# STUDIES OF CATECHOLAMINE METABOLISM IN MYOCARDIAL INFARCTION

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The urinary excretion and the plasma concentration of catecholamine have been evaluated as an index of sympathetic activity, however the determination of catecholamine content of various organs including heart is not yet accepted for the clinical use, because of a hazard or technical difficulties to obtain the specimen. Previous studies on catecholamine contents in various organs were limited in experimental animals. Therefore, in our present studies, authors have challenged to measure the myocardial catecholamine in experimental animals and patients for the purpose to know the pathophysiological significance or sympathethic activity in cardiovascular diseases, especially in myocardial infarction.

The method used for determining catecholamine content in organs was followed by Crout's one. Various kinds of experimental animals were used for determining the normal level of catecholamine in organs. Twenty-four hour observation on the postmortem changes was made in catecholamine content of rabbit organs that were placed in room temperature. The experimentally produced myocardial infarction was produced in rabbits by ligation of the descending branch of the left coronary artery. The operation was performed through a left thoracotomy, under the anesthesia with urethane. The development of myocardial infarction was confirmed by the serial changes of electrocardiogram after the ligation of coronary artery. These rabbits were used for the measurement of myocardial catecholamine during 14 days after the ligation of coronary artery. Measurements were applied to other organs such as adrenal glands, spleen, lungs and kidneys. Concerning catecholamine contents in myocardium in man, autopsy was attempted in six cases within three hours after death and myocardial biopsy was carried out in 21 cases with acquired cardiac valvular diseases and in 80 cases with congenital heart disease at surgical intervention.

The highest level of myocardial catecholamine was observed in specific part of right auricle that was presumed the sinus node, and a small amount of catecholamine was observed in valves. Determinations of catecholamine contents in the specimen taken from the right atrium at cardiac surgery have been made in the acquired and congenital heart disease, demonstrating a significant difference between these two groups. Catecholamine content was more than 2.0 mcg/gm in 6 of 80 cases with congenital heart disease including atrial septal defect, ventricular septal defect, pulmonary stenosis and tetralogy of Fallot, showing a marked increase particularly in atrial septal defect and ventricular septal defect. On the other hand, it was less than 1.0 mcg/gm in 14 of 21 cases with valvular diseases, indicating a considerable decrease. It is interesting to note that the remarkable difference of catecholamine content can be seen in the right atrial muscle between two groups of the heart disease, although there are no great differences of urinary excretion of catecholamine. The myocardial catecholamine in the autopsied cases was found to be 0.52-1.51 mcg/gm in the auricle, 1.11-2.02 mcg/gm in the papillary muscle in three cases of malignancy. No great difference was demonstrated between the right and the left heart, catecholamine content was greater in the ventricle than that in the auricle. It would be attributable to the postmortem events, the racial difference or the malignant tumor. In one case of myocardial infarction, it is noteworthy to see that catecholamine was reduced but its value was greater in the infarcted area than in the noninfarcted area. In the rest of the other two cardiac diseases, catecholamine contents in myocardium were reduced in any parts of the heart.

In order to follow the postmortem variation of myocardial catecholamine, measurements have been made on the rabbit hearts which were kept in room temperature (20°C) for 3, 6, 9, 12, and 24 hours after the animals were sacrificed. Each group consisted of three rabbits. Catecholamine content was seen gradual decrease from 1.6 mcg/gm to 1.2 mcg/gm in the left ventricular myocardium in the course of 24 hour observation, but remarkable reduction was found in the atrium between 3 and 9 hours after death, namely, from 2.0 mcg/gm to 1.0 mcg/gm. Almost no essential changes of catecholamine in ventricular myocardium was observed in the first 3 hours. It is justifiable to consider that there is no great reduction in myocardial catecholamine, if the measurement is made within 3 hours after death. The observations indicated that the difference of catecholamine content in auricle between the autopsied case and experimental animals is due to the post-mortem process.

The determination of catecholamine in myocardial infarction is one of the challengable problem. Although no demonstrable change in the urinary excretion of the pressor hormone was seen in the old myocardial infarction without anginal pain, it was found to be remarkably increased immediately after onset of more than 150 mcg/day in norepinephrine and about 40 mcg/day in epinephrine. The urinary excretion was usually restored to the normal range in one week or two. Attention has to be aroused to the postmortem determination of the catecholamine content in myocardium in one autopsy case of myocardial infarction described previously. In order to know variations of catecholamine in myocardial infarction the catecholamine content in myocardium has been measured not only in the infarcted area but also in the non-infarcted area. The rabbit hearts were used to make measurements on 3, 7, and 14 days after ligating the anterior descending branch of the coronary artery. The catecholamine content of myocardium was found to be remarkably reduced to 1.35 mcg/gm in the infarcted area, and to 1.10 mcg/gm in the non-infarcted area 6 hours after the coronary ligation respectively. The further diminutuion followed down to 0.5 mcg/gm in the former on 14th day. In the non-infarcted area the greater reduction was seen within 3 days after the coronary ligation and followed restoration to the previous level on 14th day. The results stated above can make it understandable that the myocardial catecholamine was less in the non-infarcted area than that in the infarcted area of the autopsied cases with myocardial infarction.

Catecholamine content of the adrenal gland was remarkably decreased in the first three days and hardly found to restore, if any, in the course of 14 day obstruction. It is suggested that catecholamine in the adrenal gland is released almost as much amount as produced for supplementing the myocardial storage which was considerably depleted following myocardial damage. Therefore, the delayed restoration of catecholamine store in the adrenal gland can be considered as an effect of homeostatic mechanism. This hypothesis is supported by the fact that catecholamine content in the spleen which is not affected by ligating the coronary artery got increased from 7th day of the

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coronary obstruction, indicating uptake of released catecholamine from the adrenal gland. Another example can be shown for supporting the hypothesis. Replacement of circulating catecholamine with epinephrine takes place associated with inevitable augmentation in urinary excretion of epinephrine together with the resultant decrease in norepinephrine when epinephrine is infused at a rate of 5 to 20 mcg/min to healthy persons. From above it would be reasonable to conclude that the non-infarcted area restores its function by repleting with norepinephrine synthesized in its own tissue to the storage which was depleted of catecholamine for 3 days after the coronary obstruction.

The uptake of catecholamine from the circulating blood utilizes an active transport mechanism, namely the amount of catecholamine taken up from circulating blood by myocardium depends upon the coronary blood flow and the density of sympathetic nerve endings. This myocardial catecholamine taken up from the circulation is released by sympathetic nerve stimulation. From these points of view, attempts have been made to observe how much amount of catecholamine can be taken by the heart with myocardial infarction after infusing catecholamine. Norepinephrine was infused for 30 minutes at a rate of 3 mcg/kg/min in 2 different stages after the ligation. Immediately after the infusion, the heart was removed and measured the catecholamine content in myocardium. In the early stage. 3 days after coronary ligation, the catecholamine content in infarcted area was markedly increased from 1.21 to 1.77 mcg/gm, while in non-infarcted area from 0.83 to 1.16 mcg/gm. However, in the later (14 days later), these phenomena were reversed, namely, the increased catecholamine content in infarcted area was increased a bit but remarkable in non-infarcted area.

The pathophysiological significance of sympathetic activity in heart failure has been investigated previously, it has been suggested that the hyperactivity of sympathetic nervous system, evaluated by the increased urinary and plasma catecholamine levels, the decreased catecholamine content of myocardium and the reduced uptake of infused norepinephrine in the myocardium. exists under the failing condition. Furthermore, the cardiac decompensation was aggravated by the use of adrenergic blocking agents, such as reserpine and b receptor blockade, therefore it was speculated that the hyperactivity of sympathetic nervous system contributed to the improvement of the cardiovascular disturbance. In the present study of myocardial infarction, the similar changes in catecholamine metabolism to those of heart failure was observed clinically and also experimentally. The decreased catecholamine content and a little uptake of exogenously administered norepinephrine in the non-infarcted area may suggest an increased turnover of norepinephrine of myocardium induced by the sympathetic hyperactivity.