Experimental Studies on the Effects of Sympathetic Nerve Stimulation and Catecholamines on Cardiac Action, with Special Reference to Coronary Circulation, Mechanical Efficiency and Electrocardiogram

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In order to investigate the pathologic physiology of coronary insufficiency of neurohormonal origin, the experimental studies were carried out on dogs. The relationships among cardiac work, cardiac oxygen uptake, cardiac mechanical efficiency and electrocardiograms, and the effects of administrations of adrenaline and noradrenaline and of electrical stimulations of the cervical and spinal sympathetic nerves, were studied. In an early stage of all experiments, the electrocardiogram showed a coronary insufficiency pattern in accordance with increase in cardiac efficiency. In many cases, this insufficiency pattern disappeared with restoration of the original state or decrease in cardiac efficiency.

The study of coronary insufficiency was started by Heberden, who first introduced the name “angina pectoris” in 1768. Coronary insufficiency is caused in most cases by coronary artery disease, but the term coronary insufficiency designates a functional disturbance of coronary circulation; therefore this disorder can also be involved with neurogenic, endocrine and/or humoral factors. In 1867, Nothnagel offered the concept of “angina pectoris vasomotorica”, and in 1931 this concept was ascertained by Edens. In recent years, Prof. Maekawa has approached this type of angina from the viewpoint of the spinal control of coronary circulation. He has stated that neurocirculatory asthenia and allied diseases may occur on a structural basis of subclinical arachnoiditis adhesiva cerebrospinalis and that the localization of arachnoiditis may play a crucial role in the mechanism of “Organselektion”.

There have been numerous reports that patients with neurocirculatory asthenia and allied diseases may frequently show coronary insufficiency pattern in the electrocardiograms and positive Master's exercise test which is similar to that in patients with coronary artery disease.

On the other hand, it has been reported by many investigators that the coronary insufficiency pattern is produced with the administration of sympathomimetic drugs or with stimulation of the sympathetic nerves. Moreover, Hayase showed experimentally that electrical stimulation of the spinal sympathetic nerves (upper thoracic segments) brought about a coronary insufficiency which is the same in electrocardiographic pattern as that induced with the stimulation of the cervical sympathetic nerve or intracoronary injection of catecholamines.

In general, coronary insufficiency pattern in electrocardiogram is considered to represent a myocardial ischemia caused by the unbalance between cardiac oxygen demand and oxygen supply, but the details

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of this mechanism remains yet unexplained. Rein (1931)\(^{30}\) showed that coronary insufficiency might be caused by the poor increase in coronary flow as compared with the increase in cardiac work. Milles (1937)\(^{30}\) made a detailed study on the electrocardiographic changes induced by adrenaline and concluded as follows: the electrocardiographic changes caused by adrenaline were ascribed to its increasing the myocardial requirements for oxygen beyond the available supply, thus resulting the functional anoxemia of the myocardium. And Raab and Lepeschkin (1950)\(^{30}\) stated that the characteristic depression and/or inversion of the T wave elicited by sympathomimetic amines were attributable to the specific action of these amines upon the myocardial cell metabolism, and this chemical action resulted in excessive, wasteful oxygen consumption by the heart muscle and consecutive myocardial hypoxia, despite simultaneous coronary dilatation which did not suffice to compensate fully for the rapid consumption of oxygen.

However, in order to investigate the pathologic physiology of the acute coronary insufficiency of neurohormonal origin, cardiac oxygen utilization as well as hemodynamics must be determined continuously. Therefore, in the present study, a cuvette oximeter was devised which is available for continuous measurement of the oxygen level of coronary sinus blood, and the effects of sympathetic nerve stimulation and catecholamines on coronary circulation and electrocardiograms were studied.

**Material and Methods**

Dogs weighing from 10 to 20 Kg. were anesthetized with pento-barbiturate injected intravenously. Artificial respiration was maintained through an endotracheal tube with oxygen, and the left chest was opened in the fourth intercostal space. These animals were heparinized prior to the first blood vessel cannulation. Figure 1 shows a schematic representation of the experimental arrangement.

Mean blood pressure was measured with an electric manometer (strain gauge type) in the right carotid artery. The left subclavian loop was exposed and the aortic arch was freed from the surrounding tissues by blunt dissection and then was cut at its distal part. Two glass tubes with an internal diameter of 8.5 mm. were inserted into the proximal and distal cut ends of the aorta, respectively. The inserted portion of these glass tubes had been bent at an angle of 30 degrees to the long axis for facilitating the insertion into the aorta. These glass tubes were connected with a rotameter through polyethylene tubes for cardiac output measurement. These procedures were done as quickly as possible, and the blood circulation through the rotameter circuit were resumed within 5 minutes. The cardiac work was calculated from the product of mean blood pressure and cardiac output in KgM/min., and the kinetic energy factor was neglected. The peripheral vascular resistance was calculated from the ratio of mean blood pressure to cardiac output in dynes sec./cm\(^5\).

The modified Harrison-Morawitz cannula was inserted into the coronary sinus via the right jugular vein. After the cannula was in place, the rubber balloon, which was tied near the distal end of the cannula, was inflated to hold the cannula in position and to prevent the escape of blood from the coronary sinus except through the cannula. Through this cannula, the coronary sinus blood was successively led to the handmade cuvette oximeter (see appendix) and to an electromagnetic flowmeter, and was finally returned into the left jugular vein. In each experiment, coronary venous blood was taken more than 2 times for oxygen analysis by the manometric method of Van Slyke and Neill,\(^{30}\) and

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the working oxygen-saturation curve for the cuvette oximeter was calibrated. Arterial blood was also taken more than 2 times in each experiment for oxygen measurement with the same method. Since the oxygen level of the arterial blood was revealed to change very little through each experiment, the mean value of the arterial oxygen levels was assumed to represent the arterial oxygen value throughout an experiment. Thus, the coronary arteriovenous oxygen difference could be measured continuously. The cardiac oxygen uptake was calculated from the product of coronary arteriovenous oxygen difference and coronary flow in cc/min. The cardiac mechanical efficiency was calculated from the ratio of cardiac work to the product of oxygen uptake and 2.057. The total coronary flow was calculated on the assumption that the blood flow through the coronary sinus is about 60 per cent of the total coronary flow.

Unipolar leads were taken on the left and right sides of the chest with two electrocardiographs having a 60 cps. filter. To prevent the influence of any electric-field changes upon the electrocardiograms and to avoid radiative loss of the body temperature, the opened chest was closed.

Thus in these animals, mean arterial blood pressure, cardiac output, coronary sinus flow, oxygen saturation of coronary sinus blood and two leads of electrocardiograms were recorded simultaneously on an electromagnetic oscillograph. Since the oxygen saturation curve had a time delay compared with other recordings, corrections were made.

For electrical spinal stimulation, a raminectomy was done before thoracotomy and a concentric stimulating electrode was inserted into the spinal cord (D1) and was fixed by the method of Hayase and Matsuda.

Coronary Sinus Catheterization

For coronary sinus catheterization, which began with Morawitz, the Courmand catheter has generally been used since Goodale's and Bing's works in man as well as in the dog. But in this experiment, the Harrison-Morawitz cannula, which was modified by this author, was used to lead the coronary sinus blood to the cuvette oximeter and flowmeter successively, and there was no escape of blood from the coronary sinus except through the cannula. This modified cannula was made of a thin brass tubing with an internal diameter of 3.5 mm. Two smaller brass tubings were entirely sealed into the wall of the cannula and were available for inflating the balloon and obtaining the samples of mixed venous blood, respectively.

Insertion of the cannula into the coronary sinus via the right jugular vein was carried out before thoracotomy under fluoroscopic guidance, or after thoracotomy. The insertion before thoracotomy could be done somewhat easily as compared with that after thoracotomy. In this case, however, the cannula, which had been inserted into the coronary sinus, sometimes slipped out of position during the succeeding operative manipulation. Moreover, a fairly long time elapsed up to the completion of operative manipulation after the insertion of cannula, so the coronary system might suffer a excess load before the beginning of experimental procedure. Therefore, in this experiment, the insertion of cannula into the coronary sinus was mainly done after all the operative manipulations were completed, i.e., just before the beginning of experimental procedure. After thoracotomy, however, fluoroscopic guidance was frequently unreliable for the insertion of cannula. And it appeared to be due to the changes of the heart position, so a great deal of skill was required for successful insertion of cannula after thoracotomy. The insertion of cannula into the coronary sinus was confirmed by autopsy after experiment in all cases.

RESULTS

(1) Administration of Small Doses of Catecholamines

Intravenous injection of small doses of adrenaline (2 μg./Kg./5 min. and 3 μg./Kg.) and noradrenaline (5 μg./Kg./2 min., 3 μg./Kg./2 min. and 4 μg./Kg./3 min.) were carried out in 2 and 3 mongrel dogs respectively. A representative case will be described at first.

No. 754-4 (figures 2 and 3)

Thirty microgram (2 μg./Kg.) of adrenaline was intravenously injected during 5 minutes. The blood pressure began to increase 1 minute after the beginning of injection, and reached its maximum (247 per cent of the control value) after 5 minutes. Here all values are given as per cent of the control. The heart rate increased very slightly up to 2 minutes, and then decreased below the control value corresponding with marked elevation of blood pressure. After 6 minutes the heart rate reduced to the minimal level (78 per cent). The cardiac output decreased slightly at first, whereas the blood pressure began to increase. After 2 minutes, however, the cardiac output began to increase, and after about 6 minutes it reached 159 per cent of the control value. Therefore, the peripheral vascular resist-
Fig. 2. Original recording of a representative experiment with a small dose of adrenaline (2μg./Kg./5min., intravenously) (No. 754-4). Mean blood pressure (BP); cardiac output (CO); coronary sinus flow (CF); percentage oxygen saturation of coronary sinus blood (O₂ Saturation); electrocardiograms recorded at the right (R) and left (L) sides of the chest. 1: 5' after the beginning of injection, 2: 20', 3: 40', 4: 1', 5: 1' 20'', 6: 1' 40'', 7: 2', 8: 2' 20'', 9: 2' 40'', 10: 3', 11: 3' 20'', 12: 3' 40'', 13: 4', 14: 4' 20'', 15: 4' 40'', 16: 5', 17: 5' 30'', 18: 6', 19: 6' 30'', 20: 7', 21: 7' 30'', 22: 8', 23: 8' 30'', 24: 9', 25: 9' 30'', 26: 10'.

Fig. 3. Graphical representation of figure 2. For details see text.

Anance began to increase after 1 minute, and it reached the maximum level (212 per cent) after 2 minutes, when the cardiac output showed its minimal value in spite of marked elevation of blood pressure. Then the peripheral vascular resistance declined gradually, indicating some undulation. These results are interpreted to mean that the elevation of blood pressure in this case was primarily due to vasoconstriction. The cardiac work, which was calculated from the product of mean blood pressure and cardiac output, increased gradually and reached 366 per cent of the control value after 5 minutes. The coronary flow showed a slight and transient decrease at 1 minute 20 seconds, when the blood pressure began to increase. Then the coronary flow increased gradually and reached its maximum (206 per cent) after 5 minutes 30 seconds. The oxygen content of coronary sinus blood decreased slightly up to 1 minute 40 seconds. Then it began to increase and reached the maximum (164 per cent) after 5 minutes. The oxygen uptake of the myocardium increased in spite of the decrease in oxygen extraction and reached 178 per cent of the control value after 4 minutes 40 seconds. This increase in oxygen uptake was attributable to the remarkable increase in coronary flow.

The cardiac mechanical efficiency began to increase about 1 minute after the beginning of
injection. After 6 minutes it reached the maximum level (220 per cent). This augmentation of cardiac efficiency was brought about by more marked increase in cardiac work than in oxygen uptake. In the electrocardiograms, a slight depression of the S–T segment was observed from 3 to 6 minutes, when the cardiac efficiency remained elevated. The height of T wave diminished slightly at first, but it increased after about 4 minutes.

The results observed in all of the 5 experiments with small doses of catecholamines, are summarized graphically in figures 4 and 5. As can be seen in these figures, no essential difference was found between the effect of adrenaline and that of noradrenaline on the hemodynamics and oxygen metabolism in the myocardium. With noradrenaline, however, the heart rate changed a little. In general, the effect of noradrenaline on the hemodynamics and oxygen metabolism was milder than that of adrenaline. The electrocardiographic changes observed in these experiments, will be described in detail later on.

**Fig. 4.** Effects of small doses of adrenaline on hemodynamics and cardiac oxygen metabolism. The ordinates indicate the values given as per cent of control. The abscissae indicate the lapse of time.

**Fig. 5.** Effects of small doses of noradrenaline on hemodynamics and cardiac oxygen metabolism.

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Intravenous injection of large doses of adrenaline (60μg./Kg., 30μg./Kg. and 20μg./Kg.) and noradrenaline (30μg./Kg., 25μg./Kg. and 25μg./Kg.) were carried out in 3 and 3 mongrel dogs respectively. A representative case will be described at first.

No. 750–5 (figures 6 and 7).

Five hundred microgram (60μg./Kg.) of adrenaline was injected intravenously. The heart rate, blood pressure and cardiac output began to increase within 20 seconds. After 50 seconds, however, the heart rate began to decrease, and after 1 minute 50 seconds it reduced to the minimal level (83 per cent of the control value). On the other hand, the blood pressure continued to increase and reached its maximum (435 per cent) after 3 minutes 30 seconds. The cardiac output, which reached the maximum (144 per cent) after 40 seconds, decreased rapidly corresponding with marked elevation of blood pressure. From 1 minute 30 seconds to 5 minutes the cardiac output maintained the minimal level (40 per cent), and then it gradually returned to the control level. Therefore, the peripheral vascular resistance increased rapidly after 1 minute. It showed the maximum level (1000 per cent) after 4 minutes, when the blood pressure reached its maximum and the cardiac output showed its minimal value. These results are interpreted to mean that, in this case with large dose of adrenaline, a marked and long sustained vasoconstriction occurred in a rather retarded fashion, as compared with that in the case with small dose.
of adrenaline. That is, in the latter case, the cardiac output decreased at first, while in the former case, the cardiac output distinctly increased during the first 1 minute.

The cardiac work began to increase after 20 seconds, and maintained a high level of about 210 per cent of the control value from 40 seconds to 1 minute 10 seconds after the beginning of injection. This augmentation was due to an increase not only in blood pressure but also in cardiac output. Then the cardiac work declined and showed only 110 per cent after 1 minute 30 seconds. This decline was due to a rapid and marked decrease in cardiac output in spite of remarkable elevation of blood pressure. At last, the cardiac work increased again gradually and reached 223 per cent after 6 minutes 30 seconds, and then gradually approached the control level. This second increase in cardiac work was due to returning of cardiac output to the control level, though the blood pressure began to decline. Thus, rapid and marked decrease in cardiac output exerted a great influence on the changes of cardiac work. In this case with large dose of adrenaline, the maximum level of cardiac work did not synchronize with that in blood pressure, unlike in the case with small dose of adrenaline.

The coronary flow increased gradually at first, but the oxygen level of coronary sinus blood decreased slightly up to 1 minute. Then these two variants increased rapidly and markedly in parallel with elevation of blood pressure. The coronary flow reached the maximum (850 per cent) after 3 minutes 30 seconds, when the blood pressure showed its maximum value. On the other hand, the oxygen level reached 245 per cent of the control value after 1 minute 20 seconds. Then it continued to increase and finally reached outside of the galvanometer scale from 1 minute 30 seconds to 6 minutes after the beginning of injection. The oxygen uptake of the heart increased and reached 234 per cent after 1 minute 20 seconds. This increase in oxygen uptake depended on that in coronary flow. The cardiac efficiency increased at first and reached 159 per cent after 40 seconds, and then it decreased below the control value. In the electrocardiograms, a coronary insufficiency pattern was apparently presented after 30 seconds, and then it was gradually improved in accordance with a fall of the cardiac efficiency.

The results observed in all of 3 experiments with large doses of adrenaline are summarized graphically in Figure 8. In all the cases, characteristic changes were remarkable decrease in cardiac output and marked increase in oxygen level of coronary sinus blood. The cardiac work showed less increase than in the cases with small doses of adrenaline. This was due to a decrease in cardiac output. In 2 of 3 cases cardiac efficiency changed as follows: 1) increased 2) decreased below the control levels 3) increased again 4) approached the control levels. The increase in the first stage was due to the more prominent increase in cardiac work than in oxygen uptake. The decrease in the second stage was due to the fact that the cardiac work declined because

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Fig. 8. Effects of large doses of adrenaline on hemodynamics and cardiac oxygen metabolism.

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of a remarkable decrease in cardiac output, while the oxygen uptake increased markedly because of a prominent increase in coronary flow. The increase in the third stage was due to re-augmentation of cardiac work. In one case, the cardiac efficiency showed only and transiently increased in the initial stage and then decreased for a longer period of time. In general, the effect of noradrenaline on hemodynamics and cardiac oxygen metabolism was milder than that of adrenaline. But no essential difference was found between a decrease through all stages, being due to marked increase in cardiac oxygen uptake.

The results with large doses of noradrenaline are summarized in figure 9. In all of 3 cases, the heart rate changed very little. In 2 cases, the cardiac work slightly these two amines, as in the cases with small doses.

(III) Stimulation of Cervical Sympathetic Nerve

Electrical stimulation of the subclavian loop was carried out in 7 animals with commercial alternating current, 60 cycle per
second, with a voltage ranging from 3 to 10 volt, for the period of 15 to 30 seconds. A record taken from one of these experiments can be seen in figures 10 and 11. The results observed in all of 7 experiments are summarized graphically in figure 12.

The blood pressure increased during the stimulation in all cases. Upon removal of the stimulation, it began to decrease and returned to the control level. The heart rate increased in all cases during the stimulation. After the cessation of stimulation, it fell below the control value in 3 cases. Increase in cardiac output occurred at the time when the blood pressure began to rise, and the cardiac output reached the maximum within 13 seconds after the beginning of the stimulation. The peripheral vascular resistance increased in 4 cases and decreased in 3 cases during the stimulation. However, the change of this variant was slight. In all of 7 experiments, the cardiac work increased during the stimulation. With the cessation of stimulation, it began to decrease and returned to the control level.

The coronary flow began to increase within 8 seconds after the beginning of stimulation, and reached the maximum at the late stage of stimulation or just after the cessation of stimulation. The oxygen level of coronary sinus blood decreased slightly in 6 cases during the stimulation. The oxygen uptake increased in parallel with the augmentation of coronary flow. In general, it sustained the high level even after the cessation of stimulation. The cardiac efficiency increased with the stimulation because of a marked increase in cardiac work. In the late stage of experiments, however, it fell below the control value, due to the fact that the oxygen uptake remained elevated after the cessation of stimulation.

(IV) Stimulation of Spinal Sympathetic Nerve

Electrical stimulation of the spinal sympathetic nerves was carried out in 4 animals with a commercial alternating current, 60 cps., with a voltage ranging from 5 to 10 volt, for 15 seconds. A record taken from one of these experiments can be seen in figures 13 and 14. The results observed in all of 4 experiments are summarized graphically in figure 15.

In all cases, the blood pressure incr-
eased with the stimulation and remained high after the cessation of stimulation. The average increase in blood pressure was 52 per cent. The heart rate increased in 2 cases during the stimulation. The cardiac output underwent a transitory and slight fall just after the beginning of stimulation, then it increased slightly. In all but one case, the peripheral vascular resistance increased during the stimulation and remained high even after the cessation of stimulation. In one case it changed very little. In all of 4 experiments, the cardiac work augmented during the stimulation by 45 to 81 per cent, average 63 per cent. In general, the effects of the spinal sympathetic stimulation on blood pressure and cardiac output made their appearance in a rather retarded fashion in comparison with the quick appearance of the effects in the cases of peripheral sympathetic stimulation. Therefore, the observed increase in cardiac work with the spinal sympathetic stimulation was retarded in its appearance, larger in its magnitude and longer in its duration, as compared with the peripheral sympathetic nerve stimulation.

In all cases, the coronary flow began to increase within 10 seconds after the be-

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myocardial oxygen uptake increased in parallel with the increment of coronary flow. In 3 cases, the cardiac efficiency slightly increased during the stimulation, due to a larger increase in cardiac work than in oxygen uptake. After the cessation of stimulation, it fell below the control value in 3 cases, due to the fact that the increase in oxygen uptake lasted longer in its duration than that in cardiac work.

The changes in hemodynamics and oxygen metabolism of the heart with the administration of catecholamines and electrical sympathetic nerve stimulation are schematically summarized in table I.

(V) Coronary Insufficiency Pattern in Electrocardiogram

As briefly mentioned in the representative cases, the effects of catecholamines and electrical stimulation of the sympathetic nerve on coronary circulation were also studied referring to the electrocardiograms. That is, the height of the T wave and the deviation of the S–T junction were measured consecutively. The electrocardiograms were taken through an unipolar lead from the left side of the chest. The cases in which accurate measurement failed were omitted from the subject. But in the cases of spinal sympathetic nerve stimulation, accurate measurement could not be done during the stimulation due to unavoidable alternating current disturbance. These measurements were performed in 19 cases which consisted of 2 cases with small doses of adrenaline, 3 with small doses of noradrenaline, 2 with large doses of noradrenaline, 2 with large doses of noradrenaline, 6 with cervical sympathetic stimulation and 4 with spinal sympathetic stimulation (figure 16).

1) Administration of Catecholamines

Small Doses of Adrenaline. In one case the height of T wave began to increase just after the beginning of injection, and it reached the maximum (143 per cent of the control level) after 1 minute. And no depression of S–T junction was observed. Thus, in this case any coronary insufficiency...
Table I Schematic Representation of the Effects of Catecholamines and Stimulation of Sympathetic Nerves on Hemodynamics and Cardiac Oxygen Metabolism

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<td>Coronary Sinus Oxygen</td>
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<td>Cardiac Oxygen Uptake</td>
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<td>Cardiac Efficiency</td>
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↑ increased  ↓ decreased  → no significant change

Pattern was not induced. In another case, however, the height of T wave slightly diminished up to 3 minutes, then it increased and reached the maximum (153 per cent) after 6 minutes. The S–T junction became depressed (claw form) after 3 minutes, and it remained depressed during the succeeding 3 minutes.

Small Doses of Noradrenaline. In the first case the T wave changed very little. But the depression of S–T junction (trough form), which had been observed before the injection, aggravated after the injection and showed the maximum depression (150 per cent of control level) after 2 minutes. In the second case, the following changes were observed with the lapse of time: a) increase in the height of T wave with improvement of the depression of S–T junction (sickle form), b) diminution in the T-height below the control level with aggravation of S–T depression, c) increase in the T-height with improvement of S–T depression. In the third case, the height of T wave diminished extremely after 1 minute, then it increased and reached 169 per cent of the control level after 2 minutes 40 seconds. The depression of S–T junction (wing form) aggravated from 1 to 4 minutes after the beginning of injection.

Large Doses of Adrenaline. In all of 2 cases, the T wave diminished in amplitude at first and reached the minimal level (average 57 per cent of the control level) after about 1 minute. In the latter half of experiments, however, the T wave increased.
in amplitude. On the other hand, the depression of S–T junction aggravated in accordance with a diminution of the height of T wave, and the former improved in parallel with an increase in the latter.

Large Doses of Noradrenaline. In all of 2 cases, the T wave diminished in amplitude at first, but then increased. In one case, the depression of S–T junction (wing form), which had been observed before the injection, much more aggravated after the injection in accordance with a diminution of the height of T wave. In another case, however, the S–T junction changed very little during the experiment.

2) Electrical Stimulation of Sympathetic Nerve

Stimulation of Cervical Sympathetic Nerve. In 3 of 6 cases, the height of T wave diminished and reached the minimum level just after the beginning of stimulation. In other 3 cases the T wave increased in amplitude with the stimulation. During the latter part of stimulation or after the cessation the T wave increased in all of 6 cases. In 3 cases, in which the T wave increased in amplitude, no S–T depression was presented. In 2 of other 3 cases, in which the height of T wave diminished with the stimulation, the S–T junction became depressed (wing form) as the T-height diminished.

Stimulation of Spinal Sympathetic Nerve. The T wave diminished in amplitude during the stimulation in 3 of 4 cases. After the cessation of stimulation, it remained slightly diminished in all but one case. The S–T junction changed as follows: In 2 cases no depression was observed. In one case the depression (wing form), which had been observed before the stimulation, aggravated during the stimulation. And in 1 case it rather improved with the stimulation.

The T wave and S–T junction generally showed different reactions in case by case even with the same stimulation. But these observations can be summarized as follows. The height of T wave: With the administration of small doses of catecholamines the height of T wave increased slightly in many cases. In a few cases, however, it diminished definitely just after the injection. With large doses of catecholamines it diminished at first, then increased. With the stimulation of cervical sympathetic nerve, it diminished in 3 of 6 cases and increased in remaining 3 cases. But during the latter part of stimulation or after the cessation it increased in all cases. With the stimulation of spinal sympathetic nerve it diminished. The S–T junction: In general, the S–T junction became depressed in parallel with diminution in the height of T wave, and the depression improved in parallel with increase in the height of T wave. In a few cases
cases, however, a depression of S–T junction was observed when the T wave unchanged in amplitude or even when the T wave increased.

(VI) The Correlation between Cardiac Efficiency and Coronary Insufficiency Pattern

It was described in the representative cases that the coronary insufficiency pattern in the electrocardiograms had been observed to be in accordance with increase in the cardiac efficiency. In order to investigate this problem further on, the correlation between the cardiac efficiency and the height of T wave or the depression of S–T junction was studied in individual case. This study was carried out in 19 cases. All cases could be classified into the following 3 groups on the basis of correlation between the cardiac efficiency and the height of T wave. That is: 1) group with a negative correlation, 2) group with a positive correlation, and 3) group without significant correlation. The details are given as below.

1) Group with a negative correlation

In 10 of 19 cases, a negative correlation was observed between the cardiac efficiency and the height of T wave. That is: 1 case injected with small dose of adrenaline, 2 cases with small dose of noradrenaline, 2 cases with large dose of adrenaline, 1 case with large dose of noradrenaline, 3 cases with the stimulation of the cervical sympathetic nerve and 1 case with the stimulation of the spinal sympathetic nerve. A representative case will be described.

No. 745–3 Electrical stimulation (10 volt, for 30 seconds) of the cervical sympathetic nerve. The time course changes in the cardiac efficiency, in the height of T wave and in the depth of S–T depression are shown in figure 17(A). As can be seen in this figure, the T wave changed in contrast with the cardiac efficiency. That is, the T wave diminished in amplitude when the cardiac efficiency increased, and the T wave increased when the cardiac efficiency decreased. On the other hand, the depth of S–T depression increased (which means to aggravate) when the cardiac efficiency increased, and it decreased (which means to improve) when the cardiac efficiency decreased. These relations are shown in figure 17 (B). Thus, the height of T wave showed a negative correlation to the cardiac efficiency, and the depth of S–T depression showed a positive correlation to the cardiac efficiency.

In this group, as shown in the above representative case, the coronary insufficiency pattern appeared or aggravated in accordance with an increase in cardiac efficiency. Moreover, this insufficiency pattern disappeared or improved in accordance with a decrease in the cardiac efficiency.

2) Group with a positive correlation

A positive correlation was observed in only 2 cases: that is, 1 case injected with

Fig. 17. A case in which a negative correlation was observed between cardiac efficiency and height of T wave. (No. 745–3. Stimulation of cervical sympathetic nerve, 10 Volt, for 30 seconds.) (A) Changes in the cardiac efficiency, tension equivalent of oxygen consumption, height of T wave and depression of S–T junction with the lapse of time. (B) Correlation between the cardiac efficiency and height of T wave. (C) Correlation between the tension equivalent of oxygen consumption and height of T wave.

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3) Group without significant correlation

In 7 of 19 cases, the height of T wave did not show any significant correlation as a whole to the cardiac efficiency all through the period of experiment. But this group could be classified into the following 2 subgroups: a) cases in which a circle was generated on the graph which shows the relationship among the height of T wave, cardiac efficiency and the lapse of time, and b) cases showing a negative correlation in the early stage and a positive correlation in the later stage of the experiment.

Subgroup a): Such a phenomenon was observed in 2 cases; that is, 1 case injected with large dose of noradrenaline and 1 case with the stimulation of cervical sympathetic nerve. A representative case will be described. No. 749–9 Noradrenaline 25µg./Kg. The time course changes in the cardiac efficiency, in the height of T wave and in the depth of S–T depression are shown in figure 19 (A). It seems that the T wave

small dose of adrenaline and 1 case with small dose of noradrenaline.

A representative case: No. 754–4 Adrenaline 2µg./Kg./5 min. As can be seen in figure 18 (B), the height of T wave showed a positive correlation to the cardiac efficiency in contrast with the case of group 1). That is, the T wave increased in amplitude when the cardiac efficiency increased. Here, however, the time course changes in these 2 variants must be considered (figure 18 (A)). That is, during the early stage of the experiment (from 1 minute to 2 minutes 30 seconds after the beginning of the injection), the T wave changed in contrast with the cardiac efficiency, same as the case of group 1). But later on, the T wave changed in parallel with the cardiac efficiency.

Thus, even in this group, the height of T wave showed transitorily a negative correlation to the cardiac efficiency in the early stage of the experiment, though, as a whole, it showed a positive correlation all through the period of experiment.

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and S–T depression changed independently of the cardiac efficiency. As can be seen in figure 19 (B), however, a circle could be generated on the graph which shows the relationship among the height of T wave, cardiac efficiency and the lapse of time. Thus, in this case the relation of the height of T wave to the cardiac efficiency is not simple.

Subgroup b): Such a phenomenon was observed in 5 cases, i.e., 2 cases with the stimulation of cervical sympathetic nerve and 3 cases with the stimulation of spinal sympathetic nerve. Figure 20 shows a representative case (No. 755–2) which had an electrical stimulation (5 volt, for 15 seconds) of the spinal sympathetic nerve. All through the period of the experiment, any significant correlation was not observed between the height of T wave and cardiac efficiency (figure 20 (B)). But the time course changes in these 2 variants (figure 20 (A)) must also be considered, as in group 2). That is, in an early stage of the experiment the T wave changed in contrast with the cardiac efficiency, and in the later stage it changed in parallel with the cardiac efficiency.

As mentioned above, all experimental cases were classified into 3 groups on the basis of the correlation between the height of T wave and cardiac efficiency. The most interesting fact, which was observed throughout these 3 groups, was that the height of T wave changed in contrast with the cardiac efficiency and the degree of S–T depression changed in parallel with the cardiac efficiency at least in an early stage of the experiment. That is, in this stage, a negative correlation was observed between the height of T wave and the cardiac efficiency in all of 3 groups. In group 1), this phase showing a negative correlation (negative phase) was long in its duration and followed by a phase showing a positive correlation (positive phase) of short duration. In group 2), the negative phase was shorter and followed by the positive phase of longer duration. And in group 3), the negative phase was followed by the positive phase of nearly the same duration. Thus, the proportion of the duration between the negative and positive phases decided the whole correlation between the height of T wave and the cardiac efficiency. After all, it might be concluded that the appearance of coronary insufficiency pattern was closely related to increase in cardiac efficiency.

**DISCUSSION**

In the present study, responses of animals to administration of catecholamines and sympathetic nerve stimulation with various methods were observed. The most outstanding finding throughout these observations was the fact that there was an intimate relationship between the cardiac efficiency and coronary insufficiency pattern of electrocardiogram. The effects of catecholamines on the electrocardiogram have been studied by many investigators, including Kahn,10 Levine,
Katz, Milles, Raab, Hayase, and others and today it is well recognized that these drugs bring about the coronary insufficiency pattern, i.e., deviation of the S–T junction and diminished amplitude or inversion of the T wave. On the other hand, Rothberger, Raab, Ikeda, Hayase, and Suwo induced the similar changes in electrocardiograms with electrical stimulations of the peripheral sympathetic nerves. Moreover, Hayase and Ueda presented the same changes with electrical stimulations of the spinal sympathetic nerves. In the present study, a coronary insufficiency pattern of electrocardiogram was observed in almost all the cases except a few ones with small doses of catecholamines.

In general, the coronary insufficiency pattern is considered to represent a myocardial ischemia, and many studies on the electrocardiographic changes induced by low oxygen gas inhalation support this consideration. And it is believed at present that the myocardial ischemia is caused by unbalance between the cardiac oxygen demand and oxygen supply. The relation of cardiac work to the oxygen consumption can be expressed by the values for cardiac mechanical efficiency. So the relationship between the coronary insufficiency pattern of electrocardiogram and changes in cardiac efficiency will be discussed below.

Before the discussion on this problem, the experimental conditions of present study must be considered. It was very difficult to perform the present experiments under perfectly physiological conditions, because the operative manipulation was large, and the blood pressure, cardiac output and coronary flow showed low values as compared with the values generally accepted. On the other hand, a part of the blood stream to the cranium and arms escaped from the measurement of cardiac output, so the actual values for cardiac output, cardiac work and cardiac efficiency might be higher than the observed values. Although these disadvantages might disturb the accurate determination of the absolute values for the circulatory variants, they would not interfere with pursuing the hemodynamic changes with the lapse of time and comparing these changes with those in electrocardiograms.

As already mentioned, all experimental cases could be classified into three groups on the basis of the correlation between the cardiac efficiency and the height of T wave. And it was commonly observed throughout these three groups that the T wave changed in contrast with the cardiac efficiency just after the administration of catecholamines or just after the beginning of the electrical stimulation of sympathetic nerves. That is, in the early stage of the experiments, a coronary insufficiency pattern of electrocardiogram appeared or aggravated in association with increase in the cardiac efficiency.

With the electrical stimulation of sympathetic nerves, Gollwitzer-Meier and Krüger observed a decrease in oxygen level of coronary venous blood, increase in cardiac oxygen consumption and decrease in cardiac efficiency. Shipley and Gregg demonstrated that the cardiac work, coronary flow, coronary A–V oxygen difference and cardiac oxygen consumption were increased as the result of cardiac nerve stimulation. Eckstein, et al. also observed a decrease in coronary sinus oxygen content and they concluded as follows. “Nerve stimulation markedly increases myocardial oxygen consumption and coronary flow and produces small increases in work. Even after cardiac work is markedly reduced nerve stimulation elevates cardiac oxygen consumption and coronary blood flow. Sympathetic nerve stimulation by releasing an adrenaline-like substance renders the heart anoxic and inefficient.”

In the present experiments, sympathetic nerve stimulation elevated cardiac oxygen uptake, due to decrease in coronary sinus oxygen content and increase in coronary flow. The stimulation, however, produced more marked increase in cardiac work than that in oxygen uptake. Moreover, it was interesting to note that cardiac oxygen uptake began to increase later than cardiac work and it remained elevated even after the cessation.
of the stimulation, whereas cardiac work began to fall during the stimulation. (This time-discrepancy between the increase in cardiac work and in oxygen uptake was similar to the phenomenon observed by Gollwitzer-Meier, et al.\textsuperscript{69} with the administration of adrenaline in the denervated heart.) Therefore, cardiac efficiency increased rapidly just after the beginning of stimulation or during the early part of stimulation, then it fell gradually and decreased below the original level during the latter part of stimulation or after the cessation. This decrease in cardiac efficiency during the latter part of experiments seemed to be coincident with the conclusions of Gollwitzer-Meier and of Eckstein that the stimulation of sympathetic nerves reduced cardiac efficiency. But I would rather consider that the initial increase in cardiac efficiency was an original phenomenon induced by the sympathetic nerve stimulation, and that the subsequent decrease was a secondary phenomenon.

On the other hand, the effects of adrenaline on coronary circulation have been studied by many investigators. Gremel\textsuperscript{60} showed a decrease in cardiac efficiency in the heart-lung preparation. Gollwitzer-Meier and Kroetz\textsuperscript{62} presented the following results in the innervated heart in situ. With large doses of adrenaline, which brought about a strong "Entlastungsreflex", a decrease in cardiac output and small increase in work were induced, but the oxygen consumption was reduced due to increase in coronary venous oxygen content, and therefore the cardiac efficiency was augmented. The administration of small doses of adrenaline, which brought about a weak "Entlastungsreflex", increased the cardiac output and work, but it produced no increase in coronary venous oxygen content, and therefore it increased markedly the oxygen consumption and reduced the efficiency. Thus it produced the same changes as observed in the denervated heart. Feinberg, et al.\textsuperscript{65,66} also demonstrated increase in coronary venous oxygen content and decrease in A–V oxygen difference.

In the present experiments, the increase in coronary sinus oxygen content was observed in almost all cases with the administration of catecholamines, and it was especially conspicuous in the cases of large dose administration. But in my experiments, the oxygen uptake was augmented due to remarkable increase in coronary flow, and because of marked increase in cardiac work the efficiency was augmented. Even in the cases with large doses, an initial increase in the efficiency was observed, though in the second stage of the experiments the efficiency was reduced due to marked decrease in cardiac output.

Thus, the original effects of catecholamines and of sympathetic nerve stimulation observed in my experiments must be considered as follows: they increased cardiac work more markedly than oxygen consumption, i.e., they augmented the efficiency.

Numerous reports on close correlation between the coronary flow and oxygen consumption have appeared in the literature.\textsuperscript{68} But Katz, et al.\textsuperscript{68} noted that this relation was altered by hypoxemia, catecholamines and increased stress. In these instances, they observed an abnormal increase in coronary flow associated with visually observed arterIALIZation of the coronary venous blood, that is, the "stress-adapting mechanism" or "spontaneous change". The heart appeared to become more efficient in the utilization of oxygen under these conditions. This observation may suggest the possibility that the heart has recourse to a stage of anaerobiosis, and in this regard it is in accord with the result of my experiment.

It is of value to know the cost of the cardiac effort in terms of energy expended, and I discussed as above this problem from a viewpoint of the mechanical efficiency. Here I would reconsider the meaning of the cardiac mechanical efficiency. The efficiency of the heart is expressed with the ratio of external work to energy utilization. The external work is represented by the product of mean arterial blood pressure and cardiac output. On the other hand, the energy utilization is generally represented by the oxygen consumption, because the latter is the best available, though a rather remote,
index of the conversion of chemical energy into mechanical effort. The heart, however, consumes oxygen not only to perform external work but also to maintain its architecture. Therefore, rise of the efficiency may occur due to decrease in proportion of the oxygen consumption not used for external work, the "maintenance oxygen," and it seems reasonable that in calculating the efficiency of the myocardium, the oxygen uptake by the heart performing no work should be subtracted from the oxygen usage of the beating heart.

Although the oxygen consumption is an adequate index of the myocardial energy expenditure, the external work accounts for only a small fraction of the total oxygen consumption of the heart. And the cardiac output is poorly correlated with myocardial oxygen consumption, while blood pressure and heart rate are highly correlated. Gerola, et al. stated that the usual calculation of cardiac external useful work gave no weight to the heart rate, an important determinant of myocardial oxygen consumption, and at the same time, it emphasized cardiac output, a component having little influence on cardiac oxygen requirement. Therefore, they designated the product of arterial blood pressure and heart rate as an adequate index of cardiac oxygen consumption.

On the other hand, Sarnoff, et al. obtained the "tension-time index" (mean systolic pressure times duration of systole) from the area under the systolic portion of the aortic pressure curve, and they stated that the tension-time index in mm Hg seconds was an index of the total tension developed by the myocardium per beat, and that in any given functional state of the beating heart, the tension-time index was the principal, if not the sole, determinant of myocardial oxygen utilization. Thus, they noted that the ratio of tension-time index to myocardial oxygen consumption provided an internal efficiency index.

Now the tension on the wall of a spherical container equals half the product of the internal pressure and the radius. On the assumption that at the onset of systole the ventricle resembled a sphere, Rodbard, et al. estimated the radius of the ventricular chamber from the relationship that the volume of a sphere is equal to $4/3\pi r^3$. Thus they calculated the tension and noted that the tension in the heart was a primary factor in the determination of the myocardial energy requirements measured in terms of its oxygen utilization. On the basis of these calculations, Seki obtained the tension equivalent of oxygen consumption, and in a study of induced anoxemia, he observed a higher correlation of the tension equivalent of oxygen consumption than the work equivalent of oxygen consumption to the electrocardiographic changes.

The results of my experiments should be reanalyzed here from these viewpoints. In the present study, changes in the heart rate were relatively little as compared with those in other parameters, except in a few cases with the stimulation of spinal sympathetic nerve and with large doses of adrenergic. Therefore, it can be considered that the influence of the heart rate upon the myocardial oxygen consumption was comparatively little in the present experiments. In order to study the changes in cardiac effort in terms of the tension, the myocardial tension was calculated using Rodbard's formula:

$$T = \frac{P \cdot r}{2} \times \text{Heart Rate}$$

in which $T$ is myocardial tension per minute; $P$ is mean blood pressure; and $r$ is radius ($\approx \frac{8}{1.6} \sqrt{\text{stroke volume}}$). On the basis of this calculation, the correlation between the tension equivalent of oxygen consumption (ratio of oxygen consumption to myocardial tension) and the height of $T$ wave or the depression of $S$-$T$ junction was investigated in each experimental case. In the majority of the cases, this correlation was found to be only little different from that between the cardiac efficiency and coronary insufficiency pattern (figures 17, 18, 19 and 20). Particularly, just after the beginning or during an early part of experi-

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ments, there was a positive correlation between the tension equivalent of oxygen consumption and the height of T wave in all experimental cases.

Therefore, it can be considered that increase in the cardiac efficiency during the early part of experiments indicated a less oxygen utilization for each unit of cardiac performance, and that the observed coronary insufficiency pattern of electrocardiogram was the manifestation of this anaerobic process.

With the administration of catecholamines and the stimulation of sympathetic nerves, the cardiac work was increased rapidly. Considering the changes in cardiac efficiency, it may be said that the processes of mechanical energy production of the myocardium was affected by these procedures. Namely, these procedures forced the biochemical reactions towards an anaerobic phase temporarily, and then the reactions swung back towards an aerobic phase. In accordance with these changes in the processes of energy production, coronary insufficiency pattern may appear or disappear in the electrocardiogram. These observations were quite in accord with the study of Kawai, which showed that changes in the S–T segment was indeed improved with an increase in the left ventricular work equivalent of oxygen.

The purpose of this work was to study the correlation between the coronary insufficiency pattern of electrocardiogram and the oxygen metabolism in the heart with special reference to its mechanical effort. Although a close relation was found between these two phenomena during the early part of the experiment, the study of the oxygen metabolism alone was not enough, of course, to elucidate sufficiently the changes in electrocardiogram. The use of the value of oxygen consumption as an index of energy production, without regard to the kinds of substrates that are metabolized, is justified on the basis of a first approximation. Of course, it is not the absolute one. A number of investigators have contributed toward the elucidation of carbohydrate and non-carbohydrate metabolisms of the heart, and the works of Bing and associates are especially noteworthy in this field. Further studies on the heart's high-energy phosphate exchange will contribute much toward the elucidation of coronary insufficiency.

**Summary**

In order to investigate the pathologic physiology of coronary insufficiency of neuro-hormonal origin, the experimental studies were carried out on dogs. Arterial blood pressure, cardiac output, coronary flow, oxygen level of coronary sinus blood and electrocardiograms were recorded simultaneously. The relationships among cardiac work, oxygen uptake, cardiac mechanical efficiency and electrocardiograms, and the effects of administrations of adrenaline and noradrenaline and of electrical stimulations of the cervical and spinal sympathetic nerves, were studied.

1. Small doses of adrenaline increased the cardiac work remarkably and the oxygen uptake moderately. The increase in cardiac work was due to both increases in blood pressure and in cardiac output, and the increase in oxygen uptake was mainly due to increase in coronary flow. There was increase in cardiac efficiency.

2. Large doses of adrenaline brought about increases in cardiac work and in oxygen uptake. The increase in cardiac work chiefly depended on elevation of the blood pressure. The cardiac output markedly decreased. It was characteristic that the coronary flow and the oxygen level of coronary sinus blood increased rapidly and remarkably. The cardiac efficiency considerably changed with the lapse of time. That is, it increased in the first phase of reaction, decreased in the second phase and increased again in the third phase.

3. In general, no essential difference was found between the effect of noradrenaline and that of adrenaline on the hemodynamics, except on the heart rate.

4. With the stimulation of the cervical sympathetic nerve, the cardiac work and oxygen uptake increased rapidly. The cardiac work began to decrease during the

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latter part of the stimulation or upon removal of the stimulation, but the oxygen uptake remained elevated even after the cessation of stimulation. Therefore, the cardiac efficiency increased rapidly during the first half of the stimulation and then decreased gradually. During the latter half of the stimulation or after the cessation of stimulation the cardiac efficiency decreased in all cases. The oxygen level of coronary sinus blood decreased slightly in 6 of 7 cases.

5. With the stimulation of the spinal sympathetic nerve, the cardiac work and oxygen uptake increased gradually, and this was true even after the cessation of stimulation. The increase in the cardiac work was mainly due to increase in blood pressure. The cardiac output decreased just after the beginning of stimulation, but it then increased slightly. The increase in oxygen uptake was the resultant of increase in the coronary flow. In most cases, the cardiac efficiency increased during the stimulation and decreased after the cessation of stimulation.

6. In an early stage of all experiments, the electrocardiogram showed a coronary insufficiency pattern in accordance with an increase in the cardiac efficiency. In many cases, this insufficiency pattern disappeared with restoration of the original state or decrease in the cardiac efficiency.

(Appendix) Cuvette Oximeter

The oximeter is a device capable of providing a continuous indication of the percentage oxygen saturation of blood. Although a pioneering investigation of the absorption spectra of hemoglobin and its derivatives was made by Vierordt and Hübner, the fundamental work in blood oximetry was performed by Nicolai, Kraemer and Matthes. Thereafter many investigators, including Drabkin, Millikan, Lowry, Hartman, Wood, Sekelj and others, have contributed much toward the development of this field, and the oximeter is now widely used in clinical and experimental studies.

The development of oximetry, however, is prominent particularly in the field of earpiece type, which is used for photometric determination on the blood circulating in the intact ear. But in the field of cuvette oximeter many problems remain yet to be resolved. In general, the path of cuvette is so narrow that the blood can not flow spontaneously and naturally through the cuvette, and blood samples can be introduced into the cuvette usually by suction or from a syringe by positive pressure. Therefore, it is very difficult to determine the oxygen level of coronary sinus blood continuously without influencing the coronary flow. So in the studies of coronary circulation the oxygen level of coronary sinus blood has been generally analysed merely intermittently with the manometric method, except in the works of Gollwitzer-Meier and Alella, who used the Kramer's oximeter, and of Sarnoff and McKeever, who used the cuvette densitometer. However, in order to study the effect of sympathomimetic drugs and sympathetic nerve stimulation on coronary circulation, which may be varied in a short time, it is indispensable to determine continuously not only the blood pressure, cardiac output and coronary flow but also the oxygen level of coronary sinus blood. So in the present study a cuvette oximeter applicable for this purpose was devised and described below.

1) The Filter-Phototube System

The simplified spectrophotometry is based upon the assumption that the blood has only two colour components, oxyhemoglobin and reduced hemoglobin each with a specific absorption spectrum. Oxyhemoglobin solution transmitted approximately 70 per cent of the incident red light of a wavelength of approximately 640 mμ, whereas reduced hemoglobin absorbed practically all the light of this wavelength. On the other hand, the absorbing capacities of these two colour components are the same at a wavelength of approximately 800 mμ. Therefore, the output of the phototube activated by the light of a wavelength of 640 mμ (the red
system) is a function of both the degree of oxygen saturation and the amount of total hemoglobin. And the output of the phototube activated by the light of a wavelength of 800 m\(\mu\) (the infrared system) reflects only the amount of the total hemoglobin and is independent of the degree of oxygenation. Therefore, the degree of oxygen saturation can be determined by taking the difference between the outputs of these two systems or more accurately by taking their ratio.

With reference to the study of Kuma, the filter-phototube systems of the oximeter of this study were constructed: the infrared system consisted of an argentum-caesium phototube (PT-17 V\(_1\)), having a peak sensitivity to a wavelength of 800 m\(\mu\), and a Walz R\(_2\) filter which transmits light of a wavelength greater than 600 m\(\mu\). The red system consisted of a stibium-caesium phototube (#7209 A) and the Walz R\(_3\) filter, which was the same as used in the infrared system. A tungsten lamp (6 volt, 50 c.p.) was used as the light source.

2) The Cuvette

In general, the polythene tube cuvette has been widely used. However, so as not to influence the original flow of coronary sinus blood when the cuvette is connected with the Harrison-Morawitz cannula inserted into the coronary sinus, the path of the chamber must be sufficiently broad. On the other hand, in order to determine accurately the oxygen level of coronary sinus blood, the path of the chamber must be narrow. In the present study, the polythene tube cuvettes with various diameters were used at first, but these cuvettes could serve not both of these principal objects. So the following cuvette (1 mm. in depth) was constructed.

A thin opaque celluloid plate (1 mm. in thickness), the central portion of which was bored 27 by 80 mm. in dimensions, was interposed between two transparent plastic plates (5 mm. and 2 mm. in thickness, respectively). These three plates were firmly conjoined. Thus, the bored portion of the opaque celluloid plate formed a chamber (27 mm. in width, 80 mm. in length and 1 mm. in depth), its ceiling and floor being covered by a transparent plastic plate respectively. Both ends of this chamber connected with two brass tubes (4 mm. inside diameter), the entry and exit tubes. In order to minimize the resistance to blood flow in the tube-chamber junctions, the ceiling and floor plastic plates in these places were hollowed semi-fusiformly.

Thus, the coronary sinus blood could pass through this cuvette with its original flow. As compared the flow of coronary sinus blood led to the flowmeter through this cuvette with that led to the flowmeter directly without passing through the cuvette, no difference was detectable between the two. The above mentioned light source, filter, cuvette and phototubes are arranged as shown in figure 21.

3) The Amplifying and Recording System

The outputs of the phototubes were led successively to the pre-amplifier (figure 22) and to the D. C. amplifier, and recorded by an electromagnetic oscillograph (Yoko-

![Fig. 21. Schematic drawing of optical system.](image)

![Fig. 22. Circuit diagram of pre-amplifier.](image)
gawa). Thus, the changes in the R-system and the IR-system could be recorded continuously. However, the changes in the IR-system were very little throughout an experiment, so in the present study only the changes in the R-system was recorded continuously, and the values for the IR-system were occasionally recorded to check the constancy of the amount of hemoglobin or to indicate variations in it.

4) Calibration

The calibration curves were constructed from the oximeter readings and from the values determined with the Van Slyke manometric method of analysis on simultaneously withdrawn blood samples. It was desirable that once the calibration curve was constructed, the percentage oxygen saturation values were determined only photoelectrically by using this calibration diagram. In the oximeter of this author, however, the stability of the instrument was not so complete, due to the wideness of path of the cuvette. So the calibration was particularly carried out in each experiment for accurate determination.

The oxygen saturation curve recorded by the electromagnetic oscillograph had a time-delay compared with other phenomena recorded simultaneously. So the calibration curve for the time-delay was constructed from values for the blood flow.

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