Cardiomyopathy of the Aging Human Heart
Myocyte Loss and Reactive Cellular Hypertrophy

Giorgio Olivetti, Massimo Melissari, Joseph M. Capasso, and Piero Anversa

To determine the effects of aging on the human myocardium, 67 hearts were obtained from
dividuals who died from causes other than cardiovascular disease. The age interval examined
was 17–90 years. Regression analysis demonstrated that the aging process was characterized by
a loss of 38 million and 14 million myocyte nuclei/yr in the left and right ventricular
myocardium, respectively. This loss in muscle mass was accompanied by a progressive increase
in myocyte cell volume per nucleus in both ventricles. Left ventricular myocytes enlarged by 110
μm³/yr, whereas right ventricular myocytes increased by 118 μm³/yr, resulting in a preservation
of ventricular wall thickness. However, the cellular hypertrophic response was unable to
maintain normal cardiac mass. Left and right ventricular weights decreased by 0.70 and 0.21
g/yr, respectively. In conclusion, loss of cells and enlargement of the remaining myocytes may
represent the structural basis for the reduced compensatory capacity of the aged heart and
together may contribute to the development of myocardial dysfunction and failure in the

One of the major difficulties encountered in
the study of the effects of age on the
cardiovascular system is the differentiation
of the aging process itself from the presence
of specific disease states. Atherosclerosis, diabetes, and
ischemic heart disease are common events in hu-
mans, and the severity of these pathological
conditions increases with age. Because the contribution
of these variables to the alterations of the aged myocardium
cannot easily be separated from the aging
phenomenon alone, the changes of the heart
throughout life are therefore the result of multifac-
torial events in which aging plays an important but
indistinguishable role. There is no temporal refer-
ence point that can be used to distinguish between
maturational changes beyond sexual maturity and the
aging changes per se, since they are both controlled
by time as a critical factor. Thus, the issue of
whether aging of the heart has to be regarded as a
successful adaptation or as a progressive disease state
remains a matter of controversy, with data being
accumulated in support of the former and the
latter. However, it is well established that in both
humans and animals myocyte proliferation occurs
shortly after birth and that the growth of the
heart, during the relatively early phases of postnatal
life and long before sexual maturity is reached, is
controlled by hypertrophy of myocytes and hyper-
plasia of capillary endothelial and interstitial
fibroblasts. Although DNA synthesis with ploidy
formation in adult human cardiac myocytes has been
described, this phenomenon does not alter the
number of muscle cells and/or muscle cell nuclei in
the tissue, so that the total number of myocytes or
myocyte nuclei in the ventricle can be used as an
absolute reference parameter for the evaluation of
the effects of aging on the myocardium. This
approach was used in the present investigation to
determine whether myocyte cell loss accompanies
the life span of humans and may constitute the underly-
ing cause for the occurrence of congestive heart
failure in the elderly.

Materials and Methods

Study Design and Selection Criteria

Sixty-seven human hearts were collected from a
total number of 1,176 autopsies performed at the
University Hospital of Parma Medical School during
1988 and 1989. All 67 hearts were collected within 24
hours after death. These cases were assumed to
represent normal aging according to preautopsy cri-
teria, autopsy criteria, and histological criteria, which
are listed below.

Preautopsy criteria for inclusion in the study. These
criteria were as follows: 1) sudden death associated
with traumatic injury, 2) death within 5 days after hospitalization in which medical history and laboratory and physical findings excluded cardiovascular disease processes, 3) no previous medical record of hypertension, diabetes, or ischemic heart disease, 4) body weight not in excess of 20% or lower than 20% of the optimal weight according to sex, height, and age, and 5) absence of clinically recognized systemic disorders such as malignant neoplasia, connective tissue diseases, genetically linked illnesses, and acquired immunodeficiency syndrome.

**Autopsy criteria for exclusion from the study.** These criteria were as follows: 1) atherosclerosis of the major coronary arteries resulting in discrete reductions of vessel diameter >30% (this assessment was performed by sectioning the coronary arteries perpendicular to their course with cuts ~0.5 cm apart and comparing vessel diameter at the atherosclerotic region with that above and below the atherosclerotic plaque; when a constricted site was found, a segment of the vessel was removed, maximal and minimal internal diameters were determined using a dissecting microscope having an ocular micrometer accurate to 0.05 mm, and the geometric mean value was calculated; a similar procedure was followed above and below the constriction), 2) severe atherosclerosis of the epicardial arteries and aorta with its major branches, 3) aortic aneurysms, 4) valvular abnormalities including atherosclerotic lesions at the insertion of the cups, 5) acute and/or healed myocardial infarction, 6) heart weight >500 g, which has been considered to correspond to pathological hypertrophy, 7) diffuse emphysema and chronic inflammatory processes of the respiratory system, and 8) presence of an unrecognized malignant neoplasm with multiple metastatic localizations.

**Histological criteria for exclusion from the study.** These criteria were as follows: 1) neoplasms of the hematopoietic system, 2) amyloidosis, tuberculosis, and sarcoidosis, 3) diffuse interstitial and perivascular fibrosis of the myocardium, 4) thickening and hyalinosis of the intermediate-sized vessels of the coronary tree, 5) multiple foci of replacement fibrosis greater than 2 mm in diameter, 6) presence of inflammatory cells in the myocardial interstitium, and 7) sites of myocytolytic and contraction band necrosis.

By applying these three sets of criteria, the initial selection of 238 cases was reduced by 103 cases at the autopsy. After histological examination, only 67 (44 males and 23 females) of the remaining 135 hearts were used for quantitative analysis. Importantly, the selection process using light microscopic observation of tissue sections was accomplished in a coded fashion so that the two observers (G.O., M.M.) involved in the screening were unaware of the characteristics of the cases under study.

Briefly, the major causes for exclusion at the gross morphological level were severe atherosclerosis of the aorta and epicardial coronary arteries, including coronary occlusion and myocardial infarction (81 cases), cardiac hypertrophy with heart weight >500 g (four cases), severe pulmonary emphysema (16 cases), and diffuse neoplasia (two cases). By histological examination, 66 cases were excluded because of diffuse morphological damage of the myocardium, and two cases were excluded as a result of cardiac amyloidosis.

**Preparation of Myocardial Specimens**

After excision of the heart, the great vessels were trimmed off, the blood was removed by opening atrial and ventricular chambers, and the weight was recorded. This initial heart weight measurement included the epicardial fat and both atria. Subsequently, the atria were dissected along the atrial ventricular groove, and the coronary arteries were cut perpendicular to their course for the assessment of the degree of atherosclerosis. The epicardial fat was then carefully removed, the valves were cut free, and the weights of the left ventricle inclusive of the septum and right ventricular free wall were determined. Ventricular mass volume was then computed by dividing ventricular weight by the specific gravity of muscle tissue, 1.06 g/ml.

The two ventricles were sliced into nine to twelve 10-mm-thick sections, perpendicular to the major axis of the heart from the apex to the base. Wall thickness was estimated by averaging 10 equally spaced measurements from each of the two middle tissue sections of each ventricle, which represented the portion of the ventricle halfway between the base and the apex of the heart. These determinations were restricted to the free wall of both ventricles. Moreover, the trabeculae carnea and papillary muscles attached to the wall were not included in the assessment of wall thickness. Subsequently, the two middle slices of the free wall of each ventricle were cut radially to obtain tissue fragments extending from the endocardial to the epicardial surface. These samples were fixed in 10% buffered formalin and embedded in glycol methacrylate. At the time of embedding, each specimen of the left ventricle was divided in two regions comprising the epimyocardium and endomyocardium. This procedure was necessary because of the difficulty of embedding the thick left ventricular wall in a single mold. The fragments of the right ventricle were left intact. An additional sampling of two tissue blocks from each slice of each ventricle and two from the interventricular septum was obtained and embedded in paraffin for further estimation of the presence of myocardial fibrosis and tissue injury. The methacrylate-embedded material was used for quantitative analysis of the myocardium (see below).

**Tissue Sampling**

Twelve randomly chosen plastic-embedded tissue blocks, six from the endomyocardium and six from the epimyocardium of each left ventricle, were sectioned at a thickness of 1.0 μm using a JB 4 microtome (Du Pont, Newtown, Conn.) and stained with hematoxylin and eosin. Four blocks from the right ventricular free wall of each heart were sectioned...
and stained in an identical manner. The two blocks of tissue embedded in paraffin from each slice of each ventricle were also sectioned and stained with hematoxylin and eosin and trichrome. Thus, the qualitative assessment of myocardial structural integrity was performed in 14–20 separate sections of the free wall of each ventricle and septum. This sampling was assumed to provide an accurate evaluation of histological damage in each heart.

Morphometric sampling at a magnification of ×1,000 consisted of counting the total number of myocyte nuclear profiles [N(n)] in a measured area (A) of tissue sections in which cardiac muscle fibers were sectioned transversely. A square tissue area equal to 10,036 μm² was delineated in the microscopic field by an ocular reticle (No. 105844, Wild Heerbrugg Instruments, Inc., Farmingdale, N.Y.) containing 42 sampling points. One hundred fields, 50 from the endomyocardium and 50 from the epicardium, were evaluated in each ventricle of each heart to determine the mean number of nuclear profiles per unit area of myocytes [N(n)].

The volume percent of myocytes in the tissue [V(m)] was obtained by counting the fraction of points overlaying the myocyte compartment in each of the 100 fields examined.18,23 Similarly, the volume fraction of the interstitium was evaluated from the number of points lying over this tissue component.

Average nuclear length (Dn) was determined from 50 measurements from each region of each ventricle, which were made at a magnification of ×1,250 in longitudinally oriented myocytes and viewed with a microscope having an ocular micrometer accurate to 0.5 μm. Only those nuclei in which the nuclear envelope was sharply defined at both ends and in which clusters of mitochondria were clearly visible in the areas adjacent to the nuclear edges were measured.18,23

The regional data were then combined to yield the average measurement of the number of myocyte nuclei per unit volume of myocytes [N(n)] in the ventricle using the equation 18,23

\[ N(n)_v = N(n)_i / D_n \]  

The aggregate volume of myocytes in the ventricle [V(m)] was then derived from the ventricular volume measurement (V) and V(m):

\[ V(m) = V \times V(m)_v \]  

The total number of myocyte nuclei in the ventricle [N(n)] was computed from N(n) and V(m):

\[ N(n)_v = N(n) \times V(m)_v \]  

V(m) divided by N(n) yields the average myocyte cell volume per nucleus [V(m)] in the ventricle in each heart:

\[ V(m)_n = V(m)_v / N(n)_v \]  

**Statistical Analysis**

All morphometric data were collected blindly, and the code was broken at the end of the experiment. Correlation coefficients between each set of data and age were determined by linear regression analysis.24 Comparisons between slopes were made by the analysis of covariance,24 and values of p<0.05 were considered to be significant.

**Results**

During a period of −2 years, 1,176 autopsies were performed at the University Hospital of Parma Medical School. This number included the autopsies executed in the Department of Pathology as well as those carried out by the medical examiner. Sixty-seven cases, which represented 5.7% of the autopsies, were considered to be characteristic of normal aging according to the criteria described in “Materials and Methods.” In these patients, death was not the result of primary heart disease processes or the consequence of major risk factors of coronary artery disease, including hypertension, diabetes, obesity, and/or severe atherosclerosis. The autopsy report and the histological examination of all organs excluded diffuse, metastatic malignant neoplasms and chronic inflammatory states.

Tables 1 and 2 show the characteristics of the patients studied within different decades and the patient distribution according to the terminal event.
In the 39 individuals who died suddenly as a result of traumatic injury, a complete medical history could not be obtained. Their suitability for investigation was based on the absence of a previous hospital record and on the fact that the autopsy failed to reveal underlying pathological processes, with the exception of the damage associated with the acute trauma. Since, from available information, systemic hypertension could not always be excluded, careful histological examination of the kidney and brain was performed. In no instance were lesions of intermediate and small-sized arteries and arterioles of brain and kidney tissues found, strongly suggesting that hypertension was not present in these individuals. Acute infection was found to be present in 10 of the 67 cases, whereas brain hemorrhage, pulmonary thromboembolism, and gastrointestinal hemorrhage occurred in six, eight, and four patients, respectively. These 28 cases, in which death occurred in association with a disease condition, were included in the study since the pathological states developed only terminally and, at most, had little effect on the heart.

The relation between body weight and aging in the 67 cases examined indicated that body weight decreased by 113 g/yr, but this change was not statistically significant. By plotting the individual values of heart weight inclusive of the atria and epicardial fat as a function of age, it was found that heart weight increased by an average 0.36 g/yr (data not shown). However, this increment was also not statistically significant.

When the muscle mass of the left ventricle and septum combined were examined in the absence of epicardial fat, a statistically significant decrease in this weight parameter was demonstrated with aging (Figure 1). From the value of the slope it could be seen that left ventricular and septal weight diminished by 0.70 g/yr. A similar phenomenon was observed in the right ventricle (Figure 2), but the decrement in weight was only 0.21 g/yr. Thus, the reduction in weight of the left ventricle was threefold greater than that of the right ventricle ($p<0.001$).

Although ventricular weight and body weight changed in a similar fashion with age, the ratios of left ventricular weight/body weight and right ventricular weight/body weight continued to decrease from 17 to 90 years of age. The change in the left side of the heart ($-0.006$ g/kg/yr) was greater than that in the right side ($-0.002$ g/kg/yr) ($p<0.001$).

The effects of aging on the thickness of the left and right ventricular free walls were also examined. In both instances, wall thickness remained essentially constant up to 90 years of age. Throughout the life interval studied, wall thickness measured 13.6±1.5 mm in the left ventricle and 4.9±1.1 mm in the right ventricle.

Light microscopic examination of the methacrylate- and paraffin-embedded tissue sections failed to reveal foci of replacement fibrosis $>2$ mm in diameter or diffuse interstitial and perivascular fibrosis. It should be pointed out, however, that isolated areas of reparative fibrosis were occasionally seen in the endomycocardium of the left ventricle and the left portion of the interventricular septum. In no case were amyloid deposits detected in the wall of the intramural branches of the coronary tree and/or in the interstitium.

The morphometric analysis of the volume fractions of myocytes and interstitium in the myocardium demonstrated that the muscle cell compartment varied with aging (Figures 3 and 4). This parameter was found to increase in both ventricles. Consequently, a statistically significant decrease was measured in the volume percent of the interstitium as a function of age (data not shown). However, the lack of perfusion fixation in the preparation of the tissue prevented a detailed estima-
tion of the vascular and nonvascular components of the extracellular space of the myocardium.

The primary determinations used for the quantitative measurements of the changes in myocyte cell size and number involved the evaluation of the number of myocyte nuclear profiles per unit area of myocytes. In both ventricles, this parameter decreased with age, but this change was statistically significant only in the right ventricle (left ventricle, 1.1/mm²/yr, r=0.20, p>0.05; right ventricle, 1.8/mm²/yr, r=0.31, p<0.05). In contrast, the longitudinal diameter of myocyte nuclei increased, but only in the left ventricle (left ventricle, 0.015 μm/yr, r=0.26, p<0.05; right ventricle, −0.006 μm/yr, r=0.15, p<0.2). These changes resulted in a reduction in the number of myocyte nuclei per unit volume of myocytes with aging in both ventricles. In the left side, the numerical density of myocyte nuclei per cubic millimeter of myocytes diminished by 132 nuclei/yr (r=0.28, p<0.05) and in the right side by 143 nuclei/yr (r=0.27, p<0.05).

By plotting the total number of myocyte nuclei in the left ventricular myocardium of each heart as a function of age (Figure 5), it was found that these two variables were inversely related. Aging was accompanied by a decrease in myocyte nuclei of 38 million/yr. A comparable analysis in the right ventricle showed a loss of 14 million myocyte nuclei/yr (Figure 6). By comparing the slopes of the two ventricles, a 2.7-fold greater magnitude of myocyte nuclei loss was detected in the left myocardium; this difference was statistically significant (p<0.001).

Figure 7 depicts the changes in myocyte cell volume per nucleus with aging in the left ventricle. This cellular parameter increased by 110 μm³/yr, from 17 to 90 years of age. Myocyte cell volume per nucleus was also augmented in the right ventricle, and the degree of enlargement was 118 μm³/yr (Figure 8).

To determine the relation between myocyte growth and ventricular dimension, the ratio of myocyte cell volume per nucleus/ventricular volume was calculated in each heart for both ventricles. In the left ventricle, the positive linear correlation demonstrated an augmentation of this ratio of 1.77 μm³/ mm³/yr (r=0.48, p<0.001). A larger change in this slope was measured in the right ventricle where the myocyte cell volume/ventricular volume ratio increased by 4.46 μm³/ mm³/yr (r=0.45, p<0.001). The differential response of the left and right sides of the heart was statistically significant (p<0.001). Moreover, these two linear correlations demonstrate that ventricular volume changes with aging cannot be equated with myocyte cell changes with aging.
Aging and Ventricular Weight

It is a general conviction that cardiac hypertrophy develops with age. Studies in humans have suggested that heart weight increases by 1 g/yr in men and 1.5 g/yr in women. These observations are in agreement with the current study, in which a consistent loss in myocardial mass was found. However, in previous reports, little attention was given to the effects of pathological states of the heart and blood vessels on cardiac size. Normal aging was not distinguished from the superimposition of hypertension, valvular disorders, diabetes, and ischemic heart disease, which all increase in the elderly. Moreover, these aging-associated events affect the absolute weight of the heart and its major subdivisions.

Another potential source of difference between the current results and previous observations may lie with the modality of evaluation of the heart. We carefully dissected the epicardial fat tissue before weight measurements, whereas it was kept as part of the ventricular mass in the larger population studies. In addition, a recent analysis of data from the Framingham study indicates that cardiac hypertrophy is not a necessary consequence of the aging process of the heart in humans. Such a conclusion was derived from echocardiographic evaluation of left ventricular mass in healthy individuals.

Although a reduced capacity of the aged heart to adapt to a mechanical stress has been repeatedly shown, cardiac pump performance at rest is preserved in the elderly. Thus, there is no functional basis supporting the possibility of a hemodynamic overload with age, which could sustain growth mechanisms in the myocardium and organ hypertrophy. Similar observations have been made in different animal models, in which normal physiological responses of the aged heart have been found in terms of global cardiac function, muscle mechanics, and cell mechanics. These in vivo and in vitro studies tend to favor the concept that the alterations in the isotonic and isometric contraction characteristics of the aging myocardium represent adaptive compensatory phenomena that result in energy preservation. It should be pointed out, however, that prolongation of contraction duration and depression in the velocity of shortening and relengthening of muscles from aging rat hearts have been interpreted as factors that may increase the magnitude of systolic and diastolic stress in the intact ventricle. This condition would provide a mechanical stimulus for myocardial growth.

Aging and Myocyte Number

The present results have demonstrated that 38 million and 14 million myocyte nuclei are lost each year from the left and right ventricles during the life span of humans beyond sexual maturity. Because the number of nuclei in adult human ventricular myocytes does not change in the absence of severe cardiac hypertrophy, these losses in nuclei correspond to equivalent losses in myocytes. This kind of evaluation is based on the assumption that muscle cells do not regenerate in the adult aging myocardium and that the cells are lost in a permanent manner without the possibility of myocyte nuclear and cellular hyperplasia when adulthood is reached.

Although ploidy formation may take place in the aging human heart, this phenomenon at the chromosome level increases the amount of DNA per nucleus, but it does not imply alterations in the
number of myocyte nuclei in the tissue. However, polyploidy could also result from fusion of nuclei in the cells. Were myocyte nuclear hyperplasia to occur, the calculations derived here would represent an underestimation of the magnitude of cell loss with aging. In contrast, increases in the number of multinucleated myocytes with time would result in an overestimation of the extent of myocyte loss derived from nuclear values. In this regard, cardiac hypertrophy has been shown to be accompanied by an alteration in the proportion between mononucleated and binucleated ventricular myocytes in humans.33,34 Binucleated cells are a small fraction of the myocyte population in the normal adult heart, but they increase significantly in hypertrophy (for review see Reference 13). Since cellular hypertrophy develops with aging, it cannot be excluded that variations in nuclear number within myocytes may have concomitantly occurred.

The data in Figures 5 and 6 indicate that the hearts of young adults from 17 to 30 years of age, possess an average value of 6.0×10^2±1.8×10^2 and 2.2×10^2±0.7×10^2 myocyte nuclei in the left and right ventricular myocardium, respectively. Similar results have been previously reported,14,35 although nuclear measurements were interpreted as cellular values. Between 65 and 90 years of age, 4.0×10^2±1.3×10^2 and 1.4×10^2±0.4×10^2 nuclei were still present in the left and right ventricles, respectively. Thus, these changes imply a 33% and 36% aggregate loss of nuclei in the left and right ventricles, respectively, during these age intervals. The factors responsible for the loss of nearly 35% of the cells in the ventricles are at present unknown. Ischemic injury may be a likely mechanism, since it has been suggested by Rakusan13 that capillary density decreases with aging. The reduced concentration of capillaries can be expected to produce a decrease in the endothelial surface accessible for oxygen exchange in the tissue and a greater diffusion distance for oxygen transport to the myocytes.36 These capillary characteristics may represent the structural basis for local ischemia, resulting in scattered loss of myocytes throughout the wall in the aging heart. A similar detrimental effect of aging on the capillary microvasculature and the ventricular myocytes has been described in rats.3,5,15,19-21 Moreover, a decrease in coronary vascular reserve and an increase in minimal coronary vascular resistance have been reported in the same animal model,8 suggesting an increased vulnerability potential of the myocardium to ischemic episodes with aging.

The loss of ventricular myocytes with aging documented here is in contrast with previous observations in human hearts from birth to senescence.42,43 The number of cells in these studies was found to remain constant in both the left and right ventricles up to 90 years of age. However, hearts with concentric and eccentric hypertrophy associated with valvular defects, hypertension, chronic pulmonary diseases, and congenital abnormalities were included in the quantitative analysis.42,43 Although this difference is difficult to explain, the possibility may be raised that a cellular hyperplastic response in the hypertrophied ventricles19 may have contributed to mask the phenomenon of cell loss demonstrated in the present investigation.

Aging and Myocyte Reactive Hypertrophy

The current results show that myocyte cell volume per nucleus increased as a function of age but that the magnitude of cellular hypertrophy was inadequate to preserve ventricular weight. This observation indicates that the changes in ventricular mass cannot be assumed to reflect comparable adaptations at the cellular level and that the lack of organ hypertrophy does not exclude cellular hypertrophy. Moreover, this growth response of the myocyte population may provide the structural basis for the maintenance of wall thickness with aging.

The mechanisms implicated in myocardial cellular hypertrophy in the aging human heart are currently unknown. There are no functional alterations that can be linked to the increase in myocyte volume. Systemic and cardiac hemodynamic parameters as well as body mass were not found to be abnormal with aging. It should be pointed out, however, that loss of myocytes in the ventricle can be expected to generate an increase in work load on the surviving cells proportional to the amount of myocyte loss.36 A similar phenomenon has been shown to be operative in experimental cardiomyopathies,44 in aging,5 and after acute45 and chronic23 myocardial infarction in animal models. Thus, the diffuse focal loss of cardiac cells observed in the human heart would leave a larger stress on the remaining myocytes, which undergo reactive hypertrophy in response to the increased load. Since this process occurs in the presence of normal arterial and ventricular pressures, the resulting condition can be defined as normotensive overload at the cellular level.

It is not clear whether cell loss with aging leads to a pressure and/or volume overload stress on the myocardium. Previous reports in animals, however, have indicated that the alterations in muscle mechanics,46,47 in coronary blood flow hemodynamics,8 and in the quantitative properties of myocyte shape59 with aging are consistent with an augmentation in the afterload on the myocyte population. The preservation of ventricular wall thickness in the aging human hearts is also suggestive of a prevailing expansion in the transverse diameter of the surviving cells and a pressure-overload type of hemodynamic stress.36

The current results have demonstrated that the aging process of the heart in humans is characterized by an increase in the volume fraction of myocytes in the myocardium and a corresponding decrease in the relative amount of the interstitium. A similar adaptation of the ventricular tissue has been shown to occur in experimental pressure-overload hypertrophy.18 It should be pointed out, however, that the reduction of the interstitium does not imply a decrease of either the relative and absolute concentration of connective tissue. Although an expansion in
the content of collagen has been suggested to take
place in the human heart,\textsuperscript{48,49} contrasting
results have also been reported.\textsuperscript{60} Thus,
whether aging in humans is associated with significant changes in myocardial
collagen remains a matter of controversy.

**Limitations of the Study and Conclusions**

There are several limitations in the current
investigation that must be acknowledged: 1) The number
of cases was relatively small and gender differences
could not be evaluated. 2) Medical history was not
available in a considerable number of patients, and in
these cases the possibility of an underlying disease
process could not be excluded with certainty in spite
of a complete anatomic and histological examination.
3) The effects of diet, smoking habits, and living
conditions could not be evaluated. All these factors
may have influenced the accumulated results.

Although these limitations have to be considered,
the results of the present study suggest that aging of the
human heart appears to be characterized by myocyte
loss, reactive myocyte cellular hypertrophy, and reduc-
tion in ventricular mass. These cellular processes may
represent the underlying cause for the onset of myo-
cardial dysfunction and failure in the elderly.

**References**

2. Lakatta EG, Yin FCP: Myocardial aging: Functional alter-
ations and related cellular mechanisms. \textit{Am J Physiol} 1982;242:
H927–H941
3. Lakatta EG, Mitchell JH, Pomerance A, Rowe GG: Human aging:
change in structure and function. \textit{J Am Coll Cardiol} 1987;10:42A–47A
H: Morphological and contractile characteristics of rat myo-
cytes from maturation to senescence. \textit{Am J Physiol} 1989;257:
H259–H265
loss and myocyte hypertrophy in the aging rat heart. \textit{J Am Coll Cardiol} 1986;8:1441–1448
Effect of age on the development of cardiac hypertrophy
produced by aortic constriction in the rat. \textit{Circ Res} 1987;61:
337–345
adaptation to volume overload in the rat. \textit{J Clin Invest} 1988;
81:1850–1857
in morphology and function of myocardial cells in Fischer 344
9. Anversa P, Puntillo E, Nikitin P, Olivetti G, Capasso J,
Sonnenblick EH: Effects of age on the mechanical and structural
properties of myocardium of Fischer 344 rats. \textit{Am J Physiol} 1989;
256:H1440–H1449
10. Claycomb WC: Biochemical aspects of cardiac muscle differ-
etiation: Decarboxylase activity synthesis and nuclear and
cytoplastic deoxyribonucleic acid polymerase activity. \textit{J Biol
Chem} 1975;250:3229–3235
postnatal development in the left and right ventricular myo-
cardium in the rat: I. Hypertrophy, hyperplasia, and bunucle-
of the Heart in Health and Disease." New York, Raven Press,
Publishers, 1984, pp 1–24
13. Rakusen K: Cardiac growth, maturation and aging, in Zak R
(ed): "Growth of the Heart in Health and Disease." New York,
14. Adler CP, Costabel U: Cell number in human heart in
atrophy, hypertrophy, and under the influence of cytostatics.
\textit{Recent Adv Stud Cardiol Struct Metab} 1975;6:343–355
15. Sandritter W, Adler CP: Polyploidyization of heart muscle
cells as a prerequisite for heart growth and numerical
hyperplasia in heart hypertrophy. \textit{Recent Adv Stud Cardiol Struct Metab}
1978;12:115–127
16. Takano T, Nayanishi K, Fukuda M, Fujita S: Cytofluori-
metric nuclear DNA determinations in infant, adolescence,
17. Vliegen HW, Vossepoel AM, Laarse A, Eulderink F, Corne-
lisse CF: Methodological aspects of flow cytometric analysis
of DNA polyplody in human heart tissue. \textit{Histochemistry} 1986;
84:348–354
Anversa P: The cellular basis of wall remodeling in long term
19. Linzbach AJ: Heart failure from the point of view of quanti-
tative anatomy. \textit{Am J Cardiol} 1960;5:370–382
metric study on 55 human hearts. \textit{J Mol Cell Cardiol} 1971;2:99–110
ventricular hypertrophy: A cytometric study on 42 human
hearts. \textit{J Mol Cell Cardiol} 1977;9:763–775
22. Mendez J, Keys A: Density and composition of mammalian
muscle. \textit{Metabolism} 1969;9:184–188
infarction in rats: Infant size, myocyte hypertrophy, and
Iowa, Iowa State University Press, 1980, pp 175–193
25. Linzbach AJ, Akuomoa-Boateng E: Die Alternsveranderun-
gen des menschlichen Herzens: I Das Herzgewicht im Alter.
\textit{Klin Wochenschr} 1973;51:156–165
26. Smith HL: The relation of the weight of the heart to the weight
of the body and the weight of the heart to age. \textit{Am Heart J}
1928;4:79–93
27. Hegglin R: Uber Organvolumen und Organgewicht: Nebst
Bemerkungen uber die Groebenbestimmungsmethoden. \textit{Z
Konstitutionslehre} 1934;18:110–134
weight of the human heart: I. Normal cases. \textit{Arch Pathol}
1959;68:58–73
29. Dannenberg AL, Levy D, Garrison RJ: Impact of age on
echocardiographic left ventricular mass in a healthy
population (the Framingham Study). \textit{Am J Cardiol} 1989;64:
1066–1068
incidence of isoprotein-induced ventricular fibrillation in
EG: Use of fibul length to quantify cardiac hypertrophy:
Application in the aging rat. \textit{Am J Physiol} 1982;243:
H941–H947
32. Yin FCP, Spurgeon HA, Weisfeldt ML, Lakatta EG: Mechani-
cal properties of myocardium from hypophrophied rat hearts:
A comparison between hypertrophy induced by senescence
33. Horta W: Quantitative histologische Untersuchungen an
34. Schneider R, Pfister P: Die Zahl der Kerne in isolierten Zellen
des menschlichen Myocards. \textit{Virchows Arch [B]} 1973;12:
238–258
35. Sandritter W, Adler CP: Numerical hyperplasia in human
heart hypertrophy. \textit{Experimentia} 1971;27:1435–1437
of the myocardium during physiologic growth and induced
cardiac hypertrophy. \textit{J Am Coll Cardiol} 1986;7:1140–1149

Olivetti et al Aging of the Human Myocardium
Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy.
G Olivetti, M Melissari, J M Capasso and P Anversa

Circ Res. 1991;68:1560-1568
doi: 10.1161/01.RES.68.6.1560

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/68/6/1560

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/