Myosin Isoenzymic Changes in Several Models of Rat Cardiac Hypertrophy

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SUMMARY We studied the effect of chronic mechanical overloading on the isoenzymic composition of rat cardiac myosin in several experimental models: aortic stenosis (AS), aortic incompetence (AI), aortocaval fistula (ACF), overload of the non-infarcted area after left coronary ligation (INF), and overload of the spontaneously hypertensive rats (SHR). Samples of the left and right ventricles were isolated from these hearts, and myosins were analyzed by electrophoresis in non-dissociating conditions. The myosin isoenzymes were called VI, V2, and V3 in order of decreasing mobility, according to the nomenclature of Hoh et al. Controls of the Wistar and Wistar Kyoto (WKY) strains were almost exclusively VI. A slow age-dependent shift toward V3 was observed in the left ventricles of adult Wistar rats, which at 30 weeks of age (body weight 600 g) contained approximately 15% of this form. In all models of cardiac hypertrophy, an isoenzymic redistribution was observed with a significant increase in V3. The level of V3 was statistically correlated with the degree of hypertrophy in the AS, (n=11, r=0.8, P<0.05), the AI (n=14, r=0.88, P<0.001), and the AS + AI (n=14, r=0.69, P<0.01) but not in the ACF (n=16, r=0.48). The isoenzymic changes could account for the decreases in both myosin ATPase activity and cardiac contractility described previously in our laboratory and by others. They also demonstrate that changes in myosin isoenzymes represent a general response of the rat heart, to chronic mechanical overloading.


HYPERTROPHY is a fundamental adaptive response of the heart to an imposed work overload. The intrinsic contractile state of such hypertrophied hearts has been the subject of considerable and often contradictory investigation. It is generally admitted that the velocity of shortening of cardiac fibers is modified to variable degrees, depending on the inciting stimulus: for example, it is enhanced in response to thyroxin intoxication (see Morkin, 1979), and markedly depressed in chronic pressure induced hypertrophies (see Maughan et al., 1979). The close relationship between the shortening velocity of these hearts and their myosin ATPase specific activities has recently been mentioned by Scheuer and Bahn (1979) in a comprehensive review: increased performance is associated with increased ATPase activity and, conversely, hypotroctile states are accompanied by depressed activity.

Isoenzymic changes in myosin, which can account for the enzymatic alterations, have been described recently in two models of cardiac hypertrophy. In response to thyroxin administration, euthyroid rabbits (see Morkin, 1979) and hypophysectomized rats (Hoh et al., 1978) both synthesize an isoenzyme of high ATPase activity. We have found, in rats, that, in gross cardiac hypertrophy induced by aortic stenosis or aortic incompetence, an isoenzyme exhibiting a low activity is predominant (Schwartz et al., 1978; Lompré et al., 1979). In the rat, these isoenzymes (VI and V3 according to the nomenclature of Hoh et al.) display different electrophoretic mobilities under non-dissociating conditions (Maughan et al., 1979). The close relationship between the shortening velocity of these hearts and their myosin ATPase activities has recently been mentioned by Scheuer and Bahn (1979) in a comprehensive review: increased performance is associated with increased ATPase activity and, conversely, hypotroctile states are accompanied by depressed activity.

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The present study was undertaken to determine
whether, in rats, the synthesis of the isoenzyme of low activity V3 occurred also in other models of chronic mechanical overloading, and whether these isoenzymic changes were correlated with the increase in cardiac mass. For this purpose, mechanical overload of various types was produced in rats. The myosin isoenzymes of the corresponding hearts were investigated by their migration in gel electrophoresis (Hoh et al., 1978; d’Albis et al., 1979).

**Methods**

**Experimental Groups and Surgical Procedures**

This study included 65 operated male Wistar rats and 15 controls, plus eight spontaneously hypertensive rats (SHR) of the Wistar Okamoto strain and seven Wistar Kyoto normotensive controls (WKY). The rats were housed in air-conditioned quarters in group cages with no more than six rats per cage and were provided food (Extralabo M 25 pellets) and tap water ad libitum.

Surgical procedures were carried out under anesthesia (Pentobarbital, 40 mg/kg, ip, or ether for myocardial infarctions) on animals that weighed 200-220 g (approximately 6 weeks old) and that were allowed to breathe spontaneously.

Constriction of the aorta (AS) was performed in 11 rats as described by Cutillieta et al. (1978) for the ascending aorta, except that the partially occluded week hemoclip was positioned around the upper part of the abdominal aorta. Aortic incompetence (AI) was induced in 14 rats by the method of Jouannot et al. (1973): a stiff polyethylene catheter was introduced in the right carotid artery and the patency of the fistula was assessed by the increase in differential aortic pressure. In 14 animals, these two procedures were combined (AS + AI) (Jouannot et al., 1973): the aortic stenosis was induced first, and the incompetence, 2-3 weeks later.

Left ventricular infarction was induced in 10 rats (INF) by a method similar to those previously described (see Pfeffer et al., 1979a): each rat was anesthetized with ether and a left thoracotomy was performed. The heart was exteriorized by gentle pressure on the right side of the thorax. The left coronary artery was ligated between the pulmonary artery and the left atrium. The heart was returned to its position and the thorax rapidly closed after pressing on it to empty the remaining air from the pleural cavity.

In all these groups, the animals were killed at various times after surgery (3 to 28 weeks, see Table I).

In 16 rats an aortocaval fistula (ACF) was produced by slightly modifying the procedures of Hatt et al. (1979) and Flaim et al. (1979): the aortocaval pedicle was reached through an abdominal midline incision and, under a dissecting microscope, the part between the origin of the renal arteries and the aortic bifurcation was carefully dissected from the posterior layers. Small vascular bulldog clamps were positioned on the two vessels from the right to the left, one over the aortic bifurcation and the other beneath the origin of the renal arteries. By a right-to-left rocking motion of approximately 90° of the two clamps, the vena cava was brought above the aorta. A longitudinal 2- to 3-mm-long incision was made on the vein with a razor blade fragment and the inside of the vein washed with Ringer’s solution. This incision allowed us to reach the medial common wall and a microsurgical suture (9-0 Ethilon, Ethicon) was passed through this double layer. The suture then was pulled so that the common wall protruded in the middle of the phlebotomy (Fig. 1). This protruding area was resected under the suture with microscissors and the vein closed with an overseam clamp. Clamps were removed and the patency of the fistula was assessed by the appearance of the vena cava which was stretched, reddish, and pulsatile. The abdominal incision was closed and the rat was allowed to recover. Since it has been impossible to standardize the size of the

**Table 1: Body and Ventricular Weight Ratios of Control Rats and Rats with Myocardial Hypertrophy**

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>No. of rats</th>
<th>Duration of overload (wks)</th>
<th>Age at study (wks)</th>
<th>Body wt at study (g)</th>
<th>Ventricular wt at study (g)</th>
<th>Hypertrophy (%)</th>
<th>(Ventricular wt/body wt) x 10^6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>6</td>
<td>6-13</td>
<td>200-450</td>
<td>0.80-1.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>9</td>
<td>15-30</td>
<td>490-680</td>
<td>1.20-1.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI</td>
<td>7</td>
<td>3-14</td>
<td>266-400</td>
<td>0.73-1.58</td>
<td>27-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI</td>
<td>4</td>
<td>25-26</td>
<td>489-700</td>
<td>2.20-2.40</td>
<td>40-86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS + AI</td>
<td>6</td>
<td>5-23</td>
<td>370-440</td>
<td>1.30-1.80</td>
<td>28-72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS + AI</td>
<td>6</td>
<td>5-10</td>
<td>530-670</td>
<td>1.55-2.50</td>
<td>8-93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACF</td>
<td>8</td>
<td>5-14</td>
<td>280-460</td>
<td>1.65-1.87</td>
<td>63-116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF</td>
<td>16</td>
<td>12</td>
<td>480-650</td>
<td>1.45-2.23</td>
<td>25-97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF</td>
<td>7</td>
<td>12</td>
<td>517-709</td>
<td>1.41-3.00</td>
<td>0-99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>8</td>
<td>8-10</td>
<td>517-709</td>
<td>0.83-1.30</td>
<td>0-99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>8</td>
<td>8-10</td>
<td>270±9*</td>
<td>0.81±0.03*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as ranges or as mean ± 1 se(*) AS = aortic stenosis; AI = aortic incompetence; ACF = aortocaval fistula; INF = left ventricular infarction; WKY = Wistar Kyoto; SHR = spontaneously hypertensive rats of Wistar Okamoto strain*
fistula, the overload was presumed to be highly variable, and all animals of this group were killed approximately at the same time after surgery (12 weeks).

The 15 controls were unoperated rats of the same strain, kept under identical housing conditions as the operated rats. In order to fit approximately the age and weight of the operated animals, 8- to 30-week-old rats were used [body weight (BW) from 300 g to 680 g].

The male spontaneously hypertensive rats (SHR) of the Wistar Okamoto strain and their controls of the Wistar-Kyoto strain (WKY) were a gift of Prof. P.Y. Hatt and were taken from a breeding stock originally provided from Iffa Credo (Paris). They were housed in Prof. P.Y. Hatt's animal house, and killed at 12 months of age.

All animals were killed by a blow to the head. They were weighed (BW) and the heart was rapidly excised. Atria and great vessels were removed. The ventricles were opened, washed with saline, blotted dry, and weighed (ventricular weight, VW). For some experiments, the right ventricle was dissected along its septal insertion from the rest of the ventricular mass. The ventricles were frozen in liquid nitrogen within 2 minutes and stored at −20°C.

The myocytes were prepared from isolated hearts and perfused with hyaluronidase (0.1% wt/vol) and collagenase (0.05% wt/vol) according to Cutilletta et al. (1977). The cells were stored at −20°C in the presence of 50% (vol/vol) glycerol.

Estimation of Heart Hypertrophy

The degree of hypertrophy as a result of AS, AI, AS + AI, and ACF was calculated using a regression curve BW/VW established in 152 controls from the same strain (Berson and Swynghedauw, 1973). For each rat, the theoretical heart weight was: ThW (g) = (1.20 × BW) + 197 × 10⁻³. The percentage of hypertrophy was (VW – ThW) × 100/Thw.

For the rats that underwent an experimental myocardial infarction, no reliable means of expressing hypertrophy of the noninfarcted area could be found. Only the rats showing evidence of a large ventricular infarction (scar assessed by marked thinning and pale color of the wall, >7 mm in diameter) were kept for the study and the percentage of hypertrophy was calculated as above.

For the SHR and WKY, the VW/BW ratios were calculated.

Analytical Procedures

Crude tissue extracts were obtained from samples of about 100 mg crashed in liquid nitrogen and extracted for 20 minutes at +4°C with 4 volumes (wt/vol) of a slightly modified Guba's solution (Guba et al., 1968) [0.3 M KCl, 0.1 M PO₄H₂K, 0.05 M PO₄H₂K, 0.001 M MgCl₂, 0.01 M P₂O₅Na₄, 1% (wt/vol) Azide Na, 1% (vol/vol) 2-mercaptoethanol]. The homogenate was centrifuged 20 minutes at +4°C and 30000 × g and the supernatent stored at −20°C in 50% (vol/vol) glycerol.

Polyacrylamide gel electrophoresis in non-dissociating conditions was performed in a Pharmacia apparatus (GE-411) which allows thermostating and recirculation of the buffer between the anodic and the cathodic reservoirs, according to Hoh et al. (1978), except that the running buffer contained, in addition to 0.02 M NaPO₄; 10% (vol/vol) glycerol, 0.001 M EDTA, 0.01% (vol/vol) 2-mercaptoethanol, pH 8.5 (d'Albis et al., 1979). Cylindrical polyacrylamide gels (60 mm × 5 mm) were prepared with 3.88% (wt/vol) acrylamide, and 0.12% (wt/vol) N,N'-methylene bisacrylamide. Each gel was loaded with approximately 1–2 μg of myosin, i.e., 30 μl of a 40-fold dilution of the crude extract with 0.01 M NaPO₄; 50% (vol/vol) glycerol, traces of bromophenol blue, pH 8.5. Temperature of the electrophoresis buffer was maintained between +1 and +3°C, and gels were run at a constant voltage of 14 V/cm for 20 to 24 hours.

Staining and destaining of the gels were carried...
out according to Hoh et al. (1978) in a Hoefer Scientific Instruments apparatus. Densitometric tracings of the gels were obtained with a Gilford Spectrophotometer model 240 equipped with a Hewlett-Packard 70-44A multirecorder tracing table. The relative amount of each isoenzyme was calculated from the height of each peak. Results were expressed as percentages of V3. Reproducibility of the whole procedure, calculated according to Henry (1964) was equal to 9% (16 pairs of duplicates). Results were expressed as the mean ± se. When two groups of data were compared, statistical comparisons were carried out by Student's t-test. Regression lines were calculated using the method of least squares. Statistical significance was considered to be $P < 0.05$.

Results

Magnitude of Hypertrophy

Table 1 shows that the experimental devices we used allowed us to obtain a wide range of hypertrophies, up to approximately 120%. The most important increases in cardiac mass were obtained with the two-step procedure using AS and AI. The degree of hypertrophy was not related to the duration of hemodynamic overload, which was probably due to the technical difficulties in imposing overloads reproducible from one animal to the other. The INF group also displayed significant degrees of hypertrophy (up to 66%) despite the important myocardial defect induced by the infarction itself. This indicated that the remaining tissue was, in fact, more hypertrophied than was reflected in our calculated values. In the SHR group, the VW/BW ratio was significantly increased, as compared with their WKY controls ($P < 0.001$).

Signs of heart failure (dyspnea, prostration of the animal, ascites, pleural effusion) were never noted, except in a few animals exhibiting more than 100% hypertrophy. None of the INF displayed any of these signs.

Myosin Isoenzymic Patterns

Gels typical of the LV of control animals and of rats submitted to each type of overload are shown in Figure 2. In controls, the predominant form was V1, in close agreement with Hoh et al. (1978) and with previous observations from our laboratory made on sham-operated animals of the same rat strain (Lompré et al., 1979). An isoenzymic redistribution in favor of the slow migrating form V3 was observed in all the models we studied. The electrophoretic mobility of each isoenzyme (V1, V2, and V3) was identical in controls and in experimental animals of the Wistar strain as well as in the SHR and WKY rats.

Electrophoresis of myosins obtained from myocytes of a control heart (BW 500 g) and a hypotrophied heart (AS, 96% hypertrophy, approximately same BW) are shown in Figure 3. Both patterns were in close agreement with those observed above with the whole ventricular tissue, and this established that the isoenzymic changes occurred in the muscle cells themselves.

Relationship between the Degree of Hypertrophy and Isoenzymic Shift

A significant correlation was found (Fig. 4) between left ventricular V3 and the degree of heart hypertrophy for AS ($n = 11$, $r = 0.61$, $P < 0.05$), for AI ($n = 14$, $r = 0.88$, $P < 0.001$), and for AS + AI ($n = 14$, $r = 0.68$, $P < 0.01$), and this showed that the increase in ventricular mass and the appearance of V3 were simultaneous. A very important reversal of the isoenzymic pattern was observed for the bulky hearts (approximately 60% of V3 for 100% hypertrophy), in close agreement with our previous observations. In contrast, the correlation was not significant for the ACF ($n = 16$, $r = 0.46$), and the extent of the isoenzymic shift was small: out of 13 hypertrophied hearts, values between 35 and 40% were observed in only three animals, whereas all others contained between 15 and 22% V3, which is
equal to or only slightly different from controls of the same body weight (see Fig. 5). No hypertrophy was found in three animals, possibly because the fistula was spontaneously obstructed: two of them exhibited a normal isoenzymatic pattern, and the third one contained 20% V3, which is slightly above controls.

An equivalent correlation seemed to exist in the INF, but was not statistically significant \( (n = 10, r = 0.6, 0.05 < P < 0.1) \). The average amount of V3 was 29 ± 2%, which represented a mean 3-fold increase as compared to controls of the same body weight. As compared to the WKY, an approximately 4-fold increase in V3 was observed in the SHR, whose LV myosin contained 35 ± 2% V3 \( (P < 0.001) \).

**LV-RV Differences**

During growth (Fig. 5) the amount of the slow migrating form V3 progressively increased in the LV of control animals, whereas the amount of the fast form was depressed in a parallel manner. The increase in V3, though small, was significantly correlated with the increase in BW \( (n = 15, r = 0.73, P < 0.01) \). In contrast, no significant relationship was found in the RV, whose V3 seemed to remain approximately constant \( (n = 9, r = 0.2) \). LV of 1-year-old WKY rats contained slightly less V3 than did 6-month-old Wistar controls (9% and 16%, respectively).

Table 2 shows the differences in the amounts of V3 between left and right ventricles in controls and in some experimental animals, as a function of the amount of V3 in the left ventricle: all right ventricles contained less V3 than did the left. In the ACF...
group, the LV-RV difference was small and of the same order of magnitude as for the elder controls. In the AS, AS + AI and INF, LV V3 increased before RV V3; RV V3 was only 15%, when LV V3 was already about 35%. Further increase in LV V3 was accompanied by a similar increase in the RV, and again the LV-RV differences were small.

For the SHR, the approximately 4-fold increase in LV V3 as compared with the WKY controls (see above) was accompanied by an equivalent increase in RV V3, \( P < 0.001 \), and thus, the LV-RV difference was slightly increased (Fig. 6).

**Discussion**

From this study, it appears that, in the rat, synthesis of a cardiac myosin isoenzyme V3 is a general process occurring in cardiac myocytes with hypertrophy due to chronic mechanical overload (Fig. 2). Recent observations from our laboratory (Lompré et al., 1979) have shown that myosins obtained from gross cardiac hypertrophies, which displayed a low Ca\(^{2+}\) ATPase activity as compared with myosins from control hearts, contained predominantly the V3 form. On the other hand, hypothyroid rats also contain a V3 form of low activity (Hoh et al., 1978; Pope et al., 1980), and there is now evidence from one- and two-dimensional peptide maps that it is the same isoenzyme that is synthesized in AS, AI, AS + AI, aging and hypothyroidism (Klotz et al., 1981; Schwartz and Whalen, unpublished observations).

It thus seems reasonable to assume that the V3 band we found in ACF, INF, and SHR is also the same. Since it is generally admitted that contractile element shortening capacity is correlated with the ability of myosin to hydrolyze ATP (Barany, 1967; Delcayre and Swynghedauw, 1975), our findings thus provide a molecular basis for declines in both ATPase activity and myocardial contractility previously observed in the same animal species in similar models, i.e., aortic banding or aortic regurgitation (Berson and Swynghedauw, 1973; Jouannot et al., 1975; Schwartz et al., 1978), left ventricular infarction (Pfeffer et al., 1979a), and genetic hypertension (Pfeffer et al., 1979b; Medugorac, 1980; Mayr et al., 1980; Lecarpentier, unpublished observations).

The statistical correlation between the amount of V3 and the degree of hypertrophy in the AS, AI, and AS + AI groups (Fig. 4) is in close agreement with our previous findings using an immunochromatographic approach (Schwartz et al., 1978). This shows that, in these types of overloaded rat hearts, an increase in protein synthesis is accompanied by the synthesis of a different myosin form. It is not clear whether or not such a relationship also exists in the other groups. In the ACF, the relationship was not significant and the shift seemed less pronounced (Fig. 4). One explanation for this smaller increase in V3 would be that, by plotting total ventricular hypertrophy against LV V3, we have overestimated the degree of hypertrophy of the LV in this model as compared with the others. To compensate for this overestimation, the origin of the abscissa, for the ACF, may be considered to be shifted to the right (Fig. 4), and, under these conditions, the magnitude of the isoenzymic shift would be equivalent to that of the other models for equivalent LV hypertrophies. Another possibility is that, in this kind of overload, V3 is not synthesized to the same extent or with the same time course as in the other models. This would be consistent with data of several authors showing, for other animal species, a normal or only slightly modified ATPase activity and con-

<table>
<thead>
<tr>
<th>Controls</th>
<th>ACF (n = 9)</th>
<th>AS, AS + AI (n = 15)</th>
<th>INF (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV V3 (%)</td>
<td>LV-RV</td>
<td>LV V3 (%)</td>
<td>LV-RV</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>7</td>
<td>5</td>
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<td>10</td>
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<tr>
<td>20</td>
<td>15</td>
<td>20</td>
<td>18</td>
</tr>
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</table>

**TABLE 2** Comparison of the Amounts of V3 (%) in Left and Right Ventricles from Normal and Hypertrophied Rat Hearts.
tractile function after atrioventricular block (Tur- 
ina et al., 1969), atrial septal defects (Cooper et al., 
1973; Carey et al., 1979), and aortocaval fistulas (see 
Ross, 1974). In this hypothesis, the moderate isoen-
zymic shift we observed in the ACF might be due to 
the fact that the hearts we studied were over-
loaded more severely and for a longer period than 
in the above reports. Indeed, contractility was found 
to be impaired in one dog with a large chronic 
fistula (Ross 1974) and in several dogs submitted to 
an aorto caval shunt over a 12-week period (Pinsky 
et al., 1979).

In the INF group, our data suggested that V3 per-
centage and the degree of hypertrophy were also 
related, although this relation was not statistically 
significant. Further investigations with a more pre-
cise evaluation of the tissue hypertrophy of the non-
infarcted ventricular area may give a better answer 
to this question.

Our results in the control Wistar group revealed 
a small and progressive age-dependent increase in 
the percentage of V3 in the LV (Fig. 5). Hoh et al. 
(1978) had also observed this phenomenon, but 
these authors did not analyze RV and LV sepa-
rately. Although both sets of data are qualitatively 
in agreement, the maximal value of LV V3 never 
exceeded 15% in our study (Fig. 5), whereas it 
reached 30% in the report by Hoh et al. for animals 
of similar ages. It is difficult to compare precisely 
the two groups of controls, since the BW were not 
reported by Hoh et al. One might only hypothesize 
that housing conditions, and especially physical 
activity, interfere with the isoenzymic pattern. This 
points out the need for control animals, not only of 
the same age and weight, but also bred under the 
same conditions as the experimental ones. In the 
same way, it is possible that the small differences 
that we observed between the WKY and the Wistar 
controls (Figs. 5 and 6) were also due to different 
housing conditions, although the hypothesis of 
strain differences cannot be ruled out. The amount 
of V3 which we found in the 22- to 30-week-old 
animals (Fig. 5) is insufficient to induce a detectable 
decrease in the overall enzymatic activity of the 
whole myosin. However, this is probably the begin-
ing of the process which leads, in older animals, to 
decreases in both ATPase activity of myosin and 
velocity of shortening of the cardiac muscle (Alpert 
et al., 1966; Chesky and Rockstein, 1977).

It has long been known that decreases in ATPase 
activity and myocardial contractility also occur 
after chronic mechanical overload in other animal 
species, such as rabbits (see Maughan et al., 1979), 
dog (Wikman-Coffelt et al., 1978), cats (Chandler et 
al., 1967; Skelton and Sonnenblick, 1974; Carey et 
al., 1978), and humans (Alpert et al., 1962; Leclercq 
et al., 1976; Strauer and Burger, 1980). Recent data 
indicate that adult animals of these species (espe-
ially rabbits) contain a predominant isoenzyme of 
the V3 type, whereas young animals contain both 
V1 and V3 (Hoh and Yeoh 1979; Lompré et al., in 
press). In view of these findings, decreases in ATP-
ase activity could be due (1) to the use of very 
young animals at the time of surgical procedure, (2) 
to the synthesis of a yet unknown isoenzyme of lower ATPase activity but displaying a charge anal-
ogous to that of V3, or (3) to biochemical mecha-
isms other than isoenzymic change. This remains 
to be determined.

We can only speculate on the mechanisms un-
derlying the isoenzymic shift in the rat species. 
Pressure overload recently has been proposed as an 
obligatory trigger for the decrease in myosin ATP-
ase activity in the cat (Carey et al., 1979). Indeed 
pressure overload could be one of the triggers that 
all models of our study—except perhaps the ACF— 
have in common. This process would also be in-
volved in the Al which may be considered as a 
combination of pressure and volume overload, and 
in the LV of aging rats, since the increase in the 
higher frequency terms of the aortic input imped-
ance induces a pressure overload on this ventricle 
(Yin et al., 1980). However, it is probable that other 
triggers also exist, for example, in the ACF or in the 
right ventricles of the SHR which also display sig-
nificant increase in V3 (Fig. 6).

It is interesting to note that, except for young 
rats (Fig. 5), all RV studied here contained less V3 
than the corresponding LV. In all experimental 
models except the ACF, the LV-RV differences 
should be explained by the fact that overload of the 
LV was always the primary event, the RV being 
affected only later. The difference was more sur-
prising for the ACF since, theoretically, both ven-
tricles were equally affected. The slight differences 
we have found might be due either to a difference 
in the stress imposed on each ventricular wall for 
apparently equivalent overloads, or to the RV con-
tractile reserve postulated by Wikman-Coffelt et al. 
(1979). Nevertheless, it appears that isoenzymic 
changes can be a selective and sensitive regional 
response.

The present findings show that myosin isoen-
zymic redistribution is, like hypertrophy, a general 
response of the rat heart to sustained mechanical 
overload. Together with the data of Hoh et al. 
(1978), this strongly suggests that the type of myo-
sin isoenzyme present is an important determinant 
of the contractile activity of the cardiac muscle. 
There is evidence to suggest that, in other states 
associated with modified contractile performance, 
changes in myosin form also occur (see Scheuer and 
Bahn, 1979; Malhotra et al., 1979). Further investi-
gation of the molecular events which trigger the 
transformation of cardiac myosin may thus bring 
new insights into the biochemical basis of heart 
failure.

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