# CARDIAC ACCELERATION BY ANGIOTENSIN II IN DOGS

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**Summary:** The effects of angiotensin II on heart rate of dogs were studied by intravenous and intracerebroventricular routes.

Following differences were noticeable when the results obtained with intracerebroventricular were compared with those obtained after intravenous administration. The onset of tachycardia was less as compared to the intravenously administered angiotensin. The dose required to produce tachycardia was less and the magnitude of tachycardia was also greater with intracerebroventricular administration. The initial bradycardia observed with intracerebroventricular or intravenous administration of angiotensin, could be prevented by using the mechanical buffering device. The spinal cord transection at $C_2$ level and bilateral vagotomy abolished the tachycardia.

It is speculated that angiotensin acts centrally either on the hypothalamic or medullary accelerator neurones (central sympathetic structures) and produces some degree of increased adrenergic neuron discharge which is responsible for cardiac acceleration in dogs.

**Key words:** angiotensin intracerebro-ventricle increased sympathetic activity

## INTRODUCTION

In the anaesthetized cats intraventricular angiotensin produces an increase in heart rate (8, 13). In the intact unanesthetized animals, the influence of the peripheral circulation, nervous system as well as release of adrenaline from suprarenals are also operative (3, 7). In addition to its direct stimulant action on the smooth muscles of arterioles, angiotensin has also been reported to activate the cardio-acceleratory nerves, either centrally or peripherally (1,8,13). It would be of considerable importance to work out the mechanism (s), involved in the cardiac actions of angiotensin.

## MATERIALS AND METHODS

Male and female dogs weighing between 10-14 *kg* were used in the present study. They were anaesthetized by 10% chloralose solution in normal saline administered intravenously (80-100 *mg/kg*). In order to prevent clotting, heparin (3-4 *mg/kg*) was administered intravenously. The standard dose of 1 *µg* per *kg* angiotensin-II (hypertensin, Ciba) diluted in a volume of 2 *ml* with 0.9 per cent of sodium chloride solution was used while a dose of 4.0 *µg* made up in a volume not more than 0.2 *ml* was injected into the lateral cerebral ventricle.

For determination of heart rate and rhythm continuous electrocardiographic tracings were taken beginning at least 10 seconds before intravenous injection of angiotensin II and continued for 1-2 minutes after injection. This was followed by recordings at one minute interval upto 5 minutes and thereafter, the records were taken at 7,10 and 30 minutes. In

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all the dogs, a constant ventilation of the lungs was maintained with the artificial respirator. The mechanical blood pressure buffering device was used according to Varma *et al.* (12). The cannulation of lateral cerebral ventricle was done according to the technique of Bhargava and Tangri (5). The denervation of the heart was done by exposing and sectioning both the vagi high in the neck and dorsal laminectomy was done by exposing the spinal cord and transecting at $C_1$ level after ligating it.

## RESULTS

*Effects of intravenous and intracerebroventricular administration of angiotensin II prior to and following the buffering of blood pressure*: In ten noral anaesthetized dogs without the buffering of blood pressure, administration of angiotensin produced initial slowing followed by increase in heart rate with a maximum average value of $135.20 \pm 12.38$ beats per minute (Table I, Fig. 1). When angiotensin was administered following buffering of blood pressure, the initial slowing of heart rate was not observed and magnitude of tachycardia was much more marked (Mean $140.00 \pm 11.44$ beats per minute). The maximum increase in heart rate was observed within 5 minutes. The tachycardia persisted for 30 minutes after injection. Repeated injections of angiotensin produced the same degree of tachycardia when injected at interval of one hour.

In five anaesthetized dogs, angiotensin administered into lateral cerebral ventricle following buffering of blood pressure produced a significant tachycardia with a maximum mean value of $144.32 \pm 16.82$ beats per minute from a control mean value of $104.64 \pm 12.00$ beats per minute. The initial bradycardia was not observed in all these dogs.

*Effects of angiotensin II administered into lateral cerebral ventricle prior to and following bilateral vagotomy*: Following angiotensin II administration into lateral cerebral ventricle of ten anaesthetized dogs, there was an initial bradycardia followed by tachycardia, which appeared within 30 seconds, reaching a maximum mean value of $138.42 \pm 13.92$ beats per minute from a control mean value of $100.25 \pm 14.99$ beat per minute (Fig. 1). After vagotomy, when angiotensin was administered into lateral cerebral ventricle it produced tachycardia, with maximum mean value of $173.82 \pm 14.28$ beat per minute from a control mean value of $130.22 \pm 11.20$ beat per minute (Table I, Fig. 1). There was no initial bradycardia in all the dogs. The tachycardia appeared within 20 seconds and persisted for 30 minutes.

*The effects of intraventricular and intravenous administration of angiotensin following spinal cord section and bilateral vagotomy*: There was no change in heart rate from control mean value, when angiotensin was administered into lateral cerebral ventricle, following spinal section at $C_2$ level and bilateral vagotomy in five anaesthetized dogs. In the same dogs intravenous administration of angiotensin also did not cause any tachycardia (Fig. 1).

The effect of angiotensin II administered into lateral cerebral ventricle following prior treatment with (A) Reserpine (1 *mg* intraventricular), (B) Propranolol (2.5 *mg/kg*) and (C) Guanethidine (10 *mg/kg*) slow i/v.

(A) Reserpine was introduced into lateral cerebral ventricle 24 hours prior to angiotensin administration in five dogs. The usual tachycardia was not observed and heart rate remained at control level (Mean 90.46±18.25 per minute) (Table I, Fig. 1).

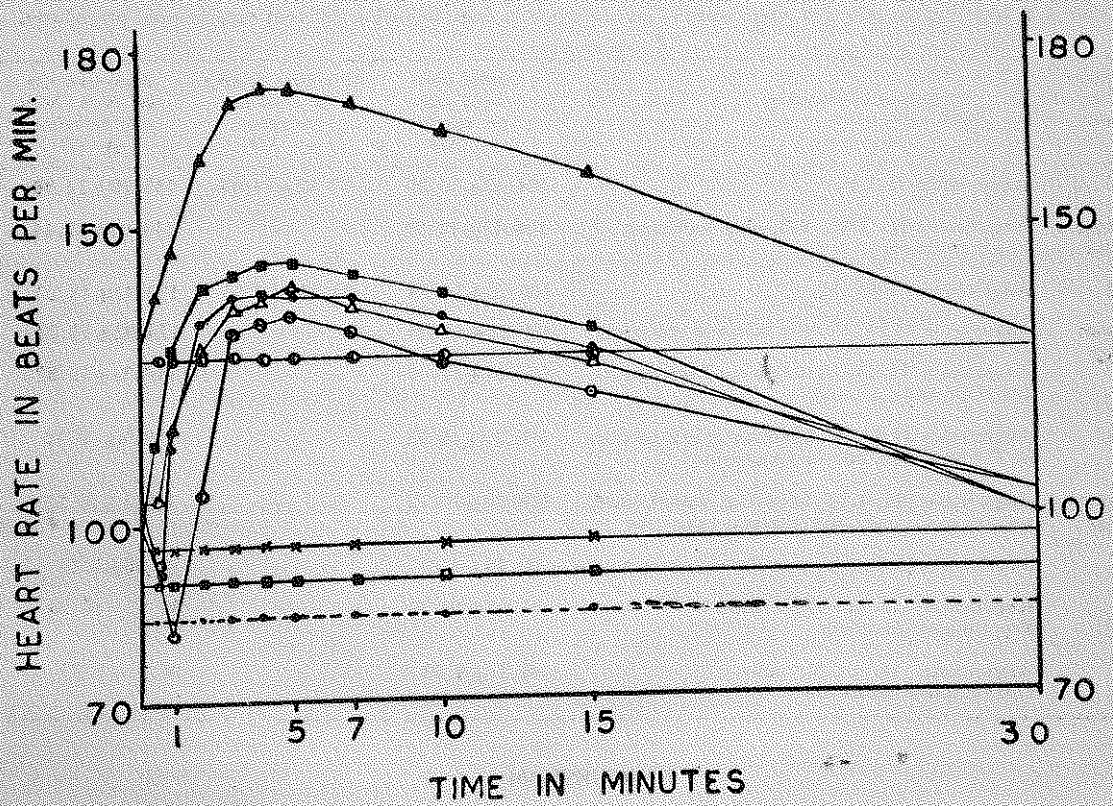


Fig 1: Cardioacceleration by angiotensin II

- — Angiotensin II intravenous (I.V.)
- — Angiotensin II I.V. following buffering of blood pressure.
- — Angiotensin II intracerebroventricular (I.C.V.).
- — Angiotensin II I.C.V. after bilateral vagotomy.
- — Angiotensin II I.C.V. following buffering of blood pressure.
- — Angiotensin II I.C.V. following spinal section at $C_2$ level and bilateral vagotomy.
- — Angiotensin II I.C.V. after treatment with reserpine.
- — Angiotensin II I.C.V. after propranolol treatment.
- — Angiotensin II I.C.V. after guanethidine treatment.

(B) In five dogs propranolol was injected slowly intravenously dissolved in 20 *ml* of normal saline. After half an hour angiotensin was introduced into the lateral cerebral ventricle. The heart rate was not altered (Table I, Fig. 1).

(C) In five dogs guanethidine was injected intravenously. Angiotensin was introduced into the lateral cerebral ventricles after half an hour (4, 6). There was no increase in heart rate (Table I, Fig. 1).

TABLE I : Showing the effects of angiotensin II on heart rate in dogs, following different experimental procedures.

| *Number of experiments* | *Experimental procedures* | *Control mean heart rate per minute* ± *SD* | *Maximum slowing of heart rate per minute* ± *SD* | *Maximum rise in mean heart rate per minute* ± *SD* |
|---|---|---|---|---|
| 10 | Angiotensin II I.V. | 104.42±10.29 | 82.42±14.84 | 135.20±12.38 |
| Same dogs | Angiotensin II I.V. following buffering of blood pressure | 104.42±10.29 | — | 140.00±11.44 |
| 10 | Angiotensin II I.C.V. | 100.25±14.99 | 92.26±12.54 | 138.42±13.92 |
| Same dogs | Angiotensin II I.C.V. after bilateral vagotomy | 130.22±11.20 | — | 173.82±14.28 |
| 5 | Angiotensin II I.C.V. following buffering of blood pressure | 100.64±12.00 | — | 144.32±16.82 |
| 10 | Angiotensin II I.C.V. following spinal section at $C_2$ level and bilateral vagotomy | 128.20±10.52 | — | 128.5±10.52 |
| Same dogs | Angiotensin II I.V. following spinal cord section at $C_2$ level and bilateral vagotomy | 128.20±10.52 | — | 128.5±10.52 |
| 5 | Angiotensin II I.C.V. after Reserpine treatment | 90.46±8.25 | — | 90.46±8.25 |
| 5 | Angiotensin II I.C.V. after Propranolol treatment | 84.52±10.26 | — | 84.52±10.26 |
| 5 | Angiotensin II I.C.V. after Guanethidine treatment | 96.21±9.73 | — | 96.21±9.73 |

## DISCUSSION

In the present study it has been observed that intravenously administered synthetic angiotensin produces initial transient slowing, followed by an increase in heart rate above the control level, persisting for about 30 minutes. The initial decrease in heart rate is produced by reflex activation of pressoreceptors due to the elevated blood pressure (11).

In our experiments, this reflex cardio-inhibition appears to be mediated via vagus nerve as bilateral vagotomy abolished this effect (Fig. 1, Table I). That the cardio-inhibition is produced by stimulation of the pressoreceptors, is evident from the studies in which the increase in blood pressure was prevented by use of the mechanical buffering device. In these experiments, the increase of blood pressure was insignificant when angiotensin was injected intravenously, thus the effective stimulus of the pressoreceptors, at whatever site they may be located,

was absent. The cardio-inhibition was abolished and the heart rate was observed to increase from the very beginning in such experiments. The increase in heart rate is not related to depression of vagal inuflences as is evident from the fact that bilateral vagotomy did not alter the magnitude of tachycardia induced by intravenous angiotensin. Angiotensin when introduced intravenously does not seem to exert a direct peripheral action on the myocardium and sinoatrial node, since it had no effect on the heart rate in spinal and vagotomized dogs. The cardiac acceleration produced, therefore, is likely to be through the stimulation of sympathetic system either peripherally or centrally.

A direct stimulant action of angiotensin on the superior cervical ganglion of cat has been reported by Lewis *et al.* (9,10). Hence, it seems that two opposing factors are operating on the heart rate when angiotensin is administered. The reflex vagal activation tries to decrease the heart rate and the other cardioaccelerator influences are tending to increase the rate. The initial bradycardia is obtained because the vagal influences predominate but these are short lived. When the vagal influence wears out, the acceleratory effect becomes apparent and prolonged, so that tachycardia results (11). Our results suggest that cardioacceleratory influences are due to increased sympathetic activity induced by angiotensin.

In those experiments in which angiotensin was introduced into the lateral cerebral-ventricle in a dose of 4-$\mu g$, tachycardia was observed (Fig. 1, Table I) and the tachycardia was of greater magnitude in dogs having a lower resting heart rate. The onset of tachycardia was within 30 seconds when angiotensin was administered into lateral cerebral ventricle as compared to the onset of about 1 minute with intravenously administered angiotensin. These findings favour the concept that angiotensin exerts its action centrally rather than peripherally (8). In these experiments, the initial a slowing was present but was much less in magnitude as compared to the bradycardia produced by intravenous administration of angiotensin. That this immediate bradycardia is related to rise in arterial blood pressure is demonstrated by the fact that the initial slowing was absent when angiotensin was introduced into the lateral cerebral ventricle while blood pressure rise was buffered by mechanical buffering device (Fig.1,Table I).

The fact that repeated intraventricular administration of angiotensin at one hour intervals produced similar tachycardia indicates that the phenomenon of tachyphylaxis was not a complicating factor under these experimental conditions.

Central vagal cardio-inhibitory neurons are not affected by angiotensin since bilateral vagotomy did not modify the tachycardia produced by angiotensin in any way (Fig. 1, Table I). Administration of propranolol intravenously half an hour bef re, blocked the cardio-accelerator action of intraventricularly administered angiotensin. This would suggest that tachycardia is due to a direct action of angiotensin on cardio-accelerator neurons in the central nervous system. The peripheral leakage of angiotensin was ruled out by injecting it into the lateral cerebral ventricles in dogs having spinal cord transected. In such dogs, angiotensin

failed to produce tachycardia. Angiotensin when introduced intravenously after spinal section and bilateral vagotomy in dogs, produced no change in heart rate (Fig. 1, Table I). This demonstrates that actions on heart rate are of central origin.

It is presumed that angiotensin acts directly or indirectly on central sympathetic structures, thereby inducing prolonged increase in heart rate. This is further supported by the fact that pretreatment with intraventricular reserpine and intravenous guanethidine abolished the tachycardia produced by intraventricularly administered angiotensin. This would also suggest that epinephrine and/or norepinephrine may be the chemical mediator responsible for the action of angiotensin on heart rate.

Benetato *et al.* (2) observed that under cross circulation conditions centrally administered angiotensin was capable of releasing catecholamines from peripheral stores. Feldberg and Lewis (7) also have shown that angiotensin is capable of directly releasing adrenomedullary catecholamines.

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