Nagoya J. med. Sci. 29: 155-165, 1966.

INVESTIGATION OF THE CARDIOVASCULAR ACTION OF SYMPATHETIC AMINES USING TWO KINDS OF STRAIN GAUGE INSTRUMENT

ATSUSHI SEKIYA, MITSUYOSHI NAKASHIMA, AND ZENGO KANDA

Department of Pharmcology, Nagoya University School of Medicine
(Director: Prof. Zengo Kanda)

SUMMARY

Ventricular responses of a few catecholamines in rabbits were studied with the use of various parameters: blood pressure, systemic output or stroke volume, heart rate, ventricular contractile force and change of segment length of ventricular muscle. In recording ventricular contraction, two kinds of apparatus, strain gauge compass and arch, which we devised, were used. Simultaneous recordings of these various factors permit characterization and direct comparison of the nature and sequence of left ventricular responses by infusion of catecholamines.

Epinephrine or norepinephrine, in smaller dose produced almost the same changes in ventricular contractile force and segment length of ventricular muscle. However, in the course of a short time after the administration of the large dose of these drugs, the change of coutractile force by means of strain gauge arch was significant, but the change of muscle segment length measused by means of strain gauge compass was more complicated and gave us much information of cardiac function. Namely, there were a decrease of stroke deflection with a decrease of stroke volume and a downward displacement of systolic and diastolic excursion curve which meant heart dilatation.

By the administration of methoxamine, the changes of muscle segment length were more marked than the changes of contractile force.

By the administration of isoproterenol, the changes of contractile force were more marked than the changes of muscle segment length changes.

The use of such two kinds of strain gauge apparatus may be valuable for observing the cardiac performance more precisely.

INTRODUCTION

For the study of the cardiac function, cardiac contractile force is one of the most significant circulatory parameters. However, as Cotten and Bay[1] said, a real cardiac movement or changes of the muscle segment are sometimes needed. Thus, the newer method for direct measurement of heart movement in animals[2] was reported in our previous paper.

The strain gauge arch[3][4] by which contractile force was measured is one

関谷　淳，中島光好，神田善吾
Received for publication June 4, 1966.

of the recorders of isometric contraction. Our apparatus is a sort of recorder of isotonic contraction.

Studies of the action of several catecholamines on the cardiovasular system have been made with many kinds of circulatory parameters by authors[5)6)]. In our experiments changes in ventricular muscle segment length were recorded with our apparatus and changes in ventricular muscle tension by means of an arch form strain gauge, and the cardiac output or the stroke volume, the blood pressure and the heart rate were measured simulaneously.

A Comparison was made among the results obtained by these various methods in relation to a few catecholamines actions.

METHODS

Rabbits were anesthetized with urethane and maintained under artificial respiration with room air.

The pericardium was opened widely and systemic output (cardiac output minus coronary blood flow) or stroke volume was measured with an electromagnetic flowmeter MF-2 (Nihon Kohden Co.) as illustrated in Fig. 1.

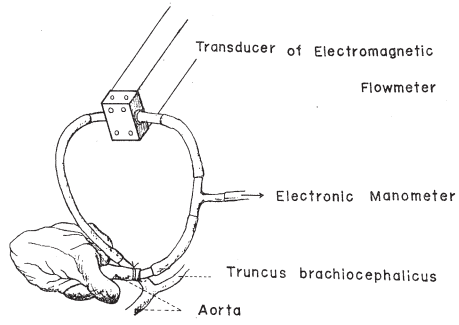

FIG. 1. Drawing of the method of measuring arterial pressure and systemic outflow or stroke volume.

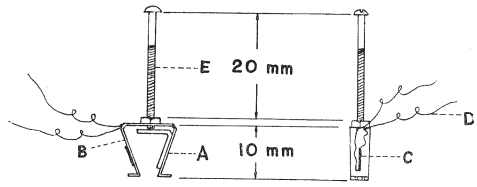

FIG. 2. Drawing of modified strain gange arch.
A: Rigid leg, B: Pivoted leg,
C: Semiconductor strain gange,
D: Lead wire, E: Set screw.

Namely, right and left vena cava anterior and vena cava posterior were transiently obstructed and ascending portion of the aorta was incised and two cannula were inserted into the two aorta ends, the probe of electromagnetic flowmeter being arranged between cannula.

Simultaneoualy aortic pressure was measured with electronic manometer through Y-type cannula from this blood path. Heart rate was recorded with a pulse rate tachometer RT-2 (Nihon Kohden Co.). The segment length of ventricular muscle was recorded with strain gauge compass reported previously[2)]. The force of ventricular contraction was measured with the instrument which was made in our laboratory, imitating strain gauge arch[3)4)] basically as illustrated in Fig. 2. A phosphor-

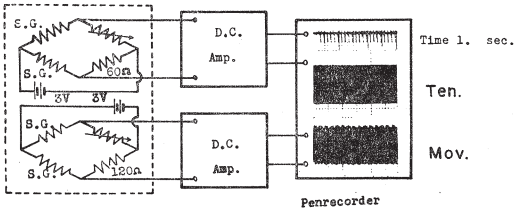

FIG. 3. Drawing of recording apparatus concerning with strain ganges.

bronze plate of 0.35 mm in thickness was used to make the arch. This arch consists of a fixed leg and a pivoted leg to which is cemented one semiconductor strain gauge (4×0.5 mm 60 Ω). The distance between the legs can be altered by means of a set screw.

The gauge is put together with other resistances forming Wheatstone bridge (Fig. 3). A three-volt cell was used as a source to this bridge. The output was carried to a D.C. amplifier. This device recorded an essentially isometric contraction similar to that described for the strain gauge arch[3)4)].

The two legs of the arch were attached to the left ventricle with cotton suture which penetrated deeply into the ventricle muscle. An attempt was made to align the axis of the arch with the longitudinal axis of the ventricle. Considerable care was taken to avoid the inclusion of any visible coronary vessels within the sutures during attachment of the arch to the ventricle. When the arch was attached to the ventricle, the muscle between the two legs of attachment was thus stretched by approximately 30 to 40 percent of the end-diastolic length. Thus the recording of myocardial adjustments secondary to changes in total peripheral resistance and heart size were minimal because of the extended initial length of the muscle segment[1)5)].

All changes in blood pressure, stroke volume, heart rate, ventricular muscle length and ventricular contractile force were recorded simultaneously on a multichannel inking oscillograph.

Epinephrine, norepinephrine, isoproterenol and methoxamine were administered to each rabbit. Drugs were injected into the femoral vein. Each intravenous injection was made as rapidly as possible and the tubing was flushed immediately with normal saline. In all cases the animal had returned to control levels prior to injection of the next drug.

RESULT

Epinephrine: The administration of epinephrine, 0.3-1.0 γ/kg caused the changes in the parameters shwon in Fig. 4 and Fig. 5. There was an increase in aortic blood pressure, stroke volume and systemic output with an increase in myocardial deflection and contractile force. As illustrated in Fig. 6, 7 and 8, epinephrine, 3 γ/kg produced the following changes. Heart rate first increased

transiently and gradually decreased in company with the increase of blood pressure. This is a reflex bradycardia because of the increase in blood pressure. Then the heart rate increased again. Blood pressure increased markedly, and the increase in systemic outflow was not excellent.

In some cases systemic outflow or stroke volume decreased. Ventricular contractile force always increased. The figure of ventricular movement registered by the compass type gauge showed the downward displacement of both levels of end diastolic volume and end systolic volume. This means heart dilatation.

But the amplitude decreased slightly in some cases. Epinephrine 10 γ/kg produced a marked increment of blood pressure, while a decrease in systemic output which was followed by an increase was found. Ventricular contractile force increased greatly, but on the other hand the record of ventricular movement showed the heart dilatation and the decrease of the amplitude (Figs. 9 and 10).

Norepinephrine: Norepinephrine produced approximately the same changes in ventricular contractile force, blood pressure, stroke volume and ventricular muscle segment length as those which occurred with epinephrine. The pressor action of norepinephrine was generally more intensive than that of epinephrine

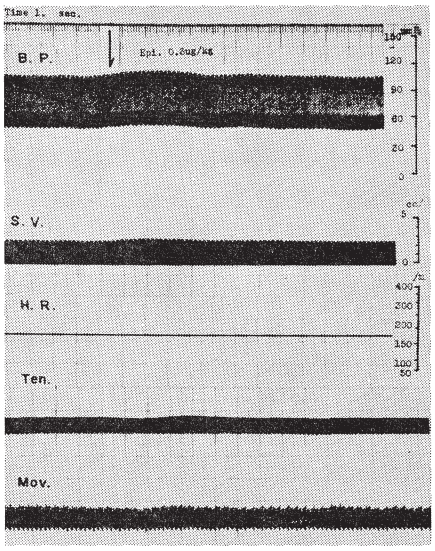

FIG. 4

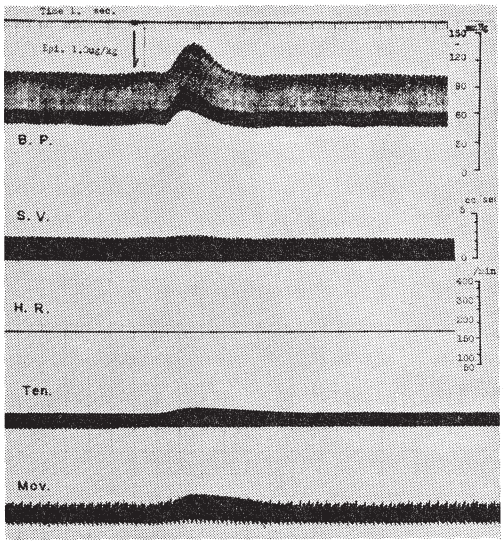

FIG. 5

FIG. 4. The effects of epinephrine, 0.3 γ/kg in the rabbit.
B.P.: Blood pressure, S.V.: Stroke volume, H.R.: Heart rate,
Ten.: Ventricular muscle tension,
Mov.: Ventricular muscle movement.

FIG. 5. The effects of epinephrine, 1.0 γ/kg in the rabbit.

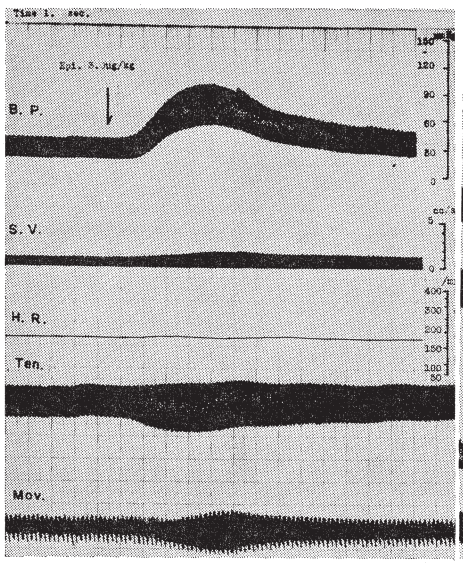

FIG. 6. The effects of epinephrine, 3.0 γ/kg in the rabbit.

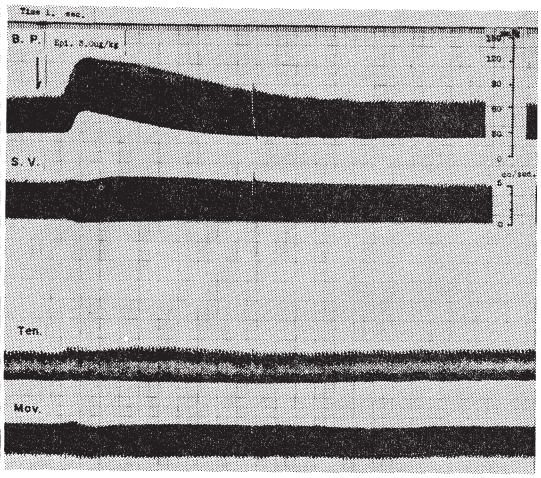

FIG. 7. The effects of epinephrine, 3.0 γ/kg in the rabbit.

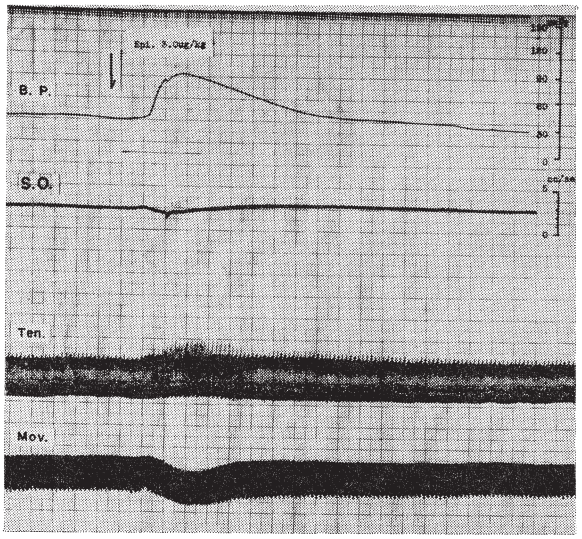

FIG. 8. The effects of epinephrine, 3.0 γ/kg in the rabbit.
S.O.: Systemic oufflow.

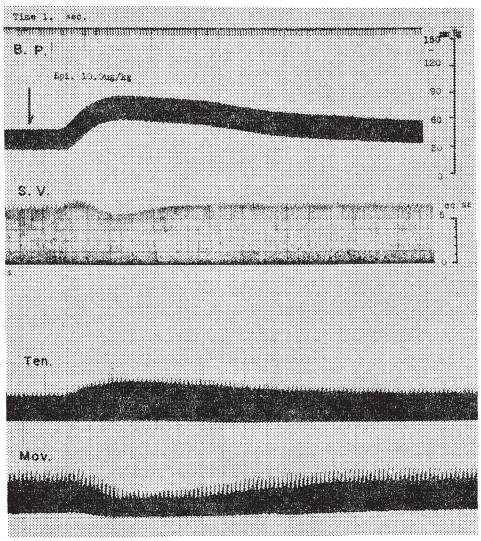

Fig. 9. The effects of epinephrine, 10 γ/kg in the rabbit.

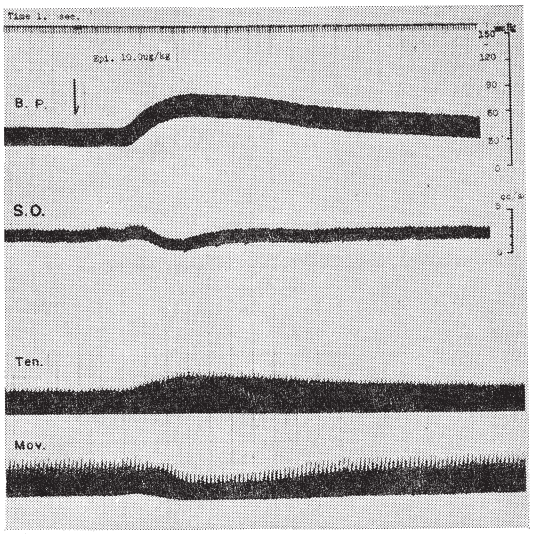

FIG. 10. The efiects of epinephrine, 10 γ/kg in the rabbit.

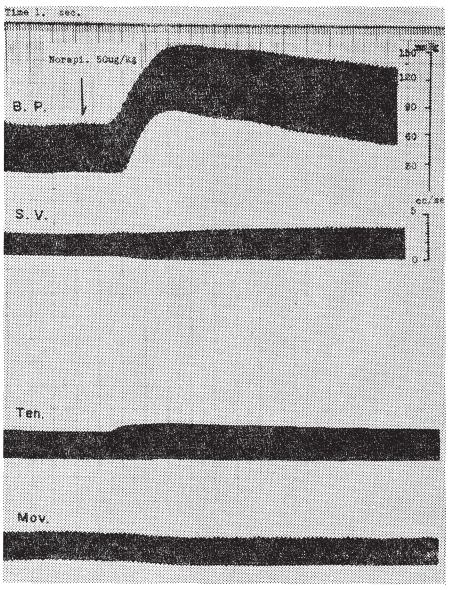

Fig. 11. The effects of norepinephrine, 50 γ/kg in the rabbit.

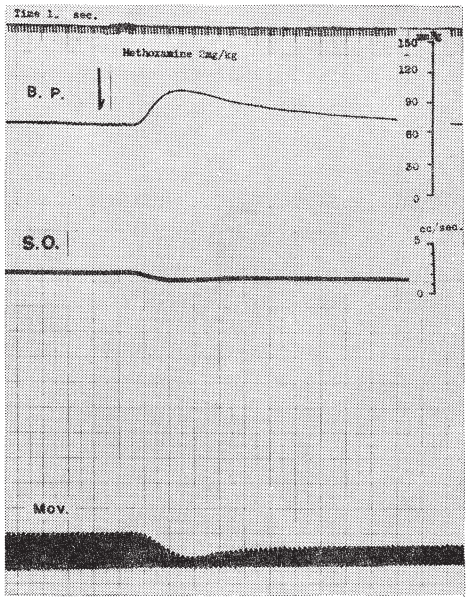

FIG. 12. The effects of methoxamine, 2 mg/kg in therabbit.

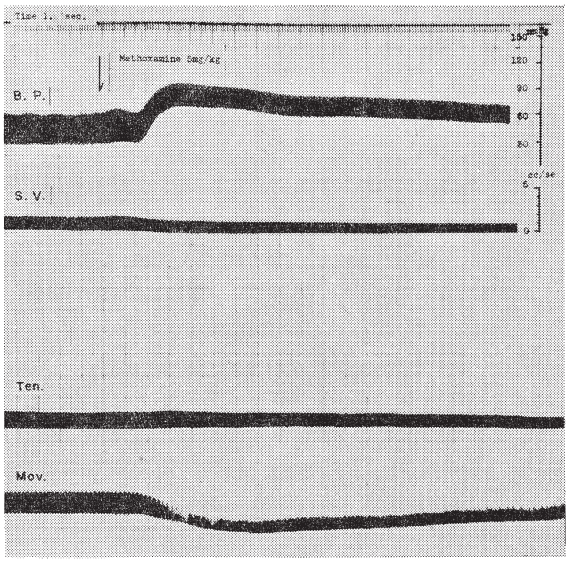

FIG. 13. The effects of methoxamine, 5 mg/kg in the rabbit.

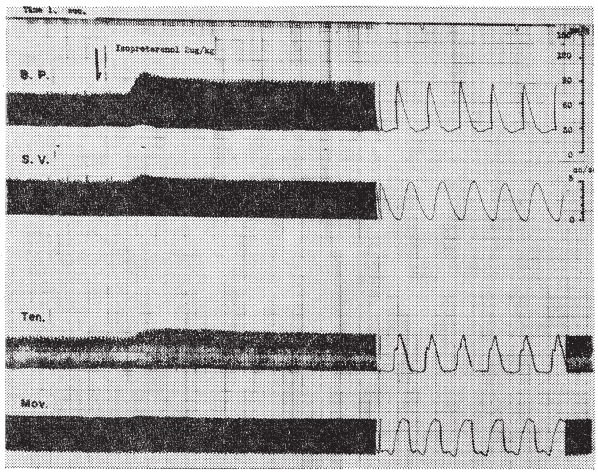

FIG. 14. The effects of isoproterenal, 2 γ/kg in the rabbit.

and it caused a reflex bradycardia more often because of the remarked increase in peripheral resistance. With intact vagi, a reflex bradycardia caused a marked derease in systemic output and stroke volume. After section of the vagi, heart rate increased, with a censequent rise in systemic output. But the increment of systemic outflow and ventricular contractile force were less than that of epinephrine. The change of ventricular movement was also less apparent than that of epinephrine (Fig. 11).

Methoxamine: Figures 12 and 13 are an illustration of the cardiovascular effect of methoxamine. Methoxamine is primarily a vasopressor agent which has little direct effect on the myocardium.[7] Blood pressure increased continuously. Ventricular dilatation and a decrease of ventricular movement were marked. These were caused by an increment in peripheral resistance. This caused a decrease in ventricular force which was accompanied by a decrease in stroke volume and systemic output.

Isoproterenol: Isoproterenol is a vasodilator and, in addition, has a powerful positive inotropic effect similar to that of epinephrine and norepinephrine.[8] This drug also produces a positive chronotropic effect.

Administration of isoproterenol caused a marked increase in force of contraction which was accompanied with an increase in systolic volume and systemic outflow. Ventricular movement slightly increased. The more complete systolic ejection was produced. In most cases, blood pressure decreased. But in rabbits whose blood pressure prior to administration of drug was low an increment of blood pressure often appeared (Fig. 14).

DISCUSSION

The contractile force is obviously one of the most critical functions of the circulatory system. However, *in situ*, a real cardiac movement or change of muscle segment is very significant as an index of cardiac function. Blood flow, which is responsible for oxygenation, and the removal of metabolites from tissue, has also a great significance. There are many reports on cardiac performance using these circulatory parameters. Epinephrine, which is known to increase heart contractile force several-fold, may at the same time produce a decrease in cardiac output through the predominance of its constricting action on the peripheral vascular bed.[9]

There is a direct relationship between the contractile force and the end diastolic length of the segment of ventricular muscle during the changes produced by norepinephrine. However, there is no consistent relationship between the contractile force and the systemic output or stroke volume.[10]

In our experiments it was observed after the administration of considerably large doses of epinephrine, that while the contractile force was stronger than before, peripheral resistance was very high, the left ventricle was temporarily dilated and could not contract or stroke out the blood sufficiently. Such results were also reported by others.[10,11] In these cases, it cannot be said that the heart function is better than control. Thus, if we observed not only the contractile force but also the muscle movement of the ventricle, the heart performance would be more precise.

Thus, change in the ventircular movement, heart rate, blood pressure, stroke output or systemic output and ventricular muscle tension were recorded

simultaneously. Comparison was made among the results given by the various methods regarding the catecholamines action.

Drugs, such as epinephrine and norepinephrine, have both actions of stimulating myocardial contractility and of vasoconstriction. By administration of smaller doses of epinephrine increment of contractile force was able to overcome the increase in total peripheral resistance, and the blood pressure and stroke volume increased. This increase of stroke volume was due to the increment of stroke deflection; the level of end diastolic volume did not change, but the level of end systolic volume showed upper excursion. The increase of stroke volume was produced by more emptying, in other words, by more complete systolic ejection. In some cases, the transient upperward displacement of diastolic level following its underward excursion were observed. Then, the increase in stroke volume was due to two effects: greater diastolic distension and more complete systolic ejection.

The Starling concept has generally been interpreted as implying that the normal ventricle tends to empty itself almost completely and to increase in diastolic volume as the stroke volume increases. Roentgenographic evidence from dogs[12] and men[13] shows that increased stroke volume is not always accompanied by diastolic distension. Stroke volume can be increased by greater diastolic distension or by more complete systolic ejection. For this reason, the factors which influence both diastolic and systolic volumes must be considered.

Rushmer[14] says that as factors affecting diastolic volume, there are effective ventricular filling pressure, ventricular distensibility and atrial contraction. Factors which influence ventricular systolic ejection are arterial pressure and myocardial contractility. The effectiveness of atrial contraction in filling the ventricles was shown by Sarnoff[15] and Linden.[16] When ventricular diastolic pressure is low or in the normal range, atrial systole produces a large increment in fiber length.

An increase in the concentration of epinephrine produced the large increase of peripheral resistance. The positive inotropic effect cannot overcome this peripheral resistance. Therefore, in spite of the marked increment of cardiac contractile force, stroke volume decreased markedly. At the same time it was found that heart dilatation, the decrease of stroke deflection, and underward displacement of the level was significant. That is, heart expansion was found. Rushmer[17] also found that end-diastolic ventricular diameter and circumference were increased by epinephrine and norepinephrine.

Wiggers[18] says that the use of ventricular volume curves, introduced by Henderson, remains one of the most useful methods for analyzing the responses of the ventricles to mechanical, humoral and nervous influences. Our compass-type strain gauge may also be one of the most useful methods to measure parameters of cardiac function.

West and Rushmer[17) 19)] found that epinephrine and norepinephrine have very similar effects on the canine heart. The same effects were also observed on the rabbit heart. Vasopressor drugs which produced little inotropic effect, such as methoxamine, markedly increased total peripheral resistance, producing a reflex bradycardia and resistance to systolic ejection which so altered stroke volume and heart rate that cardiac output was significantly decreased. The increment in peripheral resistance caused a slight decrease in ventricular tension at the same time with marked ventricular length change. Ventricular dilatation and decrease of systolic deflection of ventricular muscle were very significant.

Isoproterenol, a synthetic substance which produces peripheral vasodilation and a powerful stimulating effect on myocardium, produces a dramatic tachycaradia and a reduction in systolic and diastolic diameter[17)].

An increment of contractile force, an upper excursion of systolic and diastolic level and an increment of stroke deflection with increase of stroke volume were also observed. But the change of ventricular tension was more marked than the change of ventricular movement.

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