Quantitative Analysis of Cardiac Hypertrophy Due to Pressure Load in Reference to the Relations of Blood Pressure, Left Ventricular Weight and Left Ventricular Capacity

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ARAI, S., NAKAMURA, T. and SUWA, N. Quantitative Analysis of Cardiac Hypertrophy Due to Pressure Load in Reference to the Relations of Blood Pressure, Left Ventricular Weight and Left Ventricular Capacity. Tohoku J. exp. Med., 1976, 118 (4), 299-309 — In almost all the cases of cardiac hypertrophy due to sustained hypertension, left ventricular capacity is increased in proportion to increased left ventricular weight, even in the absence of manifest cardiac insufficiency. The condition is regarded as the general expression of cardiac response to pressure load, and the concept of "isomorphic hypertrophy" is proposed. Concentric hypertrophy of the current concept is observed only on rare special occasions, and its role in cardiac adaptation to pressure load is obscure. The increase in myocardial mass is sufficient to maintain the work done by a unit myocardial volume at a normal level. However, the calculation on pertinent models demonstrates that hypertrophied hearts of any type expel the normal stroke volume with smaller shortening of muscle fibers under larger stress, which is further elevated with the progress of cardiac contraction. Because the maximum force generated by muscle fibers declines with advancing cardiac contraction, hypertrophied hearts harbor a latent risk of mechanical insufficiency. Even under pressure load, ventricular dilatation seems to precede the reinforcement of ventricular wall in the development of cardiac hypertrophy. A common mechanism may be therefore assumed underlying the development and performance of all types of hypertrophied hearts, regardless of the difference in the character of physical loads. — cardiac hypertrophy; concentric hypertrophy; pressure load; ventricular capacity; heart weight

It is at present generally accepted that the heart responds to persistent pressure load with concentric hypertrophy, which is characterized by thickening of the ventricular wall without corresponding increase in the ventricular capacity. This condition is regarded as presenting an essential contrast to eccentric or dilatation hypertrophy due to volume overload, where the increase in ventricular capacity predominates over thickening of the ventricular wall. It is further generally assumed that the two types of cardiac hypertrophy are two adaptation processes of the heart entirely different in nature corresponding to different

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physical loads. Concentric hypertrophy in this sense would be quite effective in compensating pressure overload, because the component of increase in intramural tangential stress due to enlarged ventricular radius is absent or only insignificant, and such a mechanism is usually explicitly acknowledged in the interpretation of cardiac activity in concentric hypertrophy.

In routine autopsy studies concentric hypertrophy is immediately diagnosed on macroscopical observation. However, the designation of this pathological change is not always an exact one, because cardiac hypertrophy due to pressure load may be often associated with more or less pronounced increase in ventricular capacity, even before there is any sign of cardiac insufficiency in clinical records or autopsy findings. In view of this experience, it seems necessary to re-examine the current concept of concentric hypertrophy by pertinent quantitative analysis of autopsied hearts.

The reports of exact measurement of ventricular capacity of autopsied hearts have been unexpectedly few in number. The only intensive investigation of this problem was probably that of Kyriileis (1963), who studied the change of cardiac configuration in the course of postnatal development. However, his interest was focussed on the normal cardiac development, and the investigation was not intended for the analysis of hypertrophied hearts. The present study is therefore planned to provide information about the relation of the quantity of ventricular mass with ventricular capacity in cardiac hypertrophy due to pressure load in the state of rigor mortis.

On the other hand, systolic blood pressure level in life was correlated with left ventricular weight in another series of autopsy cases. On the basis of the results from the two investigations, mechanical characteristics in the development and activity of hypertrophied hearts are discussed, using physical models for different types of cardiac hypertrophy.

**Materials and Methods**

From the autopsy cases of patients over 20 years of age and with miscellaneous diseases including essential and renal hypertension, the hearts were taken out of the thoracic cavities by routine techniques. The younger age group was not used, because the heart weight could not simply be correlated with blood pressure level in the course of normal development. The cases of clinically noticed chronic cardiac insufficiency and those of extreme anemia or metabolic disorders which might influence heart weight were also excluded from the present study. The blood was let flow out from the cardiac orifices without opening left ventricular cavity. Blood clots were removed manually or with the aid of forceps as much as possible. The organ was then weighed, and if the heart weight was lower than 200 g, the case was not used for further studies, as extremely low heart weight is usually associated with some cachectic condition, which might lower cardiac weight irrespective of blood pressure level. Each of the selected hearts was placed without opening the left ventricle in a sufficiently large vessel containing 10% formalin solution under care to avoid distortion and fixed for about a week.

The heart was then severed at the atrioventricular border. The mitral and aortic valves were macroscopically examined for valvular disorders. If any valvular disorder was found, the case was excluded from the study. After macroscopical observation the mitral valves were excised at their roots to provide easy access to the left ventricle. The
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free portion of the right ventricle is then dissected, and the net weight of the left ventricle including the ventricular septum was measured. Immediately after the measurement, the left ventricle was gently filled with water insoluble plastic material, and the ventricular capacity was estimated from the quantity of plastic material consumed for replenishment. The left ventricle was then sliced by a number of parallel transverse sections and examined for stenosing coronary sclerosis, myocardial necrosis, scars and other myocardial damages which might cause ventricular dilatation. If any pathological change of this character was discovered, the case was excluded from further studies. In the consequence of the above-mentioned selection processes, 67 hearts could be submitted to the examination. They consisted of practically normal adult hearts and functionally and anatomically well-preserved hypertrophied hearts due to pressure load.

In another series of autopsy cases, the heart weight was correlated with blood pressure, with the purpose of obtaining the quantitative relation of increase in myocardial mass with pressure load. The group comprised 93 selected hearts consisting of practically normal adult hearts and those from cases of essential or renal hypertension, without complicating myocardial damage or valvular disorders and also free from other diseases, which might cause deviations in the blood pressure-cardiac weight relation. In all the selected cases, clinical records of repeated blood pressure measurements were available, so that the estimation of representative systolic blood pressure level of individual cases in life was made possible. The hearts were examined by routine autopsy techniques. The left ventricular weight was accordingly not directly measured in this series, but it was estimated from the total heart weight by the use of the regression equation proposed by Arai et al. (1968).

**RESULTS**

*Left ventricular weight and left ventricular capacity*

In the present study, left ventricular capacity is defined and estimated on the assumption of fully developed rigor mortis. This condition of the left ventricle develops rapidly after death and attains its maximum already within the first postmortem hour in usual autopsy cases. Its resolution seems to depend upon a number of different factors and to be different from case to case, but complete resolution takes place in about 24 hours. It is quite possible, however, that in several postmortem hours the heart is in some intermediate stage from fully developed rigor mortis to its complete resolution. Partly resolved rigor mortis may induce more or less pronounced enlargement of the ventricular capacity and cause deviation in the estimates of this quantity. As a preliminary examination, the ratio $V_L/W_L$, or the ratio of left ventricular capacity to left ventricular weight, was plotted against the postmortem time in hours at the start of autopsy, and the result is demonstrated in Fig. 1.

In the great majority of cases the autopsy was started within 5 postmortem hours, and in this range of postmortem time there is no tendency toward elevation or depression of the ratio. Even after that time, the ratio seems to be practically constant so far as the present specimens are concerned, although a very limited number of autopsy cases after 5 hours do not allow any general comment on rigor mortis in this stage. Consequently, possible influence of partly resolved rigor mortis may be disregarded, and $V_L$ is plotted against $W_L$ in Fig. 2 on a logarithmic coordinate system.
Fig. 1. Rigor mortis of the left ventricle is assessed by $V_L/W_L$, the ratio of ventricular capacity to weight, and correlated with postmortal time at the start of autopsy.

Fig. 2. Left ventricular capacity $V_L$ in ml is correlated with net left ventricular weight $W_L$ in g on a logarithmic coordinate system. ● The normotensive and the great majority of hypertensive cases making together a common group. ○ and ⬤ The cases of exceptionally low $V_L/W_L$. ○ Dissecting aneurysm. ● Chronic glomerulonephritis. A linear regression is noticed in the group of ●, and the regression equation is $Y=1.171 \times X-1.419$, where $X$ and $Y$ are log $W_L$ and log $V_L$, respectively.
It is immediately noticed in Fig. 2 that the scatter of individual values are relatively large. This is presumably due to extreme narrowing of the left ventricle in fully developed rigor mortis, and possible individual differences in the ventricular capacity in life are accentuated, especially when the small quantity is expressed with its logarithm. Nevertheless, a roughly linear regression is observed in the diagram for the common group of the hearts from normotensive and the great majority of hypertensive cases. The coefficient of regression is about 1.17. The result is very important, because it demonstrates an increase of left ventricular capacity approximately in proportion to the increase of left ventricular contractile mass. When the left ventricular weight attains to \( n \) times the normal, the left ventricular capacity is also enlarged to more than \( n \) times the normal. It is, of course, conflicting with the current concept of concentric hypertrophy.

Notwithstanding this conclusion, there are 4 exceptional cases in the present specimens, in which the behavior of the left ventricle conforms perfectly to the classical concept of concentric hypertrophy. The left ventricular capacity remains almost unchanged, while the ventricular weight is elevated. The ratio \( \frac{V_L}{W_L} \) is accordingly very low in these cases. They constitute a group distinctly separated from the other cases, and there are no transitional cases which would link them with the majority. Three out of the 4 cases were those of dissecting aneurysm, and the other was that of a 69-year-old male with non-fatal chronic glomerulonephritis. Death ensued upon complicating pneumonia in the latter case. The prevalence of dissecting aneurysm in the exceptional cases is noteworthy.

**Blood pressure and left ventricular weight**

Left ventricular weight \( W_L \) was calculated from the total heart weight \( W \) with the regression equation of Arai et al. (1968),

\[
Y = 1.261X - 0.952,
\]

where \( X \) and \( Y \) are log \( W \) and log \( W_L \), respectively. The result is correlated with representative systolic blood pressure \( P_{sys} \) in Fig. 3 on a logarithmic coordinate system.

From Fig. 3 it is evident that the hearts of pressure load together with ones from normotensive cases make a single group exhibiting a roughly linear regression. The regression coefficient is equal to 1.004. It is thus demonstrated that in hypertensive cases the heart weight attains to \( n \) times the normal on an average, when systolic blood pressure is elevated to \( n \) times the normal. The result shows that pressure load is perfectly compensated, so far as the mass of the myocardial layer is concerned. Whether the mechanical condition in the performance of hypertrophied hearts is also restored or not is an entirely different problem, which is to be discussed in detail in the subsequent section.
Fig. 3. The left ventricular weight $W_L$, calculated from the total heart weight, is correlated with representative systolic blood pressure $P_{sys}$ in life in mmHg on a logarithmic coordinate system. Notwithstanding relatively large scatters of individual values, a linear regression is still noticed. The regression equation is $Y=1.004 \times X + 0.079$, where $X$ and $Y$ are $\log P_{sys}$ and $\log W_L$, respectively.

**DISCUSSION**

The result of the present study on the relation of ventricular weight and capacity casts serious doubt upon the current concept of concentric hypertrophy as the general form of cardiac adaptation to persistent pressure load. It would be hardly acceptable that the hearts in the present specimens were already in the state of secondary dilatation, which had developed on primarily concentric hypertrophy in the strict sense; there was any sign of cardiac insufficiency neither in clinical records nor in autopsy findings. Consequently, the following hypothesis seems more reasonable: The heart responds to pressure overload not only with an increase in contractile mass, but also with corresponding growth of the ventricular cavity from a very early stage of structurally fixed adaptation. In this type of cardiac hypertrophy, the heart retains approximately a shape geometrically similar to that of the normal heart, and the condition may be most aptly called "isomorphic hypertrophy".

The meaning of the exceptional cases of very low $V_L/W_L$ is still utterly obscure. It is rather improbable that these hearts represent the initial stage of cardiac adaptation to pressure load, in view of already long standing pathological process. However, the prevalence of dissecting aneurysm in the present specimens suggests that the shape of the left ventricle is in some way influenced by physical properties of the aorta. This interesting problem awaits further examinations. In the other case of chronic glomerulonephritis, the aorta was not submitted to histological examinations, and it is not clear whether this case can also be interpreted on the same basis. In any way, we think concentric hypertrophy as a general form of
Cardiac hypertrophy due to pressure load rather dubious.

Cardiac hypertrophy is considered to be a morphological adaptation of the heart to compensate increased load, because the quantity of contractile mass is increased. However, it is still to be examined, in what respect the load is compensated. The work $A$ done by the left ventricle in the course of a single heart beat is expressed as

$$A = -\int_{V_{\text{min}}}^{V_{\text{max}}} P dV,$$

(2)

where $P$ is intraventricular blood pressure as a function of volume $V$ of the ventricular capacity; $V_{\text{max}}$ and $V_{\text{min}}$ are the volumes of the ventricular cavity at the beginning and end of ventricular contraction, respectively. The sign of minus indicates that the work is performed by diminishing the ventricular capacity. When $V_{\text{max}} - V_{\text{min}} = \Delta V$ and the mean intraventricular blood pressure is $\bar{P}$, (1) is written as

$$A = \bar{P} \Delta V.$$

Now, we suppose a model of ventricular performance, in which intraventricular blood pressure is assimilated by a linear function of $V$. If in a case of hypertension systolic and diastolic blood pressures are 240 mmHg and 120 mmHg, respectively, in contrast to a normotensive case of 120 mmHg systolic and 60 mmHg diastolic blood pressures, and if the stroke volume $\Delta V$ remains unchanged in hypertension, the work done by the whole left ventricle would be exactly twice the normal.

On the other hand, the present study revealed that the left ventricular weight would be on an average exactly twice the normal value under this condition. Consequently, the work done by a unit volume of the myocardial layer is not at all increased even under such an excessive pressure load. In this respect, cardiac hypertrophy seems to compensate completely the abnormal condition.

However, when the work is analyzed as the product of contraction or shortening $\Delta L$ of muscle fibers and the force $F$ generated by them across a transverse sectional plane of unit surface area, the proportion of $\Delta L$ and $F$ in hypertrophied hearts is quite different from that in normal hearts. In order to visualize the essential mechanism in the performance of hypertrophied hearts, some calculations on a pertinent model would be of great help. The ventricular cavity is much smaller in the state of rigor mortis than that of systolic phase in life and its value cannot be used immediately in the model. In regard to this quantity in life, however, there are a number of clinical investigations. In the present theoretical treatment, the ventricular capacity at the end-systolic phase and stroke volume are assumed to be 50 ml each for the normal adult heart, according to the report of Dodge and Sandler (1974).

In Fig. 4, the models are presented for normal and hypertrophied hearts. The left ventricle is assimilated by a thick-walled cylinder. It is also possible to use models of sphere or ellipsoid of revolution. However, whatever of these
Fig. 4. Ventricular model of a thick-walled cylinder is presented. a) Illustration and explanation of the geometrical and mechanical quantities of the model and their relations. $W_L$: mural mass or weight of the left ventricle. $V$: ventricular capacity. $r$: internal ventricular radius. $T$: thickness of ventricular wall. $h$: height of the ventricle as assimilated by a cylinder. $P$: intraventricular pressure. $A$: work done by the whole ventricle. $A_0$: work done by unit volume of ventricular wall. $T$: intramural tangential stress. $F$: stress of muscle fibers across a transverse section of unit surface area. b) Transverse sections of the cylindrical models under different conditions are illustrated in the upper part. The surface area of black rings enclosed by external and internal circumferences corresponds to $W_L$ and are treated as an invariable quantity throughout ventricular dilatation and contraction. In the lower part of the diagram, the scale on the left side gives intraventricular pressure in mmHg, ventricular weight in g and ventricular capacity and stroke volume in ml. $W_L$: left ventricular weight. $V_0$: ventricular capacity in the end-systolic phase or residual blood volume. $\Delta V$: stroke volume. $P$: systolic and diastolic blood pressures.

models may be used makes no essential difference in the conclusion, and the present model is preferred on account of its easy treatment. Hypertrophy is classified into three types. Concentric hypertrophy reproduces the current concept, and the ventricular wall is thickened, while the ventricular capacity is
Fig. 5. The results of calculation on the models of Fig. 4 are presented. $F$: contractile force of muscle fibers across a transverse section of unit surface area. $L$: length of muscle fibers. $F_{\text{max}}$: the maximum contractile force that would be generated at a muscular length of $L$ as a linear function of $L$. The mean shortening $\Delta L$ of muscle fibers of each model in the course of ventricular contraction is obtained from $\Delta L = A_0 \int_{L_{\text{min}}}^{L_{\text{max}}} F \, dL$, where $F$ is $F$ at the middle zone of the ventricular wall as a function of $L$; $L_{\text{max}}$ and $L_{\text{min}}$ are the length of muscle fibers at the middle zone in diastole and systole, respectively. $L_{\text{max}}$ being assumed to be the same in all models; and $A_0$ is the work done by a unit volume of ventricular wall, which is assumed to be the same in all models.

The results of calculation on these models are illustrated in Fig. 5. The diagram is drawn on the assumption that the work done by a unit volume of contractile mass is an invariable quantity throughout normal hearts and all types of hypertrophied heart. The surface areas enclosed under the curves of $F$ are accordingly the same in all the models. The characteristic mechanism in the performance of hypertrophied hearts is clearly demonstrated by the analysis; the hearts expel the same quantity of blood with smaller shortening of muscle fibers under larger stress with advancing enlargement of the ventricular cavity. This tendency is already noticed in the model of classical concentric hypertrophy, on account of the enlargement of the external diameter of the ventricle.

The higher intramural tangential stress in hypertrophied hearts is produced by the following mechanism. In the model of a cylinder, tangential stress $T$ is given by the product of intraventricular pressure $P$ and ventricular radius $r$ as

$$T = Pr.$$ (3)
If the thickness of the ventricular wall is \( t \), the tangential stress counterpoised by a shell of unit thickness is

\[
T/\tau = Pr/\tau.
\]  

(4)

Now, suppose that intraventricular pressure \( P \) is \( n \) times the normal pressure \( P_0 \) or \( P = nP_0 \). The ventricular weight or myocardial volume will be then \( n \) times the normal, according to the result of the present study. If the heart retains its shape geometrically similar to the normal, then we obtain

\[
\tau = r_0 \sqrt{n}
\]

(5)

and

\[
\tau = \tau_0 \sqrt{n},
\]

(6)

\( r_0 \) and \( \tau_0 \) being the ventricular radius and wall thickness of the normal heart, respectively.

Consequently,

\[
T/\tau = nP_0(r_0/\tau_0)
\]

(7)

is derived immediately from (4), (5) and (6). The expression (7) shows that the tangential stress required from a myocardial layer of unit thickness is not compensated, if cardiac hypertrophy is accompanied by a growth of ventricular cavity, as it is the case with autopsied hearts.

Further it is noteworthy that in hypertrophied hearts the stress or the force required from muscle fibers is augmented with the progress of ventricular contraction, while it is essentially unchanged in the normal heart. This imposes quite an unfavorable condition on the heart muscle, because the maximum contractile force generated by the muscle fibers declines with the progress of ventricular contraction. There is accordingly a good reason to assume that the heart muscle may succumb to the load before the normal stroke volume is obtained. The residual blood volume is elevated, and the heart has to start the next contraction from stronger stretch of muscle fibers. As the ventricular dilatation advances, it enhances in turn intramural tangential stress and finally leads to cardiac insufficiency. The principle of such an interpretation is in complete agreement with the view of Linzbach (1958, 1960). The only difference is that we regard isomorphic hypertrophy instead of classical concentric hypertrophy as the standard form of cardiac adaptation to pressure load. In our conclusion, therefore, cardiac hypertrophy due to pressure load is exposed to larger risk of mechanical insufficiency than was assumed in previous investigations.

The calculation on the model has thus disclosed common characteristics in the performance of hypertrophied hearts of any type; smaller contraction of muscle fibers under larger stress and increase of load on muscle fibers with the progress of cardiac contraction. The result suggests, on the other hand, an important mechanism in the development of cardiac hypertrophy in general. An increase of load, of whatever nature it may be, lets the heart start the contraction from a state of more or less over-stretched muscle fibers or from a larger end-diastolic ventricular cavity, because the contractile force generated by muscle fibers is so
raised as to overcome the increased load. Owing to the larger ventricular cavity at the start of ventricular contraction, the ventricle can expel the normal stroke volume already after a smaller contraction than the normal one. This seems to be the most important adaptation mechanism, because it dispenses with the terminal phase of muscular contraction, where declining contractile force would not always meet progressively rising requirement. Even to pressure load, the first step of cardiac adaptation must be ventricular dilatation, and there is no fundamental difference in the pathogenesis of hypertrophy, whether it is incited by pressure load or volume load. The ventricular dilatation is then followed by reinforcement of the myocardial layer by means of the increase of contractile mass, and the well-known configuration of cardiac hypertrophy is accomplished.

However, the thickening of the ventricular wall does not attain to such an extent as to lower the stress of individual muscle fibers to the normal level, as demonstrated in Fig. 5. Cardiac hypertrophy is after all an imperfect or defective compensatory process requiring a larger stretch of individual muscle fibers in the initial systolic phase. The reserve capacity of muscle fibers is reduced and the heart is exposed to latent risk of mechanical insufficiency before a necessary stroke volume is obtained. It is further to be pointed out that cardiac hypertrophy due to pressure load is not a process opposite to dilatation hypertrophy induced by volume load. The former represents rather an intermediate form between the normal and the latter. This view is also supported by the study of Tezuka (1975), who demonstrated that the myocardial muscle fiber orientation in isomorphic hypertrophy occupied an intermediate position between normal hearts and dilatation hypertrophy.

References