Cardiac Hypertrophy Is Not a Required Compensatory Response to Short-Term Pressure Overload

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Background—Cardiac hypertrophy is considered a necessary compensatory response to sustained elevations of left ventricular (LV) wall stress.

Methods and Results—To test this, we inhibited calcineurin with cyclosporine (CsA) in the setting of surgically induced pressure overload in mice and examined in vivo parameters of ventricular volume and function using echocardiography. Normalized heart mass increased 45% by 5 weeks after thoracic aortic banding (TAB; heart weight/body weight, 8.3±0.9 mg/g [mean±SEM] versus 5.7±0.1 mg/g unbanded, P<0.05). Similar increases were documented in the cell-surface area of isolated LV myocytes. In mice subjected to TAB+CsA treatment, we observed complete inhibition of hypertrophy (heart weight/body weight, 5.2±0.3 mg/g at 5 weeks) and myocyte surface area (endocardial and epicardial fractions). The mice tolerated abolition of hypertrophy with no signs of cardiovascular compromise, and 5-week mortality was not different from that of banded mice injected with vehicle (TAB+Veh). Despite abolition of hypertrophy by CsA (LV mass by echo, 83±5 mg versus 83±2 mg unbanded), chamber size (end-diastolic volume, 33±6 μL versus 37±1 μL unbanded), and systolic ejection performance (ejection fraction, 97±2% versus 97±1% unbanded) were normal. LV mass differed significantly in TAB+Veh animals (103±5 mg, P<0.05), but chamber volume (end-diastolic volume, 44±6 μL), ejection fraction (92±2%), and transstenotic pressure gradients (70±14 mm Hg in TAB+Veh versus 77±11 mm Hg in TAB+CsA) were not different.

Conclusions—In this experimental setting, calcineurin blockade with CsA prevented LV hypertrophy due to pressure overload. TAB mice treated with CsA maintain normal LV size and systolic function. (Circulation. 2000;101:2863-2869.)

Key Words: hypertrophy ■ cyclosporine ■ calcineurin

Cardiac hypertrophy is a homeostatic response to elevated afterload that develops in response to pressure or volume overload, loss of contractile mass (prior infarction), or mutations of contractile (and other) proteins. This tenet is based on the long-held principle that ventricular geometry and wall thickness change to maintain systolic stress within normal limits. Although hypertrophy is thought to compensate for hemodynamic stress, echocardiographically documented myocardial hypertrophy is an independent risk factor for cardiovascular morbidity and mortality. Because hypertrophy imparts coincident risk of heart failure and sudden death stemming from malignant ventricular arrhythmias, the distinction between "compensatory" and pathological hypertrophy is uncertain.

A number of stimuli are known to induce cardiomyocyte hypertrophy in vitro. These primary stimuli, which include hormones, cytokines, growth factors, vasoactive peptides, and catecholamines, trigger intricate reaction cascades with multiple interacting branching points. Studies in vivo using a physiologically relevant stimulus (pressure overload) have identified 4 means of preventing cardiac hypertrophy apart from lowering blood pressure: inhibition of ACE, Gαq, calcineurin, or c-Jun NH2-terminal kinase.

Calcineurin participates in hypertrophic signal transduction in models of cardiac and skeletal muscle biomechanical stress. In this study, we used cyclosporine (CsA), a specific inhibitor of calcineurin, as a tool to examine morphological and functional effects of pressure overload on the heart in the presence and absence of left ventricular hypertrophy (LVH). We tested the classic hypothesis that hypertrophy is a necessary compensatory mechanism for pressure overload by analyzing myocardial function in vivo by echocardiography.

Methods

Thoracic Aortic Banding

Increased pressure in the proximal aorta was induced by means of thoracic aortic banding (TAB) (Figure 1A) according to protocols approved by the institution’s Animal Care and Use Committee. Male mice (C57Bl6, 6 to 8 weeks old) were anesthetized with ketamine (100 mg/kg IP) plus xylazine (5 mg/kg IP). The mice were orally

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This article has an Online-only Figure, which can be found at http://www.circulationaha.org

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Conscious sedation was achieved with midazolam 0.2 to 0.3 mg SC. Echocardiography was performed using a 13-MHz transducer (Sequoia 256, Acuson, Mountain View, Calif) connected to a high-resolution video recorder (S-VHS). Mice were intubated with 20-gauge tubing and ventilated (Harvard Apparatus Rodent Ventilator, model 687) at 120 breaths per minute (0.1-mL tidal volume). A 3-mm left-sided thoracotomy was created at the second intercostal space. The transverse aortic arch was ligated (7-0 Prolene) between the innominate and left common carotid arteries with an overlying 27-gauge needle, and then the needle was removed, leaving a discrete region of stenosis. The chest was closed, and the left-sided pneumothorax was evacuated. Some mice were subjected to a sham operation in which the aortic arch was visualized but not banded. Perioperative (24 hours) and 1-week mortalities were each <10%.

On the morning of postoperative day 1, banded and sham-operated mice were randomized to receive either CsA 25 mg/kg SC twice daily or an equal volume of vehicle SC twice daily. Postmortem blood samples were collected, and CsA trough levels were 2.6 ± 0.2 μg/mL (n = 11), a level 150-fold higher than the IC50 for calcineurin inhibition in mice (18 μg/L) and higher than that reported to inhibit 90% of total calcineurin phosphatase activity in the heart.21,19,20

Hemodynamics and Morphology

In 11 mice anesthetized with ketamine (90 mg/kg IP) and acepromazine (1.8 mg/kg IP), the right and left carotid arteries were exposed and cannulated with fine catheters pulled from Microrenathane tubing. Blood pressure was recorded simultaneously in both carotid arteries. After the study period, the heart was removed from heparinized (500 U) mice euthanized with a lethal dose of pentobarbital (150 mg/kg). The heart and 1 cm of aorta (including the stenotic segment) were rapidly excised. The banding ligature was removed, and the heart was blotted dry and weighed. Data are reported as heart mass (rather than LV mass) to allow for retrograde-perfusion enzymatic dissociation of myocytes.21 The surface area of a 2D silhouette of the myocyte was estimated by measurement of the length and width of 10 randomly selected myocytes from endocardium-enriched and epicardium-enriched fractions. Our reported 2D surface area (length × width) is directly proportional to the surface area of a cylinder (2πr × radius × length).

Echocardiography

Conscious sedation was achieved with midazolam 0.2 to 0.3 mg SC. The anterior chest was shaved, and prewarmed ultrasonic gel was applied. Views were taken in planes that approximated the parasternal short-axis view (chordal level) and the apical long-axis view in humans. The apex was visualized in all mice. Transthoracic echocardiograms were recorded with a 13-MHz probe on a Sequoia 256 Acuson echocardiograph at a frame rate of 162 frames per second.

Diastole, designated as the time when LV volume was greatest, was identified in both short- and long-axis projections. In the short-axis view, the endocardial and epicardial silhouettes were manually traced by use of the “leading edge–to–leading edge” convention. The papillary muscles were not visualized in the chordal level short-axis views we obtained. In the long-axis projection, LV length was measured for both endocardial and epicardial surfaces by measuring from each respective location at the cardiac apex to the center of the mitral valve plane. LV mass and volumes were calculated by the area-length method.22 Heart rate was determined by measuring cycle length of pulse-wave Doppler interrogation of mitral inflow.

In 11 mice of 6 to 8 months old. After echocardiographic examination, the animals were euthanized, and left ventricles were dissected, blotted dry, and weighed.

Statistical Methods

Data are reported as mean ± SEM. Statistical significance was analyzed by Student’s unpaired t test or 1-way ANOVA followed by Bonferroni’s method for post hoc pairwise multiple comparisons. Statistical significance was defined as a value of P < 0.05.

Results

Cardiac Hypertrophy in Pressure-Overload Mice

TAB produced a large pressure gradient between the left and right carotid arteries (Figure 1B; peak systolic gradient, 70 ± 14 mm Hg; n = 6). Measurements at different times after surgery (n = 11, 4 hours to 5 weeks) revealed no significant change in pressure gradients over time.

During the 5 weeks after banding, heart mass increased 66%, from 135 ± 3 to 224 ± 28 mg (P < 0.05). The mice grew...
and gained weight during the course of the study, and as a control, we measured heart mass as a function of body mass (HW/BW). HW/BW increased from 5.7 ± 0.1 to 8.3 ± 0.9 mg/g (45% increase, P < 0.05) (Figure 1C). Other methods of controlling for the size of the mouse gave similar results. Heart weight normalized to tibia length (HW/T) increased 62%, from 8.0 ± 0.2 to 13.0 ± 0.7 mg/mm, P < 0.05) (Figure 1D). Normalized heart mass did not increase significantly in sham-operated mice killed at 5 weeks (HW/BW, 5.57 ± 0.01; HW/T, 8.0 ± 0.14; n = 20; Figures 1C and 1D).

Total heart length (base to apex) normalized to tibia length increased from 0.46 ± 0.01 to 0.55 ± 0.02 mm/mm (P < 0.05). Heart weight measured at the level of the AV groove and normalized to tibia length increased from 0.325 ± 0.007 to 0.40 ± 0.02 mm/mm (P < 0.05). ECG in alert, unrestrained mice revealed resting heart rates that were similar (655 ± 82 bpm, n = 3) to those of control mice (668 ± 30 bpm, n = 10).

Increases in heart size and mass may be the result of changes in either myocyte or nonmyocyte fractions of myocardium. To investigate this, individual ventricular myocytes were enzymatically dissociated and examined microscopically (Figure 2A). Myocyte 2D surface area (myocyte length × width) was similar in endocardial and epicardial fractions and in unoperated and sham-operated mice (Figure 2B). In contrast, 2D surface area increased in myocytes isolated from hearts subjected to TAB (Figure 2B). Cardiomyocyte enlargement was proportional to normalized heart mass in endocardial and epicardial cell fractions (Figure 2C). Histological examination of the hypertrophied myocardium did not reveal evidence of significant tissue fibrosis or myofibrillar disarray (data not shown).

Effects of CsA
Mice injected with CsA (TAB + CsA) and vehicle (TAB + Veh) tolerated mechanical loading equally well, with no detectable clinical differences (lethargy, tachypnea, impaired mobility, edema). Body mass continued to increase normally (Figure 3C), and the mice did not exhibit signs of cardiovascular compromise (effusions, ascites, hepatic congestion). One-week and 5-week mortality were each <10% in both groups.

CsA blocked the development of hypertrophy, as measured by HW/BW (Figure 3A) or HW/T (data not shown). At every time point up to 5 weeks, HW/BW and HW/T in TAB + CsA animals did not differ significantly from control. In contrast, there was a significant increase in heart mass in TAB + Veh mice from 1 to 5 weeks after banding (Figure 3A). Similarly, heart dimensions were not significantly different in TAB + CsA mice compared with controls, whereas these values increased significantly in TAB + Veh mice after banding (data not shown).

Short-axis sections through the heart at the level of the papillary muscles (Figure 3B) revealed thickening of the LV wall in the TAB + Veh hearts, whereas hearts from TAB + CsA mice were indistinguishable from hearts from control mice. Hearts from TAB + CsA mice were similar in appearance to hearts from age-matched unoperated mice.

The 2D surface area of myocytes isolated from TAB + CsA mice did not differ significantly from that of myocytes isolated from unoperated animals but was significantly greater in cells isolated from TAB + Veh mice (Figure 4A). The surface area of myocytes subjected to TAB + CsA was proportional to normalized heart mass (Figure 4B) and was well described by regression lines derived from the TAB + Veh hearts (Figure 2C), even though no hearts larger than HW/T = 9 were ever observed.

CsA had no effect on the transstenotic aortic pressure gradient. Systolic gradients measured in 5 mice subjected to TAB + CsA for 2 to 5 weeks were 77 ± 11 mm Hg, which was
not significantly different from the gradients measured in TAB+Veh animals (70±14 mm Hg, n=6).

In Vivo Function
To test the hypothesis that hypertrophy is an obligatory adaptive response, we studied in vivo cardiac function by transthoracic echocardiography (Figure I; this figure can be found online at http://www.circulationaha.org). Echocardiographic measurements provided a reliable estimate of LV mass (Figure 5A). These findings document the fidelity of endocardial and epicardial edge identification and support the validity of measurements of LV cavity volume. Under these recording conditions, there were no significant differences in heart rate (TAB+Veh, 645±28 bpm; TAB+CsA, 656±16 bpm; control, 626±16 bpm), and these values do not differ from those measured electrocardiographically in the absence of sedation (see above).

2D echocardiography was performed to evaluate systolic function and chamber size (Figures 5B and 5C) in animals subjected to TAB+Veh (n=6) versus TAB+CsA (n=7). As expected from postmortem data, LV mass by echocardiography at 3 weeks was significantly greater in mice subjected to TAB+Veh (103±6 mg, n=6) than in animals subjected to TAB+CsA (83±5 mg, n=3, P<0.05). LV mass in TAB+CsA mice was not significantly different from that of age-matched control values (83±2 mg, n=7).

End-diastolic volumes were not significantly different in all 3 groups at 3 weeks (TAB+Veh, 44±6 μL; TAB+CsA, 33±6 μL; control, 37±1 μL), indicating the absence of chamber dilation. Similarly, ejection fractions (TAB+Veh, 92±2%; TAB+CsA, 97±2%; control, 97±1%) and cardiac output (TAB+Veh, 24±4 mL/min; TAB+CsA, 21±3 mL/min; control, 23±3 mL/min) were not significantly different. Studies in TAB+CsA mice (n=4) at 1 to 2 weeks revealed similar evidence of preserved LV chamber size and systolic function (LV mass, 73±5 mg; end-diastolic volume, 31±7 μL; ejection fraction, 99±1%). In only 1 of 25 mice imaged at 4 weeks after surgery was systolic dysfunction observed, and this mouse (LV mass, 148 mg; end-diastolic volume, 107 μL; end-systolic...
The efficacy of CsA abolition of the hypertrophic response in our model is verified by 3 independent methods. First, gross pathology indicated no difference with respect to heart mass in banded mice treated with CsA compared with unbanded mice. By examining multiple time points during development of hypertrophy, we found that statistically significant differences appear as early as 1 week, the earliest time point examined. The curves continue to diverge at least as late as 5 weeks after banding. Second, the dimensions of myocytes isolated from banded mice treated with CsA were similar to those in unbanded mice. Third, in vivo echocardiography demonstrated that LV mass in banded mice treated with CsA was similar to that obtained from unbanded controls.

This is the first report of abolition of pressure-overload hypertrophy by calcineurin blockade in mice exposed to pressure overload. CsA blocked hypertrophy in all 34 mice studied, including 4 mice studied at 5 weeks. There was no evidence of nonspecific toxicity, because we observed no effects on normal growth, weight gain, or physical activity (similar to observations by others).6,12,20

Calcineurin inhibition does not prevent hypertrophy in all models of pressure overload. To date, 6 complete reports (including this work) and 2 letters have been published pertaining to the effects of calcineurin inhibition on pressure-overload hypertrophy: 3 groups report profound inhibition of hypertrophy (this work and References 7 and 9), 3 report no effect,20,23,24 and 2 detect an intermediate response.8,19 The 3 positive studies have been in different species (Sprague-Dawley7 and Wistar9 rats and C57Bl6 mice [this report]) subjected to different operations (suprarenal aortic banding7,9 and TAB [this report]).

Reasons for the contradictory findings are unclear. Technical differences among published reports are significant in terms of species, strain, age, surgical procedure, and the timing, dosage, and route of administration of CsA. Some groups have reported elevated mortality in mice treated with CsA.7,8,19,23 and it is possible that selecting CsA-treatment survivors may favor animals with relatively greater heart size. Surgical technique is also important25; for example, suprarenal aortic banding is associated with elevated plasma renin activity, unlike banding of the ascending aorta.26 Nuclear factor of activated T cells (NFAT) translocation to the nucleus is transient,13 and timing of the initiation of calcineurin inhibition may be crucial.

Zhang et al19 report LV mass normalized to body weight and pressure gradient (LVW/BW/gradient), arguing that this latter factor accounts for the potential influence of a smaller stimulus to hypertrophy. In our study, simultaneous carotid pressure measurements in anesthetized mice revealed similar transstenotic pressure gradients in TAB+Veh and TAB+CsA mice. This finding was extended to conscious, sedated mice in that we measured similar cardiac outputs inTAB+Veh and TAB+CsA mice, indicating that the pressure gradients (which vary as the square of cardiac output in the presence of a fixed stenosis) were similar. Ding et al20 report a 72% decrease in LV calcineurin activity in hypertrophied hearts; given this, one would not expect a significant impact from further calcineurin inhibition using CsA.

**Discussion**

The most important finding of this study is that abolition of the hypertrophic response to systolic pressure overload does not result in LV decompensation. This finding is supported by 6 independent lines of evidence. First, there was no clinical or actuarial evidence of heart failure in CsA-treated mice. Second, postmortem gross anatomy demonstrated no signs of cardiac dilatation or evidence of heart failure (eg, effusions, ascites, edema). Third, postmortem cardiac histopathology revealed an absence of myocardial fibrosis or other evidence of myocyte damage. Fourth, examination of single myocytes revealed normal cell size and microscopic appearance. Fifth, pressure gradients measured across the surgically induced stenosis were similar in the presence and absence of hypertrophy. Sixth, echocardiography consistently demonstrated maintenance of normal systolic function in CsA-treated mice.

**Structural Consequences of Calcineurin Inhibition**

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**Functional Consequences of Calcineurin Inhibition**

Compensatory hypertrophy putatively develops to facilitate ejection performance of the overloaded ventricle by normal-
izing systolic and diastolic wall stress. We tested this idea by imposing a condition of elevated afterload while blocking the compensatory response. As expected, mice subjected to TAB+Veh exhibited significantly increased LV mass, and measures of systolic performance were preserved. On the basis of Laplace’s law, we predict that ventricular wall stress is elevated in TAB+CsA mice (elevated systolic pressure without a change in ventricular radius or wall thickness). If hypertrophy were a necessary compensatory response, we might predict that TAB+CsA mice would develop LV systolic dysfunction, chamber dilatation, and myocyte lengthening. Our results indicate that none of these occurred. Similarly preserved systolic function in the setting of pressure overload but without hypertrophic compensation was recently reported by 2 other groups.9,10 Maintenance of cardiac output in the face of increased afterload but without change in end-diastolic or end-systolic volumes implies a positive inotropic effect. Homeometric autoregulation (Anrep effect) was first described in 191227,28 and has been reported in a variety of working heart models.25,29–32 Our findings are consistent with a sustained Anrep effect. Additional work will be necessary to test this hypothesis.

None of the animals in this study developed heart failure. Meguro et al8 reported a 7-fold increased risk of death from heart failure (defined as presence of pleural effusion and increased lung weight) after banding in mice treated with CsA, and most of this excess mortality appeared to occur in the first 2 to 3 days after surgery. This is somewhat surprising, because these investigators reported only a modest decrease in ejection fraction (~78% in TAB versus 66% in TAB+CsA, data taken from their Figure 2), and LV volumes were not reported. These investigators also reported an all-cause 10-day mortality of 43% in TAB mice and 72% in TAB+CsA mice, which is markedly higher than ours (~10% in each group), suggesting significant differences in perioperative milieu.

Our echocardiographic measurements were performed under conditions of conscious sedation so as to maintain physiological heart rates, ventilation, and inotropic state. We observe cavity near-obliteration at end systole (Figure 1), accounting for ejection fractions ~90%. These values may be artifactually inflated; although LV short- and long-axis silhouettes were consistently visualized, the area-length method does not account for residual blood pooled beneath the mitral and aortic valves. Nevertheless, the physiological conclusions derived from these measurements are valid.

Ejection-phase indices of murine LV function in studies that used general anesthesia are generally lower than in our study. General anesthetics directly depress myocardial contractility, and positive-pressure ventilation is known to perturb cardiac function. Furthermore, the adequacy of systemic oxygenation and acid-base balance during general anesthesia is difficult to assess in mice and is seldom reported. Yang et al33 performed echocardiography in conscious, sedated, minimally restrained mice, and they report ejection fractions similar to those in our study. Thus, it appears that normal conscious mice have significantly higher ejection fractions than anesthetized mice.

Perspective
Even though calcineurin is activated in heart failure in humans,34 envisioning use of CsA as treatment for hypertrophy or heart failure is problematic.35,36 Nevertheless, our data support the hypothesis that activation of a calcineurin transcriptional pathway mediates at least an early component of pressure-overload hypertrophy. Furthermore, the major implication of the findings is that hypertrophy is not a necessary adaptive response to elevated cardiac workload in this model.

Note Added in Proof
Bartunek et al37 have shown that rats rendered hypertensive by L-NAME infusion (an inhibitor of nitric oxide synthase that also suppresses protein synthesis) maintain left ventricular systolic performance despite the absence of hypertrophic compensation.

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