between renal and cardiovascular disease, investigators have debated the relationship between the renal vasculature and hypertension. Although it appears that essential hypertension precedes and induces morphologic microvascular disease in the kidney, functional vascular abnormalities may precede not only the onset of morphologic changes, but the onset of clinical hypertension as well (1, 2).

It is unusual to find a normal renal arterial tree devoid of dynamic abnormalities in vascular tone in hypertension patients (3). Numerous studies have demonstrated functional abnormalities in vascular tone in all categories of hypertensive patients, ranging from pre-hypertensives (4) (normotensive offspring of hypertensive patients) to established hypertensives (2, 5–11). In established hypertensives, renal vascular resistance (RVR) (5, 6) is typically increased along with decreased renal plasma flow (RPF) (7–10). Not only have these changes in RPF and RVR been demonstrated early in the majority of young hypertensives (2), but even hypertensives with normal renal vascular tone at rest have exaggerated responses to exogenous vasodilators (1). Lastly, RPF of normal offspring of hypertensive parents differs from that of other normotensive subjects (4). All these changes may occur with relative preservation of glomerular filtration rate (GFR).

Enhanced renal blood flow (RBF) variability in hypertensive patients (1, 2), asymmetry of perfusion between paired hypertensive kidneys, and ameliora-

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tion of increased RVR by vasodilators (2) all support the concept of functional, rather than fixed, renal hemodynamic abnormalities in hypertension (3).

α-Adrenergic participation may be an important factor in the generation of abnormal renal vascular tone and reactivity in early essential hypertensives (1). In laboratory animals, direct electrical stimulation of efferent renal nerves results in reduction of RBF and GFR; these changes are abolished by α-adrenergic blockade with phentolamine or phenoxybenzamine (11). Although its actions are still controversial, endogenous norepinephrine appears to constrict the afferent arterioles preferentially, decreasing both GFR and RBF, while angiotensin II constricts the efferent arteriole, maintaining glomerular hydrostatic pressure and thus GFR (12, 13). While α-adrenergic tone is important in maintaining renal vascular tone in non-basal states, the β-adrenergic system may also participate by regulating renin release (11).

Functional abnormalities in the adrenergic system resulting in dynamic reduction in RBF with preservation of GFR may occur in early hypertensives (1–3). Studies by Hollenberg et al (1) indicate an exaggerated increase in RBF in response to α blockade with phentolamine in early hypertensives versus normotensives, while patients with advanced nephrosclerosis have a reduced response consistent with fixed structural lesions (1).

Although drug therapy has significantly reduced the morbidity and mortality in moderate and severe hypertension (14), and only recently has been demonstrated to benefit mild hypertension (15), adverse drug reactions may negate any potential therapeutic effect. If patients with early essential hypertension have adrenergically mediated and reversible renal vascular abnormalities, the use of adrenergic antihypertensive agents may affect RBF. Such drugs may, in theory, either potentiate or ameliorate the renal vascular abnormalities, perhaps either hastening or preventing the progression of fixed nephrosclerotic changes.

In this paper, we will review the effects of commonly used adrenergic antihypertensive agents on renal hemodynamics and GFR, with a major emphasis on β blockers.

DRUGS INTERACTING WITH α-ADRENERGIC RECEPTORS (Table 1)

α-Adrenoceptor Agonists

CLONIDINE Clonidine is an α_2 agonist whose hypotensive action is generally thought to be the result of its direct agonist effect on central adrenergic receptors that increase baroreceptor sensitivity, inhibit sympathetic outflow, and perhaps increase parasympathetic outflow to the heart. In addition, it may act on peripheral α_2 receptors to decrease norepinephrine release, and, in large

Table 1 Effect of oral α adrenergic drugs on renal hemodynamics[a]

Drug	Author	GFR	RBF	RVR	FF	Number of patients	Duration
Clonidine	Onesti (18)	↔	↔	↔	NR	7	acute
	Cohen (19)	↔	↔	↓	↔	13	1 month
	Thananopavorn (20)	↔	↔	↔	↔	16	1 week
α-methyl dopa	Mohammed (25)	↔	↔	NR	NR	8	10 days
	Grabie (23)	↓	↔	NR	NR	10	8 days
	Sannerstedt (26)	↔	↔	NR	NR	11	—
	Cruz (24)	↓	↔	↔	↓	6	12 days
Guanabenz	Bosanac (27)	↓	↓	NR	NR	8	acute
	Bosanac (27)	↔	↔	NR	NR	8	3 days
	O'Connor (28)	↔	↔	↓	↔	10	5–7 weeks
Prazosin	Maxwell (30)	↔	↔	NR	NR	4	acute
	Koshy (31)	↔	↔	NR	NR	14	8 weeks
	Preston (32)	↔	↔	↓	↔	10	1 month

[a]↔ no change; ↑ increased; ↓ decreased; NR: not reported.
GFR: glomerular filtration rate; RBF: renal blood flow; RVR: renal vascular resistance; FF: filtration fraction.

doses, may even stimulate post synaptic α_1 receptors, paradoxically elevating blood pressure (16).

In dogs (17), intrarenal arterial administration of clonidine not only decreased RBF without affecting GFR but increased blood pressure, while intravenous administration decreased RBF without affecting either GFR or blood pressure. This may be explained by the fact that clonidine acts predominantly at post-synaptic α receptors in the former instance, while acting in addition at presynaptic and central sites in the latter instance (17).

However, human studies have shown that neither acute nor chronic oral clonidine disturbs RBF and in fact may decrease RVR in hypertensive patients (18, 19). Onesti et al (18) reported that acute oral clonidine reduced mean arterial pressure (MAP) without affecting RBF or GFR in seven hypertensive patients. In addition, it preserved RBF and GFR despite an acute reduction in MAP that occurred with upright posture. Cohen et al (19) reported that in 13 hypertensive patients, chronic (one month) oral clonidine reduced MAP and RVR without affecting RBF or GFR. More recently, Thananopavorn et al (20) reported similar findings in 16 essential hypertensives. Thus, it appears that oral clonidine in humans, unlike parenteral clonidine in animals, decreases RVR to preserve RBF.

Both Campese et al (21) and Thananopavorn et al (20) found a correlation between the reduction in MAP and plasma free catecholamines during cloni-

dine therapy, while Cohen et al (19) found a correlation between reduced RVR and plasma renin activity (PRA), perhaps an indirect marker of sympathetic activity, suggesting that clonidine reduces RVR by inhibiting sympathetic outflow or renin angiotensin vasoconstrictor tone.

α-METHYL DOPA Although α-methyl dopa's hypotensive actions were initially thought to reflect its role as a false transmitter, its major action is now generally considered to be as a central α agonist (22), perhaps via its metabolite α-methylnorepinephrine.

Grabie et al (23) and Cruz et al (24) reported studies assessing the effects of α-methyl dopa on renal hemodynamics in patients with normal baseline GFR. They both found a preservation of RPF, but with a reduction in GFR and filtration fraction (FF). This suggests that α-methyl dopa may act at the efferent arteriole to preserve RPF but at the expense of decreasing GFR, perhaps by decreasing glomerular capillary hydrostatic pressure.

In contrast, Mohammed et al (25) reported a preservation of both GFR and RPF in six hypertensive patients with mild renal impairment. Sannerstedt et al (26) also reported a preservation of RPF and GFR in 11 hypertensive patients. However, all six of those patients with baseline GFR greater than 100 ml/min had a reduction in GFR.

Although all these studies were relatively short-term (less than 10 days), they suggest that patients with normal baseline renal hemodynamics may be susceptible to a functional decrement in GFR, while those with baseline renal impairment may be relatively resistant to these dynamic changes. Longer-term studies are required to determine if these functional changes persist.

GUANABENZ Guanabenz is a recently released central α agonist. One study by Bosanac et al (27) reported a decrease in RPF and GFR in eight hypertensive patients after acute oral guanabenz therapy. However, after three days of guanabenz monotherapy, the GFR and RBF returned to baseline. O'Connor et al (28) reported that guanabenz during chronic (5–7 weeks) therapy in 10 hypertensive patients not only preserved RPF and GFR but reduced RVR. Although the reduced RVR did not correlate with the hypotensive effect, and thus was not paramount to its hypotensive action, it may be important in preserving RBF despite a reduction in systemic perfusion pressure.

α-Adrenoceptor Antagonists

There are currently two orally administered peripheral α antagonists commercially available.

PHENOXYBENZAMINE Phenoxybenzamine, an α_2 blocker, is used almost exclusively for management of hypertension in patients with pheochromocy-

toma. There are no recent published studies evaluating its long-term effects on renal hemodynamics.

PRAZOSIN Prazosin, a post-synaptic α_1 adrenergic blocking vasodilator (29), is widely used in essential hypertension.

Maxwell (30) reported that acute intravenous and acute and chronic oral prazosin had no effect on GFR or RBF in essential hypertensive patients. Subsequent chronic studies done by Koshy et al (31), Preston et al (32), and O'Connor et al (33) confirmed these findings while demonstrating a reduction in RVR (32, 33). Since prazosin reduced RVR without affecting filtration (32, 33), it may act directly on the afferent arteriole to reduce afferent and total RVR, perhaps via post-synaptic α_1 blockade in the afferent arteriole. This is consistent with the observation that the endogenous sympathetic neurotransmitter and α agonist norepinephrine modulates RVR chiefly at the afferent arteriole.

Summary of α-Adrenergic Drugs

Although it is impossible to draw definitive conclusions from a limited number of short-term studies, it appears that peripheral α-adrenergic antagonists preserve renal hemodynamics, while central α-agonists have varying effects. Both acute and chronic clonidine preserve renal hemodynamics. Chronic guanabenz preserves renal hemodynamics, while acute guanabenz does not. In contrast, α-methyl dopa appears to decrease GFR despite preservation of RPF in nonazotemic patients, while renal hemodynamics in patients with nephrosclerosis are unaffected by α-methyl dopa. Pharmacologic properties that account for differences between these α agonists are not readily apparent.

β-ADRENOCEPTOR ANTAGONISTS (Table 2)

The β-adrenergic system may influence renal perfusion and GFR through its effects on cardiac output, renin release, and β-mediated vasodilation (34). β blockade suppresses cardiac output and inhibits β-mediated vasodilation. Both these effects could impair renal perfusion. On the other hand, most β blockers inhibit renin release with a resultant decrease in local angiotensin II production, which may increase renal perfusion and perhaps GFR. In addition, renin suppression could alter sodium and potassium balance because of reduced aldosterone release. Therefore, the net effect of β blockers on renal function is often difficult to predict.

The variable effects of individual β blockers (35) on cardiac output (36) and renin release (37), as well as variability in such properties as cardioselectivity (35, 37, 38), hydrophilicity (38), and intrinsic sympathomimetic activity (35), may result in different effects on RPF and GFR.

Table 2 Effect of various β blockers on renal hemodynamics[a]

Drug	Author	GFR	RBF	RVR	FF	Number of patients	Duration
Propranolol	Wilkinson (45)	↓ 15%*	NR	NR	NR	15	2 months
	Bauer (72)	↔[†]	↓ 15%[††]	↔	↔	14	5–6 months
	Ibsen (46)[b]	↓ 13%**	NR	NR	NR	19	4 months
	Falch (48)[c]	NR	↓ 20%[§]	NR	NR	13	8 months
	O'Connor (49)[d]	↓ 12%*	↓ 15%[††]	↑	↔	15	1 month
	Falch (47)	NR	↓ 13%	NR	NR	11	2 weeks
	Bauer (50)[f]	↓ 27%[†]	↓ 20%[††]	NR	↔	8	—
	Danesh (55)	↔	↔	↔	↔	7	5 weeks
Atenolol	Dreslinski (57)	↔*	↔[§]	NR	NR	10	4 weeks
	Wilkinson (45)	↔*	NR	NR	NR	17	2 months
	Falch (56)	NR	↔[§]	NR	NR	13	4 months
Nadolol	O'Connor (51)[d]	↔[†]	↔[††]	↔	↔	10	6 weeks
	Textor (52)[d]	↔[§]	↔	↔	NR	15	4 weeks
	Textor (53)	↔[§]	↔	↔	NR	13	2 months
	Britton (54)[e]	NR	↓ 31%[§]	NR	NR	6	2–4 weeks
	Danesh (55)	↔	↑ 18%[§]	↓	↓	7	5 weeks
Metoprolol	Sugino (59)	↔*	↔[††]	↔	↔	9	5–7 weeks
Pindolol	Wainer (44)	↔[†]	↔[††]	↔	NR	10	6 months
	Wilcox (58)	↔	↔	NR	—	—	—
Acebutolol	Dreslinski (60)	↔*	↓ 18%[§]	NR	NR	11	4 weeks

[a]* clearance of creatinine; ** clearance of ^{51}Cr-EDTA; † clearance of inulin; †† clearance of paraaminohippurate; § clearance of orthoiodohippurate; NR: not reported. GFR: glomerular filtration rate; RBF: renal blood flow; RVR: renal vascular resistance; FF: filtration fraction.

[b]GFR improved two months after withdrawal of drug

[c]RBF decreased progressively: 11% at one month, 21% at eight months

[d]inverse correlation between baseline RBF and RBF change

[e]When separated into high/low baseline cardiac output and RBF, those with high cardiac output and RBF had a decrease in RBF of 41%

[f]Normotensive subjects

All of the following studies were done on non-azotemic essential hypertensive patients unless otherwise noted.

Acute Parenteral β Blockers

Acute intravenous β blockers suppress cardiac output but increase systemic vascular resistance (SVR). Except in high-renin hypertension, baseline MAP remains unchanged (39). As SVR decreases toward or below baseline values with chronic therapy, a reduction in MAP occurs (39). The elevated SVR is believed to be the result of unopposed α-mediated vasoconstriction after acute intravenous β blockade (39). The mechanism for the reduction in SVR with chronic therapy remains unclear. A similar phenomenon appears to occur in the renal vasculature. In studies using Xenon washout to determine RPF, Sullivan

et al (40) found a 14% reduction in RPF with an increased RVR following intravenous propranolol, while Foley et al (41) found a similar decrement with intravenous cardioselective metoprolol. In contrast, Foley et al found a 13% increment in RPF with nadolol (41). Hollenberg et al (42), using a Xenon washout technique, also found a RPF increment (26%) in response to intravenous nadolol. Using paraaminohippurate (PAH) clearance, Wainer et al (43) found that intravenous pindolol, a β blocker that differs from others in that it has intrinsic sympathomimetic activity (ISA), decreased GFR without affecting RPF. This decrement in GFR returned to baseline with chronic therapy in these same patients. Lastly, Zech et al (44) demonstrated a 16% reduction in RBF with intravenous atenolol, a cardioselective hydrophilic β blocker. The studies by Foley et al (41), Sullivan et al (40), and Wainer et al (43) reported no change in MAP following parenteral β blockers, while Hollenberg et al (42) and Zech et al (44) did not report blood pressure.

Thus, it appears that all β blockers reported except nadolol impair renal hemodynamics with acute parenteral administration. Since blood pressure did not change in these studies, the increased RVR that occurred is likely analogous to the increased SVR that occurs with parenteral β blockers—unopposed α-adrenergic vasoconstriction. The one exception is nadolol, which increased RPF in two separate studies. The mechanism by which intravenous nadolol increases RPF is presently unknown.

Chronic Oral β Blockers

Although acute parenteral β blockers reduce RBF, the potential long-term effect on renal hemodynamics is more important clinically during chronic oral therapy. In seven studies (33, 45–49, 55) of oral propranolol therapy, GFR was determined in five studies (33, 45, 46, 49, 55), with four reporting reductions in mean GFR ranging from 10–27% (33, 45, 46, 49). RBF was determined in five studies (33, 47, 48, 49, 55), with four (33, 47, 48, 49) finding a mean decrement ranging from 13–26%. In only one study (55) was propranolol shown to preserve GFR and RBF. In one other often-quoted study, Bauer (50) demonstrated a reduction in both GFR and RBF in normotensives. RBF returned to baseline two months following cessation of therapy. While creatinine clearance also returned to normal, the decrement in inulin clearance persisted. However, since these were normotensive subjects, the findings may not be relevant to a consideration of propranolol's effect on renal hemodynamics in hypertensives, since normal baseline hemodynamics differ from those of hypertensive patients (1).

Renal hemodynamic studies on the other β blockers with differing pharmacologic properties have had variable results.

Nadolol, a noncardioselective β blocker that is considerably less lipophilic than propranolol (36, 39), did not decrease mean GFR or RBF in five separate

studies (51–55). In fact, it actually increased RBF in two studies, by 18% and 31% respectively (54, 55).

Atenolol, whose properties are similar to nadolol's except for its cardioselectivity, did not affect GFR or RBF in three studies (45, 56, 57).

Two separate studies (44, 58) reported that pindolol, which differs from propranolol in that it lacks membrane-stabilizing activity (MSA) but has ISA, did not reduce GFR or RBF.

Metoprolol, which is cardioselective but lacks MSA, ISA, and hydrophilicity, did not affect RBF or GFR in one study (59).

Finally, acebutolol, a β blocker not presently available in the USA, in a single study reduced RBF without affecting GFR (60). Acebutolol is one of three β blockers (acebutolol, alprenolol, oxyprenolol) that share MSA with propranolol. Alprenolol was assessed in one study (61), but the results are not easily interpretable, since the study was done while the majority of patients were on hydralazine. There are no published studies on renal hemodynamic effects of oxprenolol.

PATHOPHYSIOLOGY OF VARIABLE EFFECTS OF β BLOCKERS UPON THE RENAL CIRCULATION

Systemic Hemodynamics

Since RBF accounts for 20% of cardiac output (62), any drug that reduces cardiac output would be expected to reduce RPF and thus GFR. This relationship has been previously described (63). However, even though all β blockers reduce cardiac output, not all of them reduce RBF. The observation that some β blockers do not reduce RBF suggests that suppression of cardiac output is not pivotal in the reduction of RBF, or that certain β blockers contain intrinsic properties that preserve autoregulation of renal perfusion in the face of altered systemic hemodynamics. For example, intravenous doses of propranolol insufficient to reduce cardiac output or heart rate have been shown to reduce renal perfusion (64). The altered intrarenal hemodynamics may be a function of intrinsic pharmacologic properties of the β blocker.

While cardiac output reduction may be instrumental in reducing renal perfusion during acute parenteral β blocker administration, these effects on renal hemodynamics may be overcome by chronic renal perfusion autoregulation.

Plasma Volume

Intravascular volume contraction might contribute to impaired renal perfusion. Tarazi et al (65) demonstrated an 8% mean reduction in plasma volume with chronic propranolol monotherapy. However, more recent studies have noted neither contraction nor expansion of plasma volume (46, 48, 49, 57, 59, 66,

67). Thus, volume depletion alone cannot be considered a factor in reducing renal perfusion during β blockade.

Pharmacologic Properties (Table 3)

CARDIOSELECTIVITY β_2 adrenergic receptors have been demonstrated in the renal vasculature. Blockade of these vasodilatory receptors may result in unopposed α-adrenergic vasoconstriction. It has been proposed that propranolol-induced renal hemodynamic changes could be secondary to unopposed α-adrenergic renal vasoconstriction (33, 49). This is partially supported by the fact that atenolol and metoprolol, cardioselective β blockers, preserve RBF (45, 56, 57, 59). However, nadolol, a non-cardioselective β blocker, has been repeatedly demonstrated not only to preserve RBF but actually to augment RBF. Thus, although cardioselectivity may be important, it is not the only factor influencing RBF.

ISA β blockers with ISA might be expected to spare the effects of unopposed α-adrenergic vasoconstriction. This may be why pindolol preserves GFR and RBF (44, 58). However, nadolol, which preserves RBF, is not only non-cardioselective but also lacks ISA. In addition, acebutolol has ISA but has been reported to reduce renal perfusion (60).

HYDROPHILICITY Hydrophilic β blockers, as determined by low partition between octanol and water (38), have difficulty crossing cellular membranes. Thus, unlike lipophilic β blockers, they are not metabolized by the liver, are excreted unchanged by the kidney, reach most compartments of the body with relative difficulty, and have long plasma half lives (38). The most hydrophilic β blockers, atenolol and nadolol, have both been demonstrated to preserve RBF. Whether and how this preservation of RBF is related to hydrophilicity is not established. In contrast, some lipophilic β blockers, such as pindolol and metoprolol, preserve renal perfusion (44, 58, 59), while the lipophilic β blocker propranolol diminishes RBF (49).

MEMBRANE-STABILIZING ACTIVITY Propranolol and acebutolol are the β blockers that most consistently reduce RPF during chronic oral monotherapy (49, 60). In addition, both have MSA (Table 3), although the renal perfusion effects of other β blockers with MSA have not been determined. However, MSA, also known as a local anesthetic effect or quinidine-like effect, does not seem to occur at β-blocker doses used for hypertension (35). Since MSA has no known effects on renal perfusion or autoregulation, it cannot be definitively implicated in RBF decrements.

Table 3 Pharmacologic properties of various β blockers[a]

Agent	Cardioselectivity	ISA[b]	MSA	Hydrophilicity
Propranolol	–	–	+	–
Nadolol	–	–	-	+
Atenolol	+	–	–	+
Metoprolol	+	–	–	
Pindolol	–	+	–	
Timolol	–	–	--	
Acebutolol	+	+	+	–

[a] + present; – absent
[b]ISA: intrinsic sympathomimetic activity; MSA: membrane stabilizing activity.

Renal Vasoactive Hormones

RENIN-ANGIOTENSIN SYSTEM In sodium-depleted states, the renin system—via angiotensin II—tends to decrease RBF (13). Therefore, suppression of renin might tend to increase RBF. However, despite propranolol's well-described inhibition of renin release (66, 67), it decreases RBF. In addition, there has been no correlation between suppression of plasma renin activity and change in RBF (43, 49, 56, 57, 60).

KALLIKREIN-KININ SYSTEM Urinary kallikrein is produced in the distal renal tubule and cleaves kininogen to yield kinins—vasodilatory peptides. Evidence suggests that in man, renal kallikrein-kinin system activity correlates with RBF (68, 69) and may modulate RVR. It is of interest that black hypertensives are both poorly responsive to propranolol (70) and deficient in renal kallikrein excretion (68, 69), suggesting a relationship between the two. O'Connor & Preston (49) reported a reduction in urinary kallikrein excretion with propranolol monotherapy, while kallikrein measured by the same technique did not change with nadolol monotherapy (51). Although there was not a significant correlation between change in RBF and change in urinary kallikrein excretion during propranolol therapy, the study does suggest that reduction in kallikrein may play some role in the RBF decrement by interfering with a possible compensatory vasodilator system.

Patient Characteristics

PATIENT SELECTION Two reported crossover studies allowed for control of patient selection variables. In one (55), nadolol statistically enhanced RBF. Following a washout period of six weeks, propranolol did not affect RBF. However, there was no significant difference between RBF after nadolol and RBF after propranolol. Since this is the only study reporting preservation of RBF with propranolol, it suggests that patient selection may be important in demonstrating these changes.

On the other hand, Wilkinson et al (45) conducted a similar study comparing the effects of atenolol and propranolol on GFR. They found that atenolol preserved GFR while propranolol decreased it, with a significant difference between GFR on propranolol versus atenolol. Although they did not measure RBF, based upon other studies the altered GFR is presumably a reflection of altered renal hemodynamics. Thus, patient selection is not the only important factor governing renal response to β blockade.

AGE Although it is known that RBF decreases with age (9), even in normotensives, none of the β blocker studies correlated the renal hemodynamic changes with age. The importance of this factor thus remains unknown.

PRETREATMENT RBF Until recently, most investigators have overlooked the potential relationship between baseline RBF and altered RBF induced by β blockers. As suggested by Hollenberg's study (1), patients with more advanced nephrosclerotic changes are relatively impervious to dynamic changes induced by antiadrenergic drugs. O'Connor and Preston (49) demonstrated an inverse correlation between baseline RBF and RBF decrement in response to propranolol; i.e. those patients with the highest pretreatment RBF had the greatest fall in RBF on treatment. O'Connor et al found a similar correlation in reevaluating their data in patients studied while on nadolol (71), as well as a similar correlation in Textor's published data on nadolol (71). However, a similar correlation was not found by Sugino et al in patients studied while on metoprolol (59), nor by Bauer (72) in propranolol-treated hypertensives.

In addition, although Britton et al (54) reported an increase in mean RBF in essential hypertensives treated with nadolol, when they divided the patients into those with high and low baseline cardiac output and mean RBF they found that those with high baseline values had a decrement in RBF (41%) while those with low baseline values had a mean increment in RBF (31%).

Since other investigators have not routinely assessed this correlation, it is not possible to comment on whether differences in pretreatment renal function may account for changes seen with propranolol in other studies. Nonetheless, it appears that pretreatment RBF may be an important predictor of renal perfusion impairment after propranolol (49).

UNDERLYING RENAL INSUFFICIENCY Although Warren et al (73) reported marked deterioration in renal function in three azotemic patients after β blockade, the risk may have been overemphasized (74). The paucity of similar reports in the literature suggests it is a rare occurrence. This is consistent with the notion (49) that patients with advanced nephrosclerosis are relatively protected from the dynamic alterations in renal perfusion induced by propranolol.

NEPHROTOXICITY There is no evidence that propranolol or other β blockers are nephrotoxic. In the studies cited above, when both GFR and RBF were measured the decrement in GFR was commensurate with the decrement in RBF. None of our patients whose GFR decreased with propranolol (49) had any evidence of renal parenchymal disease (i.e. urinary cells, casts, or proteinuria).

Clinical Importance

One limitation of all the studies cited is the duration of therapy. The longest study period was eight months, which is far shorter than the natural history of hypertension or its usual duration of treatment. Although one study (48) demonstrated a progressive decrement in RBF while on propranolol, decreasing by 11% at one month and a further 10% at eight months, the cumulative data are insufficient to determine the role, if any, of propranolol in hastening the progression of nephrosclerosis.

Despite the reduction of both RBF and GFR, the clinical impact of propranolol on renal function remains unclear since the usual clinical indices of renal function, blood urea nitrogen and serum creatinine concentrations, do not change with therapy (33, 49). Longer-term studies are needed to determine if RBF and GFR decrements after propranolol could progress toward azotemia.

The reversibility of propranolol's effects on renal hemodynamics has yet to be determined conclusively. Ibsen et al (46) reported an improvement in GFR with cessation of therapy. Bauer et al (50) found a persistent decrease in inulin clearance in normotensives after cessation of propranolol; on the other hand, Bauer et al (72) found a persistent decrease in renal blood flow two weeks after cessation of propranolol in hypertensives.

The use of vasodilators in concert with β blockers may confer renal hemodynamic protection, although once again the data is limited. Falch et al (47) reported that the addition of propranolol to hydralazine did not reduce RBF, but following cessation of hydralazine, RBF did decrease.

There is insufficient data to indicate whether factors such as chronicity of hypertension, concomitant use of other medications, dose of β blockers, duration of therapy, or intravascular volume status confer protection or predispose patients to β-blocker–induced decrements in renal hemodynamics.

Although there is one report of profound renal functional deterioration after propranolol (73), preexisting renal insufficiency might actually confer protection against the dynamic changes induced by propranolol in these patients, who would be expected to have the least reactive renal vasculatures (49). Perhaps the patients we should be most concerned with are early hypertensives with intact renal vascular reactivity. Nonetheless, we would not proscribe the use of propranolol in such patients (74). However, if a patient's renal function

deteriorates without apparent cause on propranolol therapy, one may consider changing therapy to another β blocker or to another category of drug altogether.

SUMMARY

Peripheral α antagonists not only preserve renal hemodynamics, but decrease RVR and maintain renal perfusion autoregulation in the face of decreased systemic perfusion pressures. On the other hand, central α agonists appear to have variable effects. Clonidine preserves RBF and GFR both acutely and chronically, guanabenz decreases RBF acutely but not chronically, and α-methyl dopa preserves RBF but decreases GFR.

β blockers also have variable effects on RBF: the most-often–studied β blocker, propranolol, has reduced RBF by 10–20% while other commonly used β blockers, such as nadolol and metoprolol, may preserve RBF. This may reflect propranolol's inability to maintain renal perfusion autoregulation in the face of decreased systemic blood pressure. This failure of propranolol is not completely understood but may be a function of its lack of cardioselectivity or ISA (49). It is also possible that inhibition of renal vasodilators such as the kallikrein-kinin system plays a role (49).

Finally, it appears that patients with normal renal vascular tone may be at highest risk to suffer decrements in RBF with β blockers. Perhaps most importantly, the clinical impact of propranolol's effect on renal function is unclear, since the reductions in GFR have not in general been sufficient to produce azotemia.

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