Role of Cardiac Factors in the Initial Hypotensive Action by Beta-Adrenoreceptor Blocking Agents

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SUMMARY The blood pressure decrease after beta-blockade is delayed and there are little data on the hemodynamic events associated with the initial decrease in blood pressure. The present study measured the hemodynamics of the initial hypotensive action of timolol maleate, a nonselective beta-adrenoreceptor blocking agent, in 10 patients with essential hypertension. Frequent measurements were made for the first 30 hours of treatment, and follow-up measurements made at 3 and 6 weeks. Before treatment, mean arterial blood pressure, cardiac output, and arteriovenous oxygen difference were 115.9 ± 9.1 mm Hg, 4.65 ± 1.05 liter/min, and 55.0 ± 9.6 ml/liter, respectively. At 3 hours after the first dose of timolol, blood pressure had fallen 13.5 ± 8.2 mm Hg (p < 0.05). This was preceded by an initial decrease in cardiac output, which was not associated with a simultaneous decrease in blood pressure, and by an increase of arteriovenous oxygen difference. The early, statistically significant, decrease in cardiac output was followed by a return to normal output, which coincided with the onset of blood pressure reduction. The magnitude of the initial decrease of cardiac output and of the initial increase in arteriovenous oxygen difference was significantly correlated to the later decrease in blood pressure (7 hours after first dose). These hemodynamic observations are consistent with the notion that early underperfuions of tissue play a role in the initial hypotensive action of beta-blockers. After 6 weeks, the blood pressure remained lower but the cardiac output was again decreased at that point. As with many antihypertensive agents, there was a difference between the early and late hemodynamic pattern. Only the early pattern was consistent with a peripheral adjustment of circulation to the decreased cardiac output. The early responders tended to remain responsive in the later phase. We speculate that the initial response is important and sets into motion some secondary adjustments that later alter the hemodynamic picture. (Hypertension 6: 145-151, 1984)

KEY WORDS: beta-adrenoreceptor antagonists, essential hypertension, autoregulation, norepinephrine

The mechanism that accounts for the lowering of arterial blood pressure when hypertensive patients take beta-adrenoreceptor blocking agents is not known. A number of theories have been proposed. The most important are the renin theory, the central action theory, the baroreceptor theory, and the cardiac theory. These various theories have been reviewed by a number of authors who concluded that the evidence for them is conflicting, or that there are insufficient data available to adequately evaluate them.1-7

In a review of their experience in a clinical trial with timolol and its antihypertensive action, Julius and Simon8 concluded that the most attractive hypotheses were those that took into account the observation that beta-adrenoreceptor blocking agents that lower blood pressure have as a common property, beta, blockade. At the same time, beta-adrenoreceptor blocking agents vary greatly with regard to their other properties.

These observations led to the conclusion that theories that account for the action of beta-adrenoreceptor blocking agents by their effect on the heart are those most likely to explain the mechanism for the reduction in blood pressure. The heart is the only site in the human that clearly has a preponderance of beta, receptors and thus is the most likely site for the action of agents having as a common property beta, blockade. Other sites at which beta, receptors exist may also be important; however, theories based on the action of the beta-adrenoreceptor blocking agents at those sites will not be readily testable until the role of the extracardiac beta, receptors is more clearly defined. In contrast, the theories based on blockade of cardiac beta, receptors are testable.

Two distinct cardiac theories were proposed in the earlier analysis by Julius and Simon.8 Perhaps the more
widely known is the theory that lowering cardiac output (CO) triggers a peripheral vascular adjustment, but equally as probable is the theory that the stimulus for the reduction in blood pressure is increased intracardiac pressure in the right atrium resulting from the negative inotropic effect of beta-blockers. The increased intracardiac filling pressure and cardiac distention may then be detected by the low pressure cardiac receptors and provide the stimulus for a reflex reduction in blood pressure. To test these two hypotheses, the experimental data that are needed include measurements of CO, oxygen (O₂) consumption, blood pressure, and cardiac distention as reflected either by cardiac filling pressures or measuring cardiac chamber dimensions. These measurements need to be made serially in the initial phase of blood pressure reduction following administration of a beta-adrenergic blocking agent.

Despite numerous hemodynamic studies on the effects of beta-adrenergic blocking agents, only one other study has measured the hemodynamics at the time that the initial reduction in blood pressure occurred. Almost all studies have been restricted to measurements of the changes that occur within 1 hour after intravenous administration of a beta-adrenergic blocking agent or to the measurement of the changes that occur weeks to years after chronic oral administration of these agents. We undertook the current study to examine the hemodynamic events occurring at the time of the initial blood pressure reduction and to examine the cardiac theories for hypotensive action of the nonselective beta-adrenergic blocking agent, timolol maleate.

Methods

We studied 10 patients (seven men and three women) with mild to moderate hypertension. The mean age of the patients was 38 years, and the mean duration of their hypertension was 4.8 years. Secondary hypertension was excluded by clinical and laboratory evaluation, including renal arteriography when indicated. None of the patients had known coronary or valvular heart disease, cerebrovascular or renovascular disease, renal insufficiency, or electrolyte abnormalities. All subjects signed an informed consent form approved by the institutional review committee.

Study Plan

The 10 hypertensive subjects discontinued all antihypertensive medications and were followed for a 3-week period. During this run-in period, they measured their blood pressure at home with an aneroid sphygmomanometer twice daily. During the last week of the run-in period, the patients were maintained on a 20 mEq sodium diet supplemented with sodium chloride capsules containing 100 mEq sodium. Plasma renin activity (PRA) was measured at the end of the run-in period.

Three weeks after discontinuing their medications, the patients were admitted to the Clinical Research Center. A 120 mEq sodium diet was continued throughout the in-hospital phase of the study. Fluids were available as desired. Meals were provided three times a day, and the patients went from the laboratory to the Clinical Research Center dining room at 1200 for lunch and 1800 for dinner. On their first hospital day, they were familiarized with the Hemodynamic Laboratory where the procedures were to be performed, and on the second hospital day, they were taken there at 0730 after having had a light breakfast. Baseline recumbent invasive and noninvasive hemodynamic measurements were obtained 30 minutes after all catheters were introduced. Timolol 40 mg was then given orally for the duration of the study at a dose of 20 mg twice daily. Serial hemodynamic measurements were obtained at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 26, 28, 30 and 32 hours after the initial dose of timolol. Only the baseline and immediate post-timolol hemodynamic data were obtained by both invasive and noninvasive techniques. At the conclusion of the 32-hour serial hemodynamic measurements, the patients were discharged from the hospital. The study was continued for an additional 6 weeks during which time the patients continued to take timolol 20 mg orally twice daily. During this follow-up period as outpatients, they underwent noninvasive tests at the end of the 3rd and 6th weeks to assess hemodynamics, PRA, and plasma norepinephrine (NE) concentrations. These measurements were made at 0830 hours after the subjects had fasted overnight.

Hemodynamic Measurements

Arterial blood pressure was measured directly through an 18-gauge, 2-inch Teflon catheter placed in the brachial artery and connected to a Statham P23Db transducer. Arterial blood pressure was also measured using an automated ultrasonic cuff device (Arteriosonde, Roche Medical Electronics, Cranbury, New Jersey). Mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one-third of the pulse pressure. Both measurement techniques were used for the baseline measurements and for up to 3 hours after timolol was administered. The correlation between the direct and indirect methods was r = 0.948 for the systolic pressure and r = 0.931 for the diastolic pressure. CO was measured using the indocyanine green dye dilution method and the carbon dioxide rebreathing technique. The correlation for the two techniques was r = 0.770. Total peripheral resistance (TPR) was calculated in arbitrary units by dividing the MAP by the CO. O₂ consumption was measured using timed collections of expired air and measurement of the O₂ content difference of the inspired and expired air corrected for temperature, barometric pressure, and humidity. The arteriovenous oxygen (A-V O₂) difference was calculated as O₂ consumption divided by CO, with the result expressed in milliliters of O₂/liter blood.

Echocardiographic Measurements

The echocardiographic studies were performed with a Smith-Kline Instruments 20A M-mode echocardiogram.
graph (Sunnyvale, California). Measurements were made using the leading-edge-to-leading-edge convention. Ejection fraction was calculated from end-systolic and end-diastolic volumes calculated according to the formula of Teicholz et al. and Kronik et al.

Plasma Renin and Plasma Catecholamine Determinations

PRA was measured using a radioimmunoassay technique. Plasma catecholamine concentrations were measured using a radioenzymatic assay.

Data Analysis

The daily home blood pressure measurements for the 3-week run-in period and the 6-week follow-up period were averaged for each week. The data from the 3- and 6-week revisits were also averaged to provide a single revisit data point. Measurements of the same variable obtained at different times were evaluated using an analysis of variance for repeated measures, but restricted to comparisons among baseline, 1 hour, 10 hours, 32 hours, and 6 weeks post-timolol. Correlations were performed using a linear correlation analysis.

Results

The MAP prior to treatment was 115.9 ± 9.1 mm Hg. Following treatment with timolol, the MAP was significantly lower, decreasing a mean of 18.8 ± 10.7 mm Hg at 6 weeks \((p < 0.05)\). The onset of the reduction was at 3 hours after the first dose of timolol, and a near maximum blood pressure reduction of 14.1 mm Hg \((p < 0.05)\) was achieved by 10 hours (Figure 1). The early reduction in blood pressure, i.e., the reduction in pressure at 5 to 10 hours, correlated with the reduction in blood pressure at the late follow-up \((r = 0.657, p < 0.05)\).

The time courses for the other hemodynamic variables were different from the course observed for the MAP. Heart rate was reduced nearly maximally by the first hour and, thereafter, remained significantly reduced \((p < 0.05)\) for the remainder of the study. CO also fell significantly \((p < 0.05)\) in the first hour, but thereafter recovered toward baseline. At 10 hours, CO exceeded the baseline value \((p < 0.05)\), before a second and sustained reduction occurred. A-V \(O_2\) difference increased maximally in the first hour, returning toward baseline in the following hours. Even at the late follow-up, however, the A-V \(O_2\) difference was still greater than at the baseline measurement. The changes in A-V \(O_2\) difference were not statistically significant (Figure 1).

The left ventricular end-diastolic diameter, measured by echocardiography, rose following timolol administration, although this increase was not statistically significant. The changes in left atrial diameter were also not significant, although there was a sustained rise after timolol. Left ventricular ejection fraction was sharply decreased \((p < 0.05)\) following timolol administration and reached its nadir at 1 hour. The left ventricular ejection fraction recovered toward baseline after the first hour.

To help interpret our data, the hemodynamic events can be arbitrarily divided into three phases: 1) a phase of immediate cardiac blockade (acute, 0.5 to 1 hour); 2) an early phase in which the initial reduction in blood pressure occurs (early, 5 to 10 hours); and 3) a late phase of sustained blood pressure reduction (late, 3 to 6 weeks). The acute cardiac blockade was marked by a statistically significant reduction in heart rate, ejection fraction, and CO, and by a rise in A-V \(O_2\) difference, although the change in this derived parameter did not achieve statistical significance. At that time there was no reduction in arterial blood pressure and TPR showed a trend toward being increased.
The early phase in which the blood pressure reduction first occurred was characterized by a correction of CO and A-V O₂ difference toward the baseline pretreatment values, while heart rate continued to be maximally reduced. The changes in TPR were not statistically significant, but TPR decreased and fell below the baseline pretreatment value.

In the late phase, the blood pressure was significantly (p < 0.05) reduced about 20% below the pretreatment level. This was associated with a reduction in CO of 8% and an increase in A-V O₂ difference, both of which were not statistically significant. TPR in our patients was slightly though not significantly reduced at this stage.

Correlations of Late Hemodynamic Changes (6 Weeks) with Early Hemodynamic Changes (5 to 10 Hours)

Early and late changes of blood pressure were significantly correlated (r = 0.637, p < 0.05). Thus, patients who had a large initial reduction in blood pressure also tended to be those with the greatest reduction of blood pressure at the later follow-up. Similarly, the early and late changes in heart rate, left atrial diameter, ejection fraction, and A-V O₂ difference were correlated (Table 1).

Correlations of Acute (0.5-1 Hour) Hemodynamic Changes with the Early (5-10 Hour) Reduction in Blood Pressure

The acute reduction in CO and acute rise in A-V O₂ difference in the first hour following timolol were both correlated to the early reduction in blood pressure observed from 5-10 hours (Table 2 and Figure 2). These correlations were statistically significant for the maximum of the acute change in CO and A-V O₂ difference occurring at either 0.5-1 hour compared to the maximum of the reduction in blood pressure at 5, 8, or 10

Table 1. Correlations of Early with Late Hemodynamic Changes

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
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<tbody>
<tr>
<td>MAP</td>
<td>0.637</td>
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</tr>
<tr>
<td>Heart rate</td>
<td>0.946</td>
<td>&lt;0.01</td>
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<tr>
<td>Left atrial diameter</td>
<td>0.674</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.865</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A-V O₂ difference</td>
<td>0.7507</td>
<td>&lt;0.05</td>
</tr>
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</table>

Table 2. Correlations of Acute Hemodynamic Changes with the Early and Late Reduction in Mean Arterial Pressure

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
<th>r</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.151</td>
<td>NS</td>
<td>0.497</td>
<td>NS</td>
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<tr>
<td>CO</td>
<td>0.659</td>
<td>&lt;0.05</td>
<td>0.665</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>A-V O₂ difference</td>
<td>-0.841</td>
<td>&lt;0.01</td>
<td>-0.457</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>0.063</td>
<td>NS</td>
<td>-0.431</td>
<td>NS</td>
</tr>
<tr>
<td>LV diameter</td>
<td>-0.098</td>
<td>NS</td>
<td>-0.304</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.153</td>
<td>NS</td>
<td>0.441</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 2. Correlation of the early reduction of mean arterial blood pressure with the acute fall in cardiac output (left graph) and with the acute rise in arteriovenous oxygen (A-V O₂) difference (right graph) after treatment with timolol 40 mg by mouth. The early reduction in blood pressure was calculated as the mean of the blood pressures measured at 5-10 hours after beginning treatment subtracted from the baseline value. The acute reduction of cardiac output (CO) was calculated as the mean of the COs measured at 0.5 and 1 hours after beginning treatment subtracted from the baseline value. The acute rise in A-V O₂ difference was similarly calculated as the difference of the baseline value and the mean of the values measured at 0.5 and 1 hour after beginning treatment.
MECHANISM OF EARLY BLOOD PRESSURE REDUCTION BY TIMOLOL

TABLE 3. Plasma Renin Activity (PRA) and Plasma Norepinephrine (NE) Concentration at Baseline and at 6 Weeks Following Institution of Antihypertensive Treatment with Timolol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (upright)</td>
<td>3.3±3.0</td>
<td>1.1±0.8*</td>
</tr>
<tr>
<td>PRA (recumbent)</td>
<td>1.2±0.7</td>
<td>0.8±0.7</td>
</tr>
<tr>
<td>NE (upright)</td>
<td>771±381</td>
<td>712±269</td>
</tr>
<tr>
<td>NE (recumbent)</td>
<td>413±167</td>
<td>438±143</td>
</tr>
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</table>

*p < 0.05 for difference between baseline and 6 weeks.

hours, and for the mean of the acute (0.5-1 hour) change in CO compared to the mean of the early (5-10 hours) reduction in blood pressure. The acute changes in heart rate, ejection fraction, left atrial diameter, and left ventricular end-diastolic diameter did not correlate to the early change in blood pressure.

Correlations of Acute (0.5-1 Hour) and Late (6 Week) Hemodynamic Changes with the Late (6 Week) Reduction in Blood Pressure

The acute decrease in CO correlated with the late reduction in blood pressure ($r = 0.665, p < 0.05$). None of the other acute hemodynamic changes and none of the late hemodynamic changes correlated significantly with the late reduction in blood pressure (Table 2).

Plasma Renin and Plasma Norepinephrine

PRA and plasma norepinephrine (NE) concentrations at baseline and 6 weeks after beginning timolol are shown in Table 3. Only the upright PRA decreased significantly from baseline to follow-up ($p < 0.05$). The baseline upright PRA and NE were positively correlated with the resting heart rate, as was the recumbent PRA ($p < 0.05$, Table 4). The baseline MAP was positively correlated to the upright and recumbent NE, and the baseline CO was significantly correlated to the recumbent NE concentration (Table 4). The acute decrease in heart rate was correlated to both the upright and recumbent baseline PRA and NE, and the acute decrease in CO was correlated to the recumbent NE concentration. The acute rise in A-V difference, however, was not related to the baseline PRA or NE (Table 4). The early and late changes in MAP were not significantly correlated to the baseline PRA, and the late change in blood pressure was also not correlated to the decrease in PRA. There was a correlation, however, between the baseline plasma NE concentration and the reduction in blood pressure observed at late follow-up (Table 4).

Discussion

Before discussing the specific hypotheses examined in this study, let us underscore our data that confirm a number of previous negative observations about the mechanism of blood pressure reduction by beta-blocking agents. Suppression of PRA by beta-blockers has been proposed as an important mechanism for reduction of blood pressure.\textsuperscript{1} There is not wide agreement, however, that this is the case,\textsuperscript{2} and a lack of correlation of the baseline PRA with the subsequent reduction in blood pressure, as in this study, has often been observed. The findings in this study do not support the hypothesis that blood pressure reduction by beta-
blockers is largely through a reduction in PRA. The baseline PRA and NE concentrations both seem to reflect sympathetic tone since they are correlated to heart rate. There was indeed a correlation of the baseline NE to the subsequent reduction in MAP. This observation has been made previously for a number of antihypertensive agents, including the beta-blockers, and may be evidence for a neurogenic mechanism for hypertension. Since we observed a correlation between chronic blood pressure reduction and the plasma NE only, it is conceivable that in the chronic phase blood pressure reduction is in part the result of blockade of neurogenic mechanisms.

Several previous studies have measured the hemodynamic events occurring within 1 to a few hours, and at periods of a few weeks and longer, after administration of beta-blockers. The acute reduction of CO, heart rate, and ejection fraction observed in this study has been well documented in other studies, as has the lack of an immediate reduction in blood pressure. Also well recognized is the late finding of a moderately reduced CO associated with an increased A-V O₂ difference, although in our study these changes were not statistically significant. Previous studies as well as ours have uniformly failed to find a correlation of the late reduction in blood pressure with the reduction in CO measured during the phase of late blood pressure reduction. In this and in other studies it remains true that the significant reduction in blood pressure observed in the late phase for a group of patients must be accounted for by the combined effects of changes in CO and TPR. When the patients are divided into responders and nonresponders, the decrease of CO is similar, and the blood pressure difference is accounted for by a difference in TPR. Not only a decrease of CO but also an adjustment of TPR is required for chronic blood pressure lowering with beta-blockers.

The principal aim of this study was to describe the sequence of hemodynamic events associated with the onset of the blood pressure reduction by the beta-blocking agent timolol. The major reason for obtaining these data was to determine if these events were consistent with either an adjustment of the peripheral circulation to the underperfusion of the body (widenning of the A-V O₂ difference) or the cardiac low pressure receptor hypothesis for the antihypertensive action of beta-blockers, as previously discussed.

The hypothesis that an increase in the intracardiac filling pressures following administration of beta-blockers could lower arterial blood pressure by an increased stretch of cardiopulmonary mechanoreceptors could not be confirmed in our study. We found no correlation of the early or late fall in MAP with the changes in the echocardiographically measured left atrial or left ventricular end-diastolic diameters. The changes in left atrial and left ventricular end-diastolic dimension were small and not statistically significant.

Only one previous study has measured hemodynamic changes during the initial phase of blood pressure reduction. In that study of the effects of atenolol in hypertensive patients, Simon et al. showed that the initial reduction in CO was followed by a return of CO toward baseline. The unique findings of our current study are that the magnitude of the initial reduction in blood pressure is significantly correlated to the magnitude of the immediate reduction in CO and to the immediate rise in A-V O₂ difference that preceded the blood pressure reduction. We interpret these findings as being consistent with the so-called autoregulatory hypothesis for the initial hypotensive action of beta-blockers in hypertension.

The term autoregulation is used for convenience, but may be misleading. In the strictest sense, autoregulation refers to the ability of an isolated tissue or organ to maintain constant flow in spite of changing perfusion pressure. It has been postulated, and experimentally proven, that the whole body possesses the ability to autoregulate. Two types of total body autoregulation have been described, short-term and long-term. The short-term type appears within hours of over- or underperfusion and is considered a rapid adjustment reflecting a summation capacity of local tissues to autoregulate. The relationship of this short-term total body autoregulation to local autoregulation, however, has not been defined and it is therefore more appropriate to use the term of adjustment of the peripheral circulation to altered flow.

Long-term autoregulation occurs over days and weeks and entails not only local flow changes, but a number of secondary adjustments, including alterations in the intravascular or "effective" blood volume. The relationship between the two types of total body autoregulation is not clear, but both seem to be "directly or indirectly related to the oxygen delivery and are local in origin." The observations in our study do not allow assessment of long-term autoregulation. However, since the fall of blood pressure related to the initial underperfusion of tissues (widenning of the A-V O₂ difference), the findings are explainable in terms of a short-term adjustment of the peripheral vasculature.

At 10 hours, CO was increased significantly compared to baseline. In the context of autoregulation, this would seem difficult to explain since an overshoot would not be expected, as CO returned to normal. Calculation of the A-V O₂ difference, however, shows that there was no overshoot. The ratio of CO to O₂ demand did not correct completely, and although the changes in A-V O₂ difference never reached statistical significance, they were at all times greater than baseline. Thus, the rise in CO at 10 hours is probably explained by an increase in O₂ demand (Figure 1), thus the change in O₂ consumption. The rise in O₂ con-
sumption at 5-10 hours is probably not explained by an effect of timolol.

Review of the literature did not uncover any likely pharmacologic mechanism for this observed rise in O₂ consumption. Diurnal variation in O₂ consumption, perhaps related to activity and eating, is a possible explanation. Lund-Johansen also found an increase in O₂ consumption with eating, similar to that in this study, which was associated with a substantial decrease in vascular resistance, but not with a large fall in blood pressure. Beta-adrenergic blockade does not interfere with the ability to substantially increase the blood pressure during exercise in spite of a fall in vascular resistance and an increase of O₂ consumption. Thus, it appears unlikely that the initial fall in blood pressure in this study is related to the food-induced alteration in vascular resistance or O₂ consumption.

The major positive finding of this study is that the hemodynamic sequence of events is consistent with a peripheral adjustment to the decreased CO as the mechanism for the early hypotensive action of timolol. This sequence was found only in the early phase of blood pressure lowering; later the relationship was obscured. The CO in the late phase was reduced, but it settled at an intermediary level between its nadir with acute blockade and the pretreatment levels.

An alteration of the hemodynamic picture in the course of antihypertensive treatment is not unusual. With diuretics, the initial fall of plasma volume and CO is followed by a late volume repletion and a decrease of the vascular resistance. It is interesting to note that in spite of an apparent change in the hemodynamics, there is a good correlation in our study between the early and late blood pressure responses to timolol, similar to that with diuretics. The early, and presumably tissue underperfusion-related, lowering of the blood pressure appears to bear relevance to the late reduction of blood pressure.

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