Pressor Mechanisms Induced by Intracranial Compression

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A sudden rise in intracranial pressure initiates a three-fold cardiovascular response in the dog. Within one second after the onset of compression, the blood pressure rises sharply, presumably as a result of a direct neurogenic stimulus to the arterioles; the pressure then levels off in a few seconds. A second pressor effect is apparently due to the secretion into the blood stream of graded amounts of nor-epinephrine-like materials at the onset of compression; this rise is delayed about 12 seconds, a period perhaps associated with its circulation to the arterioles. In some experiments, a heart rate increase occurs at this time. It is shown by a special technique that the circulating blood volume increases about 10 per cent during this period. With the offset of compression all these effects disappear in the same order. The potential role of these mechanisms in the blood pressure regulating complex is discussed.

The technic of intracranial compression lends itself admirably to the study of some of the mechanisms involved in the regulation of the blood pressure. This is so since the intensity of the pressor response can be shown to be related to the degree of the compression.1, 2 The stimulus can thus be graded in terms of millimeters of mercury and can be compared with an equidimensional response in blood pressure.

At the turn of the century Cushing1 demonstrated that the pressor response was dependent on a disturbance in the blood supply to the brain. He interpreted his findings as demonstrating that the stimulus for the rise in pressure was the production of an ischemia or anemia of the brain. His general results have been confirmed by numerous investigators2-11 who have added significant information concerning the pathways involved. Thus, it has been shown that intracranial compression can produce a blood pressure rise even when most of the brain anterior to the medulla has been removed.9 The pressor response does not occur if the sympathetic nervous system is eliminated surgically or pharmacologically by section of the spinal cord or by block of its outflow by local anesthetics.1, 2, 6, 8 Further, an association between the blood pressure adjusting mechanisms of the carotid sinus region with those of intracranial compression is shown by the fact that denervation of the carotid sinus enhances the pressor response to intracranial compression.2, 5

Our studies2 have shown that the data of Cushing as well as of others can be reinterpreted as indicating the presence of a pressor receptor mechanism inside the cranium. This receptor appears to be responsive to differences in the relative pressure existing between that in the blood vessels and that in cerebrospinal fluid. Thus, a rise in the intracranial pressure may be considered the equivalent of a relative fall in the pressure inside cephalic blood vessels. In this way a baroreceptor is stimulated, setting a chain of pressor reactions into motion.

In the present study we undertook to determine more accurately the types of pressor mechanisms induced by intracranial compression. Evidence has already been presented to show that in the chick, the pressor response is due primarily to the release of graded amounts of a pressor material into the blood stream depending on the degree of compression. The presence of a relatively long lag, before the onset of the pressor response, suggested the operation of a hormonal factor. The active material was shown to be pharmacologically similar to norepinephrine. However, the very short duration of the lag of the

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response in experiments on rabbits and dogs raised the question that pressor mechanisms other than those dependent on circulating pressor materials\textsuperscript{12, 13} must be involved in these species. Experiments were therefore undertaken in dogs to analyze the mechanisms available for the production of the rise in blood pressure.

I. "Intact" Preparations

Methods and Results

Twelve dogs weighing 6 to 20 Kg. were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram). A hole was trephined in the parietal bone near the midline of the skull and the dura was incised. A metal pipe was fitted into the trephine hole and connected to a reservoir of saline. Other details of the preparation have been described previously.\textsuperscript{2, 12, 13} Both vagus nerves were then cut and the trachea was cannulated for positive pressure respiration. The femoral artery was cannulated for blood pressure registration and attached to a Sanborn electromanometer. Simultaneous blood pressure and intracranial pressure recordings were made on a direct writing twin-visocardiette (Sanborn).

Blood pressure response. The intracranial pressure was raised within the course of a second or so to either 200 or 250 mm. Hg, a level considerably above the arterial blood pressure. The onset of the pressor response to this intracranial compression became manifest within two or three heart beats, usually, within one second (fig. 1). Occasionally, this immediate response was absent.

After another 10 to 25 seconds, when the pressor response appeared to be leveling off, a second, delayed blood pressure response with an increased slope usually appeared (fig. 2), and the blood pressure increased to a higher level, usually sufficient to overcome the intracranial compression.

At the onset of intracranial compression there was usually a slow fall in blood pressure to the control level. However, occasionally there were variations in this pattern, with the occurrence of either a rapid fall or of a prolonged pressor response, maintaining the blood pressure at its heightened level for 20 to 30 seconds before the onset of a gradual decline to the control level. The heart rate response to compression was variable.

Comment. The immediate blood pressure rise occurring with the onset of intracranial compression.
compression makes it appear unlikely that ischemia or anoxia acts as the triggering device activating the blood pressure regulating mechanism. Instead, it supports the concept that a mechanism depending on pressure sensitivity is involved. The immediate response also indicates that a direct neurogenic vasoconstrictor action on the systemic arterioles is operative.

The increased slope of the blood pressure curve seen 10 to 20 seconds following the onset of the first rise may depend in part on the delayed action of a circulating pressor material. This is in line with evidence from earlier experiments on the chick which had suggested that intracranial compression may trigger the release into the systemic venous blood stream of graded amounts of a pressor agent.

To obtain further information on the nature of these responses, the venous return was measured by modifying the preparation described above.

II. "Open Chest" Preparation

Method and Results

The chest was opened in the third or fourth intercostal space. The superior and inferior venae cavae were cleaned, and the phrenic nerve was dissected away. The azygous vein was ligated at its junction with the superior vena cava. To permit the collection of both superior and inferior vena cava blood the right external jugular vein was isolated and a long polyethylene catheter of 6 or 8 mm. internal diameter was inserted into it (fig. 3). Ligatures were placed above and below the junctions of the right atrium with the vena cava to prevent caval blood flow from passing directly into the right heart. The venous return was collected by means of slight suction (4 to 5 mm. Hg) into a calibrated bottle reservoir. It was then pumped at a constant rate through a meter pump (Maisch) through a flow meter (rotameter) and then returned to the right heart via a cannula tied into the right auricle.

With this preparation it was possible to measure the entire venous return except for the relatively small volume returning to the heart via the coronary sinus, Thebesian veins, and the bronchial arterial supply. Volume calibrations of the reservoir bottle permitted a measure of changes in the venous return from the constant volume being returned to the heart by the metering pump arrangement.

1. Blood pressure response. As in the "intact" preparations, the pressor response usually began immediately following the onset of compression (fig. 4). However, significant differences in the character of the blood pressure responses were seen in these open-chest preparations, when compared with those obtained in the "intact" dog. The time of onset of the second, (delayed) rise could be made out occasionally and then without the clear separation of slope seen in the more intact preparations. In the open-chest animal the response was usually less in degree than in the intact dog.

When the intracranial compression was released, the blood pressure began to fall more sharply than in the intact preparations. In the course of 10 seconds or so the pressure often fell to the original level or even markedly below this level. In the latter instances, the pressure then slowly regained its original control value. Sometimes, an overshoot to a new

![Diagram of apparatus for measuring the venous return](https://example.com/image.png)

**Fig. 3. Apparatus for measuring the venous return and maintaining a constant volume input into the right heart. Flow passes through venae cavae into catheter and thence to reservoir. It is then pumped via a constant output pump through a flowmeter into the right atrium. Details in text.**
level somewhat higher than that obtaining prior to stimulation was observed.

A greater degree of blood pressure instability was noted in the open-chest preparation. Commonly, a slow fluctuation of the blood pressure level was present, suggesting the operation of a level-seeking device.

B. Heart rate. A gradual rise in heart rate sometimes began about 15 seconds after the onset of compression (fig. 4). The data are tabulated in table 1 which shows the rise in 7 of 12 successive trials. After a lag following the offset of compression, the heart rate returned to control levels.

C. Venous return. Previous studies from this laboratory have suggested that the pressor response to intracranial compression might be dependent in part on a mobilization of a volume of blood from the periphery.13 This possibility could be tested in the present preparation since a measure of the venous return is provided.

The slight negative pressure applied to the great veins pulls blood from these vessels and their tributaries, presumably to a constant degree. The returned blood is then collected in the reservoir (fig. 3). The constancy of output volume from the pump which takes reservoir blood and passes it into the right atrium makes it possible to measure variations in the venous return. Thus, changes in the level of the blood in the reservoir reflect a difference between the constant rate being ejected by the pump and the potentially variable volume being returned from the veins. An increased venous return is evidenced by a rise in the level of the reservoir while a decreased venous return presents itself as a fall in this level.

At the onset of the intracranial compression no immediate change in venous return was noted (fig. 4). The blood level in the reservoir gradually but consistently began to increase 50 to 100 ml over the course of 10 to 20 seconds.

The special design of our apparatus withheld this added volume from the circulation. It thus separated the potential effects of this enhanced return from other pressor and cardioaccelerating mechanisms.

No immediate change in the reservoir level was seen at the offset of intracranial compression. After about 15 to 25 seconds, however, a time when the arterial tension had usually fallen sharply from the maximal pressure levels, the reservoir level began to fall. This fall was rapid at first and then took place more gradually as the blood pressure approached control levels (fig. 4). In other experiments a more striking volume effect was seen.

At the end of the compression period the blood pressure fell more sharply than in the “intact” preparations, and sometimes fell markedly below the original control levels. The venous reservoir level also began to fall sharply indicating that less blood was returning to the veins than the constant volume being metered by the pump into the right heart. This would suggest that to halt the sharp fall in pressure, a vasoconstriction was induced which had the
effect of holding blood on the arterial side of the circulation, thereby reducing the venous return to the heart. As the blood pressure finally returned to and was maintained at the normal levels, the amount of blood in the reservoir also gradually returned to its control volume.

**Discussion**

The present studies provide new information concerning factors initiating the pressor response to intracranial compression as well as an analysis of the mechanisms whereby the rise in blood pressure is accomplished. From the data of our experiments it appears that there are three distinct types of pressor mechanisms involved in the response to intracranial compression. These are summarized in figure 5.

The very brief lag from the onset of compression, less than one second in duration, argues against the possibility that the pressor effect depends upon the development of an ischemia or anemia of the brain. Instead this evidence is in accord with our previous interpretation that the response depends upon a mechanoreceptor which reacts immediately to a change in the balance of pressures inside and outside a sensing arterial wall inside the cranium. The immediacy of the response also shows that a direct nervous connection from receptor to effector must be in operation.

There was also a very short delay, of the order of about one second, after the release of intracranial compression before the onset of the fall in blood pressure, especially in the open-chest preparations. This finding also fits with the evidence that the direct neurogenic vasoconstriction operative during compression ceases almost instantaneously with the return of the intracranial pressure to normal levels.

The second phase of the rise in blood pressure response occurs about 10 to 15 seconds after the onset of intracranial compression. The lag is consistent with our earlier interpretations that a pressor material released into the venous system by the intracranial stimulus is delayed by the amount of time required for circulation to its site of action at the arterioles.

It is of interest to note the similarity between the delayed response and the entire pressor response to intracranial compression which was seen in the chick. It would appear that in the dog the direct vasoconstrictor response is an additional mechanism added to
that present in the chick, providing a more highly developed and faster vascular response.

The increase in heart rate which sometimes occurs about the same time as the second rise in blood pressure suggests that the substance released into the circulation is one that may have a positive chronotropic effect on the heart. Heymans and Edholm in studies on intracranial pressure have demonstrated such an increased rate after an initial bradycardia. (The vagi were intact in their preparations.) The tachycardia could not have been due to the release of vagus inhibition in our experiments since our animals were all vagotomized bilaterally. It cannot be due primarily to an enhancement of venous return since this heart rate effect occurs in the open chest preparation in which the venous return is maintained constant.

In previous studies we have shown an increased flow of blood through both venae cavae beginning shortly after intracranial compression. The present experiments demonstrate that an amount of blood equivalent to about 10 per cent of the circulating blood volume is mobilized within a few seconds after compression, and added to the effective circulating blood volume.

The pressor responses were consistently greater in the "intact" preparation than in the open chest preparations. This difference must have been due in part to the fact that the enhanced venous return which certainly plays a role in the magnitude of the response was prevented from acting in the open chested preparations by virtue of its entrapment in the pump-reservoir. Other factors presumably include the relatively greater trauma as well as the loss of some vascular-control mechanisms resulting from opening the chest.

This difference between the two types of preparations was also apparent at the release of intracranial compression. In the open-chest preparation there was a very short delay, of the order of about one second, before the onset of the fall in blood pressure. It would not seem probable that in this short period the amount of blood pumped to the central nervous system could carry enough oxygen to overcome the ischemia present, because of the almost negligible diffusion during intracranial compression.

The present study demonstrates the variety of blood pressure regulating mechanisms available to the animal and set into motion by stimulation of the presumptive cephalic baroreceptors. These include direct vasocostrictor and hormonal pressor factors as well as appropriate adjustments of the blood volume.

The possible functions of the intracranial baroreceptor-pressor mechanism is also worthy of comment. It would appear unlikely that
such a sensitive pressure regulating system would have developed to meet the rare exigencies of accidental or traumatic increases in intracranial pressure. More likely, the apparatus which we have been studying is a more continually operable system serving a more significant function, probably in the normal regulation of the blood pressure which helps to adjust intracranial blood flow to need.

Similarities between the types of pressor responses induced by the nondiscriminating stimulation of concussion, in which pressor responses are sometimes present, and by localized stimulation of the brain stem suggest the operation of common pathways. Elucidation of these mechanisms may have value in improving our understanding of normal blood pressure regulating mechanisms and perhaps those involved in the genesis of systemic hypertension.

Summary

The response to intracranial compression in dogs subjected to anesthesia and bilateral vagotomy is shown to result from a combination of three types of pressor mechanisms. An immediate rise in pressure, beginning within one second of the onset of intracranial compression, indicates the activation of a direct vasoconstrictor pathway. The presence of a second delayed pressor response occurring 10 to 15 seconds after the onset of stimulation is consistent with earlier studies demonstrating that a hormonal agent may be secreted into the blood, producing a pressor effect after it circulates to the arterioles. A change in heart rate occurring at this time may represent an increase in circulating hormonal chronotropic materials.

An increase in the venous return also participates in the pressor mechanism. This was elicited by deviating the venous return through a constant output pump. An increase in return equivalent to about 10 per cent of the circulating blood volume took place about 10 to 25 seconds after the onset of compression. This indicated a mobilization of blood from the periphery which, being added to the circulating blood volume, would participate in the rise in pressure.

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Summario in Interlingua

Un subite augmento del pression intracranial resulta, in le can, in un triple responsa cardiovascular. Intra un secunda post le declaration del compression, le pression sanguine ascendente acutemente (probablemente in consequentia de un directe stimolo neurogenic del arteriolas) e tune se nivella in le curso de alium secundas additional. Un secunde effetto pressorial es apparentemente causate per le secretion a in le circulation de graduate quantitates de materiales norepinephrinioide. Iste ascendita del pression sanguine es retardate per circa 12 secundas, un periodo possibilemente associate con le circulation verso le arteriolas. In alium experimentos isto es etiam le momento del occurrence di un acceleration del battimento del corde. Per medio de un technica special nos has monstrate que durante le periodo mentionate le volumine del sanguine circulante es augmentate per circa 10 pro cento. Post le cessation del compression omne le effectos enumerate dispare in le mesme ordine. Nos discute le rolo potential de iste mechanismos in le complexo del regulation del pression sanguine.

REFERENCES

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