Circulatory and Respiratory Effects of Hypertonic Saline
with Special Reference to the Coronary Effect

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In an attempt to elucidate the mechanism of the systemic hypotension produced by the rapid intravenous injection of 20 per cent saline, experiments were made using the intracoronary injection technique and transeptal left atrial puncture in a total of 25 dogs. Accompanying apnea and bradycardia were considered to be due to the pulmonary reflex via the vagus. Scrutiny of systemic hypotension produced after injection of hypertonic saline into varying cardiovascular chambers showed that the injection into the left side of the heart also resulted in the same degree of hypotension as that of the right side, and that pressure fall was separated into early and late dips, about which the genesis was discussed and the former was attributed to the coronary effect. Electrocardiographic analysis revealed that the ST and T changes were the proof of the arrival of saline at the coronary circuit and their mechanisms were mentioned. From these results the authors emphasized the possible role of coronary effect by the agent and suggested the transient myocardial failure in the production of systemic hypotension.

It is now evident that the rapid intravenous injection of hypertonic saline produces the triad, namely systemic arterial hypotension, apnea and bradycardia.1)-10) Although the apnea and bradycardia are considered to be produced by a reflex mechanism mediated via the vagus nerve, there is no agreement about the mechanism of the arterial hypotension.2),5)-10) The purpose of this paper is to present our experiences about the hemodynamic responses and electrocardiographic changes induced by the intravenous injection of hypertonic saline, and to discuss the results in comparison with previous studies. To maintain the animals in the best physiological condition, our experiments were performed in closed-chest dogs with the aid of transeptal left atrial puncture and intracoronary injection technique.

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MATERIALS AND METHODS

Twenty-five mongrel dogs each weighing between 7.5 and 15 Kg. were anesthetized with morphine (4 to 5 mg./Kg.) and chloralose (50 mg./Kg.) or amobarbital sodium (60 mg./Kg.). With the aid of fluoroscopy, a cardiac catheter was introduced into the main pulmonary artery via the right external jugular vein, and similar catheters were also inserted into the femoral artery and the inferior vena cava. The injection of hypertonic saline and pressure recording in the left atrium were made by puncturing the interatrial septum from the right atrium as described by Ross and his associates.11),12) In some of the experiments, the intracoronary injection was performed with special catheter introduced into the circumflex branch of the left coronary artery.13),14) The location of the catheters was verified at the end of the experiments. Blood pressures were measured by 2 electromanometers, and the systemic and pulmonary arterial pressures were recorded on a 3-channel direct writer with electrocardiogram. Arterial pressure was also recorded on the sooted paper of the kymographion and at the same time the pulmonary arterial pressure was recorded with the left atrial pressure on a direct writer.

Five to 10 ml. of 20 per cent solution of sodium chloride (0.5 to 1 ml./Kg.) was injected through the catheter into the various parts of the cardiovascular system in 2 to 5 seconds. A total of 191 injections were made: 42 into the inferior vena cava or femoral vein, 49 into the pulmonary artery (partly into the pulmonary capillary), 20 into the left atrium, 3 into the left ventricle, 41 into the aorta (including 19 into the ascending aorta, 3 into the aortic arch, 10 into the descending aorta or femoral artery, and 9 into the carotid artery), and 19 into the coronary artery. In the last group, the dose of solution injected was 0.5 to 1 ml. of 10 per cent saline.

Control experiments with the same quantities of normal saline and a 50 per cent solution of glucose were performed in a total of 17 injections: 12 with normal saline and 5 with glucose.

RESULTS

(I) Control Experiments.

The injections of normal saline into the various parts of the cardiovascular system were followed by changes neither in the systemic arterial, pulmonary and left atrial pressures nor in respiration and electrocardiogram. The injections of 50 per cent glucose resulted in no changes in all experiments but one, in which a slight arterial hypotension was produced after intravenous injection.

(II) Changes in Systemic Arterial Pressures.

A total of 29 injections were made into the inferior vena cava of 18 dogs, which were followed within 3 to 8 sec. (average 5 sec.) by a fall of arterial pressure. There were usually 2 phases of pressure fall, the first was reached within 10 to 15 sec. and averaged 20 mm.Hg; the second
Fig. 1. Changes in pressure of pulmonary artery and systemic artery following the intravenous injection of 10 ml. of 20 per cent saline. Arrow indicates the time of injection.

was at about 40 sec. after injection and averaged 40 mmHg (Fig. 1). The difference in anesthesia did not influence the characteristic responses. The arterial pressure returned to the original level within 2 to 3 minutes. In 6 of 29 injections (about one fifth), the first and second fall fused to one deep depression. The hypotension was not influenced at all by the bilateral cervical vagotomy which was performed in a total of 13 experiments (Fig. 2).

The basic pattern of the pressure fall after the intravenous injection was not changed when the injection was made into the pulmonary artery, left atrium (Fig. 2, B), and left ventricle. However, the interval between the injection and the beginning of the systemic hypotension was shorter when the injection was made into the left atrium than into the pulmonary artery; in the former it averaged 1.7 and in the latter 3.4 sec.

(III) Changes in Pulmonary Arterial and Left Atrial Pressures.

Pulmonary hypertension, which corresponded in time to the first fall of the systemic arterial pressure, was seen in only 16 of 42 injections into the inferior vena cava (Fig. 3). The other pressure patterns of pulmonary artery were hypertension seen at the time of the second fall of arterial pressure in 12 instances and no changes in 14. The 3 different patterns of the pulmonary arterial pressure were of about similar incidence (Fig. 4).

Simultaneously recorded left atrial pressure demonstrated no constant tendency of the change; some increased, some decreased and the rest remained unchanged. The characteristic pattern described by Eliakim et al.,7 which showed the increased pulmonary arterial pressure and the decreased left atrial pressure, was seen in only 4 instances (about 10 per cent). Fig. 5 shows the case with a slight increase in left atrial pressure.
Fig. 2. Systemic arterial hypotension following the injection of 20 per cent saline into the inferior vena cava (A) and the left atrium (B) before and after bilateral cervical vagotomy.
Fig. 3. Changes in pressure of pulmonary artery and systemic artery following the intravenous injection of hypertonic saline. Note the marked pulmonary hypertension.

Fig. 4. Incidence of the pressure patterns of pulmonary artery, in relation to the biphasic hypotension of the systemic artery when injections were made into the inferior vena cava in a total of 42 instances.

A.P.: systemic arterial pressure.
P.A.: pulmonary arterial pressure.
Fig. 5. Changes in pressure of pulmonary artery and left atrium following the intravenous injection of 5 ml. of 20% saline.

When the hypertonic saline was injected into the pulmonary artery, the pressure patterns were approximately the same as those after the injection into the inferior vena cava. The pulmonary hypertension associated with the first fall in arterial pressure was observed in 27 of 49 injections (about 55 per cent), of which simultaneous left atrial pressure fall was observed in only 2 instances. Left atrial pressure was seen to remain the same in 10 cases and to increase in 10 others.

When the injections were made into the left atrium, pulmonary arterial pressure did not show any change in 14 instances and increased in 6. The magnitude of pressure increase was within 10 mm.Hg in 4 and about 20 mm.Hg in 2 other experiments.

(IV) Intracoronary Injection.

The concentration of the injected saline varied widely, but in most cases a 10 per cent solution was used in a dose of 0.5 to 1 ml. The systemic arterial pressure began to fall immediately after the injection, reaching its nadir in about 3 sec. in the fastest cases. The magnitude of the pressure decrease was 70 to 80 mm.Hg in the most marked cases. The second fall of the systemic arterial pressure was not observed. The depressor effect was more prominent in the 0.5 ml. of 20 per cent solution than the 1.0 ml. of 10 per cent solution. One of these experiments was shown in Fig. 6. Vagotomy did not influence the hypotension.

When the injection was made into the lower part of the ascending
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Fig. 6. Changes in systemic arterial pressure following the intracoronary injection of 10 per cent saline.

Fig. 7. Comparison of the systemic arterial hypotension following injection into the coronary artery, upper part of the ascending aorta and the inferior vena cava.
aorta near the ostium of the coronary artery, the pressure changes were similar to those observed after the intracoronary injection. Injection into the upper part of the ascending aorta or into the more distal part of the aorta resulted in a delayed hypotension as compared with the changes by the intracoronary injection (Fig. 7).

(V) Electrocardiographic Changes.

Bradycardia was always seen after the injection of hypertonic saline into the inferior vena cava and pulmonary artery, but not into the left atrium, left ventricle, coronary artery and aorta (Fig. 8). When injected into the

inferior vena cava, bradycardia appeared about 5.5 sec. after the injection and continued for 3 to 30 sec. (average 13 sec.). Injection into the pulmonary artery resulted in bradycardia within 2 to 8 sec. (average 4 sec.). The duration of the bradycardia was 30 sec. to 2.5 minutes (average 56 sec.), which was more prolonged than that by the injection into the inferior vena cava. The degree of bradycardia was a decrease of 6 to 18 beats per minute in the case of intravenous injection, and 6 to 100 beats per minute in the case of intrapulmonary injection. In general, the dogs anesthetized with morphine-chloralose showed more prominent bradycardia than those anesthetized with amobarbital sodium.

ST-segment and T-wave abnormalities occurred in all instances of the injection except for the cases where the injection was made into the upper part of the ascending aorta and its distal portion (Fig. 8). ST-segment changes were almost always depression, and rarely elevation. These changes reversed to the control level within 1 to 2 minutes, but when the injections
Fig. 9. Changes in electrocardiogram, pressure of left atrium and pulmonary artery following the intracoronary injection of 1 ml. of 5% saline.

were repeated over several times in the same dog, the changes became irreversible, and resulted in sustained ST and T changes. The time interval from the injection of hypertonic saline to the occurrence of the ST, T changes were 3 to 15 sec. (average 6 sec.) in the instance of inferior vena cava, 3 to 10 sec. (average 5 sec.) in the pulmonary artery, 1 to 7 sec. (average 3.6 sec.) in the left atrium, and 1 to 3 sec. (average 2 sec.) in the left coronary artery (Fig. 9). These ST and T changes occurred earlier than or simultaneously with the onset of systemic arterial hypotension.

Decreased voltage of the P-wave appeared earlier than the occurrence of bradycardia, and was present in almost all cases of the injection into the inferior vena cava, pulmonary artery and left atrium, but not in cases of injection into the left ventricle. Its duration and intensity did not show any uniformity and the difference due to the sites of injection was not so remarkable as the bradycardia.

The amplitude of the R-deflection was increased within 10 sec. after the injection of hypertonic saline into the cardiac cavities, irrespective of left or right heart, and partly followed by a decrease in amplitude. Intra-coronary injection revealed no changes in P-wave, no increase in R-deflection, and some showed a decrease in the amplitude of R-deflection.

There were no remarkable changes in PR-interval or QRS duration.

Arrhythmias most frequently observed were atrial and/or ventricular premature systoles, which were in short run within 10 sec. after the injection, or in frequent occurrence after about 20 to 30 sec. Differences due to the sites of injection were not found. In one dog the 6th injection of hypertonic saline made into the left atrium, resulted in ventricular
fibrillation and death. Paroxysmal tachycardia was observed in 2 other dogs. In the dogs anesthetized with morphine-chloralose, second degree atrioventricular block was often seen, which returned to a sinus rhythm after the injection.

In the bilaterally vagotomized dogs, bradycardia was completely eliminated regardless of different anesthetics. The other electrocardiographic changes, however, were not influenced.

(VI) Respiratory Changes.

The remarkable sign of respiratory effect produced by hypertonic saline was apnea. It appeared immediately after the injection into the inferior vena cava and the pulmonary artery and was considerably prolonged, but did not appear after the injection into the left atrium or into the coronary artery (Fig. 10). Similar to the bradycardia, apnea was also completely abolished by the vagotomy. No difference was found in the character of the apnea between the 2 different kinds of anesthetics. After an injection of hypertonic saline into the ascending aorta, apnea was also observed, and occurred in the delayed period.

**DISCUSSION**

In the present series bradycardia and apnea occurred only when the injection of hypertonic saline was made into the right side of the heart but
not in the left side; the effect was especially prominent in the injection into the pulmonary artery; vagotomy completely eliminated both effects; all these findings indicated the 2 responses to be effectuated by a pulmonary reflex via the vagus nerve. The systemic hypotension was not influenced by the vagotomy, and so the above responses were not consistent with the known reflexes, which include coronary chemoreflex, pulmonary depressor chemoreflex, and pulmonary depressor reflex mediated by baroreceptor.

As for the changes in the arterial pressure, injection into the inferior vena cava, pulmonary artery, and left atrium was followed in a similar pattern by the biphasic pressure fall; the second fall was deeper than the first, and in some experiments two falls fused into one. These findings are in agreement with the previous works by Binet, Muirhead, Eliakim, and Semler, although the trials of injection into the left atrium were not so found in the past. Its interpretations, however, were different. Binet and Burstein showed that pulmonary hypertension occurred shortly before the systemic hypotension and explained this by the “barrage pulmonaire” induced by the pulmonary arteriolar spasm. Eliakim and his associates observed simultaneous decrease in left atrial pressure and concluded that the systemic hypotension was caused by the spasm of the pulmonary vein-left atrial junctional muscle. He suggested the presence of a kind of receptor, sensitive to high concentrations of Na⁺ and/or Cl⁻. On the other hand, Semler demonstrated that the pressure gradient occurred between the pulmonary artery and its distal vessels and that the pulmonary block should be produced in the proximal portion to the site which was suggested by Eliakim. Read and his associates showed that the triad did not occur in a preparation perfused with a solution devoid of erythrocytes. They showed that in the perfused lung erythrocytes agglutinated transiently within 5 to 10 sec. after the injection and raised the vascular resistance, and that the vascular spasm did not occur and blood flow recovered within 60 sec.

In the present experiments when the injections were made into the inferior vena cava and pulmonary artery (91 times), the pulmonary arterial pressure increased markedly in 43 instances (Fig. 3), of which only 6 showed a decrease in left atrial pressure. Although there were few cases which were in agreement with Eliakim’s pattern, about one-half of the experiments demonstrated pulmonary hypertension which shortly preceded the systemic hypotension. The remaining one-half, however, did not show significant pulmonary hypertension. In addition, similar hypotension was reproduced even by injecting hypertonic saline directly into the left atrium and left ventricle not through the pulmonary circuit. These sorts of experiment have not been done except for that of Binet and Muirhead. Binet observed arterial hypotension by the injection of hypertonic saline into the left atrium. Muirhead showed a systemic hypotension of 34 mm. Hg on aver-
age after the injection of 50 per cent glucose into the left ventricle. Furthermore, the ST and T changes in ECG appeared almost simultaneously with systemic hypotension and when the site of injection was nearer to the coronary ostium, appearance of ST and T changes occurred earlier. These facts strongly suggested the presence of other factors besides the pulmonary block in the production of systemic hypotension, and led us to examine the effects of intracoronary injection of hypertonic saline.

The intracoronary injection of hypertonic saline was followed immediately by monophasic systemic hypotension, which is consistent with the previous work. A small dose (0.5 to 1.0 ml) of 10 per cent solution into the coronary artery was sufficient to produce the same degree of hypotension as that by intravenous injection. This dose was smaller than that of Muirhead, which was in the range of 0.23 to 0.70 ml/Kg. Injection into the upper part of the ascending aorta was followed by a similar monophasic hypotension with some time lag. Superposition of the both trancings suggested that the biphasic hypotension by the intravenous injection could be separately considered in the following manner; the first fall of hypotension was caused by the direct cardiac action through the coronary artery, and the second was produced by the peripheral action (Fig. 7). This concept differs from that of Muirhead in the interpretation of the biphasic hypotension. He considered the second fall to be caused by the coronary action of the saline. But its commencement was about 15 to 20 sec. after the injection and this interval was too long for the solution to reach the coronary beds through the pulmonary circulation.

ST and T abnormalities also appeared immediately after the injection and almost simultaneously with the systemic hypotension. Our observation demonstrated that the nearer the site of injection was to the coronary ostium, the earlier the ST and T changes appeared. For this reason, the ST and T changes might be considered to be a proof of arrival of the hypertonic saline at the coronary circulation.

Now, one problem is presented, and that is whether the ST and T changes are produced by the coronary ischemia or by the electrolyte imbalance. Using the perfused preparations, Read observed the coronary resistance to decrease in parallel with the aortic resistance. Under the condition of constant flow, the decreased resistance was a reflection of the systemic hypotension, and so the true behavior of the coronary artery was not known. The original work of Muirhead did not measure the coronary blood flow, although Walcott cited the results as coronary constrictive effect. Katz and Lindner showed the coronary dilator action of the Na ion in Langendorf's preparation, but the concentration of the solution and the rate of injection were not clearly mentioned. We also did not measure the coronary blood flow and no definite conclusion could be drawn concerning the dilator or constrictive action of the hypertonic saline to the coronary artery.
Electrocardiographic effects due to hypertonic saline are not fully understood. Scherf studied the impulse formation by the focal application of hypertonic saline and Eliakim extensively analyzed the ECG changes induced by intravenous injection of hypertonic saline but did not compare the differences due to the sites of injection. He observed the beginning of the ST and T changes to be 15 sec. after the injection, which was slightly longer than that of our experience. Prinzmetal and his associates analyzed a chemical origin of ST deviation, using the focal application and intracoronary injection of the sodium and potassium solution of varying concentrations. In nonischemic condition, a rapid injection of 5 ml. of hypertonic (even 0.9 to 1.1 per cent) saline into the artificial coronary artery circuit resulted in an immediate ST segment depression. This change progressively became more marked for 15 to 20 seconds, then on reaching its nadir gradually returned to the isoelectric line during the next 10 seconds to 2 or 3 minutes. They also observed a similar ST change in an injection of hypotonic potassium solution and explained that ST depression was related largely to the increase in ionic gradients of both potassium and sodium. According to this concept, ST depression can be explained even in the absence of myocardial ischemia.

From the above discussions, ST and T changes may be explained by the electrolyte imbalance due to hypertonic saline. However, marked hypotension produced simultaneously with or slightly later than ST and T changes can not be explained sufficiently by the electrolyte imbalance alone. On this account, any transient myocardial failure due to coronary ischemia must be considered besides the electrolyte imbalance.

As for the diminished P-waves and changes in amplitude of R deflection, the explication of their mechanism by the information of transmembrane potential and epicardial leads is still within the stage of speculation, since our results are obtained from a single limb lead.

In our experiments, injections were also made into the varying sites of the aorta for the purpose of comparison with effects of intravenous and intracardiac injection. Recently a number of papers have been presented about the peripheral action of hypertonic saline, and our experiments are in progress in an attempt to add further information.

Summary

In order to clarify the mechanism of the triad, namely apnea, bradycardia and systemic arterial hypotension, produced after the intravenous injection of hypertonic saline, intracoronary injection technique, transeptal left atrial puncture and electrocardiographic analysis were applied in a total of 25 anesthetized closed-chest dogs.

(1) Bradycardia and apnea were demonstrated by the injection of...
hypertonic saline into the inferior vena cava and pulmonary artery, but not into the left heart. Vagotomy eliminated both reactions completely. These were considered to be due to the pulmonary reflex via the vagus.

(2) Systemic hypotension had 2 dips after the injection into the right or left cardiac chamber, but after the injection into the coronary artery there was only one early dip. Injection into the distal part of the aorta also resulted in a monophasic hypotension, and its appearance was later than in the case of intracoronary injection. These 2 different kinds of monophasic dips corresponded in time and magnitude approximately to the 2 dips after the intracardiac injection. In about one-half of experiments, pulmonary hypertension occurred, and simultaneous decrease in left atrial pressure was found in only 6 of 91 experiments.

(3) In electrocardiograms, ST-segment and T-wave changes were shown to occur proportionally earlier as the site of injection approached nearer to the coronary ostium; immediately after the intracoronary injection and several seconds after the intravenous and intrapulmonary arterial injection. These changes were almost simultaneous with the first dip of hypotension.

(4) From above findings the authors emphasized the possibility that the initial dip of the arterial hypotension after the intravenous injection of the hypertonic saline was produced by the transient myocardial failure due to any myocardial ischemia and electrolyte imbalance. The mechanism of the second dip of the hypotension remained unsolved.

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