Hemodynamic Response: Decrease in Cardiac Output vs Reduction in Vascular Resistance

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SUMMARY From a hemodynamic point of view, an adequate response to antihypertensive therapy would be restoration of a normal circulatory system. In most patients with mild to moderate essential hypertension considered to need drug therapy, the cardinal hemodynamic disturbance is an increased total peripheral resistance (TPR) and a normal or reduced cardiac output (CO). During a 10- to 17-year follow-up of untreated hypertensives, a gradual increase in TPR, increase in MAP, and a decrease in CO and stroke volume (SV) were seen. Hemodynamic responses to chronic drug therapy were studied at rest and during exercise in 250 men with mild to moderate essential hypertension in WHO Stage I. A significant reduction in TPR was seen on thiazide diuretics, nifedipine and verapamil, but there was no increase of subnormal CO or SV. A greater normalization of central hemodynamics was achieved by prazosin, which induced a reduction in TPR and an increase in CO and SV, particularly during exercise. In contrast, beta-blocker therapy was associated with a chronic reduction in CO and heart rate (HR) and usually no reduction in TPR below pretreatment values. The chronic CO reduction was associated with an increase in arteriovenous oxygen difference. In 14 patients with therapy-resistant hypertension, a marked increase in TPR was found. Captopril induced a reduction in TPR with rest and exercise, and also a reduction in cardiac output. Prolonged therapy for 5 years with beta-blockers did maintain blood pressure control, but with no further decrease in TPR. In contrast, 5 years of therapy with labetalol induced a gradual fall in TPR below pretreatment levels, and a gradual increase in CO. (Hypertension 5 (supp III): III-49—III-57, 1983)

KEY WORDS hypertension • hemodynamics • diuretics • beta-blockers • prazosin • labetalol • verapamil • nifedipine • captopril

From a hemodynamic point of view, an adequate response to antihypertensive therapy could be defined as a restoration of a normal circulatory system—at rest as well as during exercise. An inadequate response would mean lack of this effect even if the blood pressure is reduced.

The central hemodynamic disturbance in most hypertensive patients considered to need drug treatment is an increased total peripheral resistance (TPR).1-3 Increased vascular resistance is generally found in most vascular beds, such as in the kidneys, splanchnic organs, and skin, and in advanced hypertension, also in the skeletal muscles. The cardiac output (CO) during rest is usually normal or reduced, and the stroke volume (SV) is subnormal. During muscular exercise, subnormal CO and SV are usually found even in mild hypertension in young persons.1

When hypertension is left untreated, the spontaneously occurring changes are characterized by a gradual fall in CO and SV and an increase in TPR—at rest as well as during muscular exercise.1 The changes in blood pressure (BP) may vary, but in most patients with mild or moderate established hypertension (not borderline hypertension), BP will increase over a 10- to 17-year period. In a 10-year follow-up of 29 patients with mild hypertension, CO fell by 20% and TPR increased by 30% during rest.1 Eight of these subjects have had a third hemodynamic study after 17 years. The changes seen at the 10-year follow-up had progressed, as shown in figure 1.

This review will first discuss how the most commonly used antihypertensive agents affect central hemodynamics during chronic treatment in typical patients with mild to moderate essential hypertension. It will also discuss whether inadequate blood pressure reduction could be due to extreme degrees of hemodynamic disturbances and/or to improper drug selection. The review will be limited to diuretics, alpha- and beta-blockers (alone or in combination), calcium antagonists, and to the converting-enzyme inhibitor, captopril.

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Hemodynamic Changes Induced by 1-Year Therapy

Over the years, we have studied the hemodynamic responses to chronic drug therapy in 250 men with mild to moderate essential hypertension (diastolic pressure 100–120 mm Hg) in WHO Stage I. Before treatment, practically all the subjects demonstrated an increased TPRI* (> 2800 dyn·sec·cm⁻²·m⁻²) at rest and also increased values during exercise. CO was normal or moderately decreased; SV was usually normal during rest and subnormal during exercise (reduced by about 20%). During exercise, the arteriovenous oxygen difference was generally increased by 10% to 15%.

Diuretics (Thiazide Diuretics and Tienilic Acid)

About 20 years ago it was shown by Conway and Lauwers that BP reduction during the first days of thiazide treatment was associated with fall in CO and no change in TRP. However, prolonged use over several months caused a fall in TPR toward normal levels and a gradual increase in CO. About 10 years later, these results were confirmed in our laboratory and we also showed that the BP control during exercise was maintained by the same mechanisms — a fall in TRP without reduction in CO. The heart rate (HR) response to exercise was unaffected. A similar hemodynamic response was later demonstrated with tienilic acid. Thus, the thiazide diuretics and tienilic acid might be said to induce at least a partial correction of the hemodynamic disturbances: partial because the subnormal SV and CO during exercise is not corrected.

Beta-Blockers

There are well-documented differences among hemodynamic responses to the different types of beta-blockers during the rest situation, but the responses during muscular exercise are largely the same, especially during chronic treatment. We have studied seven different beta-blockers in 89 patients with mild to moderate essential hypertension, all previously untreated. The typical response to chronic treatment with beta-blockers without intrinsic sympathomimetic activity (ISA) was a BP reduction of about 15% to

*TPRI = MAP × 80 / CI.
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20%, and a fall in HR and CO of about 20% to 25% during rest. During exercise, there was some compensatory increase in SV and a somewhat less reduction in CO (10% to 15%). TPR did usually not fall below pretreatment levels. Figure 2 shows the results in a group of hypertensives treated with atenolol for 1 year.\(^{15}\)

Beta-blockers with strong ISA, such as pindolol, usually maintained BP reduction during rest, with less decrease in HR and CO than from beta-blockers without ISA. TPR stayed at pretreatment levels or was only slightly reduced. During exercise (when sympathetic tone is increased), the reduction in HR was significant but usually less than on beta-blockers without ISA. SV increased (compared to pretreatment level) and TPR during exercise fell slightly below pretreatment level.

Most investigators have agreed upon these hemodynamic changes,\(^ {10-15}\) but some reports have differed and patients responding to chronic beta-blocker therapy with increase in CO and marked fall in TPR have been described.\(^ {16, 17}\) In patients with mild to moderate essential hypertension, however, this reaction pattern is rare. Figure 3 shows the individual changes in cardiac index (CI) in our series. It is seen that CI fell in most patients and the fall was greatest in those with the highest CI values. However, also in patients with rather low CI substantial reductions in CI were seen. Figure 4 shows that in this type of patient relatively few responded with reduction in TPR. Table 1 shows that the number of patients who demonstrated at least a 10% reduction in TPR at rest and during two exercise loads was relatively small.

Most studies have shown that chronic beta-blocker treatment causes little change in oxygen consumption (\( VO_2 \)) at rest as well as during exercise.\(^ {14}\) Since CI is reduced (usually 20% to 25%), this means that the arteriovenous oxygen difference is increased accordingly. The significance of this is not known. However, although many patients react to initiation of beta-blocker therapy with muscular fatigue and cold hands and feet, these complaints often disappear during chronic treatment, at least in patients with mild to moderate hypertension. Cold extremities, however, which are most likely due to reduced peripheral blood flow, are an important problem in cold climate. However, from a hemodynamic point of view, patients on chronic beta-blocker therapy have replaced their normokinetic hypertensive circulatory system by a nor-

**Figure 2.** Hemodynamic changes induced by 1-year therapy of atenolol in 13 men with essential hypertension. \( VO_2 \) = oxygen consumption. Legends are as in figure 1; ----- = before therapy; ----- = on therapy. Note the increase in SI during exercise after therapy, partly compensating the reduction in HR (see ref. 15).
motensive but hypokinetic system. It is of course important that the blood pressure × heart rate product is markedly reduced on beta-blocker therapy, especially during muscular exercise when a 40% reduction or more might be seen. This reaction is of course most adequate in patients with a compromised coronary circulation.

**Alpha-Blockers (Prazosin)**

Studies of prazosin have generally agreed that acutely as well as chronically BP is reduced entirely through reduction in TPR. HR as well as CO is unchanged during rest. During exercise, CO is increased due to an increase in SV and a slight, insignificant increase in HR. Fall in TPR is a very consistent finding. The
TABLE 1. Individual Total Peripheral Resistance (TPR) Responses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Δ TPR &gt; -10% (Rest sitting — 2 workloads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>1/13</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1/12</td>
</tr>
<tr>
<td>Timolol</td>
<td>0/16</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>4/13</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>1/10</td>
</tr>
<tr>
<td>Bunitrolol</td>
<td>0/11</td>
</tr>
<tr>
<td>Pindolol</td>
<td>3/14</td>
</tr>
<tr>
<td>Total</td>
<td>10/89 (11%)</td>
</tr>
</tbody>
</table>

results from our 1-year study are shown in figure 5. In conclusion, prazosin might be said to restore normal circulation in the majority of patients with mild to moderate essential hypertension. No reduction in renal or peripheral blood flow is seen. However, in patients with compromised coronary circulation it should be noted that the workload on the heart is reduced far less than by the use of beta-blockers, since HR is not decreased, only the BP.

Combination of Alpha- and Beta-Blockade (Labetalol)

When alpha- and beta-blockade is properly balanced, a marked reduction in BP is often achieved, the BP reduction being partly due to reduction in TPR and partly due to fall in CO 21 An increase in SV might be expected, and the decrease in CO during exercise is less than when beta-blockers are used alone.

Labetalol induced similar changes, as might be expected since this drug blocks alpha- as well as beta,- and beta,-receptors. 22-25 A substantial BP reduction might then be achieved by one single drug. In our series, the mean reduction was 23%. During exercise, CO was reduced much less than on conventional beta-blockers. 24

Calcium Antagonists (Verapamil and Nifedipine)

In recent years, the calcium antagonists have been introduced for therapy of hypertension. 26-30 These drugs reduce BP through reduction in TPR. During long-term therapy, nifedipine, 30 given in long-acting form, reduced BP 17% during rest without any significant changes in CO, SV, or HR (fig. 6). Verapamil induced similar reduction in TPR, but also about 10%
Figure 6. Hemodynamic changes during chronic treatment with long-acting nifedipine in 14 men with essential hypertension. Note the reduction in total peripheral resistance (TPRI), and no significant changes in cardiac index (CI), stroke index (SI), and heart rate (HR) (see ref. 30).

Figure 7. Individual changes in cardiac index (CI), mean blood pressure (MAP), and total peripheral resistance (TPRI) in 10 men on chronic atenolol therapy studied before therapy, after 1 year, and after 5 years. ——— shows mean values (see ref. 31).
decrease in HR. However, this was compensated by increase in SV and CO was unchanged.

Thus, the calcium antagonists (like the diuretics) maintain BP control by partial correction of the hemodynamic disturbances: only partial because the subnormal CO during exercise is not corrected.

Hemodynamic Responses to Prolonged Drug Treatment (5-6 Years)

Since at least some of the hemodynamic abnormalities in established hypertension are thought to be due to structural changes in the heart and in the resistance vessels, it could be hoped that permanent blood pressure control could induce regression of these changes and also further normalization of central hemodynamics during prolonged treatment. We have studied groups of patients treated with different beta-blockers (alprenolol, atenolol, or metoprolol) and with labetalol who have had a third hemodynamic study after 3-5 years. The results from the atenolol study (fig. 7) show that the systemic hemodynamics were practically unchanged from 1 year until 5 years after the start of therapy. Somewhat disappointingly there was no tendency for an increase in CO and SV or a decrease in TPR. On the other hand, no obvious deterioration had taken place. Similar changes were seen with alprenolol and with metoprolol. The reduction of the workload on the heart was maintained.

We have recently completed a 6-year follow-up on 15 patients with moderate hypertension treated with labetalol for 6 years. The responses were somewhat different from those seen on prolonged beta-blocker therapy. BP was controlled over these 6 years and did not change significantly. However, TPR had fallen at rest as well as during exercise, and after 6 years TPR was less than after 1 year on therapy (fig. 8). CI after 6 years was slightly higher than after 1 year, but the differences between the 1-year and 6-year results were

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**Figure 8.** Hemodynamic changes induced by 6-year therapy on labetalol in 15 men. Solid line = studied before therapy; dashed line = studied after 1 year; and dotted line = studied after 6 years. Mean values and SEM. Stars show differences between the first and the second study. Note the gradual fall in total peripheral resistance (TPRI) and a slight increase in stroke index (SI) and cardiac index (CI) during the 5 years between the second and the third study.
not statistically significant. However, the results point to a greater normalization of central hemodynamics on prolonged labetalol therapy than with prolonged beta-blocker treatment.

**Hemodynamic Characteristics and Responses in Patients with Severe Therapy-Resistant Hypertension**

Anderson et al. studied a group of patients who had shown resistance to treatment with conventional antihypertensive agents (triple therapy with diuretics, beta-blockers, and vasodilators). When therapy was stopped and blood pressure increased, the characteristic hemodynamic disturbance was a marked increase in TPR associated with a subnormal SV and CO. The BP was very high (about 230/140 mm Hg during rest). In a similar group of patients, we have confirmed these hemodynamic characteristics at rest and during mild exercise (Omvik and Lund-Johansen, 1983, unpublished results). Since, apart from structural changes in the resistance vessels, the high resistance could also theoretically be due to an overactivity in the renin-angiotensin system (not measured), the patients were treated with captopril and a diuretic. Most of the patients responded with a substantial drop in BP, with a little change in CO. During exercise, a decrease in CO was also seen. Similar responses during rest have been reported by others.

**Discussion and Conclusion**

This review has shown that most of the commonly used antihypertensive agents may control BP, but often only by partially correcting the hemodynamic disturbances. Particularly the beta-blockers will usually maintain a subnormal cardiac output at rest and during exercise, and of course a subnormal HR. The arteriovenous oxygen difference is increased at rest as well as during exercise. A greater degree of normalization of central hemodynamics is achieved by diuretics and calcium antagonists, but complete normalization of CO is usually not achieved. In our experience, the greatest normalization of central hemodynamics was achieved by the alpha-blocker, prazosin.

During prolonged treatment for 5–6 years, the beta-blockers prevented a further decrease in SV and a further increase in TPR, and thus seem to arrest or stop the changes that could have been expected in untreated patients. Prolonged therapy with combined alpha- and beta-blockade (by the use of labetalol) induced a gradual decrease in TPR and a slight increase in CO at rest as well as during exercise. Thus, combined alpha- and beta-blockade might induce more adequate responses than beta-blockers alone.

This short review discusses only the typical response in patients with mild to moderate essential hypertension. Most of these patients generally seemed to tolerate the chronic reduction in CO induced by the beta-blockers surprisingly well, generally with little restriction in their physical activity. However, in special subgroups of patients, the use of a wrong antihypertensive agent may induce inadequate responses: i.e., a decrease in CI in patients with hypertension and peripheral vascular disorders. In patients with very severe therapy-resistant hypertension, converting-enzyme inhibitors are sometimes particularly useful, at least partly normalizing central hemodynamics through reduction in TPR.

Finally, it should be emphasized that, although the responses to antihypertensive agents vary greatly from a hemodynamic point of view, other effects of the antihypertensive agents might of course have greater significance for the clinical outcome. However, at least when dealing with relatively young patients with mild to moderate essential hypertension where many years (perhaps life-long) therapy might be necessary, restoration of a normal circulatory system would seem to be the most logical way of treating this condition.

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Discussion

DISCUSSANTS: S. JULIUS
P. LUND-JOHANSEN
MUIESAN
P. SLEIGHT

JULIUS: Are lowering the cardiac output and raising the vascular resistance necessarily bad? And is lowering the vascular resistance always good for the body? For example, if one pools all the blood to the skin the vascular resistance may be low but the renal blood flow may be decreased. Tarazi's study suggests that hydralazine causes cardiac hypertrophy in site of the fact that it lowers the vascular resistance.

LUND-JOHANSEN: My philosophy is that the cardiac output should be tailored so that it gives a normal perfusion of the body. So in "healthy" patients with essential hypertension I aim at making things as normal as possible. Possibly this philosophy is wrong and it could even be better to lower the cardiac output and heart rate at rest and during exercise by, say, 20%. But the pay-off is an increased arterial oxygen difference. Patients with mild to moderate essential hypertension seem to tolerate both of these latter features surprisingly well. Finally, this type of treatment has now been in use for 20 years, but there haven't been any reports of a mysterious hypoperfusion syndrome.

MUIESAN: Which doses of nifedipine and labetalol did you use?

LUND-JOHANSEN: With nifedipine we started with 20 mg of the long acting form twice daily, raising this to a maximum total daily dose of 80 mg. With labetalol the initial dose was 100 mg twice daily increasing to 1200 mg maximum.

SLEIGHT: Could you enlarge on your statement that patients with a reduced cardiac output and a raised resistance felt surprisingly well.

LUND-JOHANSEN: Some of these subjects certainly felt dizzy and had "heavy legs" and muscular fatigue the first two to three weeks of therapy, but thereafter these sensations disappeared. Most of the subjects could participate in rather vigorous physical exercise (skiing, mountain hiking) without feeling any change in their physical working performance.
Hemodynamic response: decrease in cardiac output vs reduction in vascular resistance.
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_Hypertension_. 1983;5:III49
doi: 10.1161/01.HYP.5.5_Pt_2.III49

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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