Biphasic Change in Human Peripheral Vascular Resistance Produced by Carnigen®

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IWATSUKI, N., AMAHA, K. and KOGA, Y. Biphasic Change in Human Peripheral Vascular Resistance Produced by Carnigen®. Tohoku J. exp. Med., 1982, 138 (1), 81-85 — The response of the human peripheral vascular resistance (TPR) to carnigen® was examined on 11 patients by measuring arterial pressure change during cardiopulmonary bypass at a constant pump flow. The administration of 2 ml of carnigen into the bypass for the adult and 1 ml for the child produced an initial transient (36 sec) decrease in arterial pressure (9%) followed by a definite increase (13% at 5 min after administration). The present results, therefore, reveal that carnigen possesses a property changing human TPR in biphasic mode; a transient decrease at first followed by a definite increase.

Carnigen® has commonly been accepted for clinical use as one of the mild vasopressor agents. This drug is a mixture of suprifen, a kind of catecholamine, and a nucleotide extracted from mammalian heart muscle. Following intravenous injection of carnigen in man, blood pressure reveals a mild increase, and occasionally a transient decrease prior to eliciting the increase. The mechanisms of this transient pressure decrease have not been clarified.

The vasopressive action of carnigen has been suggested to be attributed to the increased myocardial contractility (Kenmotsu et al. 1979a) and the acceleration of ventricular function (Komarek and Mansfeld 1977; Kenmotsu et al. 1979b). On the other hand, total peripheral resistance (TPR) was reported to be rather decreased by this drug in the canine experimental study (Komarek and Mansfeld 1977). Because of this reduction in TPR, in other words, the reduced afterload to the heart, carnigen has been recommended to be the drug for choice for the treatment of cardiogenic shock (Nakao et al. 1978). However, the effect of carnigen on human TPR has not been observed. In addition, the opposite change in TPR by carnigen has been reported in the dog (Nozaki et al. 1973).

The change in arterial pressure during cardiopulmonary bypass is considered to reflect solely the change in TPR under a constant pump flow. We, therefore, administered carnigen to patients during cardiopulmonary bypass of open heart surgery to elucidate two questions; what is the response of the human peripheral

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vascular bed to carnigen and whether the initial transient decrease in blood pressure is mediated by the reduction of TPR or not.

**Materials and Methods**

Eleven patients (8 adults and 3 children) undergoing cardiopulmonary bypass for various cardiac surgery were the subjects for this study. Ages ranged from 22 to 57 years in the adults group and from 3 to 5 years in the children group, and body weight in adults was 55.2±6.4 kg (s.D.) and in children 14.4±0.9 kg, respectively.

Anesthesia was maintained with N2O-O2-halothane in 9 cases and morphine-diazepam-N2O-O2 in 2 cases until the start of bypass. During bypass 0.5–0.7% of halothane was administered to the oxygenator in all cases except for one patient to whom morphine was given. After bypass was stabilized and the aorta was cross-clamped, arterial pressures during a constant pump flow were measured continuously from a radial- or femoral-artery catheter by a transducer before and for 5 min after the injection of carnigen. Two ml of carnigen (Hoechst) in adult or 1 ml in child was administered into the reservoir of pump in bolus. The pump flows were 4.46±0.3 liters/min (s.D.) in adult, and 1.54±0.07 liters/min in child, respectively.

Total peripheral resistance was calculated as arterial pressure (torrs)/pump flow (liters/min). The data, expressed as mean±s.E., were analyzed by Student’s t-test for the paired data, and p values less than 0.05 were considered to be statistically significant.

**Results**

The administration of carnigen into the bypass produced an initial transient decrease in arterial pressure, lasted for 36.2±2.4 sec (s.E.). Then the decreased arterial pressure was followed by an obviously increased one (Fig. 1). The maximum decrease in arterial pressure was 7.0±2.2 torrs which was equivalent to 20 torrs.

![Fig. 1. Time course of changes in arterial pressure after administration of carnigen.](image)

*p<0.05, †p<0.01.

**Table 1. Percent changes in arterial pressure following administration of carnigen**

<table>
<thead>
<tr>
<th>Pre-administration</th>
<th>30 sec</th>
<th>1 min</th>
<th>3 min</th>
<th>5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>71.1 torrs</td>
<td>-9.0</td>
<td>+5.9</td>
<td>+17.2</td>
</tr>
<tr>
<td>s.E.</td>
<td>4.4</td>
<td>3.1</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>*p</td>
<td>0.05</td>
<td>0.05</td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>
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Effect of Carnigen on Vascular Resistance

The present study demonstrated that carnigen produced a transient decrease followed by an increase in total peripheral resistance (TPR) in human subject under general anesthesia. This final increase in TPR completely differs from the findings showed by Komarek and Mansfeld (1977) in dog experiments. They reported a 20% decrease in TPR in normotensive dogs and a 28% decrease in hypotensive dogs associated with 34% and 14% increases in cardiac index, respectively, following intraduodenal administration of 3 mg/kg of carnigen. In their study the TPR was calculated from cardiac output and mean blood pressure. The species difference between human and dog may be one reason for this difference in vascular reaction. However, even in the dog, Nozaki et al. (1973) demonstrated a 37% increase in TPR with a 46% increase in cardiac output by intravenous administration of 0.5 ml of carnigen during hypotension under spinal anesthesia. The differences in the experimental conditions, such as the route of drug administration (intravenous vs. intraduodenal) and the methods of TPR measurement, may be other contributing factors for this discrepancy. The administration of a drug during cardiopulmonary bypass is a simple and reliable method for evaluation of the effect of a drug upon TPR unrelated with myocardial function, because peripheral vascular function can be completely separated from cardiopulmonary function. Therefore, our results are considered to be reliable and acceptable as the data showing the properties of carnigen upon the human vascular bed.

The procedure of cardiopulmonary bypass itself has been noticed to elicit occasionally a gradual increase in arterial pressure without any drug administration (Tsuji et al. 1978). The pressure increase in the present study was only about 10 torrs. For excluding the possibility that these increases in arterial pressure in this study are rather phenomena associated with the bypass procedure, and for making the effect of carnigen conspicuous, we administered a large dose of carnigen into

| TABLE 2. Changes in total peripheral resistance (TPR) after administration of carnigen |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Adults (n=8) s.e. Mean          | Changes in TPR (torrs/liter/min) | Maximum Δ decrease | Maximum Δ increase |
| 16.5                            | -1.6 +0.7 +2.0 +2.5 +1.6 +3.4    |
| 1.4                             | 0.7 0.4 0.4 1.1 0.7 0.7          |
| p                               | <0.05 NS <0.001 <0.05 <0.05 <0.001|
| Children (n=3) s.e. Mean        | Changes in TPR (torrs/liter/min) | Maximum Δ decrease | Maximum Δ increase |
| 41.7                            | -4.6 +2.5 +12.3 +11.8 4.6 14.3   |
| 2.5                             | 1.2 2.1 4.0 4.7 1.2 4.3          |
| p                               | <0.05 NS NS <0.05 <0.05          |

to 9.0 percent decrease from the control value, and the Δ increase in arterial pressure at 5 min was 13.0±4.0 torrs (19.3 percent increase) (Fig. 1, Table 1). The calculated total peripheral resistances (TPR) are shown in Table 2. The maximum Δ decrease in TPR was 1.6 TPR units and the maximum Δ increase was 3.4 TPR units in the adults group.

DISCUSSION

The present study demonstrated that carnigen produced a transient decrease followed by an increase in total peripheral resistance (TPR) in human subject under general anesthesia. This final increase in TPR completely differs from the findings showed by Komarek and Mansfeld (1977) in dog experiments. They reported a 20% decrease in TPR in normotensive dogs and a 28% decrease in hypotensive dogs associated with 34% and 14% increases in cardiac index, respectively, following intraduodenal administration of 3 mg/kg of carnigen. In their study the TPR was calculated from cardiac output and mean blood pressure. The species difference between human and dog may be one reason for this difference in vascular reaction. However, even in the dog, Nozaki et al. (1973) demonstrated a 37% increase in TPR with a 46% increase in cardiac output by intravenous administration of 0.5 ml of carnigen during hypotension under spinal anesthesia. The differences in the experimental conditions, such as the route of drug administration (intravenous vs. intraduodenal) and the methods of TPR measurement, may be other contributing factors for this discrepancy. The administration of a drug during cardiopulmonary bypass is a simple and reliable method for evaluation of the effect of a drug upon TPR unrelated with myocardial function, because peripheral vascular function can be completely separated from cardiopulmonary function. Therefore, our results are considered to be reliable and acceptable as the data showing the properties of carnigen upon the human vascular bed.

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the bypass. Following the administration of carnigen an immediate and definite increase in arterial pressure was observed (Fig. 2). The property of carnigen increasing TPR was confirmed in man.

Following intravenous injection of carnigen in man, a transient decrease in blood pressure as shown in Fig. 3 has been frequently noticed. This decrease in blood pressure has been suggested to be mediated by peripheral vasodilatation (Yoshikawa et al. 1979). The present result proves that the reduction of TPR plays a major role for this pressure decrease, unrelated with cardiac effect. Carnigen contains nucleotide and suprifen as its components. But, there have been few studies which evaluate the cardiovascular effect of carnigen by examining the individual components, nucleotide and suprifen, separately. Kenmotsu et al. (1979a) demonstrated that suprifen exerted a positive inotropic effect mediated by a beta-adrenergic receptor stimulation of the heart. It is, therefore, reasonable to speculate that suprifen possesses a beta-action upon the vascular bed. Nucleotide is known to produce vasodilatation of a short duration. Thus, both nucleotide and beta-action of suprifen upon the vascular bed may be responsible for the mediation of the transient TPR reduction produced by carnigen. In addition, the final increase in TPR suggests that the beta-action of suprifen on the vascular bed is weak enough to be overcome by its vasoconstrictive action, or that the beta-action is only transient. Moreover, the contributing component for the carnigen-mediated

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**Fig. 2.** Effect of 4 ml of carnigen upon arterial pressure during cardiopulmonary bypass. TM, trimethaphane.

**Fig. 3.** Change in initial transient decrease of blood pressure following intravenous injection of carnigen.
TPR increase seems to be suprifen, since the only known property of nucleotide to the vascular bed is vasodilatation.

In clinical use of carnigen, it should be taken into account that a transient decrease in blood pressure may occur after intravenous injection. Since the present results indicate that this decrease in blood pressure is owing to the reduction of TPR, the injection of carnigen to a patient in a hypovolemic state may produce a severe reduction of blood pressure to a critical level, even it is only temporary. In fact, Yoshikawa et al. (1979) demonstrated the greater decrease in blood pressure in the hypovolemic patients. Another property of carnigen to be considered in clinical use is that the vasopressive action is associated with an increase in TPR, beside a positive inotropic effect to the heart. A severe increase in TPR which might happen following an injection of large dose of carnigen is undesirable to the heart in a failing or an ischemic state, because of the highly increased afterload for the heart.

The dose of 2 ml administered to a bypass circuit in this study is assumed to be equal to that of 1.25 ml injected to a vein, taking into account of the expanded circulating blood volume by priming fluid during bypass. Usually we use about 1/2–1 ml for the treatment of hypotension in adults, which is less than the dose used in this study. Therefore, changes in TPR, either decrease or increase, caused by the use of the usual clinical doses of carnigen may be less marked than that observed in this study.

In conclusion, the present study revealed biphasic changes in total peripheral vascular resistance of the human subject in response to carnigen; a transient decrease for a short duration followed by a definite increase.

References