Expression of the Vitamin D Receptor Is Increased in the Hypertrophic Heart

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Abstract—The liganded vitamin D receptor (VDR) is thought to play an important role in controlling cardiac function. Specifically, this system has been implicated as playing an antihypertrophic role in the heart. Despite this, studies of VDR in the heart have been limited in number and scope. In the present study, we used a combination of real-time polymerase chain reaction, Western blot analysis, immunofluorescence, and transient transfection analysis to document the presence of functional VDR in both the myocytes and fibroblasts of the heart, as well as in the intact ventricular myocardium. We also demonstrated the presence of 1-α-hydroxylase and 24-hydroxylase in the heart, 2 enzymes involved in the synthesis and metabolism of 1,25 dihydroxyvitamin D. VDR is shown to interact directly with the human B-type natriuretic peptide gene promoter, a surrogate marker of the transcriptional response to hypertrophy. Of note, induction of myocyte hypertrophy either in vitro or in vivo leads to an increase in VDR mRNA and protein levels. Collectively, these findings suggest that the key components required for a functional 1,25 dihydroxyvitamin D–dependent signaling system are present in the heart and that this putatively antihypertrophic system is amplified in the setting of cardiac hypertrophy. (Hypertension. 2008;52:1106-1112.)

Key Words: vitamin D • cardiac hypertrophy • nuclear receptors • BNP • cardiac myocyte

Vitamin D is a secosteroid that functions as a ligand for a nuclear receptor (vitamin D receptor, or VDR) to control the transcription of target genes in a positive or negative fashion. Vitamin D is either ingested in the diet or generated de novo through scission of cholesterol precursors in the skin by ultraviolet light. Vitamin D is activated through 2 sequential hydroxylation reactions. The first of these, a 25-hydroxylation, takes place largely in the liver to produce 25-hydroxyvitamin D. This molecule circulates bound to a plasma protein and is measured to assess the adequacy of vitamin D stores. The second hydroxylation, a 1-α-hydroxylation, takes place predominantly in the kidney to generate 1,25-dihydroxyvitamin D (VD3). It serves as the principal ligand for VDR in the nucleus (and extranuclear compartment) of target cells. Another enzyme, that are ubiquitously expressed 24-hydroxylase, is responsible for hydroxylating this ligand, leading to its inactivation and subsequent degradation.

Recent studies suggest that VD3, in addition to stimulating absorption of intestinal calcium and promoting mineralization of bone osteoid, may play an important role in controlling cardiac hypertrophy. We have shown that VD3, as well as a number of nonhypercalcemic analogues, act in both atrial and ventricular myocytes to inhibit the activation of phenotypic markers associated with hypertrophy in vitro. Endothelin (ET)-stimulated changes in fetal gene expression and promoter activity, cell size, and protein synthesis are partially reversed by VD3 or its nonhypercalcemic analogues. Similar findings have been reported by others using the cultured cardiac HL-1 myocytes. In animal studies, vitamin D deficiency in Sprague-Dawley rats leads to both hypertension and cardiac hypertrophy, whereas treatment of Dahl salt–sensitive rats with the vitamin D analogue paricalcitol reverses cardiac hypertrophy in that model. The VDR knockout mouse displays hypertension, cardiac hypertrophy with enlargement of individual myocytes, and elevations in atrial natriuretic peptide (ANP) expression. However, the elevated blood pressure precludes assigning the liganded VDR a primary antihypertrophic role at the level of the cardiac myocyte. Although VDR has been identified microscopically and functionally in the heart, our understanding of the role of the liganded VDR in the maintenance of cardiac function remains incomplete.

Although VDR is clearly present in the heart, we know little of the specific cell types in which it is expressed nor of the functional activities associated with the liganding of these receptors. In the present article, we demonstrate the presence of VDR- and VD3-dependent functional activity in both the...
myocytes and fibroblasts of the rat heart. We also demonstrate the presence of the 1-α-hydroxylase enzyme in both compartments. Noteworthy, application of a hypertrophic stimulus (ET in vitro and isoproterenol in vivo) leads to an increase in VDR gene expression with little or no effect on expression of the 1-α-hydroxylase. The results indicate that a functional vitamin D–dependent signaling system is present in both cardiac myocytes and fibroblasts and support a growing body of data defining an antihypertrophic role for this system in the heart.

Materials and Methods

Materials

ET was purchased from American Peptide (Sunnyvale, Calif). Paricalcitol and active hectorol were gifts from Joel Melnick (Abbott Laboratories, Abbott Park, III). VD3 and 25-hydroxyvitamin D3 were obtained from Calbiochem Inc (La Jolla, Calif). VDR antibody (sc-1008), procollagen I antibody (sc-8787), 24-hydroxylase antibody (a gift from Martin Hewison, Cedar-Sinai Hospital, Los Angeles, Calif), and GAPDH antibody (sc-32233) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). 25-Hydroxyvitamin D 1-α-hydroxylase antibody (PC290) was from The Binding Site (Birmingham, UK).

Isoproterenol-Induced Cardiac Hypertrophy

Wistar rats purchased from Charles River Laboratories (Wilmington, Mass) were anesthetized, and subcutaneous osmotic minipumps were implanted into the dorsum of the neck. Individual rats received vehicle alone or isoproterenol at the rate of 2.4 mg/kg per day for 7 days (n = 8 each group). Animals were weighed and euthanized by CO2 narcosis followed by bilateral thoracotomy. Left ventricles were isolated and weighed. Left ventricular weight/body weight and left ventricular weight/tibial length were measured as indices of cardiac enlargement. All experiments were approved by the institutional animal care and use committee at University of California at San Francisco (UCSF).

Cell Culture

Ventricular myocytes and fibroblasts were prepared from 1- to 2-day-old neonatal Sprague-Dawley rats (Charles River Laboratories) as described previously. Both cell types were maintained in Dulbecco’s modified Eagle’s medium H-21 supplemented with 10% enriched calf serum (Gemini Bioproducts; West Sacramento, Calif).

Immunoblotting

Myocytes and fibroblasts were changed from media containing 10% enriched calf serum to media containing 10% serum substitute12 for 24 hours. At that point, fresh media containing different concentrations of ET or VD3 were added. Cells were cultured for another 24 hours. At that point, the supernatant was divided, either anti-VDR antibody or antibody alone at 1:200 final dilution. Before being added to the membrane, the mixture was diluted to 1:5. Before being added to the membrane, the mixture was diluted to 1:5. Total protein was analyzed by Western blot with horseradish peroxidase–conjugated secondary antibodies and visualized by ECL reagent (Amersham Life Sciences; Arlington Heights, Ill). When VDR–luciferase or pcDNA3. The media were then changed to serum-free media, and the cells were treated with 10⁻⁸ mol/L VD3 or vehicle and incubated for an additional 24 hours. At that time, the cells were treated with 10⁻⁷ mol/L ET or vehicle for 1 hour. The DNA immunoprecipitation assays were performed using a modification of published methodology. Briefly, after treatment, cells were fixed with 1% formaldehyde for 15 minutes at 37°C, neutralized with 0.125 mol/L glycine for 5 minutes at room temperature, washed, lysed, and sonicated. The supernatant was preincubated with protein G sepharose beads, 2 μg salmon sperm DNA, and 100 mg/mL bovine serum albumin and shaken at 4°C overnight. At that point, the supernatant was divided, either anti-VDR antibody or normal rabbit IgG was added, and the incubation was continued at 4°C overnight. Immunoprecipitates were collected then sequentially washed as described. Bound material was then eluted with freshly made elution buffer (1% sodium dodecyl sulfate and 0.1 mol/L NaHCO₃). Cross-linking was reversed by heating the elutes at 65°C overnight. DNA was extracted, and polymerase chain reaction (PCR) was performed with the following primer pair: sense 5'-CCGGAAATGTGCGTGAATAA-3' and antisense primer present in the luciferase gene coding sequence 5'-CTTCCAGGCGATGAGTGG-3'.

Total RNA Isolation and Real-Time PCR

Total RNA was isolated from cardiac myocytes and fibroblasts and left ventricles with the RNeasy kit (Qiagen) and reverse transcribed into cDNA. Real-time PCR was performed with rat ANP (Rn00561661_ml) and GAPDH (Rn99999916_sl) Taqman primers (Applied Biosystems; Foster City, Calif) and rat VDR (sense: AGGA-CAAACCCGGCAGCCT; antisense: CTGTACCTCTCATCTGTCG). rat 1-α-hydroxylase (sense: CTGACAGACTGGATAGA; antisense: AAATCCTCCTCAGGCTTTCC), and GAPDH (sense: GA-CATGCCGCTGAGA; antisense: AAGCCAGATGGCCTTTAGTG) SYBR Green primers, ANP, VDR, and 1-α-hydroxylase mRNA levels were normalized to GAPDH mRNA expression. Real-

Immunofluorescence Analysis

Cardiac myocytes or fibroblasts were isolated as described above and plated on 4-well BD Biocat culture slides coated with fibronectin (BD Bioscience; Franklin Lakes, NJ). Cells were incubated for 48 hours and fixed using Z-Fix (Anatech Ltd; Battle Creek, Mich), followed by permeabilization with 0.1% Triton X-100. The following primary antibodies were used: rabbit anti-VDR, mouse anti-α-actinin (Sigma Aldrich; St. Louis, Mo), and mouse anti-vimentin. Anti-mouse Alexa Fluor 488 (Invitrogen; Carlsbad, Calif) and anti-rabbit Cy3 (Invitrogen) secondary antibodies were used. The slides were then mounted with Vectashield mounting medium with 4’,6-diamidino-2-phenylindole (Vector Laboratories; Burlingame, Calif). Immunofluorescent images were acquired using an Olympus IX-70 inverted fluorescent microscope.

H-Thymidine Incorporation

After serum starvation in 0.1% FBS for 12 hours, cells were treated with 10⁻⁷ mol/L VD3 for 36 hours. During the final 12 hours, they were incubated with H-thymidine (4 μCi/ml) in thymidine-free Eagle’s minimal essential medium. H-thymidine incorporation assay was performed as described previously. Transfection and Luciferase Assay

Cardiac myocytes were transiently cotransfected with a human B-type natriuretic peptide gene promoter (BNP) luciferase reporter and Renilla-Luc. VDR, or retinoid X receptor expression vectors16 using lipofectin reagent (Invitrogen) as reported previously. Twenty-four hours after transfection, cells were incubated with VD3 or 25-hydroxyvitamin D 48 hours with or without ET for the final 24 hours. At that time point, the cells were collected and lysed. Luciferase activity was measured using the Dual-Luciferase kit (Promega; Madison, Wis). BNP luciferase activity was normalized for Renilla luciferase activity.

DNA Immunoprecipitation Assay

Cardiac myocytes were transfected with -198 human BNP (hBNP)–luciferase or pcDNA3. The media were then changed to serum-free media, and the cells were treated with 10⁻⁸ mol/L VD3 or vehicle and incubated for an additional 24 hours. At that time, the cells were treated with 10⁻⁷ mol/L ET or vehicle for 1 hour. The DNA immunoprecipitation assays were performed using a modification of published methodology. Briefly, after treatment, cells were fixed with 1% formaldehyde for 15 minutes at 37°C, neutralized with 0.125 mol/L glycine for 5 minutes at room temperature, washed, lysed, and sonicated. The supernatant was preincubated with protein G sepharose beads, 2 μg salmon sperm DNA, and 100 mg/mL bovine serum albumin and shaken at 4°C overnight. At that point, the supernatant was divided, either anti-VDR antibody or normal rabbit IgG was added, and the incubation was continued at 4°C overnight. Immunoprecipitates were collected then sequentially washed as described. Bound material was then eluted with freshly made elution buffer (1% sodium dodecyl sulfate and 0.1 mol/L NaHCO₃). Cross-linking was reversed by heating the elutes at 65°C overnight. DNA was extracted, and polymerase chain reaction (PCR) was performed with the following primer pair: sense 5'-CCGGAAATGTGCGTGAATAA-3' and antisense primer present in the luciferase gene coding sequence 5'-CTTCCAGGCGATGAGTGG-3'.
antivimentin, an antibody that selectively stains these cells.19

In an effort to confirm the presence of VDR through independent methodology, we performed immunocytochemistry of both myocytes and fibroblasts (Figure 2) in culture. Myocytes were stained with antibody directed against α-actinin to demonstrate sarcomeric structure, as well the anti-VDR antibody, whereas cardiac myocytes were stained with antivimentin, an antibody that selectively stains these cells.19

In both cases, the anti-VDR antibody identified immunoreactivity in the nuclei and, to a lesser degree, the cytoplasm, of the cells. The pattern of staining in the myocytes was coarser and aggregated in selected subnuclear locations, whereas that in the fibroblasts was intense but homogenous throughout the nucleus.

To assess the effects of the liganded VDR on the nonmyocyte population in the heart, we treated cells with VD3 for 36 to 48 hours before assessing proliferative (ie, 3H-thymidine incorporation) as well as synthetic effects (ie, procollagen I levels) in these cultures. As shown in Figure 3, VD3 treatment resulted in a significant reduction in both 3H-thymidine incorporation (Figure 3A) as well as procollagen I levels (Figure 3B), demonstrating that VD3 has important biological effects in these cells and suggesting that it may have antifibrotic activity in the interstitial compartment of the myocardium.

To confirm the biological activity of VD3 in the myocyte cultures, we transfected an hBNP luciferase reporter into

Figure 2. Immunocytochemistry of VDR in cardiac cells. VDR was visualized by immunofluorescence in cardiac myocytes (100×; oil immersion) and in cardiac fibroblasts (60×). A, Cardiac myocytes were double stained with a polyclonal anti-VDR antibody, visualized with Cy3 (red)-conjugated anti-rabbit antibody, and sarcomere-staining, with monoclonal anti-α-actinin (green), visualized by AG488-conjugated anti-mouse antibody. VDR colocated to the nucleus, stained with 4’,6-diamidino-2-phenylindole (DAPI; blue). B, Cardiac fibroblasts were double stained with anti-VDR, visualized with Cy3-conjugated anti-rabbit antibody and anti-vimentin, visualized with AG488-conjugated anti-mouse antibody. VDR colocated to the nucleus stained with DAPI (n=3).
these cells. BNP gene expression and BNP promoter activity serve as surrogate markers of hypertrophy.13,20,21 We then treated them with VD3 or 1 of 2 nonhypercalcemic analogues of VD3 (ie, paricalcitol or active hectorol), followed by the prohypertrophic peptide ET. As shown in Figure 4A, treatment of cells with $10^{-7}$ mol/L ET resulted in a >2-fold increase in promoter activity in these experiments. As shown in the same panel, pretreatment with VD3 or the nonhypercalcemic analogues of VD3 resulted in a reduction in basal hBNP promoter activity and a significant reduction in the ET-dependent stimulation of promoter activity. In each case, the effective dose range was similar among the 3 VDR ligands. We also tested the ability of the VD3 precursor 25-hydroxyvitamin D to suppress basal hBNP promoter activity. As shown in Figure 4B, 25-hydroxyvitamin D also led to a reduction in hBNP promoter activity, although, perhaps, with somewhat lower potency (compare effect of $10^{-10}$ mol/L VD3 in Figure 4A with effect of $10^{-10}$ mol/L 25-hydroxyvitamin D in Figure 4B). The ability of the precursor to mirror activity of VD3 implies that these cultures may have the requisite enzymatic machinery to convert 25-hydroxyvitamin D to VD3 (ie, 1-α-hydroxylase). As shown in Figure 4C, this was confirmed by Western blot analysis and real-time PCR, which demonstrated immunoreactive 1-α-hydroxylase protein and mRNA in the myocyte cultures. In this case, protein and mRNA levels were unaffected by ET treatment. Expression of 1-α-hydroxylase mRNA was also seen in cultured fibroblasts and was not changed following ET treatment (VD3 1.14±0.17-fold induction versus control; mean±SD; n=3).

To determine whether VDR was directly associated with the hBNP promoter, we performed DNA immunoprecipitation

Figure 3. VD3 inhibits fibroblast proliferation and procollagen I synthesis. A, VD3 reduces 3H-thymidine incorporation in cultured ventricular fibroblasts. Values are normalized to controls in each experiment (n=4). B, VD3 inhibits procollagen I synthesis in cultured ventricular fibroblasts. Cells were treated with VD3 for 48 hours in serum substitute (SS) media. Procollagen I protein was detected by Western blot (n=4). Values are normalized to control in each experiment. *P<0.05 vs control. C indicates control.

Figure 4. VD3, 25-hydroxyvitamin D, paracalcitol, and active hectorol inhibit -1595 BNP promoter activity in cardiomyocytes. A, -1595 BNP-Luc and Renilla-Luc were cotransfected with VDR/retinoid X receptor (RXR) expression vectors into the myocytes. Twenty-four hours after transfection, cells were treated with different doses of VD3, paracalcitol, active hectorol, or vehicle for 48 hours and ET for 24 hours before collecting cells (n=3). BNP luciferase activity was normalized for Renilla luciferase activity. B, Ventricular myocytes were transfected with -1595 BNP-Luc, Renilla-Luc, and VDR/RXR expression vectors for 24 hours and then treated with different doses of 25-hydroxyvitamin D for 48 hours (n=5). C, 1-α-hydroxylase expressed in cardiomyocytes as assessed by Western blot and real-time PCR (n=3). *P<0.05; **P<0.01 vs control; +P<0.01 vs ET alone. C indicates control.
tion analysis of myocyte cultures, previously transfected with the -198 hBNP-luciferase reporter, and then treated them with
VD3 in the presence or absence of ET. As shown in Figure
5A, this construct responded to VD3 treatment in a qualita-
tively similar fashion to the longer promoter construct used
above. Promoter activity was reduced by \( \approx 30\% \) by VD3
treatment alone and by \( >80\% \) when the cells were cotrans-
fected with VDR and retinoid X receptor (heterodimeric
partner of VDR) before VD3 treatment. Figure 5B exhibits a
direct association of VDR with the hBNP promoter. This
association was undetectable at baseline but increased after
treatment with the VDR ligand. Treatment with ET resulted
in an increase in VDR association with the promoter, and this
was further amplified by addition of the VDR ligand.

The ET-dependent induction of VDR was an unexpected
finding and raised the possibility that the activation of
hypertrophy by ET might be the driving force behind the
increased expression of the putatively antihypertrophic VDR
(ie, a closed-loop feedback system). To test this further, we
investigated cardiac VDR expression in a rat model of
myocardial hypertrophy after 7 days of continuous isoproter-
enol infusion. This infusion reliably generates significant
increases in cardiac mass and hypertrophy-dependent gene
expression (eg, ANP) over this time interval.\(^2\) As shown in
Figure 6A, isoproterenol-treated rats experienced a signifi-
cant increase in left ventricular size when normalized either
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Figure 5. Liganded VDR inhibits hBNP promoter activity through direct interaction. A, -198 hBNP-Luc and Renilla-Luc were cotran-
sfected with or without VDR/RXR expression vectors into cardiac myocytes. Twenty-four hours after transfection, cells were treated with
vehicle or VD3 for 48 hours. BNP/Renilla activities were measured, and pooled data (n=3) are shown. *\( P<0.05; **\( P<0.01 \) vs control (C).
B, Myocytes were transfected with -198 hBNP luciferase or pcDNA3 plasmid. Cells were treated with VD3 followed by ET. DNA immu-
noprecipitation assay was performed as described in Methods (n=3).

Figure 6. Isoproterenol (ISO) induces cardiac hyper-
trophy and stimulates VDR expression in the
Wistar rat. A, Rats were infused with ISO or vehi-
cle for 7 days. Animals were euthanized, and body
weight (BW), left ventricular weight (LVW), and tib-
ial length (TL) were measured (n=7). B, Left ven-
tricular samples from control and ISO-infused rats
were homogenized in extraction buffer, and total
RNA was isolated. ANP mRNA/GAPDH mRNA lev-
els were measured by real-time PCR (n=5). C,
VDR expression was assessed by Western blot
and real-time PCR. Representative immunoblot
and pooled data (n=7) for VDR protein and mRNA
measurements are presented. C indicates control.
D, 24-hydroxylase and 1-α-hydroxylase expression
were assessed by Western blot (n=7). \(*\ P<0.01 \) vs
control.
the expression of 1-α-hydroxylase, 24-hydroxylase or GAPDH protein (Figure 6D), or the 1-α-hydroxylase mRNA (1.04±0.25-fold induction relative to control; mean±SD; n=4).

Discussion
The key findings of the present report are: (1) the demonstration of VDR in both cardiac myocytes and fibroblasts, as well as ventricular myocardium, using a combination of biochemical, immunofluorescence, and functional assays, (2) the demonstration of 1-α-hydroxylase in the same sources and 24-hydroxylase protein in the intact heart, (3) the demonstration that VDR has the capacity to bind directly to the BNP gene promoter, and (4) the finding that activation of myocyte hypertrophy, either in vitro or in vivo, is associated with a significant increase in VDR expression.

Previous studies have suggested a role of the VD3/VDR system in the control of cardiac function. Our group has shown previously that VD3 as well as less hypercalcemic analogues of VD3 demonstrate antihypertrophic activity in cultured neonatal rat cardiac myocytes. Several independent studies in adult patients have linked congestive heart failure with reduced levels of circulating 25-hydroxyvitamin D levels. Moreover, Bodyak et al recently demonstrated that the VD3 analogue paricalcitol reduces cardiac hypertrophy, without affecting blood pressure, in the Dahl salt-sensitive rat. A variety of clinical studies lend additional support. Vitamin D deficiency in early childhood is associated with significant cardiomyopathy and congestive heart failure. Several independent studies in adult patients have linked congestive heart failure to reduced levels of circulating 25-hydroxyvitamin D levels. Finally, Park et al reported that low circulating levels of VD3 in patients with chronic renal failure on dialysis are linked to the presence of ventricular hypertrophy. Remarkably, treatment of these patients with exogenous VD3 resulted in amelioration of the hypertrophy.

Immunoreactive VDR has been described in human heart and cultured cardiac HL-1 cells. To our knowledge, ours is the first report that demonstrates VDR expression in both the myocyte and cardiac fibroblast and the first to document hypertrophy-dependent stimulation of VDR expression. The presence of VDR in both myocytes and fibroblasts implies that the potential exists for widespread effects of the liganded receptor in the heart (eg, suppression of myocyte hypertrophy and interstitial fibrosis). It also engenders a need to be cautious in interpreting effects of vitamin D on the heart in the whole animal. Such effects could result from direct interactions with the cardiac myocyte, indirect hemodynamic effects (eg, reductions in blood pressure), or indirect paracrine effects resulting from ligand-dependent interactions with neighboring fibroblasts.

The presence of 1-α-hydroxylase in myocytes and fibroblasts implies that the heart has the capacity to synthesize the bioactive VD3 metabolite independent of its production in the kidney, using circulating plasma 25-hydroxyvitamin D as substrate. Similar 1-α-hydroxylase immunoreactivity has been demonstrated in inflammatory cells, breast, colon, and prostate cancer cells. This is an important consideration because it places cardiac production of VD3 outside those regulatory controls that govern renal production of the ligand. In the intact heart, local tissue VD3 levels would then be a function of endogenous synthesis (ie, cardiac 1-α-hydroxylase activity and circulating plasma 25-hydroxyvitamin D levels), delivery of circulating plasma VD3 to the heart, and degradation of VD3 (eg, through 24-hydroxylase activity).

The fact that VDR binds directly to the hBNP gene promoter indicates that at least some of the effects of VD3 operate directly at the level of target gene expression in suppressing the hypertrophic phenotype rather than indirectly (eg, through alterations in hemodynamics or inhibition of inflammatory markers associated with hypertrophy). After treatment with ET, VDR binds to the hBNP promoter in the absence of exogenous ligand, a finding compatible with either ligand-independent activity of this receptor or alternatively, low-level production of VD3 in these cultures. In any case, addition of exogenous ligand clearly amplified association of VDR with the promoter. Interestingly, treatment with ET resulted in increased VDR binding, likely reflecting the hypertrophy-dependent increment in VDR available for binding in these cultures.

Finally, the induction of VDR expression with hypertrophic stimuli in vitro or in vivo might be predicted to have important implications in terms of the regulation of the hypertrophic process. In both the neonatal rat myocyte, a traditional model for studying myocyte hypertrophy in vitro, and the in vivo model of isoproterenol-induced hypertrophy, we observed an induction of VDR gene expression. The induction appears to be somewhat selective for VDR in the nuclear receptor gene family. Other family members, most notably the peroxisome proliferators activator receptor α and thyroid hormone receptor, are downregulated in the cardiac myocyte with the development of hypertrophy. We and others have suggested that VD3 or its less hypercalcemic analogues suppress myocyte hypertrophy in vivo and in vitro. Amplification of VDR expression in hypertrophy suggests that the myocyte is attempting to close a negative-feedback loop that would serve to dampen the magnitude of hypertrophic growth. Interference with the activation of this feedback mechanism would be predicted to amplify the hypertrophic response and conceivably favor progression to cardiac decompensation and heart failure.

Perspectives
Recent studies suggest that vitamin D may play an important physiological role in controlling cardiac hypertrophy. The present study adds support for this hypothesis in demonstrating that the key components of the vitamin D–dependent signaling system (ie, VDR, 1-α-hydroxylase, and 24-hydroxylase) are present in cardiac myocytes and fibroblasts. It also demonstrates for the first time that levels of VDR are upregulated during hypertrophy, implying activation of a counter-regulatory mechanism to control growth in the hypertrophied heart. Collectively, these data suggest that the use of vitamin D, vitamin D analogues, or drugs that modulate vitamin D metabolism could be beneficial in the management of disorders associated with cardiac hypertrophy.
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Disclosures
None.

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