Nuclear Hypertrophy Reflects Increased Biosynthetic Activities in Myocytes of Human Hypertrophic Hearts

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**Background** The nucleus of the myocytes in human hypertrophic hearts is characterized by its bizarre shape and widespread clumping of chromatin. The functional significance has not been determined.

**Methods and Results** Left ventricular (LV) endomyocardial biopsies obtained from patients with dilated cardiomyopathy (DCM, n=23), postmyocarditis (n=13), hypertrophic cardiomyopathy (HCM, n=21), apical hypertrophic cardiomyopathy (APH, n=11) and hypertensive heart disease (HHD, n=11), and from nonhypertrophic hearts (controls, n=14) were examined. Myocyte size and LV mass index were similar among the hypertrophic hearts, but the nuclear hypertrophy score (grade 0–3) was highest in hearts with systolic failure (DCM and post-myocarditis) and higher in those without it (HCM, APH, and HHD), compared with controls. So were biosynthetic activities such as DNA repair/synthesis, immunohistochemically assessed by proliferating cell nuclear antigen, transcription activity by spliceosome component of 35kDa, and translation efficiency by 70kDa S6 protein kinase. There were significant correlations between nuclear hypertrophy and each biosynthetic activity. Additionally, most of the proliferating cell nuclear antigen-positive nuclei co-expressed oxidative DNA damage markers.

**Conclusion** A link is suggested between structural alteration and molecular biological events in the nuclei of myocytes from human hypertrophic hearts; the nuclear hypertrophy reflects increased biosynthetic activities of DNA repair/synthesis, transcription, and translation efficiency. (Circ J 2006; 70: 710–718)

**Key Words:** Biosynthesis; Cardiac hypertrophy; Cardiomyopathy; Heart failure; Ultrastructure

In response to various stresses, cardiac myocytes present phenotypic alterations of the cytoplasm, such as increased cell volume, increased fraction of subcellular organelles in contrast to decreased fractions of myofilaments, mitochondriosis, and intracytoplasmic vacuoles. Nuclear structure is markedly altered as well. The nuclear change has been well characterized as “hypertrophied nucleus” by the morphological hallmarks of severe crenation of the nuclear membrane (bizarre shape) and widespread clumping of chromatin. However, the significance of such dramatic alteration of the nuclear phenotype in hypertrophic hearts is largely unknown. We previously reported that hypertrophied nuclei in the myocytes of human hearts with dilated cardiomyopathy (DCM) were accompanied by increased activity of DNA repair/synthesis and widespread clumping of chromatin. However, the significance of such dramatic alteration of the nuclear phenotype in hypertrophic hearts is largely unknown. We previously reported that such a nuclear phenotype change is associated with various molecular biological alterations occurring in myocyte nuclei of pathologic hearts, which may also be related to cardiac functional alterations. Thus, the major aim of the present study was to use endomyocardial biopsy specimens from hypertrophic hearts of various etiologies to examine linkages between the structural and molecular biological alterations of the hypertrophied nuclei of cardiac myocytes of human hypertrophic hearts.

**Methods**

**Patients and Endomyocardial Biopsies**

This study was approved by the Institutional Research Committee. A total of 93 patients with hypertrophic hearts were studied (Table 1): DCM (n=23); postmyocarditis (n=13); hypertrophic cardiomyopathy (HCM, n=21); apical hypertrophic cardiomyopathy (APH, n=11); hypertensive heart disease (HHD, n=11); 14 nonhypertrophic hearts served as controls. There were 67 males and 26 females with a mean age of 58±13 years. Echocardiography, cardiac catheterization, and coronary angiography were performed and left ventricular (LV) endomyocardial biopsies were obtained. Measurements included by echocardiography, LV mass index (LVMI); interventricular septal thickness, and LV posterior wall thickness, and by cardiac catheterization, LV end-diastolic volume index, LV ejection fraction (LVEF), and LV end-diastolic pressure. Each endomyocardial biopsy was originally performed for differentiation between primary and secondary myocardial diseases. The
diagnosis of cardiomyopathies (HCM, APH, and DCM) was made principally according to the definition and classification proposed by the World Health Organization/International Society and Federation of Cardiology task force. None of the patients with cardiomyopathies had apparent hypertension. In DCM, there were no foci of inflammatory cell accumulation. The postmyocarditis group included patients who had clinical evidence of acute myocarditis more than 1 month earlier and were given the histological diagnosis of acute myocarditis by the endomyocardial biopsy. The endomyocardial biopsies at the late stage, from which the biopsied specimens were used for the present study, revealed healing, or healed myocarditis. The histological definition of myocarditis was based on the “Dallas classification system.” The HHD group included patients who had clear-cut history of chronic hypertension for 5–15 years or more (>160/95 mmHg), whose hearts were recognized as hypertrophic by cardiac imaging and whose biopsy findings ruled out any infiltrative heart disease. The control group included patients who had been clinically suspected of some cardiac disease (eg, myocarditis, sarcoidosis, or small artery disease, because of minimal ECG change, arrhythmia, or atypical chest pain), but for whom coronary angiography and biopsy findings were not diagnostic.

Endomyocardial biopsy specimens (3–5 specimens per patient) were taken from the LV posterior wall. The largest specimens were cut into 2 pieces, and the biggest were fixed with 10% buffered formalin for 24 h and embedded in paraffin for light microscopy. In the 4-μm-thick paraffin sections stained with hematoxylin-eosin or Masson’s trichrome, the transverse diameter of myocyte (mean diameter of 30–50 myocytes per specimen) was evaluated at the nuclear level. Smaller pieces were fixed with 2.5% phosphate-buffered glutaraldehyde for 4 h and 1% osmium tetroxide for 1 h and embedded in Epon for electron microscopy.

**Scoring of Nuclear Hypertrophy by Electron and Light Microscopy**

Under electron microscopy, the nuclear ultrastructure of the myocytes was assessed by 2 hallmarks indicating “nuclear hypertrophy”: severe crenation of the nuclear membrane (bizarre shape); and widespread clumping of chromatin. Based on these hallmarks, the nuclei were...
semiquantitatively scored into grades 0–3 (grade 0: no hypertrophy; grade 1, 2, and 3: mild, moderate, and marked hypertrophy) according to the method proposed by Baandrup et al5 and shown in Fig 1. Approximately 20 nuclei were evaluated per specimen and the mean value of the scoring was determined as the nuclear hypertrophy score of the electron microscopic specimen.

Similarly, nuclear hypertrophy was scored as 0–3 using the paraffin-sections stained with hematoxylin-eosin under light microscopy based on the degree of nuclear deformity and the thickness of the hematoxylin stain of nuclear chromatin (Fig 2A). We evaluated 40–80 nuclei (mean, 66) of myocytes per specimen and the mean value of the scoring was determined as the nuclear hypertrophy score of the light microscopic specimen. In addition, we evaluated nuclear size as the short diameter of the nucleus and myocyte size as the transverse diameter at the nuclear level. In cases of a bizarre-shaped nucleus, the short diameter of the hypothetical circumference of the nucleus was regarded as the nucleus size. The nuclear size—cell size ratio (N/C ratio) was calculated in the same myocytes.

**Table 2** Oral Drug Regimens Used of the Time of Biopsy

<table>
<thead>
<tr>
<th></th>
<th>Control n=14</th>
<th>HCM n=21</th>
<th>APH n=11</th>
<th>HHD n=11</th>
<th>DCM n=23</th>
<th>PM n=13</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (18)</td>
<td>20 (87)</td>
<td>10 (77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs, n (%)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>1 (9)</td>
<td>4 (36)</td>
<td>7 (30)</td>
<td>4 (31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ca2+ antagonists, n (%)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>9 (82)</td>
<td>3 (13)</td>
<td>1 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-adrenergic blockers, n (%)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>3 (27)</td>
<td>6 (26)</td>
<td>3 (23)</td>
<td>0.0542</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>1 (9)</td>
<td>1 (9)</td>
<td>9 (39)</td>
<td>4 (31)</td>
<td>0.0343</td>
</tr>
<tr>
<td>Digitalis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (30)</td>
<td>4 (31)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Anticoagulants, n (%)</td>
<td>0 (0)</td>
<td>17 (81)</td>
<td>4 (36)</td>
<td>2 (18)</td>
<td>18 (78)</td>
<td>10 (77)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. See text for other abbreviations.
Scorings were performed independently by 2 observers who were unaware of the clinical diagnosis, with the results of differences less than 5% between them for the score.

**Immunohistochemistry**

On the 4-μm-thick sections, proliferating cell nuclear antigen (PCNA), Ki-67, spliceosome component of 35 kDa (SC-35), and 70 kDa S6 protein kinase (p70S6K) were immunohistochemically stained using ABC Elite kits (Vector Lab, Burlingame, CA, USA). The antibodies to PCNA (DAKO; 1:100), Ki-67 (DAKO; 1:100), SC-35 (Sigma, St Louis, MO, USA; 1:100), and p70S6K (Santa Cruz Biotech, Santa Cruz, CA, USA; 1:100) were used as the primary antibodies. Pretreatment by microwave irradiation at 400W for 5 min was performed twice to retrieve PCNA before incubation with the primary antibody. Diaminobenzidine HCl (DAB) was the chromogen. Human tonsils were used as the positive control tissue sections. At least 50 myocytes were assessed in each preparation under light microscopy, and unanimity on the positive immunohistochemical staining was acquired for all preparations between the 2 observers who were unaware of which group the preparations belonged.

To detect the presence of oxidative DNA damage and redox/DNA repair protein, immunofluorescent stains for 8-oxo-deoxyguanosine (8-OHdG) and redox factor 1 (Ref-1) were performed using antibodies against 8-OHdG (Pharmingen, San Diego, CA, USA; 1:200) and Ref-1 (Santa Cruz Biotech; 1:200) which were secondary labeled with Alexa Fluor 568 (Molecular Probes, Eugene, OR, USA). They were double stained with fluorescent isothiocyanate-labeled anti-PCNA antibody (Santa Cruz Biotech; 1:100). The sections were observed under a fluorescent microscope. Immunohistochemistry using the ABC kit was also performed for quantitative assessment of the 8-OHdG- or Ref-1-positive myocytes, where colorization was performed with DAB.
Statistical Analysis
Values are expressed as mean±SD. Statistical comparisons were performed by Student’s t-test or ANOVA followed by Newman-Keul’s multiple comparison test for continuous variables and chi-square analysis for categorical variables. Agreement between the nuclear hypertrophy score assessed by light microscopy and that by electron microscopy was analyzed according to the Bland and Altman method of concordance.10 For the others, Spearman’s analysis was used for determining the correlation between the parameters. A p-value less than 0.05 was considered significant.

Results
Patients Profiles
Table 1 summarizes the patients’ morphological and hemodynamic findings based on echocardiography, cardiac catheterization and the histological findings of the biopsy specimens. The data reflected the typical pathophysiologic conditions of each group. Hearts with DCM and postmyocarditis showed significantly reduced contractility and a dilated cavity of the LV, compared with control hearts and hearts with HCM, APH, and HHD. However, the cardiac hypertrophy assessed by LVMI and myocyte size evaluated by the transverse diameter were similar, or rather greater, in HCM among the hypertrophic hearts, which were significantly increased compared with the control hearts.

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The oral drug regimens administered to the groups of patients at the time of biopsy are listed in Table 2. There were significant differences in the incidences of all drugs, except for $\beta$-adrenergic blockers, among the groups; the percentage of treated patients was significantly higher in the DCM and postmyocarditis groups than in the others.
**Nuclear Hypertrophy Score**

Nuclear hypertrophy was classified as normal (0), mild (1), moderate (2), and marked (3) by light and electron microscopy. Fig 2B shows the agreement between the nuclear hypertrophy score estimated by light microscopy and that by electron microscopy using the Bland and Altman method, assuring the validity of the light microscopic scoring of nuclear hypertrophy. Therefore, in the present study we used the score of the light microscopic specimens, in which immunohistochemical evaluations could also be performed using the serial sections.

The nuclear hypertrophy score was more severe in hypertrophic hearts than in nonhypertrophic hearts. As shown in Fig 3A, the nuclear hypertrophy score was significantly higher in each group of pathologic hearts (1.05±0.08 in HCM; 1.03±0.11 in APH; 1.09±0.09 in HHD; 1.18±0.11 in DCM, and 1.16±0.11 in postmyocarditis) compared with the controls (0.84±0.08). Among the pathologic hearts, the nuclear hypertrophy score was highest in the hearts with DCM and postmyocarditis, which were accompanied by ventricular dilatation and systolic dysfunction. As shown in Fig 3B, there was a similar incidence of hypertrophied nuclei with a mild or moderate grade (score 1 or 2) among all groups of hypertrophic hearts. However, the incidence of hypertrophied nuclei with a marked grade (score 3) was especially prominent in DCM (2.29±2.25%) and postmyocarditis (2.68±2.09%), both of which show ventricular dilatation and systolic dysfunction. The sensitivity and specificity of hearts with ventricular dilatation and systolic dysfunction for nuclear hypertrophy scores >1.10 were 75% and 66%, respectively, and those for the incidence of grade 3 nuclear hypertrophy >1% were 72% and 72%, respectively. A higher score of nuclear hypertrophy was accompanied by greater nuclear size (r=0.749, p<0.0001) and nuclear size-cellular size ratio (N/C ratio) (r=0.556, p<0.0001).

**Expressions of PCNA, Ki-67, SC-35, and p70⁶⁶⁶⁷K**

Myocyte nuclei that were positive for PCNA were observed in all groups including controls (Fig 4). However, we did not find any Ki-67-positive myocyte nuclei in any group. The incidence of PCNA-positive nuclei was significantly greater in the hypertrophic hearts than in the controls: 36.3±8.9% in DCM; 30.9±9.2% in postmyocarditis; 26.4±8.6% in HCM; 26.0±14.3% in APH; 25.3±8.3% in HHD; and 12.8±6.4% in the control (Fig 5). The incidence of PCNA-positive myocyte nuclei was highest in DCM and postmyocarditis among the groups. Incidences of immunohistochemically positive reactions for SC-35 and p70⁶⁶⁶⁷K showed similar patterns to that for PCNA. The incidence of the myocyte nuclei with a positive reaction was highest in DCM and postmyocarditis and significantly higher in HCM, APH and HHD compared with controls: for SC-35 and p70⁶⁶⁶⁷K, respectively, 41.0±9.4% and 45.5±9.7% in DCM; 33.9±8.5% and 34.4±8.3% in postmyocarditis; 28.2±8.3% and 30.1±9.6% in HCM; 25.1±14.1% and 30.4±14.2% in APH; 26.5±10.0% and 28.6±10.2% in HHD; and 14.0±7.1% and 16.3±7.4% in controls (Figs 4,5).

**Relationship Between Nuclear Hypertrophy and Biosynthetic Activities**

The nuclear hypertrophy score showed a strongly positive correlation (p<0.0001) with the incidence of PCNA-positive myocyte nuclei (r=0.684), and with that of SC-35-positive nuclei (r=0.681) and p70⁶⁶⁶⁷K-positive nuclei (r=0.634) (Fig 5). Thus, the specimens with a higher score of nuclear hypertrophy showed higher incidences of PCNA-, SC-35-, and p70⁶⁶⁶⁷K-positive myocyte nuclei.
There were significant correlations (p<0.0001) between PCNA, SC-35, and p70S6K expressions: r=0.956 between PCNA and SC-35; r=0.930 between PCNA and p70S6K; and r=0.940 between SC-35 and p70S6K.

**Expressions of 8-OHdG and Ref-1 and Their Relationships With PCNA Expression**

To seek the trigger(s) of increased activity of DNA repair/synthesis in hypertrophic hearts, oxidative damage of DNA and a cellular redox/DNA repair protein were investigated. All hypertrophic hearts showed higher incidences of 8-OHdG and Ref-1 compared with controls, but both 8-OHdG and Ref-1 were more greatly expressed in hearts with DCM and postmyocarditis than in the other hypertrophic hearts (Fig 6). Moreover, incidences of myocytes positive for both 8-OHdG and Ref-1 showed significant correlations with the incidence of PCNA-positive myocytes (Fig6). Fluorescence microscopy revealed that most of the myocytes positive for 8-OHdG or Ref-1 co-expressed PCNA (Figs 4G,H).

**Relationships Between Cardiac Hypertrophy, Myocyte Hypertrophy, and Nuclear Hypertrophy**

There was no significant correlation between cardiac hypertrophy (assessed by LVMI) and nuclear hypertrophy (Fig7A). Myocyte hypertrophy showed a significant correlation with nuclear hypertrophy (Fig7B1), which suggests that nuclear hypertrophy depends on myocyte hypertrophy. However, the nuclear hypertrophy score was greater in DCM and postmyocarditis than in HCM, APH, and HHD, whereas myocyte size was similar among these hypertrophic hearts. When the nuclear hypertrophy score was analyzed separately in the myocytes equal to or smaller than 20μm and in those greater than 20μm, greater scores of nuclear hypertrophy, especially grade 3, were significantly more frequently observed, even in the small sized myocytes, of the hearts with DCM and postmyocarditis (Fig7B2). Therefore, nuclear hypertrophy appeared to be a special feature of hypertrophic hearts with ventricular dilatation and systolic dysfunction, which is not always parallel to myocyte hypertrophy.

**Discussion**

The present study revealed that nuclear hypertrophy of myocytes was precisely correlated with the expressions of PCNA, SC-35, and p70S6K, independently of the etiology of hypertrophy of the heart. PCNA is a co-factor of DNA polymerase I and is required for both S-phase DNA synthesis and DNA repair. In addition, it is already known that PCNA expression can be increased without a corresponding increase in S-phase DNA synthesis. We recently reported that PCNA-positivity in the myocytes of DCM means that the myocytes are under DNA repair rather than in S-phase DNA synthesis, because those PCNA-positive myocytes were negative for Ki-67. Ki-67 is a replication-associated antigen that is a marker of DNA synthesis but not of DNA repair. The present study confirmed these
findings in other types of hypertrophic hearts in addition to DCM. We next sought the contributing factor(s) for the increased activity of DNA repair/synthesis and found that PCNA expression was strongly correlated with the expressions of 8-OHdG and Ref-1. Being oxidatively damaged, the guanosine nucleotides of the DNA are modified to form 2,5-amino-5-formamido-pyrimidine and 7,8-dihydro-8-oxoguanosine. These damaged DNA nucleotides are removed from the nucleus and the DNA is repaired by the repair mechanisms. One of the DNA repair mechanisms in oxidative modified DNA is the basic excision repair pathway in which PCNA as well as Ref-1 is involved. These DNA repair enzymes, PCNA and Ref-1, were recently reported to be increased in the nucleus of myocytes of hearts with DCM. In the present study, strong correlations were noted between expressions of PCNA, Ref-1, and 8-oxoguanosine.14 These damaged DNA nucleotides are removed from the nucleus and the DNA is repaired by the basic excision repair mechanisms. One of the DNA repair mechanisms in oxidative modified DNA is the basic excision repair pathway in which PCNA as well as Ref-1 is involved.15,16 These DNA repair enzymes, PCNA and Ref-1, were recently reported to be increased in the nucleus of myocytes of hearts with DCM.17 In the present study, strong correlations were noted between expressions of PCNA, Ref-1, and 8-OHdG, suggesting that oxidative DNA damage might contribute to increased DNA repair.

A recent study showed overexpression of SC-35 in myocytes of hearts with DCM,8 which we confirmed in the present study. An in vitro experiment reported an increase in upstream binding factor (UBF) in cultured myocytes that were rendered hypertrophic by forced contraction. UBF activates transcription of ribosomal DNA, resulting in increased ribosomal proteins. Transcription of oncogenes (eg, c-fos, c-myc) and fetal-type genes (eg, β-myosin heavy chain, β-skeletal actin, atrial natriuretic peptide) are known to be increased in experimental cardiac hypertrophy.20,21 Thus, overexpression of SC-35 may be associated with transcriptions of ribosomal DNA, oncogenes, and fetal-type genes in hypertrophied hearts. Reciprocally, the contractile myofilaments of myocytes in the heart with DCM were reported to be decreased.23-25 Thus, it is possible that transcription may be differently regulated in individual proteins. Also, the rate of degradation of the proteins may importantly affect the protein contents in the diseased hearts.

Translation efficiency from mRNA to protein is known to correlate well with phosphorylation of S6 protein, one of the ribosomal proteins. In addition, the S6 protein is phosphorylated by p70S6K.22 This kinase is activated in cardiac hypertrophy and biosynthetic activities were especially marked in hypertrophied hearts with systolic dysfunction (DCM and postmyocarditis), whereas less marked abnormalities were a feature of the other types of hypertrophied hearts without systolic dysfunction, such as HCM, APH, and HHD. Biosynthetic activity in hearts with HHD is considered to be increased in response to mechanical stretch induced by the increased wall stress. Wall stress is increased in failing hearts such as those with DCM. In addition, oxidative stress is reported to be increased and plays a pathogenic role in failing hearts; we also confirmed increased oxidative DNA damage in the present study. It is thus possible that oxidative stress, additive to mechanical stress, contributes to such marked nuclear hypertrophy and biosynthetic activities in hypertrophic hearts with systolic dysfunction (DCM and postmyocarditis).

Hypertrophied hearts can be categorized into those with systolic dysfunction showing features of low LVEF and dilatation, such as DCM, and those without it, such as HCM, compensated HHD, etc. However, both types have similar LVMI and myocyte size. Moreover, the cytoplasmic degenerative changes are similar between DCM and HCM. That is, among cardiac hypertrophy, myocyte hypertrophy, and nuclear hypertrophy, only nuclear hypertrophy can distinguish the type of cardiac hypertrophy. At present, there is no morphological marker at the cellular level that distinguishes between normal and impaired systolic function of hypertrophic hearts.28,29 That is, HCM and DCM cannot be distinguished solely by the histological findings of endomyocardial biopsies. Thus, a high incidence of marked nuclear hypertrophy of myocytes might be a special morphological feature of hypertrophic hearts with ventricular dilatation and systolic dysfunction. However, it should be cautioned that both the cell size assessed by the short-axial diameter and LVMI evaluated by echocardiography may not always correctly reflect, respectively, the cell volume and heart weight. Myocyte length was reported to be increased in failing hearts such as DCM,20 but was not examined in the present study. Also, the LVMI does not always strictly express LV weight in cases of hearts without homogeneous LV remodeling, such as HCM and APH. These should be noted as limitations of the present study.

There are several other limitations in the present study. First, small biopsy specimens do not always represent the whole myocardial lesion because the distribution of pathologic changes is not necessarily homogeneous. Second, medications were very different among the groups and their possible influence on biosynthesis in the myocyte nuclei was not ruled out.

In conclusion, nuclear hypertrophy of cardiomyocytes precisely correlated with biosynthetic activities such as DNA repair/synthesis, transcription activity, and translation efficiency, suggesting a significant linkage between structural alteration and molecular biological events in the nucleus of myocytes in human hypertrophic hearts.

Acknowledgments

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