# Maladaptive Remodeling of Cardiac Myocyte Shape Begins Long Before Failure in Hypertension

Tatsuyuki Onodera, Tetsutaro Tamura, Suleman Said, Sylvia A. McCune, A. Martin Gerdes

***Abstract***—Progression to failure in hypertension is associated with ventricular dilation, excessive myocyte lengthening, and an increase in myocyte length/width ratio. The temporal development of these changes in relation to impaired pump performance is unknown. We examined isolated myocytes from 1- to 12-month-old spontaneously hypertensive heart failure (SHHF) rats who develop heart failure at approximately 24 months of age. Left ventricular myocyte cross-sectional area reached a maximum of ≈350 to 400 $\mu m^2$ at 3 months of age and did not change significantly thereafter. Nonetheless, LV systolic wall stress, a known stimulus for myocyte transverse growth, increased progressively between 3 and 12 months of age. Unlike the situation in normally aging rats with stable body mass, myocyte length in SHHF rats continued to increase with aging ($P<0.05$ from 9 to 12 months of age). In summary, (1) left ventricular myocyte transverse growth reaches an upper limit by 3 months of age although systolic wall stress continues to rise; and (2) cell length is significantly increased by 12 months of age. This study suggests that maladaptive remodeling of cardiac myocyte shape begins long before pump failure in hypertension. Additionally, it appears that the left ventricle may be robbed of an important adaptive mechanism to normalize wall stress (eg, myocyte transverse growth) early in the progression to failure. **(*Hypertension*. 1998;32:753-757.)**

**Key Words:** heart failure ■ ventricular remodeling ■ myocytes



Chamber dilation and an increase in chamber diameter to wall thickness ratio are characteristic of heart failure in general, including failure induced by pressure overload. Changes in wall thickness and chamber diameter may reflect alterations in myocyte diameter and length, respectively, since myocytes run in a circumferential manner around a given chamber. Early compensated pressure overload leads to increased cross-sectional area (CSA) of ventricular myocytes but does not change cell length.[1–3] A maladaptive pattern of cellular remodeling, characterized by excessive myocyte lengthening, was observed in left ventricular (LV) myocytes from rats and humans with heart failure associated with hypertension.[4,5]

Although excessive myocyte lengthening from series addition of sarcomeres is clearly linked to ventricular dilation in failure, inadequate myocyte transverse growth may be a more critical early defect leading to impaired wall thickening.[4,6,7] Indeed, increasing wall thickness by myocyte cross-sectional growth is the primary mechanism of reducing systolic wall stress. At this time, it is not known when critical changes in myocyte shape leading to heart failure are initiated.

Our previous study using lean female spontaneously hypertensive heart failure rats (SHHF; a genetic model predisposed to hypertension and heart failure)[8–10] showed a significant increase in LV myocyte length from 12 months (nonfailing) to 24 months (failing) of age.[4] Myocyte CSA from both 12- and 24-month-old SHHF rats, however, was similar. On the basis of available information from normotensive controls,[11] it appeared that myocyte length was already above normal in 12-month-old SHHF rats. These results suggested that maladaptive myocyte remodeling, related to heart failure, began before 12 months of age. In this study, temporal changes in myocyte shape in SHHF rats from 1 to 12 months of age were examined to determine when maladaptive myocyte remodeling is initiated.

## Methods

### Experimental Animals

Lean female SHHF rats, who typically develop heart failure at 24 months of age, were used in this experiment. In the present study, rats at 1, 2, 3, 4, 6, 9, and 12 months of age were obtained from Genetic Models Inc (Indianapolis, Ind) and from Dr Sylvia McCune's colony at Ohio State University. All procedures were approved by the University of South Dakota Animal Care and Use Committee and followed institutional guidelines for animals.

### Echocardiography, Hemodynamics, and Wall Stress Measurements

The animals were anesthetized with an intramuscular injection of ketamine HCl (30 mg/kg) and xylazine (5 mg/kg)[4] at the time of terminal experiments. Standard echocardiography techniques were used[12] to obtain two-dimensionally targeted M-mode echocardio-

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**TABLE 1. Body Weight and Heart Weight Data**

| Age | n | BW, g | HW, mg | HW/BW, mg/g |
|---|---|---|---|---|
| 1M | 7 | 53±5 | 320±36 | 5.99±0.39 |
| 2M | 13 | 160±11* | 739±54* | 4.56±0.55* |
| 3M | 14 | 193±18*† | 785±110* | 4.06±0.28* |
| 4M | 15 | 216±12*†‡ | 857±72* | 3.98±0.33* |
| 6M | 7 | 217±7*†‡ | 1040±59*†‡ | 4.79±0.29* |
| 9M | 13 | 241±22*†‡§ | 1123±147*†‡§ | 4.67±0.45*§ |
| 12M | 7 | 295±18*†‡§‖¶ | 1475±114*†‡§‖¶ | 5.01±0.42*‡§ |

All rats are SHHF. M indicates age in months; n, number of animals; BW, body weight; and HW, heart weight. Values are expressed as mean±SD.

*$P<0.05$ compared with 1M; †$P<0.05$ compared with 2M; ‡$P<0.05$ compared with 3M; §$P<0.05$ compared with 4M; ‖$P<0.05$ compared with 6M; ¶$P<0.05$ compared with 9M.

grams from short-axis views of the left ventricle at or just below the tip of the mitral valve leaflets using a GE-RT5000 echo machine with a 7-MHz transducer.

Right ventricular (RV) and LV hemodynamics were collected as described previously.[2–4] LV systolic wall stress (meridional) was calculated from LV pressure and echo measurements of LV internal dimension and posterior wall thickness as described by Litwin et al.[12] RV wall stress was not obtained because of the inherent difficulties in collecting those data from rats.

## Myocyte Isolation and Morphometry

The hearts were quickly removed, trimmed of excess tissue, blotted, and weighed. The procedure for isolating myocytes using aortic perfusion with collagenase has been described previously.[13] Regional heart weights were not collected after collagenase perfusion because of the potential artifact added by this procedure. Myocyte volume was measured using a Coulter Channelyzer (model Z2, Coulter Corp). Cell length, defined as the longest length parallel to the longitudinal axis of the myocyte, was measured in 40 cells from each sample. On the basis of a standard equation for sample size,[14] 40 cell-length measurements reduced the sampling error to <3% for all samples. Myocyte CSA was calculated from cell volume/cell length. Thus, calculated CSA represents average values along the entire length of the myocyte. Cell width was calculated from CSA using the formula for a circle (area=$\pi r^2$, cell width=2r).

## Data Analysis

Results are presented as mean±SD computed from the average measurements obtained from each group. ANOVA was used to compare data in each group. The Scheffé test was used to examine significant differences observed with the ANOVA.[15]

# Results

All animals appeared healthy and exhibited no clinical signs of heart failure. Changes in body weight and heart weight are indicated in Table 1. Body weight increased from 1 month to 4 months of age and was relatively stable thereafter, although significant increases were observed at some time points. Heart weight increased 2.7-fold from 1 month to 4 months of age and continued to increase after 4 months of age.

LV and RV hemodynamics and LV systolic wall stress are summarized in Table 2. Aside from some minor (but statistically significant) fluctuations, LV and RV hemodynamics did not change between 2 and 12 months of age. LV systolic wall stress, however, increased by 52% in SHHF rats between 3 and 12 months of age.

Isolated myocyte data from the LV and RV are indicated in Table 3. Cell volume increased significantly during the period of physiological growth from 1 month to 4 months of age. Cell volume also increased at 4 months to 12 months of age when body mass was relatively stable. Cell length increased progressively from 1 to 12 months of age. Some fluctuations that were seen in this progression were of uncertain statistical significance. CSA increased from 1 month to 3 months of age but did not change after 3 months of age.

RV cell volume and cell length increased from 1 month to 4 months of age. Cell volume and length did not increase significantly from 4 months to 12 months, although some

**TABLE 2. LV and RV Hemodynamics and LV Systolic Wall Stress**

| Age | n | SP, mm Hg | EDP, mm Hg | +dP/dt, mm Hg/s | −dP/dt, mm Hg/s | Systolic Wall Stress, kdyn/cm$^2$ |
|---|---|---|---|---|---|---|
| LV | | | | | | |
| 2M | 10 | 130.4±7.2 | 1.7±1.6 | 5867±162 | 5640±565 | ... |
| 3M | 12 | 140.2±21.1 | 2.9±1.6 | 5737±126 | 5643±242 | 35.5±9.9 |
| 4M | 12 | 143.9±18.3 | 2.6±1.7 | 5761±160 | 5680±269 | 35.7±8.1 |
| 6M | 6 | 135.2±6.5 | 1.8±0.9 | 5783±175 | 5661±218 | 38.2±8.2 |
| 9M | 9 | 139.5±16.5 | 2.8±1.9 | 5672±118 | 5613±93 | 42.6±9.9 |
| 12M | 6 | 144.7±22.1 | 2.0±1.1 | 5752±139 | 5682±220 | 53.9±8.7†‡§ |
| RV | | | | | | |
| 2M | 6 | 27.0±5.9 | 0.2±1.1 | 1442±319 | 1182±565 | |
| 3M | 7 | 30.4±5.1 | −0.9±0.7 | 2054±326* | 1723±245 | |
| 4M | 6 | 23.8±2.4 | −0.2±1.9 | 1356±106† | 1157±123 | |
| 6M | 6 | 27.8±2.3 | 0.8±0.7 | 1751±237 | 1560±219 | |
| 9M | 7 | 28.0±3.7 | −0.8±0.9 | 1509±160† | 1286±251 | |
| 12M | 6 | 29.3±4.9 | 0.6±1.6 | 1878±341 | 1423±373 | |

All rats are SHHF. M indicates age in months; n, number of animals; SP, systolic pressure; EDP, end-diastolic pressure; +dP/dt, maximum rate of pressure development; and −dP/dt, maximum rate of pressure decline. Data were collected from anesthetized rats.

*$P<0.05$ compared with 2M; †$P<0.05$ compared with 3M; ‡$P<0.05$ compared with 4M; §$P<0.05$ compared with 6M.

**TABLE 3. Isolated Myocyte Data From Left and Right Ventricles**

| Age | n | Cell Volume, $\times 10^3$ $\mu m^3$ | Cell Length, $\mu m^2$ | CSA, $\mu m^2$ | Cell Width | L/W Ratio |
|---|---|---|---|---|---|---|
| LV | | | | | | |
| 1M | 7 | 14.1±2.7 | 89.5±7.3 | 158±33 | 14.1±1.5 | 6.41±0.87 |
| 2M | 7 | 34.6±3.2* | 118.3±7.0* | 293±29* | 19.3±1.0* | 6.15±0.56 |
| 3M | 7 | 48.8±2.6*† | 130.0±4.9* | 376±27* | 21.9±0.8* | 5.96±0.40 |
| 4M | 8 | 46.3±4.4* | 134.8±6.3*† | 343±24* | 20.9±0.7* | 6.46±0.32 |
| 6M | 6 | 53.8±8.1*† | 140.1±10.7*† | 384±51* | 22.1±1.5* | 6.37±0.61 |
| 9M | 10 | 48.7±14.3*† | 141.3±7.8*† | 344±95* | 20.7±2.9* | 6.93±1.09 |
| 12M | 5 | 67.2±6.8*†‡ | 165.1±12.4*†‡§‖¶ | 408±38*† | 22.8±1.1*† | 7.27±0.75‡ |
| RV | | | | | | |
| 1M | 7 | 12.3±2.2 | 88.3±4.6 | 139±24 | 13.3±1.1 | 6.70±0.61 |
| 2M | 7 | 24.8±2.3* | 112.4±7.3* | 221±18* | 16.8±0.7* | 6.72±0.55 |
| 3M | 7 | 27.3±2.0* | 124.1±10.5* | 223±33* | 16.8±1.3* | 7.46±1.16 |
| 4M | 8 | 24.7±3.2* | 119.7±10.9* | 204±19* | 16.1±0.8* | 7.44±0.76 |
| 6M | 6 | 25.4±3.6* | 126.5±14.4* | 203±33* | 16.0±1.3* | 7.97±1.33 |
| 9M | 10 | 22.4±5.4* | 114.8±9.7* | 193±35* | 15.6±1.4* | 7.38±0.73 |
| 12M | 5 | 26.1±2.2* | 134.0±5.0*†¶ | 195±24* | 15.7±1.0* | 8.55±0.80*† |

M indicates age in months; n, number of animals; L/W, length/width ratio; A/B ratio, ratio of major to minor transverse axis. Values are expressed as mean±SD.

*$P<0.05$ compared with 1M; †$P<0.05$ compared with 2M; ‡$P<0.05$ compared with 3M; §$P<0.05$ compared with 4M; ‖$P<0.05$ compared with 6M; ¶$P<0.05$ compared with 9M.

fluctuations were noted. CSA and cell width increased significantly only between 1 month and 3 months of age.

## Discussion

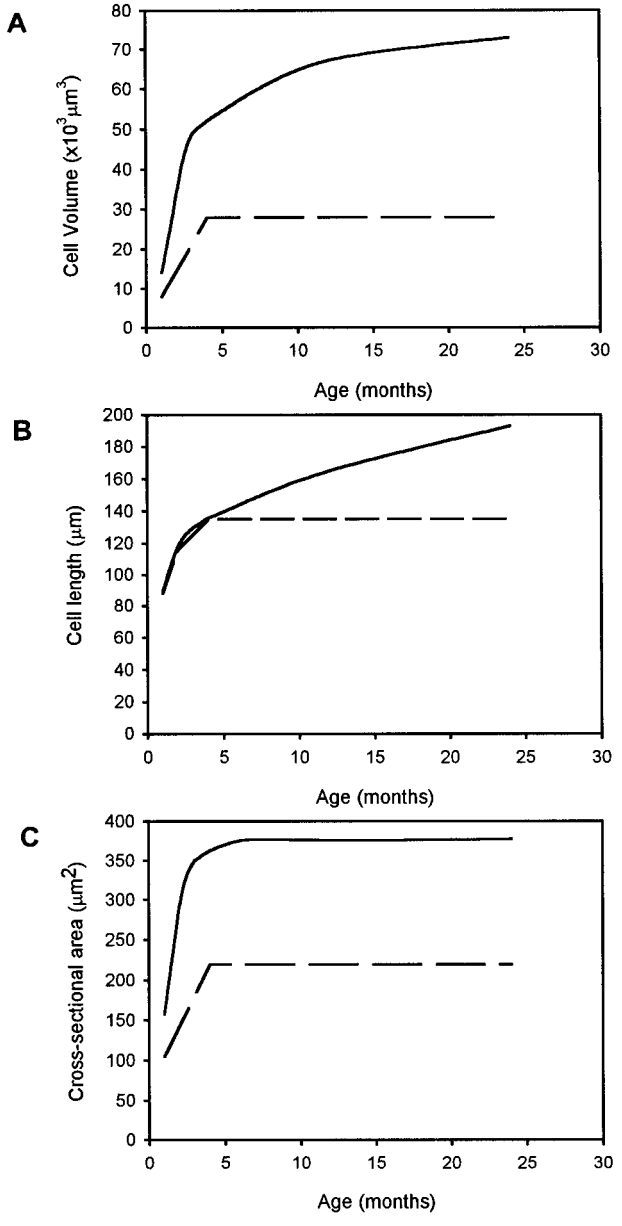
In this study, temporal changes in myocyte shape in SHHF rats from 1 month to 12 months of age were examined to determine when maladaptive myocyte remodeling begins during the progression to failure. No clinical signs of heart failure were found in these animals during these time points. The rats between 2 and 12 months of age showed elevated LV systolic pressure, but hemodynamic data suggested no impairment of LV function. RV hemodynamics did not show any signs of altered function during this period. Thus, it was concluded that all rats in this study had systemic hypertension but compensated LV and RV function.

Temporal development of important LV pathophysiological alterations in hypertension are reported here for the first time. Specifically, (1) myocyte CSA reached an upper limit of ≈350 to 400 $\mu m^2$ at ≈3 months of age; (2) systolic wall stress increased significantly between 3 and 12 months of age; and (3) myocyte length increased significantly from 9 to 12 months and continued to increase until failure. These alterations suggest that arrested myocyte cross-sectional growth may contribute to the maladaptive changes in cell shape observed in failure. This cellular alteration appears to underlie the impaired wall thickening response associated with congestive heart failure.

It is helpful to divide the rats used in this study into 2 populations based on growth and aging: a juvenile period from 1 to 4 months of age and an adult period from 4 to 12 months of age. Physiological growth contributed to the increase in heart weight between 1 month and 4 months of age. Nevertheless, some of the increase in heart mass during the period of growth was due to the superimposition of hypertension on physiological growth, as evidenced by the values for myocyte CSA. Normal values for LV myocyte CSA in rats are ≈190 to 240 $\mu m^2$. The increased value for CSA associated with normal cell length in SHHF rats at 3 to 4 months of age confirms the presence of compensated hypertrophy with concentric remodeling due to hypertension at those time points.

SHHF rats have a different genetic background than spontaneously hypertensive rats (SHR) or Wistar rats, although they were developed from SHR rats.[8–10] A good control for SHHF rats has not been identified. However, it is known that average LV myocyte dimensions from normal adult mammals are very similar. For instance, values for LV myocyte length, volume, and CSA are virtually identical in normal rats, cats, guinea pigs, hamsters, and humans.[6,13,16] Our previous experiments have demonstrated that in normal rats, cardiac myocyte dimensions do not change with aging if body mass remains stable.[11] Specifically, there was no increase in LV myocyte length, volume, or CSA in female Sprague-Dawley rats between 3 and 24 months of age. It is clear that the progressive increase in LV myocyte length in SHHF rats is abnormal. In this study, we have demonstrated that this maladaptive change in cardiac myocyte shape begins very early in the progression to failure. Temporal changes in LV myocyte shape in lean female SHHF rats and female Sprague-Dawley rats are summarized in the Figure.

Increased myocyte length reflects increased chamber diameter because myocytes run in a circumferential manner around a given chamber. Likewise, changes in wall thickness should be reflected at the cellular level by alterations in




Temporal changes in myocyte volume (A), length (B), and cross-sectional area (C) are summarized for lean female SHHF rats (solid line) and female Sprague-Dawley rats (broken line). Data were taken from this study and from References 4 and 11.

myocyte diameter or CSA. Wall stress is directly proportional to chamber pressure and radius, and inversely proportional to wall thickness based on Laplace's law.[17] Consequently, myocyte length and diameter (CSA) are the cellular analogues of chamber diameter and wall thickness, respectively. Therefore, changes in myocyte length/width ratio should be directly related to alterations in wall stress. The increase in myocyte length and myocyte length/width ratio in SHHF rats and humans with ventricular dilation and heart failure is likely to be a major contributor to elevated systolic wall stress and suggests that this cellular change is maladaptive.

Increased systolic wall stress (afterload) is known to be a powerful stimulus for myocyte cross-sectional growth.[7] LV systolic wall stress increased significantly in SHHF rats between 3 and 12 months of age. Despite a drop in LV systolic pressure with progression to failure, a further increase in LV systolic wall stress occurs in 24-month-old SHHF rats (94.9±29.2 kdyn/cm$^2$, n=4; A.M.G., unpublished results, 1998). The failure of progressively rising systolic wall stress to stimulate myocyte cross-sectional growth suggests a cellular alteration that underlies the presence of inadequate relative wall thickness in failure. Very little is known about the molecular mechanisms regulating cardiac myocyte shape. Recent evidence suggests that mechanical signals can be transmitted via intermyocyte collagen struts through membrane integrins which are linked to the nucleus by intermediate filaments.[18,19] Unfortunately, little is known about the temporal sequence of myocyte cytoskeletal changes in the transition to failure, and specific cytoskeletal changes have not been directly correlated with myocyte shape alterations in a model of heart failure. It is likely that alterations in other signal transduction pathways are also involved in the regulation of myocyte shape. G proteins have been implicated in myocyte cross-sectional growth, and the cytokine cardiotrophin-1 is believed to be involved in myocyte lengthening.[20–22] Further work into the molecular regulation of myocyte shape in the transition to failure obviously merits more attention.

It is of interest that myocyte transverse area appears to reach an upper limit of ≈350 to 400 μm$^2$ in hypertension in SHHF rats and in humans. Additionally, RV myocytes also reached this value after overloading due to LV failure in SHHF rats.[4] Although the upper limit for myocyte cross-sectional growth is not known at this time, it should be appreciated that cell volume increases by the radius cubed, whereas membrane area available for diffusion increases by only the radius squared. Nonetheless, cardiac myocytes appear to have some adaptations that allow large cell size despite having a high metabolic rate. Page and McCallister[23] investigated hypertrophy due to hyperthyroidism and pressure overload and found that myocyte surface/volume ratio was maintained due to a larger increase in T tubular surface area. Consequently, total myocyte surface area (T tubules+sarcolemma) to myocyte volume was maintained in these rat models of modest hypertrophy. It is possible that myocyte cross-sectional growth in hypertension may reach an upper limit and further stimuli for hypertrophy may be able to induce cell lengthening only. Limitations in microcirculatory growth may also play a role, since myocyte cross-sectional growth may tend to push capillaries further apart while myocyte lengthening associated with capillary lengthening may not impair diffusion of nutrients and metabolites.[24]

There was no significant change in RV cell length and length/width ratio in adult SHHF rats between 3 and 12 months of age. Our previous study demonstrated significant RV myocyte hypertrophy after LV failure in 24-month-old SHHF lean female rats. It is important to note, however, that myocyte length and width increased proportionally, suggesting an appropriate cellular response to chamber distention and pressure overload. The regional differences in cell-shape regulation suggest that local, rather than circulating, factors are involved. Because RV myocyte CSA had reached the 350 to 400 μm$^2$ range in 24-month-old rats in failure, it is likely

that further RV myocyte hypertrophy would lead to a maladaptive growth pattern. These regional differences in myocyte shape may be helpful in screening for differently expressed genes that are involved in the underlying pathology.

It should be realized that heart failure is a complex clinical entity and many factors other than myocyte shape are involved in the process. Myocardial fibrosis undoubtedly contributes to end-stage failure and diastolic dysfunction.[25] Loss of cardiac myocytes through apoptosis may also play a role.[26] It should be pointed out, however, that myocardial fibrosis is minimal (eg, collagen content increases from ≈1.5% to 2.5%) in lean female SHHF rats progressing to failure (A.M.G., unpublished observations, 1998). With respect to the issue of apoptosis, cumulative data from ongoing experiments, our previous study,[4] and from this study suggest that myocyte number remains relatively stable between 1 and 24 months of age in this model (eg, myocyte volume increase alone appears to account for the increase in heart mass). Further work is underway to clarify this important issue.

In the present study, the results from SHHF rats showed that maladaptive myocyte remodeling began long before the development of clinical signs or depressed hemodynamic function. Because humans with hypertension and hypertension-induced failure display an identical myocyte remodeling pattern,[4,5] it is likely that maladaptive remodeling in hypertensive patients may also begin long before failure. These experiments underscore the importance of treating hypertension early and aggressively to prevent maladaptive myocyte remodeling from leading to chamber dilation and failure.

In summary, morphological changes were examined in isolated myocytes from lean female SHHF rats between 1 and 12 months of age. LV myocyte CSA reached an upper value approximately twice normal at 3 months of age and did not change thereafter. LV systolic wall stress was elevated by 12 months of age and continued to rise steadily until failure. These results demonstrate that maladaptive myocyte remodeling begins long before the onset of clinical signs or depressed heart function in the progression to failure. Arrested myocyte cross-sectional growth may be an early event that precipitates the maladaptive alteration in cell shape.

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