

STUDIES ON THE MECHANISM OF FATAL ANAPHYLAXIS IN THE RABBIT*†

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INTRODUCTION

SYSTEMIC anaphylaxis in the rabbit has been reported to be characterized by pathologic-physiologic changes within the cardiovascular system.¹⁻⁴ Rabbits dying in anaphylactic shock exhibit extreme dilatation of the right auricle and ventricle, congestion of the liver, and distention of the portal vein and inferior vena cava. Airila¹ first noted the rise in pulmonary arterial pressure after the shocking injection and the fall in systemic blood pressure as soon as the high pulmonary pressure developed. Coca² stated that the altered hemodynamics in rabbit anaphylaxis resulted from contraction of the smooth musculature of the pulmonary arterioles leading eventually to obstruction of flow through the constricted lumen of the involved vessels. The pulmonary arterial bed is thus practically occluded and dilatation of the right side of the heart follows. Drinker and Bronfenbrenner,³ by direct pressure readings from the exposed pulmonary artery, recorded the rise in pressure in the pulmonary circulation and fall in systemic arterial pressure during anaphylactic shock, and by means of the Starling heart preparation then demonstrated that the heart does not suffer primary damage in anaphylaxis but is secondarily affected due to its inability to maintain the necessary pressure head to force blood through the pulmonary vessels. The experiments of Friedberger and Seidenberg⁵ demonstrated resistance to flow of antigen-containing perfusion fluid through the lung of the sensitized animal, and Grove⁶ noted constriction of isolated strips of the pulmonary artery in the Dale bath. Vallery-Radot, Halpern, and Mauric⁴ concluded that pulmonary vasoconstriction is not the only cause of a drop in systemic blood pressure, for in their experience the generalized drop in arterial blood pressure and the rise in pressure in the pulmonary artery seem to occur independently.

Auer and Robinson⁷ reported electrocardiographic disturbances in conduction in the heart of the rabbit during anaphylaxis which ranged from slight delay to partial and complete heart block. Criepp⁸ studied cardiac changes, as revealed by the electrocardiogram, in the rabbit during anaphylaxis, asphyxia, and mechanical clamping of the pulmonary artery. In all 3 states there were noted identical changes consisting of the development of conduction disturbances progressing to cardiac standstill. Criepp indicated that the cardiac changes observed were due to myocardial anoxemia and possibly cerebral anoxemia secondary to the state of asphyxia induced by anaphylaxis.

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This report deals with our attempt to study the pathologic physiology of anaphylaxis in the rabbit by electrocardiographic and pneumographic studies and by recording intracardiac pressure during anaphylactic shock.

EXPERIMENTAL PROCEDURE

The techniques of sensitization and subsequent challenge in eliciting anaphylaxis in the rabbit were carried out according to the conditions suggested by Bukantz, Johnson, and Alexander.⁹ Adult rabbits ranging in weight from 2.5 kg. to 3.5 kg. were sensitized by a single intramuscular injection of 325 mg. of bovine gamma globulin (Fraction II, Armour) absorbed on aluminum hydroxide prepared according to the method of Hektoen and Welker.¹⁰ Three to 4 weeks later fatal anaphylactic shock was induced by the intravenous administration of 500 mg. of bovine serum gamma globulin in 10 ml. of physiologic saline.

Just prior to the administration of the shocking dose of antigen, 6 sensitized animals were lightly anesthetized with intravenously administered pentobarbital sodium. This degree of anesthesia facilitated the procedures required in exposing the jugular vein and passing a catheter into the heart, but at the same time did not interfere with respiration, cardiac action, the production of anaphylaxis, or the symptoms occurring during anaphylactic shock.

Blood pressures within the right ventricle were obtained with a No. 6 ureteral catheter introduced through the exposed right jugular vein and attached to a Statham P23A pressure transducer. Recordings on a constant speed kymograph were obtained utilizing a direct coupled high gain stabilized amplifier which drove an Edin pen motor. Calibration of the transducer was obtained by standardization against a mercury column, as well as by the integral electrical calibration. Heparinized saline solution was used to fill the transducer and catheter system. Electrocardiograms employing the standard Lead II and respirations utilizing a pneumatic system were also simultaneously recorded by pen writing arms on the constant speed kymograph. Two additional rabbits were similarly studied except that pulse pressure rather than blood pressure was recorded.

Following death, the thoracic cage of each animal was opened, the heart grossly examined, and the position of the catheter checked.

RESULTS

The method of Bukantz, Johnson, and Alexander⁹ for sensitizing and challenging rabbits, which was employed in this experiment, was uniformly successful in effecting fatal anaphylactic shock in the animals studied.

The effects of fatal anaphylaxis on respiration, electrocardiographic tracings and right ventricular pressure are summarized in Table I.

In 6 rabbits there was an immediate rise in both systolic and diastolic pressure within the right ventricle reaching a maximum within 20 to 60 seconds following the administration of the shocking dose of antigen. The variations in intraventricular pressure noted at the height of anaphylaxis were related to the convulsive seizures and the marked fluctuations in respiratory movements that occurred. After the rise of intraventricular pressure to a maximum height,

TABLE I. CHANGES IN RIGHT INTRAVENTRICULAR PRESSURES, RESPIRATIONS, AND ELECTRO-CARDIOGRAPH TRACINGS DURING ANAPHYLAXIS IN SENSITIZED ANIMALS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF A SHOCKING DOSE OF ANTIGEN

RABBIT NUM- BER	CONTROL INTRA- VENTRICULAR PRESSURES (MM. HG)		INTRAVENTRICULAR PRESSURES AFTER INJECTION OF ANTIGEN (MM. HG)		TIME OF APPEAR- ANCE OF MAXI- MUM VENTRICU- LAR PRES- SURE FOL- LOWING INJEC- TION OF ANTIGEN (SECONDS)	TIME OF CESSATION OF RES- PIRATION FOLLOW- ING IN- JECTION OF ANTIGEN (SECONDS)	DURATION OF TIME FROM AD- MINISTRA- TION OF ANTIGEN UNTIL DISAPPEAR- ANCE OF INTRA- VENTRICU- LAR PRESSURES (MIN- UTES)	ELECTRO- CARDIOGRAM
	SYS- TOLIC	DIAS- TOLIC	SYS- TOLIC	DIAS- TOLIC				
1	9-10.5	4-4.5	13.5-16.5	7.5-9	20	80	8	Cardiac slowing and prolonged QRS after 2 min.
2	6.6-9.9	2.2-4.4	16.5-38.5	6.6-8.8	20	120	2	No change
3	7.7-9.9	1.1-3.6	8.8-38.5	2.2-6.6	20	70	9	Marked lowering of ST segment; otherwise not significant
4	9.6-12.8	1.8-4.8	16-17.6	8-9.6	50	130	6	No change
5	10-12.8	1-1.8	17.2-19.8	3.6-7.2	60	120	10	No change
6	12-18	3-7	16-20	6.8	60	60	4	No change

both the systolic and diastolic pressures gradually fell to zero in from 2 to 10 minutes following the intravenous administration of the antigen.

With the exception of a few terminal gasps, respirations abruptly ceased within 60 to 120 seconds after the administration of the antigen. In 1 rabbit (No. 2) respirations and intraventricular pressure changes ceased simultaneously after 2 minutes. However, in the other 5 rabbits studied, pulsatile changes in intracardiac pressure continued for a period of from 2 to 10 minutes after respirations had ceased (Fig. 1). In 2 additional sensitized rabbits, similarly studied, in which pulse pressures rather than true blood pressures were recorded, the fatal reaction to the administration of antigen was also that of a sudden respiratory arrest occurring well before the disappearance of intraventricular pressure changes.

No significant changes in the electrocardiograms were noted during anaphylactic shock. All of the major electrocardiographic changes recorded occurred after respiration had ceased and the intraventricular pressure had fallen to zero and pulsatile variations no longer occurred.

In all instances, on post-mortem inspection, the tip of the catheter was found lying inside the right ventricle. Both the right auricle and ventricle felt flabby and were enlarged to approximately 3 times their normal size.

DISCUSSION

It is recognized that the administration of certain drugs may interfere with the production of typical anaphylaxis in experimental animals. However,

Drinker and Bronfenbrenner³ did not find that the anesthesia employed in their studies interfered with the production of anaphylactic shock in rabbits, and Chase¹¹ was of the opinion that anesthetics are of low order in this regard. The effect of the anesthesia itself, together with the operative procedures involved, probably exerted no significant influence on the response of the animals to the challenge dose of antigen, since similar fatal anaphylactic shock was elicited in unanesthetized sensitized rabbits, within similar time periods, employing the same doses of antigen.

The cause of death in anaphylactic shock in the rabbit has been considered to be attributable to acute failure of the right side of the heart secondary to obstruction of blood flow in the pulmonary circuit. Further evidence for the development of right-sided heart failure is noted in this study in that increased systolic and diastolic pressures were observed to develop within the right ventricle. Though the intracardiac pressures gradually diminished to zero indicating a failing heart, it is noteworthy that in 7 of the 8 rabbits studied in this experiment respirations suddenly ceased while cardiac function as measured

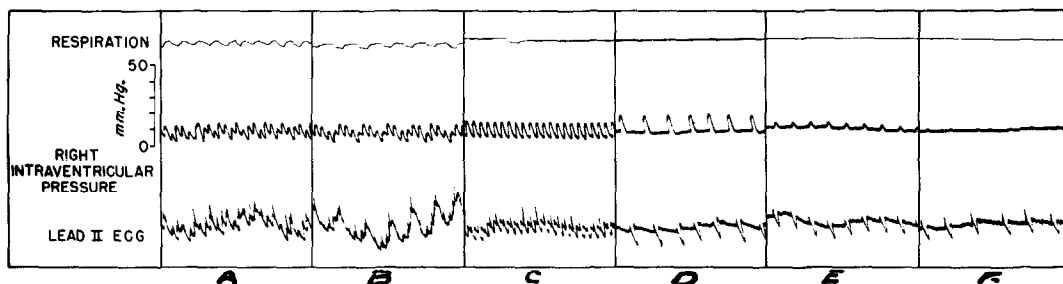


Fig. 1 (Rabbit No. 4).—Showing simultaneous recordings of respirations, right intraventricular pressures, and electrocardiographic tracing: A, during control period; B, during period of injection of shocking dose of antigen; C, 2 minutes later, showing abrupt cessation of respiration while the intraventricular pressures have risen and the electrocardiographic tracing is maintained; D, 2 minutes after respirations have ceased, increased intraventricular pressures and electrocardiographic tracing continue; E, 3 minutes after respirations have ceased, intraventricular pressures are diminishing to levels below normal; F, 4 minutes after the cessation of respiration, the intraventricular pressure has fallen to zero, the electrocardiographic tracing continues.

by right intraventricular pressure and electrocardiogram was maintained. The heart continued to beat and significant intraventricular pressures were recorded for several minutes following the cessation of respiration. The abrupt manner in which respirations stopped following the administration of the shocking dose of antigen suggests a sudden peripheral respiratory failure. The few terminal gasps that followed later were probably due to central anoxia. Continued beating of the heart following death has been previously noted in anaphylactic shock in the rabbit¹²; however, fatal anaphylaxis in the animal has always been attributed to acute congestive heart failure. Evidence of bronchospasm has not been found¹¹ and histologic study of the bronchioles and lung parenchyma showed no significant changes. Simmonds¹³ explained the absence of bronchospasm on the assumption that bronchial muscles in the rabbit are relatively too weak to be capable, by contraction, of interfering with respiration. Grove⁶ was unable to secure contraction of an isolated bronchial strip taken from a sensitized rabbit and immersed in a Dale bath with antigen added, but noted that this might indicate that the muscular tissue in the strip was so weak that its con-

traction would not be registered by that technique. The fact that major electrocardiographic changes did not occur until after respirations had ceased and intracardiac pressure changes were no longer recorded indicated that death was not due to disturbances in the conduction mechanism of the heart or myocardial damage that could be recorded by the electrocardiogram. The persistence of heart action for as long as 10 minutes following apparent peripheral respiratory failure suggests that the mechanism of death in fatal anaphylaxis in the rabbit is respiratory failure rather than acute failure of the right side of the heart.

SUMMARY

1. Right ventricular pressures and pneumographic and electrocardiographic tracings were recorded in sensitized rabbits during anaphylactic shock.

2. Following the intravenous administration of the shocking dose of antigen a rise in both systolic and diastolic right ventricular pressures was observed, followed by gradual reduction in pressure to zero.

3. In 7 of 8 rabbits studied, respirations ceased abruptly although the heart action and significant intracardiac pressure pulsations continued for as long as 10 minutes. In one animal heart action and respirations ceased simultaneously.

4. Major electrocardiographic changes did not occur until after respirations had ceased and the intraventricular pressure had fallen to zero.

5. It is suggested that the mode of death in anaphylaxis in rabbits is due, at least in part, to peripheral respiratory failure.

REFERENCES

1. Airila, Y.: *Skandin. Arch. f. Physiol.* 31: 338, 1914. Cited by Drinker and Bronfenrenner.³
2. Coca, A. F.: The Mechanism of Anaphylaxis Reaction in the Rabbit, *J. Immunol.* 4: 219, 1919.
3. Drinker, C. K., and Bronfenrenner, J.: The Pulmonary Circulation in Anaphylactic Shock, *J. Immunol.* 9: 387, 1924.
4. Vallery-Radot, P., Halpern, B. N., and Mauric, G.: Considérations sur le mécanisme de l'hypotension artérielle au cours du choc anaphylactique et histaminique chez le lapin, *Acta allergol.* 1: 85, 1948 (taken from *Allergy Abstracts* 14: 24, 1949).
5. Friedberger, E., and Seidenberg, S.: Einfluss der Umgebungstemperatur auf Immunität und Infektion, *Klin. Wehnschr.* 6: 1515, 1927.
6. Grove, E. F.: Studies in Anaphylaxis in the Rabbit; On Simmonds Explanation of Different Pathology of Acute Anaphylactic Shock in Different Animal Species; On Rôle of Unstriated Muscle in Acute Anaphylaxis in the Rabbit, *J. Immunol.* 23: 147, 1932.
7. Auer, J., and Robinson, G. C.: An Electrocardiographic Study of the Anaphylactic Rabbit, *J. Exper. Med.* 18: 450, 1913.
8. Crip, L. H.: Electrocardiographic Studies on the Effect of Anaphylaxis on Cardiac Mechanism, *Arch. Int. Med.* 48: 1098, 1931.
9. Bukantz, S. C., Johnson, M. C., and Alexander, H. L.: Unpublished observations.
10. Hektoen, L., and Welker, W. H.: Precipitin Production in Rabbits Following Intramuscular Injection of Antigen Absorbed by Aluminum Hydroxide, *J. Infect. Dis.* 53: 309, 1933.
11. Chase, M. W.: *Bacterial and Mycotic Infections of Man*, Ed. by R. J. Dubos, Philadelphia, 1948, J. B. Lippincott Company, p. 120-121.
12. Seegal, B. C.: *Agents of Disease and Host Resistance*, Ed. by F. P. Gay, Springfield, Ill., 1935, Charles C Thomas, Publisher, pp. 52-54.
13. Simmonds: Cited by Grove.⁶