CARDIOVASCULAR RESPONSES TO PHENYLEPHRINE AND SODIUM NITROPRUSSIDE DURING ACUTE CORONARY OCCLUSION IN DOGS

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Abstract: The effects of administration of pressor agent phenylephrine (PE) and depressor agent, sodium nitroprusside (SNP) (10-40 μg/kg) on arterial blood pressure (ABP) and heart rate (HR) were investigated during acute occlusion of left anterior descending coronary artery (LAD) in anaesthetized, artificially ventilated dogs with and without the influence of selective blockade of autonomic nervous system (ANS).

ABP response to PE was significantly (P< 0.05) attenuated following 4 hrs of LAD occlusion in all the four groups of animals. SNP response at higher dose (40 μg/kg) was also significantly (P< 0.05) attenuated 4 hrs after LAD occlusion in ANS intact, beta-blocked and atropinized groups. The bradycardia response to PE after LAD occlusion was abolished in vagotomized group while in the other three groups, it was significantly attenuated following 4 hrs of LAD occlusion. The tachycardia response to SNP was significantly (P< 0.05) attenuated 4 hrs after LAD occlusion in ANS intact and atropinized animals. The response was abolished in beta-blocked animals and no significant change occurred (P>0.05) in vagotomized group. This study suggests that the cardiovascular reflex effects of PE and SNP are significantly attenuated following acute LAD occlusion. Blocking any of the components of ANS changed this responsiveness.

Key words: coronary occlusion phenylephrine sodium nitroprusside arterial blood pressure baroreflex

INTRODUCTION

Coronary artery occlusion is known to activate cardiac receptors, induces various cardiovascular reflex responses (1-4) and the autonomic nervous system (ANS) plays a critical role in triggering ventricular fibrillation (5-6). Chronic myocardial infarction is reported to damage the left ventricular sensory nerve endings and impair reflexes that originate in the heart in response to change in cardiac filling (7). Acute myocardial ischemia or infarction induced by coronary occlusion provokes vagally mediated depressor reflexes originating in the ischemic myocardium (8). It has been demonstrated that vagal affarent nerves from cardiopulmonary receptors may modulate arterial baroreflex response (8-9). Studies have also been

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conducted to examine autonomic reflex mediated changes in the heart rate (HR) to discriminate patients at high or low risk of sudden death (3). Changes in HR mediated by baroreceptor reflex can provide a meaningful way to assess autonomic control of the heart (5-6).

In most of these studies in human/animal, phenylephrine (PE) and sodium-nitroprusside (SNP) are commonly used as a pressor and depressor agents respectively. The corresponding reflex changes in HR or pulse intervals (PR) are used to assess the arterial baroreflex responses (10-11). However, there is lack of information on the effect of these drugs per se during coronary artery occlusion and the role of autonomic nervous system (ANS) in modulating these effects.

Therefore, the main purpose of the present study was to investigate the effect of PE and SNP on BP and HR during pre and post left anterior descending coronary artery (LAD) occlusion in anaesthetized dogs with intact ANS, beta-blocked, atropinized and vagotomized conditions.

**METHODS**

Dogs weighing 10-15 kg of either sex were used. Animals were anaesthetized with morphine sulphate (3 mg/kg) intramuscular, followed by intraperitoneal injection of an anaesthetic mixture consisting of allobarbitalone (12.5 mg/kg), pentabarbitone sodium (7.5 mg/kg) and urethane (50 mg/kg) as per procedure described earlier (11-12). This combination of anaesthetics was used to obtain a slow HR. A tracheal cannula was inserted and the dog was artificially ventilated at a rate of 24/min with a tidal volume of about 14 ml/kg body weight. A left thoracotomy was performed in the 4th intercostal space, the pericardium was opened and LAD was exposed approximately 1 cm. beyond its origin. A thread was placed around LAD for occlusion. The arterial pressure was recorded on a two channel recorder (Beckman type RS Dynograph) with a pressure transducer (Statham P-23 Db). A rectal thermometer was used to record the body temperature which was maintained at 37-38°C. Arterial blood samples were drawn anaerobically from the femoral arterial catheter periodically and blood PO2, PC02 and pH were measured with the help of radiometer (BMS-3MK-2 blood microsystem in conjunction with PHM-73 pH/blood gas monitor) during each experiment, and blood gases were maintained within normal range by adjusting ventilation.

Experiments were carried out in four groups of animals: in the 1st group of ten dogs, the ANS was intact, in the second group of five dogs following control observation beta-blockade was done by i.v. injection of propranolol (1 mg/kg) every 20 min. In 3rd group of 5 dog, atropine (1 mg/kg) was administered to block efferent parasympathetic pathway. In 4th group of 5 dogs, bilateral vagotomy was performed. An increase or decrease in B.P. was achieved by bolus injection of a single dose of PE or SNP respectively in control as well as 4 hrs after coronary artery occlusion. The corresponding changes in HR with increase in BP were recorded.

The data from each series of experiments were analysed separately. On evidence of significant effects, individual and other appropriate comparisons were done through linear contrasts (13). The variables have been expressed throughout as mean values and the variation between animals of the same group is indicated by standard error of mean (±SEM).

**RESULTS**

1. Effect of PE on arterial blood pressure:

Intravenous administration of PE resulted in a dose-dependent increase in BP. The mean values of result obtained in this series of experiments are represented in Fig. 1.

In ANS intact animals having baseline MAP 97±3 mmHg, there was a dose-dependent increase in MAP following bolus injection. (iv) of PE, both before and 4 hrs after LAD occlusion. While no significant (P>0.05) difference in MAP at lower doses of PE (10-20 μg/kg) was found, it was significantly (P<0.05) reduced 4 hrs after LAD occlusion (Fig.1). Following administration of 10, 20, 30 and 40 μg/kg of PE, the corresponding increases in MAP in ANS intact animals before LAD occlusion were 30±2, 42±3, 61±3 and 92±4
mmHg while 4 hrs after LAD occlusion the MAP values were 33±3, 45±3, 52±2 and 74±3 mmHg respectively (Fig. 1).

In beta-blocked animals for the similar doses of PE, the ΔMAP values were 54±5, 81±4, 90±5 and 93±6 mmHg respectively before LAD occlusion and 28±3, 43±5, 60±5 and 65±5 mmHg respectively 4 hrs after LAD occlusion (Fig. 1). In atropinized animals MAP values, before LAD occlusion were 17±2, 44±4, 68±3 and 80±4 mmHg, and 25±3, 40±3, 54±2 and 64±5 mmHg respectively after LAD occlusion (Fig. 1). In vagotomized animals, for similar doses of PE, MAP values before LAD occlusion were 42±2, 68±3, 82±3 and 106±5 mmHg while post LAD values were 34±2, 63±3, 65±3 and 62±4 mmHg respectively.

In all four groups of animals, ΔMAP values were lower 4 hrs after LAD occlusion. In ANS intact, atropinized and vagotomized groups, the attenuation in ΔMAP response was more prominent at higher dose of PE (40 μg/kg), while in beta-blocked group, a distinct attenuation in MAP response was observed for all the four concentrations of PE 4 hrs after LAD occlusion.

II. Effect of PE on heart rate:

A decrease in HR was observed in all the four groups of animals following administration of PE (10-40 μg/kg). However, significant (P< 0.05) difference was observed in bradycardia response for the similar doses of PE before and after LAD occlusion (Fig. 2).

In ANS intact group, a dose-dependent decrease in HR from a control value of 108±3 b/min was observed on administration of PE. Before LAD occlusion, at 10, 20, 30 and 40 μg/kg of PE, the fall in ΔHR (ΔHR) was by 28±1, 49±2, 70±2 and 76±3 b/min respectively while 4 hrs after LAD occlusion for similar doses of PE, ΔHR values were 25±1, 40±1, 57±2 and 60±2 b/min respectively (Fig. 2).
In beta-blocked group, administration of 10, 20, 30 and 40 μg/kg of PE before LAD occlusion produced a decrease in HR by 22±2, 34±2, 38±3 and 40±3 b/min. This response was however, reduced to 11±1, 24±2, 27±2 and 28±2 b/min, 4 hrs after LAD occlusion for similar doses of PE.

In atropinized animals, PE produced a dose-dependent decrease in HR. Following administration of 10, 20, 30, and 40 μg/kg of PE, the HR before LAD occlusion was reduced by 24±2, 33±2, 42±2 and 46±3 b/min respectively while for similar doses of PE, 4 hrs after LAD occlusion, HR was reduced by 10±1, 17±1, 25±2 and 28±2 b/min respectively (Fig. 2).

In vagotomized animals, the fall in HR by PE was very small after LAD occlusion while before occlusion there was significant reduction in HR (Fig. 2). HR fell by 32±2, 50±3, 72±7 and 82±5 b/min following 10, 20, 30 and 40 μg/kg PE injections respectively before LAD occlusion while for similar doses after LAD occlusion HR fell by 9±1, 12±1, 12±1 and 14±1 b/min respectively.

III. Effect of SNP on arterial blood pressure:

Intravenous administration of SNP resulted in a dose dependent fall in BP. The mean values of results are summarised in Fig. 3.

In animals with ANS intact, a dose-dependent decrease in MAP following bolus injections of SNP (10-40 mg/kg) during pre and post LAD occlusion was observed. There was no significant (P> 0.05) effect of LAD occlusion on MAP values resulting from 10, 20 and 30 mg/kg while at 40 μg/kg of SNP a significant (P<0.05) difference was observed between pre and post occlusion values. At this dose (40 μg/kg) of SNP before occlusion, the reduction in MAP was by 58±2 mmHg from a control value of 97±3 mmHg while after 4 hrs of occlusion, same dose of SNP produced a fall in MAP by 40±1 mmHg (Fig. 3).

In beta-blocked and vagotomized animals, no significantly (P> 0.05) different hypotensive response was observed for different doses of SNP before and after LAD occlusion (Fig. 3). However, with 40 μg/kg SNP, reduction in MAP after LAD occlusion was significantly (P < 0.05) less as compared to pre-occlusion values (Fig. 3). In atropinized animals, LAD occlusion produced a significant attenuation in MAP with SNP. At 10, 20, 30 and 40 μg/kg of SNP, the corresponding ΔMAP values were 25±2, 38±3, 57±3 and 72±4 mmHg before occlusion while 34 hrs after LAD occlusion for similar doses of SNP the ΔMAP values were 17±2, 28±2, 33±2 and 45±3 mmHg respectively (Fig. 3).

IV. Effect of SNP on heart rate:

An increase in HR following administration of SNP (10-40 μg/kg) was always observed in all the four groups of animals. The results are summarised in Fig. 4.

In ANS intact animals, administration of 10, 20, 30 and 40 μg/kg of SNP, the increase in HR (ΔHR) before occlusion was by 50±2, 68±3, 77±2 and 81±3 b/min respectively. These responses 4 hrs after LAD occlusion were reduced to 29±2, 31±2, 33±2 and 45±2
alpha receptor stimulant with little effect on beta receptors of heart. A direct action on receptor accounts for the greater part of its effects, only a small part being due to its ability to release norepinephrine. Similarly, the hypotensive effects of SNP is known to be the result of direct peripheral vascular relaxation independent of sympathetic innervation (14).

In this study, we observed a significant (P< 0.05) reduction in MAP after LAD occlusion at high dose (40 µg/kg) of PE in all the groups of animals. Following LAD occlusion SNP at high doses (40 µg/kg) caused a significant (P<0.05) reduction in MAP in ANS intact, beta-blocked and atropinized animals. Reduction in BP response on administration of PE and SNP before and after coronary occlusion has been observed earlier also (2, 10-11).

The observed decrease in the responsiveness of pressor or depressor agents (PE and SNP during autonomic blockade seems to be, due to the disturbance in its vasoconstrictor or vasodilator effect. It has been reported that following coronary occlusion, vasodilator induced decrease in BP may be capable of upsetting the tenuous balance of factors controlling the extent of ischemic injury (15). Under the condition of O₂ deficiency, such as anaemia there is a decrease in cardiovascular responsiveness to selective beta-adrenergic receptor stimulation with isoproterenol and alpha adrenergic stimulation with PE (16) and to some neurotransmitters (17).

Besides neurohormonal and metabolic factors, recently, endothelium derived factor(s) (EDRF) e.g. nitric oxide (NO) and prostacycline are being considered to be effective regulators of vascular tone, BP and tissue perfussion (18-19). Various constrictor and dilator stimuli work in maintaining cardiovascular homeostasis. Under pathological conditions, whichever, stimulus (vasodilator/constrictor) dominates, it affects the cardiovascular parameters accordingly.

It is well known that abnormalities in cardiopulmonary baroreceptor mechanisms contribute to the pathophysiology of several disease states including hypertension, syncope and heart failure (20). It has also been earlier reported that there is inhibition

DISCUSSION

The pressor response of PE (10-40 µg/kg) was significantly (P< 0.05) attenuated following LAD occlusion in all the four groups of animals viz ANS intact, beta-blocked, atropinized and vagotomized animals. This study demonstrated that similar doses of PE and SNP do not produce same degree of hypertensive or hypotensive effects respectively after LAD occlusion. It is well known that PE, used mainly as a pressor agent in hypotensive states, is a powerful alpha receptor stimulant with little effect on beta receptors of heart. A direct action on receptor accounts for the greater part of its effects, only a small part being due to its ability to release norepinephrine. Similarly, the hypotensive effects of SNP is known to be the result of direct peripheral vascular relaxation independent of sympathetic innervation (14).

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It is well known that abnormalities in cardiopulmonary baroreceptor mechanisms contribute to the pathophysiology of several disease states including hypertension, syncope and heart failure (20). It has also been earlier reported that there is inhibition
of arterial baroreflex in response to an increase or
decrease in BP during acute LAD occlusion in dogs
(2, 11). The fall in HR caused by PE was significantly
(P<0.05) reduced after LAD occlusion for the same
dose in ANS intact and atropinized animals and was
almost abolished in vagotomized group. However, the
bradycardia response was significantly (P<0.05) higher
in beta-blocked animals suggesting that this reflex
inhibition of the response was mediated primarily
through vagi. The tachycardia response observed after
SNP administration (10-40 μg/kg) was significantly
(P<0.05) reduced 4 hrs after LAD occlusion in ANS
intact, atropinized and vagotomized animals while there
was no change in HR in beta-blocked group. These
observations suggest that the reflex tachycardia
response operating partly through sympathetic limb of
ANS is affected by acute LAD occlusion. Our
observations in vagotomized animals support the
contribution of vagal efferent in baroreflex mediated
tachycardia response. Our study is also in conformity
with the earlier findings that the reflex tachycardia
response to drug induced hypotension is often absent
or drastically reduced in ischemic heart disease patients
(21). The reduction in the response to PE and SNP
could be either due to reduced sensitivity of the
baroreceptors of destruction or sensory nerve endings
in the ischemic myocardium as reported earlier (7).

In our study we always observed a significant
increase in HR following occlusion of LAD in ANS
intact and beta-blocked groups while some workers
did not find any change in HR during coronary
occlusion (2, 22). The possible reason for this
discrepancy could be the higher control HR in their
animals, since it is well established that the baroreflex
sensitivity and various other reflex chronotropic
responses depend on the pre-existing vagal and sympa-
thetic tone (2, 23-24). Anaesthetics used in previous
studies e.g. pentabarbital, chloralose are known to
inhibit parasympathetic tone and increased sympathetic
efferent activity whereas in our animals under the
anaesthetic mixture, morphine-allobarbitone- 
pentabarbitone-urethane, an adequate level of resting
vagal and sympathetic efferent activity is evident from
relatively low control HR in the range of normal HR
of conscious resting dogs.

In conclusion, our study suggests that the
hypertensive or hypotensive effects of PE and SNP
respectively are significantly reduced under the
condition of acute LAD occlusion. The resulting HR
changes are also attenuated under such conditions.
Blocking any of the components of autonomic nervous
system, significantly affects the responsiveness of PE
and SNP during acute LAD occlusion suggesting the
involvement of both parasympathetic and sympathetic
efferents and vagal afferents. The vagal component
seems to play relatively larger role during coronary
occlusion.

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