On the Histological Changes of the Cardiac Muscle caused by the Experimental Uremia, a Comparative Study with those in Consequence of an Oedema or Urea-injection.

Yoshitoshi Sato*
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Abstract

1. The cardiac muscle fibres of the rabbit swell more and more in the course of the artificial uremia. In the early stage of the disease, this swelling is almost confined to the sarcoplasm, but later the fibrils take part in it also. In the latter stage of the disease, the swelling of both of these two becomes considerable, so that the muscle assumes a characterized feature. 2. The cardiac muscle fibres of the rabbit made artificially oedematous show a swelling also, but in this case the sarcoplasm takes only a little part in it. 3. The cardiac muscle of the rabbit submitted to the urea-injection bears a close resemblance to the finding seen in the case of the artificial uremia. 4. The histological changes of the cardiac muscle caused by the uremia are chiefly due to the urea or its analytic substance retained in the blood, the oedematous stagnation of water having little concern in it. In closing this paper, I wish to express my best thanks to Dr. K. Kosaki under whose guidance this work has been performed.
From the Institute of Anatomy, Okayama Medical University
(Director: Dr. K. Yagita).

On the Histological Changes of the Cardiac Muscle caused
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Yoshitoshi Satō.

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Introductory.

The histological study concerning the uremia has been under-
taken by many investigators in past. Most of them, however, aimed
to research the changes occurred in the central nervous system since
the principal symptom of uremia is nervous one, and only a few
have considered the changes of the other tissues. Therefore it is an
interesting problem to examine the histological change of the cardiac
muscle in the case of the uremia.

Korowin (1897) reported that he found a hypertrophy and an
albuminoid degeneration of the cardiac muscle in a man died of
uremia. Obata (1925) tied up both the ureters of the rabbit and after
some time examined the cardiac muscle, and found that its fibres
became indistinct, and many small haemorrhages were observed
everywhere in the muscle.

To our regret, however, no precise report on the subject is
available at present. Consequently the author has studied the
subject more exactly and some of the results will be given on the
following pages.

Technique.

As no better method has been devised since the pathogenesis of the uremia has
not as yet decidedly been testified, I had recourse to use the same method used by
the previous workers.

* This investigation was undertaken under kind guidance of Emerit. Prof.
Dr. K. Kōsaka, Ex-director of the institute.
In healthy male rabbits weighing 1800 to 2000 g., both the ureters were aseptically ligatured on the upper side of the bladder. The operated rabbits died within a few days, having shown an uremia-like symptom*.

Some of the animals were killed by the air emboly, 24, 48 and 72 hours after the ligation of the ureters. After death a piece of the cardiac muscle from the left ventricle was taken out as fast as possible and was fixed in a 10 per cent formalin solution and paraffin sections of 4¼ thickness were made. The sections were stained with eosin-haematoxylin and Mallory's connective tissue staining. Throughout the treatments a care was taken to subject all the sections for the same condition as much as possible. As the control the cardiac muscle of rabbits killed by urea-injection** and of those which produced artificially oedematous was taken***.

The finding of heart muscle.

A. 24 hours after the ligation of ureters.

The muscle fibres increase their thickness; the longitudinal arrangement of the fibrils becomes more conspicuous than the transverse striations or the intercalated discs; the latters being rather obscure than in the normal. Surrounding the nucleus, an unstained area occurs in a form of spindle. This appears to press the fibrils to the marginal portion of the fibre.

A transverse section of the muscle fibre shows a little broadening, but the boundary of each fibre is still well defined. The fibrils shown in the transverse section are also somewhat pressed to the marginal portion on account of a round unstained area surrounding the nucleus in the axis of the fibre. In this case, inspite of the thickening and widening of the muscle fibre, the swelling of the fibrils are not readily seen.

B. 48 hours after the ligation of ureters.

Swelling of the muscle fibre inclusive of the nuclei becomes more remarkable; the tissue, on the whole, being less stained, and

* 1 to 2 days after the ligation of the ureters the animal lost the appetite and became emaciated suffering from diarrhoea. Within 3 or 4 days a lethargic condition appeared and soon it proceeded to a condition of paralysis. Thus the animal came to the end. During all the process, no sign of convulsive attacks was seen. Inspite of the oedema in the whole body, the body weight decreased, probably because it had not taken enough food.

** In this case a slow injection of a 20 per cent urea solution was used, the dose of the solution being 25 cc per Kg body weight.

*** 50 cc of the physiological saline solution was injected into the abdominal cavity. The injection was repeated 6 times a day at moderate intervals. By this treatment, an increase of the body weight amounted to about 200 g after 3 days.
the muscle fibre itself being longitudinally split into loosened bundles of fibrils (so-called “Säulchen”) so that the unstained area is not only found around the nucleus but it separates the bundles of the fibrils from each other as thread-like interstices. The boundary of each fibre, the transverse striations and the intercalated discs become more obscure.

In the transverse section of the muscle fibre, the most of the fibril bundles is still seen in the peripheric portion of the fibre, but some remain in the inner part also. Beside the chief unstained area around the nucleus as is seen in the previous case, there is a net-work of the unstained substance which separates the fibril bundles from each other. The interfibular connective tissue becomes thinner, being pressed by the swollen fibres.

C. 72 hours after the ligation of ureters.

Briefly stated, changes in this case are more remarkable than in the previous case, as the swelling of the tissue elements is more intense, so that the muscle fibre splits by the hydropically swollen sarcoplasm into many smaller bundles of fibrils; the whole breadth of it being greatly increased. The boundary of each fibre is indistinct. Neither the intercalated discs nor the transverse striations are seen well. On the contrary, the longitudinal striations are observed although they are stained slightly.

In the transverse section, the fibre shows a much-increased diameter and the boundary of each fibre is hardly discernible even when the Mallory's staining is used, on account of the very thin layer of the connective tissue between the swollen fibres. The transverse section of the muscle fibre is speckled, the small fibril
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Fig. 1. Cardiac muscle from the left ventricle of a rabbit killed 72 hours after the ligation of both the ureters. Fixed with formalin; paraffin section of 4 μ thickness; stained with eosin-haematoxylin. (A) shows the longitudinal section, (B) shows the transverse. Leitz, Ocl. 6, Obj. 7; camera-length 25 cm.

bundles being separated by a net-work of the unstained sarcoplasm. Comparison with a normal cardiac muscle gives an impression that the finding in this case is much confused by the swelling of the tissue elements and the weak staining of the tissue itself*.

Just the same or more remarkable changes are seen, if the cardiac muscle of the rabbit died 72 or more hours after the ligation of ureters is examined.

D. Artificial oedema.

The cardiac muscle, on the whole, seems to be more or less loosened; the muscle fibre with its nuclei being somewhat swollen and stained diffusely. Consequently the boundary of each fibre is not readily recognizable.

However, the finding in this case is not equal to that of the previous cases. Neither the longitudinal division of the fibre nor any characteristic unstained area, such as seen in the previous cases, are found anywhere. Moreover, the transverse striations are rather visible than the longitudinal arrangement of the fibrils. Though the

* From the physical view of staining, a loose tissue rich in fluid is hard to retain the stain which escape easily on washing. On the contrary in a dense tissue poor in fluid the stain is well retained.
fibre increases its diameter pressing the surrounding connective tissue, the transverse section of the muscle fibre shows no net-work nor speckles, because of the compact distribution of the swollen fibrils in the fibre without giving the unstained sarcoplasm much space.

Fig. 2. Cardiac muscle from the left ventricle of an oedematous rabbit. (A) shows the longitudinal section, (B) shows the transverse. Treatments and enlargement are same as Fig. 1.

E. Urea-injection.

The finding in this case bears a close resemblance to that of 48 hours after the ligation of ureters.
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In short, the striking changes are the swelling of the muscle fibre which splits longitudinally into many loose bundles of the fibrils, each bundle being separated from each other by the unstained hydropic sarcoplasm, so that the longitudinal section of the muscle fibre assumes a remarkable striation, while the transverse section shows a net-work of the sarcoplasm.

Fig. 3. Cardiac muscle from the left ventricle of a rabbit put to death by urea-injection. (A) shows the longitudinal section, (B) shows the transverse. Treatments and enlargement are same as the other figures.
Discussions.

From the above results it is almost obvious to state that the cardiac muscle fibre inclusive of its nuclei swells generally in the uremia and extends in breath more and more in course of the disease, making the interstitial connective tissue thinner and thinner.

In an early stage of the disease, this swelling of the fibre is due chiefly to the hydropsy of the sarcoplasm which absorbs much water while the fibrils themselves having almost nothing to do with it. The unstained area* surrounding the nucleus and the clearer manifestation of the longitudinal striation of the fibre indicate this fact.

In the medium stage of the uremia, the swelling of the muscle fibre seems to be accounted not only for the expansion of the sarcoplasm but also for the swelling of the fibrils. In this stage, the fibrils having absorbed much water and seem to be loosened, and are united with each other to form many small bundles which are separated by the expanded sarcoplasmic septa. Both the longitudinal and the transverse section of the muscle fibre show the characteristic appearance as mentioned above.

Further the disease advances, the fibre swells more markedly, and becomes the less stainable, while the bundle of the fibrils divides into smaller ones.

In the later stage of the uremia, the cardiac muscle fibre shows the utmost swelling, the bundles of the fibrils being more minutely divided, and the connective tissue becoming only a thin layer between the extremely swollen fibres. Then the cardiac muscle, on the whole, assumes the most characterized feature.

In my opinion, the hypertrophy of the cardiac muscle noted by Korowin is not a hypertrophy in the true sense, but a hydromic swelling of the muscle fibres, at least in the case of the acute uremia.

On the other hand, Obata's report which states that the cardiac muscle becomes indistinct, is attributable I think to the fact that in the case of the uremia the swelling of the muscle fibres renders them less stainable so that their minute structure is not well discernible.

Concerning the histological changes of the cardiac muscle, there is a difference between the rabbit of the artificial uremia and that of the artificial oedema. In the former, the muscle fibrils as well as

* This area where the sarcoplasm is accumulated is seen even in the normal cardiac muscle, but it shows an evident enlargement and can be seen clearly in an early stage of the uremia.
the sarcoplasm show a hydropic swelling, while in the latter the change is almost confined to the fibrils, the sarcoplasm playing only a little part.

On the contrary, the cardiac muscle after urea-injection bears a close similarity to the finding in the case of the uremia, the swelling appearing remarkably in the fibrils as well as in the sarcoplasm.

Therefore I believe, that the change of the cardiac muscle in the case of the uremia is caused by urea itself or its analytic substance retained much in the blood at that time, and the oedematous stagnation of water has little to do with it*.

Summary.

1. The cardiac muscle fibres of the rabbit swell more and more in the course of the artificial uremia. In the early stage of the disease, this swelling is almost confined to the sarcoplasm, but later the fibrils take part in it also. In the latter stage of the disease, the swelling of both of these two becomes considerable, so that the muscle assumes a characterized feature.

2. The cardiac muscle fibres of the rabbit made artificially oedematous show a swelling also, but in this case the sarcoplasm takes only a little part in it.

3. The cardiac muscle of the rabbit submitted to the urea-injection bears a close resemblance to the finding seen in the case of the artificial uremia.

4. The histological changes of the cardiac muscle caused by the uremia are chiefly due to the urea or its analytic substance retained in the blood, the oedematous stagnation of water having little concern in it.

In closing this paper, I wish to express my best thanks to Dr. K. Kōsaka under whose guidance this work has been performed.

* There are two conflicting views concerning the pathogenesis of the uremia; the one is a mechanical theory based on the retention of water in the body, and the other is a theory of poisoning supported by the retention of nitrogen in the blood (Widal's azotemia). Among those who advocate the latter, Noorden (1912), Widal (1915), Vorhardt (1918) and others attach weight to the effect of urea, while others such as Strauss (1920), Hara (1921), H. Full (1921) and others lay stress on that of ammonia.
Muscle caused by the Experimental Uremia etc.

Bibliography.