Suppression of Class I and II Histone Deacetylases Blunts Pressure-Overload Cardiac Hypertrophy

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Background—Recent work has demonstrated the importance of chromatin remodeling, especially histone acetylation, in the control of gene expression in the heart. In cell culture models of cardiac hypertrophy, pharmacological suppression of histone deacetylases (HDACs) can either blunt or amplify cell growth. Thus, HDAC inhibitors hold promise as potential therapeutic agents in hypertrophic heart disease.

Methods and Results—In the present investigation, we studied 2 broad-spectrum HDAC inhibitors in a physiologically relevant banding model of hypertrophy, observing dose-responsive suppression of ventricular growth that was well tolerated in terms of both clinical outcome and cardiac performance measures. In both short-term (3-week) and long-term (9-week) trials, cardiomyocyte growth was blocked by HDAC inhibition, with no evidence of cell death or apoptosis. Fibrotic change was diminished in hearts treated with HDAC inhibitors, and collagen synthesis in isolated cardiac fibroblasts was blocked. Preservation of systolic function in the setting of blunted hypertrophic growth was documented by echocardiography and by invasive pressure measurements. The hypertrophy-associated switch of adult and fetal isoforms of myosin heavy chain expression was attenuated, which likely contributed to the observed preservation of systolic function in HDAC inhibitor–treated hearts.

Conclusions—Together, these data suggest that HDAC inhibition is a viable therapeutic strategy that holds promise in the treatment of load-induced heart disease. (Circulation. 2006;113:2579-2588.)

Key Words: hypertrophy ■ signal transduction ■ chromatin remodeling ■ histone deacetylases

In response to the stress of neurohumoral activation, hypertension, or myocardial injury, the heart initially compensates with an adaptive hypertrophic increase in mass. Under prolonged stress, the heart undergoes apparently irreversible decompensation that results in dilation of the failing heart. During stress-induced hypertrophy, postnatal cardiac muscle cells increase in size and activate a set of fetal genes that encode proteins involved in contractility, calcium handling, and myocardial energetics.

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Recent work has uncovered the importance of chromatin remodeling, especially histone acetylation, in the control of gene expression in heart disease. The structure of chromatin is governed by the acetylation state of nucleosomal histones, which, in turn, participates in regulating the expression of numerous genes. Histone acetyltransferases (HATs) transfer acetyl groups from acetyl coenzyme A to ε-amino groups of conserved lysine residues within nucleosomal histone tails, resulting in charge neutralization of the amino acid. The altered charge of the histone tail promotes chromatin relaxation and thus creates a local environment that accommodates transcriptional machinery. HAT activity is antagonized by histone deacetylases (HDACs), which promote nucleosomal condensation and consequent transcriptional repression. Recent studies have shown that both HAT and HDAC activities participate in regulating the hypertrophic response of the heart. Among the best characterized examples are class II HDACs; in the absence of stress signals, these enzymes interact with the MEF2 transcription factor to repress the fetal gene program and cardiac growth. Paradoxically, recent studies in vitro indicate that pharmacological inhibition of HDAC enzymatic (deacetylase) activity blunts hypertrophic growth. These surprising results suggest a potential role for HDAC inhibitors as therapy to control cardiac hypertrophy.

In the present study, we set out to explore the efficacy of HDAC inhibition (HDACi) in a surgical model of pressure overload-induced cardiac hypertrophy. Using 2 broad-spectrum HDAC inhibitors, we observed dose-responsive...
suppression of ventricular growth that was well tolerated in terms of clinical outcome and cardiac performance measures. In both short-term and long-term trials, cardiomyocyte growth was blocked by HDACi with no evidence of cell death or apoptosis. Fibrotic change was diminished in hearts treated with HDAC inhibitors, and collagen synthesis in isolated cardiac fibroblasts was blocked. Preservation of systolic function in the setting of blunted hypertrophic growth was documented by echocardiography and by invasive pressure measurements. Attenuation of the hypertrophy-associated switch of adult and fetal isoforms of myosin heavy chain (MHC) expression was detected, which likely contributed to the preservation of systolic function in HDAC inhibitor–treated hearts. Together, these data suggest that HDACi is a viable therapeutic strategy that holds promise in the treatment of load-induced heart disease.

**Methods**

**Pressure-Overload Hypertrophy Model**

Male C57BL6 mice (6 to 8 weeks old; Charles River, Wilmington, Mass) were subjected to pressure overload by thoracic aortic banding (TAB). We have shown previously that constriction to a 27G stenosis induces moderate hypertrophy (~40% increases in heart mass) without clinical signs of heart failure or malignant ventricular arrhythmia. At 3 weeks, when the hypertrophic response reaches steady state, integrity of aortic banding was confirmed by inspection of the surgical constriction and by visualization of marked differences in caliber of the right and left carotid arteries.

**Cardiomyocyte Cross-Sectional Area**

Hearts were rapidly excised and retrograde perfused (4°C) with Carson’s Modified Buffered Formalin (Richard-Allan Scientific, Kalamazoo, Mich). Hematoxylin & eosin-stained tissue sections from 3 hearts in each treatment group were studied at 200× magnification. In each field, all myocytes cut in short axis with a visible nucleus were counted (~20 cells), and 6 to 8 randomly selected fields spanning the septum, apex, and free wall were studied per tissue section. Cell borders were planimetered manually by an operator who was blinded to treatment group. ImageJ software (NIH) was used to calculate 2-dimensional cross-sectional areas.

**Echocardiography**

Transthoracic echocardiograms were recorded in conscious-sedated mice as described. Details are provided in the online Data Supplement.

**Invasive Hemodynamics**

Left ventricular pressure volume and systemic blood pressure measurements were performed as previously described. Details are provided in the online Data Supplement.

**Statistical Analysis**

Averaged data are reported as mean±SEM. Statistical significance was analyzed using a Student unpaired t test or 1-way ANOVA followed by Bonferroni method for post hoc pairwise multiple comparisons. Additional methodological details are provided in the online Data Supplement.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**HDAC Suppression Augments Histone Acetylation In Vivo**

To explore the effects of HDAC inhibitors in cardiac myocytes, we examined the acetylation state of known HDAC
targets. HDAC suppression would be expected to induce histone hyperacetylation due to unopposed HAT activity. To test this, we exposed neonatal cardiomyocytes in culture to 50 nmol/L Trichostatin A (TSA; Biomol, Plymouth Meeting, Pa; Figure 1A), an inhibitor of class I and II HDACs,13 and measured acetyl-histone-3 (H3) levels by immunoblot. As expected, TSA induced significant increases in H3 acetylation confirming the efficacy of deacetylase suppression (Figure 1B). TSA also induced increases in the acetylation of /H9251-tubulin, another HDAC substrate14,15 (Figure 1B).

To test for efficacy in vivo, mice were treated with TSA (1 mg/kg for 3 days) and euthanized at different time points after the last injection. H3 hyperacetylation was observed for 24 hours after the final injection with the drug (Figure 1C), suggesting that once daily dosing was suitable for further testing in vivo. Similar findings were observed with Scriptaid (6-[1,3-Dioxo-1H,3H-benzo(de)isoquinolin-2-yl]-N-hydroxyhexanamide) (SA; Biomol), another broad-spectrum HDAC inhibitor (data not shown).

TSA Blunts Pressure-Overload Hypertrophy

To test the effects of HDAC inhibitors on load-induced cardiac hypertrophy, mice were exposed to TAB. On the first postoperative day, mice were randomized to daily subcutaneous injections of either TSA or vehicle. A parallel group of animals was subjected to a sham operation and treated with once-daily injections of TSA or vehicle. Animals were followed for 3 weeks, a time frame similar to the HDAC inhibitor trials presently underway in clinical oncology. In these experiments, we observed that pressure overload induced by TAB was sufficient to induce H3 acetylation (Figure 1D and 1E), suggesting that chromatin remodeling is an important mechanism governing the cardiac response to stress.

Administration of TSA (2 mg/kg) resulted in a statistically significant suppression ($P<0.05$) of hypertrophic growth measured as heart mass or left ventricular (LV) mass normalized to either body mass or tibia length (Figure 2A and 2B). Treatment with lower doses of TSA (1 mg/kg and 0.5 mg/kg) resulted in similar degrees of blunted growth, suggesting that maximal antihypertrophic efficacy had been achieved at 0.5 mg/kg. TSA had no apparent effect in sham-operated mice.

TSA treatment of skin fibroblasts has been shown to suppress collagen synthesis and fibrogenesis.16 As pathological hypertrophy is typically associated with interstitial and perivascular fibrosis, we examined the effects of HDAC inhibition on TAB-induced fibrosis. Masson’s trichrome–stained tissue sections reveal interstitial fibrosis typical of pressure-overload–induced hypertrophy (left) is nearly abolished by TSA (right). D. Fibroblasts were isolated from adult murine left ventricle and exposed to TGF–/beta (5 ng/mL) for 24 hours in the presence/absence of TSA. A representative immunoblot probed for type I collagen is shown, revealing dose-responsive suppression of collagen biosynthesis. Cntl indicates control.
significantly increased in TAB ventricle. In TAB tissue (Figure 3A). As expected, cell cross-sectional area was dropout, we quantified cell cross-sectional area in sections of LV cardiomyocyte growth as opposed to apoptosis-induced cell growth seen in animals treated with TSA was due to blunted cancer therapy. To determine whether the diminished heart and several of these compounds have shown efficacy as anti-therapy. In situ DNA nick end labeling staining and DNA laddering cles, however, cardiomyocyte cell size was significantly blunted. In situ DNA nick end labeling staining and DNA laddering analysis for apoptosis revealed no significant changes in TSA-exposed heart (data not shown). Together, these data suggest that the effects of TSA derive from diminished hypertrophic cell growth rather than from TSA-triggered death of a population of cells in the heart.

A second, broad-spectrum HDAC inhibitor, Scriptaid, was tested in another series of short-term trials. Similar to the findings with TSA, banded animals treated with Scriptaid manifested statistically significantly less hypertrophic growth compared with vehicle-treated controls (Figure 4). Here, a dose-response relation was observed with greater degrees of hypertrophy suppression manifest at higher Scriptaid doses, suggesting that the serum concentrations achieved at these doses are situated on the vertical part of the dose-response curve.

Natriuretic Peptide Expression

Given that the transcriptional effects of HDAC inhibitors would be expected to augment gene expression and yet HDAC inhibitors blocked hypertrophy, we hypothesized that countervailing antigrowth pathways may be activated by these drugs. Enhanced expression of natriuretic peptides, such as atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP), is a characteristic feature of the pressure-stressed heart, and it has been postulated that they may function as part of a counterregulatory mechanism that limits growth. To test whether HDAC inhibitors altered the expression of natriuretic peptides in our model of load-induced hypertrophy, we measured steady-state levels of ANF and BNP transcript in ventricle subjected to TAB+TSA (Figure 3B).

Despite significant blunting of hypertrophic growth in TAB+TSA animals, ANF and BNP transcript levels were increased to a similar extent (P=NS) compared with TAB+Veh animals.

Functional Effects of HDAC Therapy

In numerous animal models, suppression of hypertrophic growth is well tolerated, with preservation of ventricular size and performance, despite persistence of the inciting stimulus (recently reviewed6). Our data demonstrate that HDAC inhibitors can blunt hypertrophic growth, and yet nothing is known about the tolerability of HDAC inhibitors in load-induced cardiac hypertrophy. It was therefore important to assess the impact of HDAC inhibitor therapy on cardiac function and the overall health of the mice.

TSA and Scriptaid were each well tolerated in both TAB- and sham-operated animals. Animals subjected to TAB or sham operation and subsequently randomized to TSA or vehicle injections were clinically healthy without evidence of cardiovascular insufficiency (lethargy, edema, etc). Three-week mortality was similar in all 4 treatment arms (P=NS) and less than 25% (Figure 5A).

Ventricular function was assessed by echocardiography under conditions of light sedation. We observed preservation of ventricular size and systolic function despite the presence of persistent afterload stress (Figure 5B and 5C), suggesting that under these conditions, HDAC suppression may be a viable treatment strategy.

Although ejection fraction by echocardiography is technically easy to measure, and hence frequently used as a surrogate for systolic function, it is not a true measure of intrinsic contractility because it varies with myocardial loading conditions. Additionally, ejection fraction overestimates contractility in the setting of hypertrophy because of changes in LV geometry during contraction.17,18 Thus, we also evaluated ventricular performance by means of invasive hemodynamic pressure recordings (Figure 6A). Using this sensitive method, we uncovered evidence of diminished contractile performance in TAB hearts (Table in the online Data Supplement). For example, the end-systolic pressure-volume relation (ESPVR), a load-independent measure of ventricular...
performance, was significantly decreased \( (P<0.01) \) in TAB hearts (Figure 6B). Remarkably, this measure of systolic function was preserved in TAB + TSA hearts. In sham-operated animals, TSA had no significant effect on ventricular function. Similar results were obtained when we examined maximum and minimum dP/dt. Again, evidence of diminished ventricular function was observed in TAB hearts, which was nearly completely abolished by TSA (Figure 6C).

**Myosin Heavy Chain Isoform Switching**

During hypertrophic growth of the heart, expression of the fetal isoform of MHC (β-MHC) is enhanced, and expression of the adult isoform (α-MHC) is diminished. Some evidence suggests that this stress-triggered switching of sarcomeric protein isoforms contributes to the diminution of contractile performance typically seen in hypertrophy.\(^{19,20}\) To determine whether the positive inotropic actions of TSA might be a consequence of preserved balance of MHC isoforms, we quantified the abundance of α-MHC protein in TAB hearts (Figure 7A). The increase in β-MHC protein levels was significantly blunted by TSA. Similarly, the TAB-induced decrease in α-MHC abundance was attenuated by TSA (Figure 7B). Also, TAB-induced increases in α-tubulin abundance were blocked by TSA (Figure 7C). Together, these data suggest that the dramatic effects of TSA on cardiac contractile performance may result, at least in part, from attenuated switching of contractile protein isoforms.

**Long-Term TSA Trials**

To envision HDAC inhibitors in clinical use, it is important to evaluate their long-term efficacy and tolerability. To begin to explore this, we studied animals subjected to TAB or sham operation and treated with TSA (1 mg/kg QD) for 9 weeks, a period roughly corresponding to 10 to 12 years in humans. In 2 independent trials, treatment with TSA was clinically well tolerated throughout the 9-week trial and did not alter survival: sham + Veh, 100% \((n=7)\); sham + TSA, 100% \((n=7)\); TAB + Veh, 71% \((n=11)\); and TAB + TSA, 67% \((n=13)\). On necropsy, statistically significant blunting of hypertrophic growth similar to that seen in short-term trials was observed in TSA-treated animals (Figure 8A).

To test for effects on cardiac performance, animals in all 4 treatment arms underwent echocardiography 1 day before euthanasia. Here, we observed modest declines in systolic function in TAB + Veh animals, consistent with pressure overload-induced pathological remodeling (Figure 8B). In TAB + TSA mice, declines in ventricular performance were significantly attenuated compared with TAB + Veh mice \((P<0.05)\), despite the presence of a blunted compensatory hypertrophic response. After 9 weeks of pressure overload, marked accumulation of interstitial fibrosis was observed, which was dramatically attenuated by TSA (Figure 8C). Finally, quantification of myocyte cross-sectional area revealed the expected increases in cell growth in TAB + Veh hearts \((P<0.01)\) that was significantly \((P<0.01)\) blunted by HDACi (Figure 8D). No evidence of increased apoptosis was detected by in situ DNA nick end labeling staining or by DNA laddering analysis in any of the 4 long-term treatment arms (data not shown). Together, these data suggest that TSA is capable of suppressing hypertrophic growth long term. These findings also suggest that this blunted remodeling response is associated with salutary effects on ventricular performance and pathological fibrogenesis despite persistence of increased afterload.

**Discussion**

Recent studies point to the importance of enzymes that control histone acetylation as stress-responsive regulators of gene expression in the heart.\(^{21}\) Pharmacological inhibition of HDACs blocks hypertrophic growth of cardiac myocytes in...
vitro, and some evidence suggests they block agonist-induced hypertrophy in vivo. Before the present study, nothing was known about whether these compounds impact hypertrophic growth in a physiologically relevant model of pressure overload in vivo. Here, we demonstrate that (1) 2 broad-spectrum HDAC inhibitors are capable of blunting hypertrophic growth in a model of load-induced cardiac hypertrophy, (2) HDAC inhibitors are clinically well tolerated, (3) suppression of pressure-overload hypertrophy by HDAC inhibitors is not associated with circulatory insufficiency, (4) HDAC inhibitors preserve systolic function, (5) HDAC inhibitors blunt stress-induced fibrogenesis and inhibit collagen biosynthesis in cardiac fibroblasts, and (6) HDAC inhibitors blunt pathological switching of MHC isoforms, which may contribute to their actions to preserve ventricular performance.

Class II HDACs block expression of progrowth genes through their interaction with MEF2, a transcription factor that integrates multiple Ca2+/calmodulin-dependent signals. On the basis of what is known about the interaction of class II HDACs with MEF2, however, one would predict that compounds inhibiting HDAC activity would induce hypertrophy rather than inhibiting hypertrophy as we and others have observed. The key to this paradox may lie in the fact that class II HDAC isoforms that lack deacetylase activity are also capable of blocking MEF2 transcription both in vitro and in vivo. The crystal structure of MEF2 bound to DNA was recently solved and showed that association of MEF2 with p300 and class II HDACs is mutually exclusive, as these proteins target an overlapping site on the transcription factor. Under normal circumstances, the presence of HDAC (whether active or not) is sufficient to prevent access of HAT. In response to hypertrophic stress signals, HDAC is phosphorylated and released from MEF2 and moves to the cytoplasm. Inhibition of HDAC activity at this point would have no effect on genes regulated by class II HDACs because the class II HDACs are no longer bound to chromatin. Because of this, it is likely that within the context of a hypertrophic heart, inhibition of HDAC activity has no direct effect on MEF2 transcription and therefore does not directly derepress expression of the prohypertrophic genes under MEF2 control.

In cultured neonatal myocytes, HDAC inhibition by TSA has been reported to either induce27 or blunt agonist-induced ANF expression. Working with a model of load-induced hypertrophy in vivo, we observed that activation of ANF and BNP expression was preserved in TSA-exposed hearts even though hypertrophic growth was blunted. Thus, TSA treatment dissociated activation of expression of this set of fetal genes from a progrowth response. Our finding that ANF transcription remains elevated in TSA-treated TAB hearts despite attenuation of hypertrophic growth is consistent with studies where calcineurin was inhibited by transgenic expression of glycogen synthase kinase-328 or modulatory calcineurin interacting protein-1. Indeed, it is tempting to speculate that the preservation of increased ANF expression in TSA-treated TAB hearts may participate in the antihypertrophic effects of deacetylase inhibitors. The observation that TSA diminished pathological remodeling measured as fibrotic change in the myocardium suggests that the sum of the effects of broad-spectrum HDAC inhibition is salutary and beneficial.
HDAC Targets in Hypertrophy
Despite their nomenclature, which implicates histones as a major substrate, the molecular targets of HDACs relevant to cardiac hypertrophy are unknown. Indeed, many proteins in the cell are acetylated and deacetylated by HATs and HDACs. Similar to phosphorylation, acetylation of a protein can have a wide range of effects including altering stability of the protein, changing its enzymatic activity, or facilitating new protein–protein interactions. A number of transcription factors are acetylated, as well as nuclear import factors, cell cycle regulators, and structural proteins. The attenuation of hypertrophy by HDACi that we have observed could be due to increased acetylation of one or a combination of these protein substrates.

We observed that TAB-induced afterload stress, a robust trigger of hypertrophic growth, induced histone acetylation, suggesting that chromatin remodeling is a mechanism through which transcription could be regulated in response to hypertrophic stimuli. This is consistent with a recent report demonstrating that the hypertrophic agonist cardiotoxin-1 triggers histone H3 acetylation in H9c2 cells in culture. Paradoxically, however, HDAC inhibition, which was similarly capable of provoking histone acetylation, blunted hypertrophic growth in our studies. Together, these data suggest that there are antigrowth targets suppressed by HDACs that, when released, are dominant over the progrowth genes controlled by class II HDACs. Consistent with this, recent evidence suggests that chromatin-modifying enzymes are capable of regulating both progrowth and antigrowth arms of the complex network that governs cardiac growth. Homeodomain-only protein (HOP) represses the transcriptional activity of serum response factor through its association with HDAC2, a class I HDAC. HOP overexpression induces hypertrophy, but overexpression of a mutant HOP, unable to interact with HDAC2, does not. This suggests that in this context, and in contrast to class II HDACs, this class I HDAC facilitates prohypertrophic growth. Exactly which genes are regulated by this system is not clear. However, we have conducted preliminary studies evaluating effects of TSA on the abundance and activation of ERK, JNK, p38, Akt, phospholamban, and SERCA2a, and these experiments so far have failed to reveal robust treatment effects (Y.K., J.A.H., unpublished observations).

Blunted Hypertrophic Growth
In a study designed to evaluate antihypertrophic therapy, it is critical that the imposed hemodynamic load be equivalent to the load imposed in the control group. This is best achieved by subjecting the control and treated animals to the same afterload stimuli.
across treatment groups. To assure that all animals were exposed to equivalent banding-induced stress, mice were randomized to 2 treatment groups the day after TAB surgery. For 2 important reasons, we did not measure transstenotic pressure gradients. First, transstenotic pressure gradients are a function of both the degree of vessel stenosis and the pressure generated by the left ventricle; hence, they provide an indirect measure of arterial resistance. To infer that transstenotic pressure gradients are indicative of TAB-induced stenosis, one must assume that cardiac output is unchanged by drug treatment. (As an analogy, to compare electrical resistance \( R \) in 2 circuits by measuring the voltage-drop \( V \) across each circuit, one must assume that current \( I \) is the same in both circuits; \( V = IR \).) Our findings reveal improved systolic performance in TSA-treated animals. Thus, it was clearly inappropriate to assume that cardiac outputs are equivalent in all treatment groups. Second, measurements of simultaneous transstenotic pressures are complicated by inevitable and variable declines in blood pressure from anesthesia, which renders these indirect measures of vascular resistance yet more unreliable. As a result, we adopted a previously validated strategy of banding animals by a surgeon who was blinded to treatment group followed by randomization between treatment arms.

Our findings are consistent with prior work in vitro demonstrating an antihypertrophic effect of TSA in cultured cardiac myocytes. One study, however, reported that TSA was capable of provoking cardiomyocyte growth in vitro. Although an explanation for the different observations in cell culture models is not apparent at this time, we report in the present study that both TSA and Scriptaid blunt hypertrophic growth of the heart triggered by pressure stress in vivo.

**Figure 7.** Blunted hypertrophy-associated switching of MHC isoforms in hearts exposed to TSA. Representative immunoblots from individual left ventricles treated as listed and probed for \( \beta \)-MHC (A), \( \alpha \)-MHC (B), or \( \alpha \)-tubulin (C).

**Figure 8.** Long-term treatment with TSA is well tolerated. A, HW/BW ratios in hearts treated for 9 weeks as listed. Sham + Veh, \( n = 7 \); sham + TSA, \( n = 7 \); TAB + Veh, \( n = 11 \); TAB + TSA, \( n = 13 \). B, Percent fractional shortening measured at the end of the 9-week trial reveals statistically significant attenuation of pressure overload-induced systolic dysfunction in TAB hearts treated with TSA or vehicle. C, Representative fields of Masson’s trichrome–stained tissue sections reveal marked accumulation of interstitial fibrosis (left) which is nearly abolished by TSA (right). D, Two-dimensional cardiomyocyte cross-sectional area measured as described. Sham + Veh (\( n = 552 \) cells/3 hearts); sham + TSA (\( n = 580/3 \)); TAB + Veh (\( n = 634/3 \)); TAB + TSA (\( n = 658/3 \)).
Importantly, despite blunted hypertrophic growth in the setting of persistent afterload stress, ventricular size and performance were preserved, consistent with a growing literature pointing to suppression of pathological hypertrophy as a viable therapeutic strategy.6

The efficacy of HDAC inhibitors in cancer trials stems, in part, from their ability to induce tumor cell death. In the case of pathological cardiac growth, the HDAC inhibitors TSA and Na butyrate block myocyte hypertrophic growth and histone deacetylation at doses 10-fold lower than those capable of inducing cytotoxicity.8 In experiments reported here, we found no evidence of drug-induced cell dropout or myocyte apoptosis.

Preserved Ventricular Function
We tested HDAC inhibitor therapy in both short-term (comparable in duration to the anticancer clinical trials presently underway) and long-term trials (as might be envisioned for antihypertrophy therapy). In both cases, we observed preservation of ventricular size and performance despite blunting of “compensatory” hypertrophy. This finding, in the presence of persistently elevated afterload, suggested a positive inotropic effect. This was confirmed in invasive hemodynamic studies where ESPVR, a measure of the intrinsic contractility of the left ventricle, was maintained in banded animals treated with TSA. One contributor to this action of TSA to preserve ventricular function may be its ability to blunt the pathological switch between MHC isoforms in stressed myocardium. This switch, where the adult isoform declines and the fetal isoform increases, is thought to contribute to the contractile dysfunction typically seen in hypertrophy.19,20,31 It is of interest to elucidate mechanisms whereby HDAC inhibitors attenuate hypertrophy-associated switching of sarcomeric proteins, as this property holds promise as a strategy to increase myocardial performance.

Limitations of the Study
A precedent exists in the field of clinical oncology for the therapeutic application of drugs that suppress HDAC activity. In this setting, HDAC inhibitors have been shown to upregulate cell-cycle inhibitors (eg, p21), blocking both growth and proliferation of a wide variety of cell types. Indeed, numerous clinical trials are underway to test the use of HDAC inhibitors in cancer patients, and development of new HDAC inhibitors as a viable therapeutic strategy.6 A precedent exists in the field of clinical oncology for the therapeutic application of drugs that suppress HDAC activity.6 In experiments reported here, we found no evidence of drug-induced cell dropout or myocyte apoptosis.

Hypertension-induced cardiac hypertrophy is a common disease phenotype in our society, predisposing patients to ventricular dysfunction and circulatory failure. A growing body of evidence in rodent models indicates that inhibiting pathological hypertrophy in the face of hemodynamic stress maintains cardiac performance and enhances survival, pointing to the potential therapeutic benefit of strategies that suppress the hypertrophic process.6 Indeed, while our paper was in review, Kee et al33 reported similar hypertrophy-blocking effects of HDACi in animal models of cardiac hypertrophy. On the basis of these findings, HDAC inhibition may emerge as a promising antihypertrophic therapeutic strategy.

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None.

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In response to stress, the heart initially compensates with an adaptive hypertrophic increase in mass. Under prolonged stress, the heart undergoes apparently irreversible decompensation that results in dilation of the failing heart. Thus, there is great interest in developing novel treatment strategies to block hypertrophy and prevent heart failure. In the present study, we evaluated drugs that inhibit the activity of histone deacetylase (HDAC), a molecular regulator of gene transcription. Using 2 broad-spectrum HDAC inhibitors in a surgical model of pressure-overload–induced cardiac hypertrophy, we observed dose-responsive suppression of ventricular growth that was well tolerated in terms of clinical outcome and cardiac performance measures. In both short-term and long-term trials, cardiomyocyte growth was blocked, with no evidence of cell death or apoptosis. Fibrotic change was diminished in hearts treated with HDAC inhibitors, and collagen synthesis in isolated cardiac fibroblasts was blocked. Preservation of systolic function in the setting of blunted hypertrophic growth was documented by echocardiography and by invasive pressure measurements. Attenuation of the hypertrophy-associated switch of adult and fetal isoforms of myosin heavy chain expression was detected, which likely contributed to the preservation of systolic function in HDAC inhibitor–treated hearts. Together, these data suggest that HDAC inhibition is a viable therapeutic strategy that holds promise in the treatment of load-induced heart disease. Also, as HDAC inhibition is emerging as a potentially important therapy for a number of malignant tumors, our findings have relevance regarding cardiovascular effects of these drugs in cancer patients.
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