# HAEMODYNAMIC EFFECTS OF HYPOTHALAMIC STIMULATION ON SKIN AND MUSCLE VENOUS BEDS*

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**Summary:** Twenty three points mainly located in the posterior hypothalamus were stimulated to study its effect on the pressures, flows and calculated segmental resistences of the skin and muscle venous beds of hind limbs in the dog. Stimulation of these points produced a uniform pattern of rise in pressures of the muscle veins consisting of a steep rise during stimulation followed by a rapid decline to basal level on its cessation. Skin veins, on the other hand registered a gradual increase in pressure during stimulation followed by a secondary rise during post stimulatory period. Large veins of both muscle and skin exhibited comparatively smaller pressure increases than small vein. These pressure changes were accompanied by a similar marked rise in systemic arterial pressure.

Out of 23 points, 21 points produced similar increases in the calculated resistances of skin and muscle veins. Two points produced greater increase of the skin vein resistances. Total venous resistance of the limb was therefore, raised by all the points stimulated. None of these points elicited any fall in the pressures or calculated resistances of either the muscle or skin venous bed. Muscle venous outflow always registered an inereese while the skin venous outflow recorded either a small increase or decrease or at times no change during the hypothalamic stimulation.

These findings demonstrate that hypothalamic stimulation can profoundly alter the haemodynamics of the hind limb venous beds and actively mobilize the post capillary venous sections of both skin and muscle venous beds.

**Key words:** skin venous flow; muscle venous flow; hypothalamus; posterior hypothalamus; hypothalamic control of blood flow; differential control of skin and muscle venous flow

## INTRODUCTION

Electric stimulation of the hypothalamus has been reported to provoke selective or differential changes in the precapillary resistance segments belonging to different paralled coupled vascular circuit (1,6,9,22). It is not yet experimentally demonstrated whether such controls from the hypothalamus are also applicable to the postcapillary venous beds of the parallel-coupled vascular circuits. Well known bodily responses engage veins belonging to different vascular beds differently. For example, cutaneous veins are brought into action mainly for the purpose of thermoregulation (24,25), splanchnic veins are more sensitive to blood volume changes (20) while veins belonging to skin, muscle and splanchnic beds actively constrict during exercise (2,3,17,23).

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In this study, we obtained haemodynamic data in terms of pressure, flow and resistance in the skin and muscle venous beds and studied the effect of stimulation of discrete areas of hypothalamus on these parameters. It was observed that stimulation of hypothalamus produced profound haemodynamic alterations in both skin and muscle venous beds, which were not identical and showed certain degree of differential control.

## MATERIALS AND METHODS

Mongrel dogs of either sex weighing between 7 and 15 *kg* were anaesthetised with 50-60 *mg/kg* alpha chloralose given intravenously. Anaesthesia was maintained at the same approximate level by supplementary doses of the anaesthetic (5-10 *mg/kg*) whenever required.

### Measurement of pressure, flow and resistance:

These parameters were measured in the muscle and skin venous beds of the hind limb by using a technique described earlier by Nagle *et al.* (18) after slight modification. The technique is based on the anatomical consideration that the blood flow from the paw and the skin is drained mainly through the medial and the lateral saphenous veins. The medial saphenous vein drains into the femoral vein at a level lower than the lateral saphenous vein. Thus, if the blood from the medial saphenous vein, is so diverted as to join the flow of the lateral saphenous vein, an approximately total skin and paw venous flow can be measured. Rest of the blood flow coming from the femoral vein will then represent the drainage of the blood from the bone and muscle tissue.

The data of venous flow thus differentiated when considered alongwith the pressure gradients in the skin and muscle venous bed would give the respective resistance to flow according to the following equation :

$$R = \frac{SVP - LVP}{F}$$

Where R is resistance expressed as mm *Hg/ml/min*/100 *gms* of tissue, SVP is pressure (mm Hg) in the small vein of a particular venous bed, LVP is the pressure in the large vein of that bed, and F is the venous blood flow in *ml/min*/100/*gms* of tissue.

A schematic diagram depicting the separation of the two venous beds and the sites at which pressures in the small and large veins of respective venous beds were measured is given in Fig.1. Small vein pressure was measured through polythene catheters introduced in a retrograde manner into the metacarpal vein for the skin venous bed, and a small vein draining the hamstring muscle for the muscle venous bed. Such a manoeuver never hampered the venous drainage of either tissue. This was frequently confirmed during the experiment by flushing the catheter with saline and observing free flow occuring through the collateral

vessels. This was further confirmed at the end of each experiment by injecting a solution of methylene blue which coloured various collaterals of a particular venous bed. Large skin

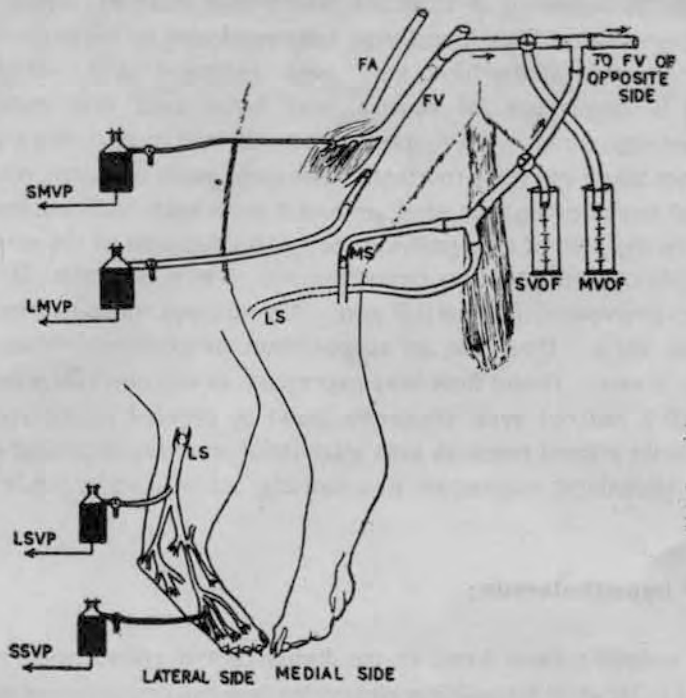



Fig. 1: Schematic diagram showing location of catheters for the measurement of pressures and flows in the skin and muscle venous beds of the hind limb of the dog.

Note the extracorporeal circuit interposed to separate the skin and muscle venous outflows, both of which were ultimately led into the femoral vein of the apposite side. Whenever desired the venous outflow of each bed was diverted to a measuring cylinder to record the respective venous outflow of skin or muscle.

| | | |
|---|---|---|
| FA | — | Femoral artery |
| FV | — | Femoral vein |
| LMVP | — | Large muscle vein pressure |
| LS | — | Lateral saphenous vein |
| LSVP | — | Large skin vein pressure |
| MS | — | Medial saphenous vein |
| MVOF | — | Muscle venous outflow |
| SMVP | — | Small muscle vein pressure |
| SSVP | — | Small skin vein pressure |
| SVOF | — | Skin venous outflow |

vein pressure was measured by threading a polythene catheter to a side branch of lateral saphenous vein. Large muscle vein pressure was similarly measured by introducing a catheter through the central end of the medial saphenous vein and lodging it in the femoral vein. All pressures, were recorded on a Grass Model 5P1 ink writting polygraph by the use of

appropriate Statham strain gauge transducers (P23 BC). Blood flow of a particular venous bed during any period was measured by collecting blood for a half min in a 10 *ml* measuring cylinder by opening a stopcock which was inserted ahead of the large vein for pressure measurement. This blood was later reinfused in the animal. At the end of each experiment, the skin of the hind limb was removed and weighed. Remaining limb tissue, that is composed of muscle and bone was also weighed. Also in a series of 7 experiments, 2 mm wide rings of small skin and muscle veins in which catheters were inserted, were taken out post-mortem. The rings were slit open with a sharp ophthalamic scissors and stretched against an illuminated scale with minimal force to measure the circumference with the help of a magnifying loop. The diameter of the small veins was then calculated by applying the equation circumference $= \pi$ x diameter. The diameters of the small veins varied between 0.75 and 0.5 mm. No rigorous measurement of the diameters of large veins was done. However, an approximate estimation indicated that these were always more than 3 mm. Blood flow was expressed as *ml/min*/100 *gms* of tissue in each case. Heparin (0.5 *mg/kg*) was routinely given to prevent clotting of blood. In all experiments systemic arterial pressure was also simultaneously recorded with the help of a P23 AC Statham transducer connected to a catheter introduced in the left femoral artery.

**Stimulation of hypothalamus:**

With the animal's head fixed in the frame of the stereotaxic instrument (INCO) holes were drilled in its skull for guiding electrodes into the posterior areas of hypothalamus. The stereotaxic coordinates were chosen as recommended by Lim *et al.* (13). Bipolar concentric steel electrodes of 0.25 mm tip diameters were lowered into the holes in steps of 0.5 mm and various points in the tracks were stimulated. Stimulation was done with square wave pulses (1.2-6V, 0.5-1 msec, 60-100 Hz) obtained from Grass stimulator model S4 through an isolation unit model SIU-4B. Each point was stimulated with the same fixed parameters of stimulation at least three times, first for recording changes in skin vein pressures, then for recording muscle vein pressures, and last for measuring venous outflow. A rest of at least 5 min, was given in between the stimulations.

**Histological confirmation of sites of stimulation:**

At the end of each experiment anodal current of 2 ma was passed for 10 secs at the tip of electrode to produce electrolytic lesion. Brain was removed, perfused and kept in 10% formol saline for 7 days. Coronal sections, 12 u thick were cut and stained with haematoxylin and eosin. These were enlarged nine times to confirm the stimulation point.

**Miscellaneous:**

All the animals were paralysed by intravenous gallamine triethiodide 2-3 *mg* per *kg* and artificially ventilated with a positive pressure respiratory pump. Body temperature of the animal was continuously monitored and maintained at 37°C.

## RESULTS

**Basal values:**

In general, the mean pressures in the skin veins were higher than the muscle veins and the venous outflow per 100 *gm* of tissue from the skin was higher than that recorded from the m iscle. The range and mean values of basal pressures, outflows and calculated resistances of skin and muscle venous beds recorded over a period of 4 to 5 hrs are given in Table I. Venovasomotor waves were not present in the muscle vein records but were

TABLE I: R inge and mean values of basal haemodynamic parameters of skin and muscle venous beds

| | *Small vein (mmHg)* | *Large vein (mmHg)* | *Outflow (m1/min/100 gm)* | *Resistance (mmHg/ml/min/100 gm)* |
|---|---|---|---|---|
| *Skin veins* | | | | |
| Range | 5 - 20 | 2 - 12 | 1.9 - 20.0 | 0.6 - 1.83 |
| Mean | 13.18 | 7.20 | 8.80 | 1.15 |
| SE | ±0.52 | ±0.61 | ±0.34 | ±0.15 |
| *Muscle veins* | | | | |
| Range | 5 - 15 | 2 - 12 | 1.75-16.0 | 0.25 - 1.70 |
| Mean | 8.90 | 5.59 | 4.41 | 0.91 |
| SE | ±0.71 | ±0.59 | ±0.08 | ±0.05 |

noticeable in a fair number of records from skin veins. The magnitude of these waves when manifest, was never more than 2-3 mm Hg.

**Responses from Hypothalamus:**

Figure 2 reproduces a polygraphic record obtained on stimulation of a locus in the posterior hypothalamus. Stimulation at such a locus always produced marked increase in systemic arterial pressure, heart rate and pulse pressure which was accompanied by an increase in the large and small vein pressures of the muscle as well as skin venous bed It may, however, be noted that the temporal pattern of the muscle vein pressor curves were

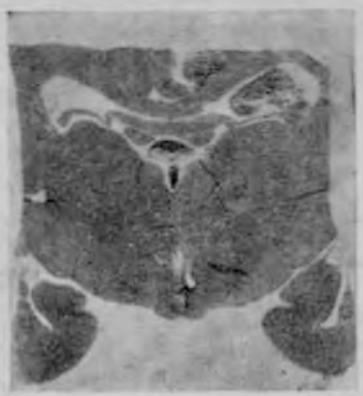
distinctly different from those of skin veins. Rise in muscle vein pressures was always stimulus bound exhibiting a steep rise during stimulation followed by a rapid decline to the basal values after the cessation of stimulation. On the other hand, the skin veins showed gradual slow rise during stimulation followed by a secondary rise during post-stimulatory period and then a slow decline to the baseline. This pattern of change in skin vein pressure has been reported earlier in response to sympathetic chain stimulation and considered to be due to disparity in the rate of inflow and outflow, the post stimulatory run-off of blood being much less than the continued inflow (12). Such a situation could result from constrictive closure of veins or their valves (5). We have earlier reported that the skin vein constriction outlasts the sympathetic chain stimulation by 60-70 sec while resistance vessels of the same bed come back to the basal level within 10-15 sec (15). Measurement of venous flow in the two beds during stimulation indicated an increase in muscle venous flow and a decrease in the skin venous flow.

A total of 23 points in various parts of the posterior hypothalamus and one point in the midlateral hypothalamus were stimulated, each producing a marked rise in the systemic arterial pressure and venous pressure curves of the type depicted in Fig.2. Polygraphic records showing the effects of stimulation of two more such loci in the hypothalamus alongwith the data on the venous outflow and resistance to flow in the respective venous beds are depicted in Fig.3. The composite data of resistance and flow changes of the muscle venous bed obtained on stimulation of all the hypothalamic loci is tabulated in Table II and that of the skin venous bed is given in Table III. It can be noted that muscle venous outflow was inveriably increased by as much as 23.8% to 63.4% while the skin venous flow either decreased or increased by a small proportion. It is interesting however, that most loci in the perifornical, lateral and mammilary regions of posterior hypothalamus produced an increase in resistance to venous outflow which was of similar approximate magnitude in the skin and muscle beds. There were however, two loci, one each in the periventricular and lateral hypothalamus, stimulation of which produced a marked increase in resistance to skin venous outflow, almost 2-3 times of resistance to flow in the muscle veins. All the 23 stimulation loci are plotted in four serially arranged coronal sections of the dogs brain in stereotaxic coordinates according to Lim *et al.* (13) as given in Fig. 4.

## DISCUSSION

Haemodynamic alterations of the venous sections recorded in this study, we believe, are mainly due to active neurogenic constrictions of veins brought about by the increased discharge of the sympathetic fibres during hypothalamic stimulations. Precautions were taken to minimise those factors which passively affect the veins. For example, extra vascular skeletal and respiratory effects were controlled by paralysing the animal and artificially ventilating it; and for tabulation of data, only records with basal transmural pressures

more than 5 mm Hg were used for at this pressures, the veins are expected to be filled and any change in their calibre would then mainly be due to neurogenic constriction (19).



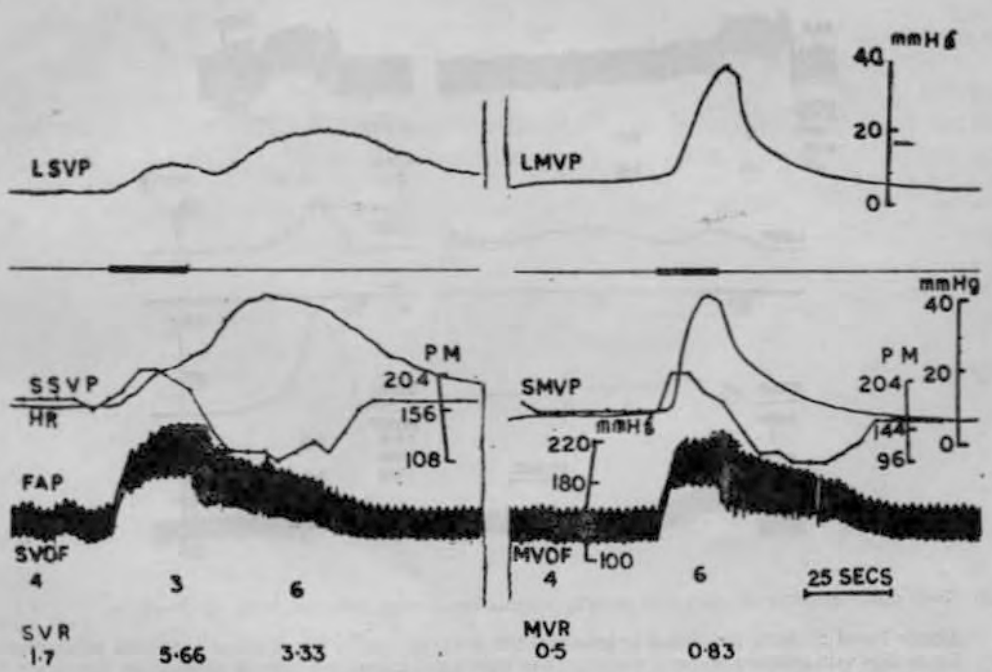



Fig. 2: Polygraphic record to illustrate typical response pattern obtained on stimulation of most of the points in the posterior hypothalamus. Note the temporal pattern of the skin and muscle vein pressor curves. Readings of venous outflow and calculated resistance to flow are given under the records. Insert on the upper side shows the histological localization of the point in the Nucleus supramamillaris. Abbreviations same as in Fig. 1. Parameters of stimulation used were 4V, 1 msec, and 80 Hz.

It has been reported that with artificial regulation of blood flow, the normal reactivity of the vascular tissue to nervous stimuli cannot be maintained for long periods of experimentation (7). Therefore, arterial inflow to the limb was purposely not regulated in our experiments to preserve the normal reactivity of the vessels. Increase in arterial flow, therefore, might have partly contributed to the total rise in the muscle venous resistance obtained by hypothalamic stimulation.

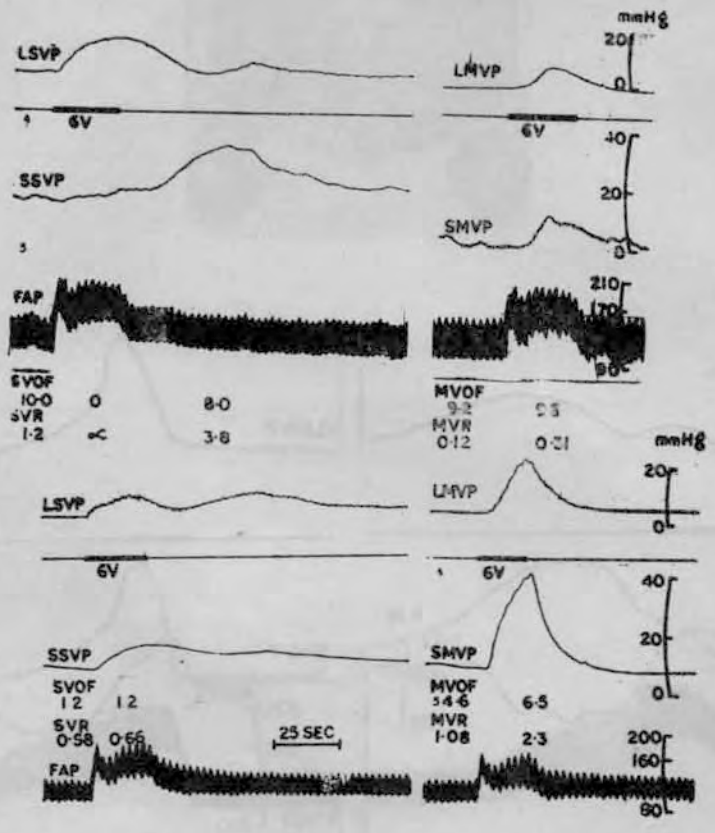



Fig. 3: Two other patterns of skin and muscle venous responses obtained from hypothalmus.

Upper Panel : Note the disparity between the onset of rise in pressures of large and small skin veins. Large skin vein pressure showed a marked rise during the stimulation period itself while significant rise in the small skin vein pressure was obtained only after the cessation of stimulation. The muscle vein pressures registered only a small rise. The calculated skin venous resistance showed infinite increase. Stimulating electrode was located in fornix.

Lower Panel : Stimulation of a point in the lateral mammillary region elicited pattern similar to depicted in Fig. 2.

Systemic arterial pressure recorded simultaneously rose markedly in response to stimulation of both the points. Stimulation pulses employed were 6V, 1 msec, and 80 Hz. Abbreviations same as in Fig. 1.

TABLE II: Mean changes in the resistance and outflow of muscle venous bed elicited on stimulation of various hypothalamic loci.

| | *Outflow (ml/min/100 gm)* | | | *Resistance (mmHg/ml/min/100 gm)* | | |
|---|---|---|---|---|---|---|
| | *Control* | *After Stimu.* | *% Changes* | *Control* | *After Stimu.* | *% Changes* |
| 1. Perifornical region (PL) (6)* | 3.08 ±0.90 | 4.73 ±0.90 | +53.90 | 1.07 ±0.19 | 2.25 ±0.41 | +90.20 |
| 2. Posterolateral hypothalamus (7) | 2.67 ±0.16 | 4.30 ±0.11 | +61.04 | 1.15 ±0.07 | 2.01 ±0.04 | +74.80 |
| 3. Mammillary area( 6) | 2.41 ±0.12 | 3.95 ±0.30 | +64.40 | 1.18 ±0.11 | 2.47 ±0.14 | +109.20 |
| 4. Periventricular area ( PM) (1) | 2.80 | 3.90 | +52.30 | 0.71 | 1.28 | +80.20 |
| 5. Posterior hypothalamic area (2) | 2.50 | 3.30 | +30.80 | 1.00 | 1.66 | +66.00 |
| 6. Perifornical region (middle hyopthalamus) (1) | 2.10 | 2.60 | +23.80 | 1.40 | 2.10 | +50.00 |

*Number in parenthesis refers to number of stimulation points in the respective region.

PL — Posterolateral
PM — Posteromedial

TABLE III: Mean changes in the resistance outflow of skin venous bed elicited on stimulation of various hypothalamic loci.

| | *Outflow (ml/min/100 gm)* | | | *Resistance (mmHg/ml/min/100 gm)* | | |
|---|---|---|---|---|---|---|
| | *Control* | *After Stimu.* | *% Changes* | *Control* | *After Stimu.* | *% Changes* |
| 1. Perifornical region (PL) (6)* | 7.83 ±1.41 | 7.91 ±1.01 | +1.09 | 0.97 ±0.90 | 1.62 ±0.27 | +66.90 |
| 2. Posterolateral hypothalamus (7) | 5.01 0.12 | 5.18 0.32 | +3.30 | 1.21 ±0.07 | 2.05 ±0.15 | +60.30 |
| 3. Mammillary area(6) | 6.00 0.20 | 6.26 0.37 | +4.30 | 1.14 ±0.03 | 2.20 ±0.27 | +92.10 |
| 4. Periventricular (PM) (1) | 5.40 | 5.00 | —7.40 | 0.83 | 3.00 | +261.40 |
| 5. Posterior hypothalamic area(2) | 6.00 | 6.85 | +14.15 | 1.12 | 1.81 | +70.70 |
| 6. Perifornical region (middle hypothalamus)(1) | 4.80 | 4.00 | —16.60 | 1.04 | 2.20 | +118.40 |

*Number in parenthesis refers to number of stimulation points in the respective region.

PL — Posterolateral
PM — Posteromedial

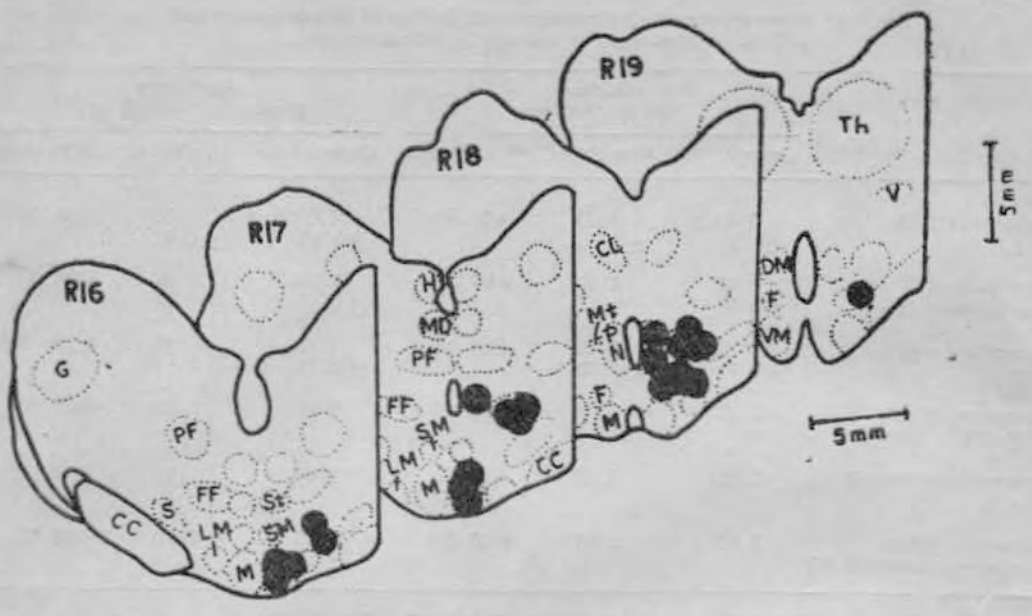



Fig. 4: Stimulation loci which produced increase in the pressure and segmental resistances of both the skin and muscle venous beds are plotted in serially arranged coronal sections of the dog's diencephalon. Note that stimulation points are concentrated in the posterior hypothalamus. Approximate outline of the principle nuclei is drawn with dotted line.

Abbreviations : Terminology from Lim *et al.* (13)

| | | |
|---|---|---|
| CC | — | Crus cerebri |
| CL | — | Nucleus centralis |
| DM | — | Nucleus hypothalamicus dorsomedialis |
| F | — | Fornix |
| FF | — | Campi foreli |
| G | — | Nucleus corporis geniculate lateralis |
| H | — | Nucleus habenulae |
| LM | — | Nucleus mammellaricus lateralis |
| M | — | Nucleus mammellaris medialis |
| MD | — | Nucleus thalamicus dorsomedialis |
| Mt | — | Tractus mammillothalamicus |
| PF | — | Nucleus perafascicularis |
| PN | — | Posterior hypothalamus |
| R | — | Rostral |
| SM | — | Nucleus supramammillaris |
| St | — | Stria terminalis |
| Th | — | Nucleus medialis dorsalis and nucleus centralis lateralis |
| V | — | Nucleus ventralis |
| VM | — | Nucleus hypothalamicus ventromedialis |

Earlier we have reported that stimulation of medulla oblongata and hypothalamus produces various patterns of circulatory responses involving differential changes in the tone of capacitance and resistance vessels of skin (16). In the present study, haemodynamic data obtained both from skin and muscle venous beds demonstrates that in the chloralose anaesthetized preparation, the pressures and resistances to blood flow in skin veins were higher than the muscle veins, indicating a higher basal tone in skin veins. This is in accord with the generally accepted view that the skin vascular section except for the shunt vessels have fairly high basal tone (10). Stimulation of all the posterior hypothalamic points investigated in the present study, increased the segmental resistances and the pressures of both the cutaneous and muscle venous beds, thus raising the total hind limb venous resistance. This would decrease the venous capacity leading in turn to increase of venous return and the cardiac output (14,11,21). If these lower limb venous responses represent the changes that may be occurring in the rest of the skin and muscle venous beds of the body, then this is what would be desired in the event of muscular exercise or elaboration of a defence reaction.

None of these points produced a fall in the muscle vein pressures and decrease in its segmental resistance. These observations corroborate earlier findings (8) that the hypothalamus induced cholinergic vasodilatation is limited only to the precapillary resistance vessels of muscle vascular bed. Constriction of post-capillary venous section instead of dilatation during exercise or defence reaction would help (i) in mobilizing the increased arterial blood flow towards the heart and (ii) more effective efflux of the fluid from the vascular bed to the metabolically highly active skeletal tissues.

The present study further demonstrates that while the resistances of both skin and muscle venous beds show a parallel increase, it is only the muscle venous outflow that registered a significantly marked increase on stimulation of posterior hypothalamus, and this was uniformly observed in all animals. The increase in muscle venous outflow may partly be due to the muscle venoconstriction but perhaps in a large measure it must have been a reflection of increased arterial inflow for stimulation of these areas does produce a dilatation of pre-capillary resistance vessels of the muscle (6,4,8).

The posterior hypothalamic loci excited in the present study did not produce any selective changes limited only to skin or muscle venous bed alone. The selective effects on the cutaneous and muscle veins perhaps would be obtained from more anterior regions of hypothalamus (16). However, dissimilar increase of the resistances of skin and muscle segment were obtained at least from two points. Our study, thus, demonstrates that the post capillary venous sections like the precapillary vascular segments of skin and muscle vascular circuits are equally strongly mobilized in cardiovascular adjustments evoked by stimulation of posterior hypothalamus.

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