# Left Ventricular Hypertrophy: A Shift in Paradigm

M.F.L. Meijs[1], L.J. de Windt[4], N. de Jonge[1], M.-J. M. Cramer[1], M.L. Bots[3], W.P.Th.M. Mali[2] and P.A. Doevendans[*,1]

*[1]From the Heart Lung Center Utrecht, [2]The Department of Radiology (W.P.Th.M.), [3]The Julius Center for Health Sciences and Primary Care, the University Medical Center Utrecht, [4]Utrecht, the Netherlands; The Hubrecht Laboratory, Royal Netherlands Academy of Arts and Sciences, Utrecht, the Netherlands*

**Abstract:** Observational studies have identified left ventricular hypertrophy (LVH) as a strong, independent risk factor for the development of heart failure (HF), coronary heart disease and stroke. LVH develops in response to hemodynamic overload. Classical conceptualization has it that LVH would start as an adaptive, beneficial response in order to normalize wall stress. With progression of the disease, deterioration to maladaptive hypertrophy, and further on to HF could occur. Recent experiments in animal models of pressure-overload and myocardial infarction now challenge this concept by demonstrating that blunting the hypertrophic response is actually associated with preserved cardiac function, and with improved survival. These findings may have profound therapeutical implications.

**Keywords**: Hypertrophy, ventricle, pathway, function, pressure overload, myocardial infarction, adaptive, maladaptive.

## A SHIFT IN PARADIGM

Heart failure (HF), or the inability of the heart to meet haemodynamic demands, can be regarded as the end-stage of various forms of cardiac disease. In the Western world, the prevalence and incidence of HF are increasing steadily (for review, see Kannel *et al*. [1]). HF is now the leading cause of hospitalization in the elderly. Survival after the onset of HF is grim, with a 5-year survival rate as low as 25% in men and 38% in women. The leading causes of HF are cardiac ischemic disease and hypertensive heart disease [2] [3]. In both pathologies, left ventricular hypertrophy (LVH) plays an important role.

LVH develops in response to increased biomechanical stress resulting from various conditions [4]. Firstly, long-term pressure overload can result from hypertension, aortic stenosis or coarctation of the aorta. Secondly, the surviving myocardium after myocardial infarction (MI) faces an increased diastolic wall stress. Thirdly, defects in genes encoding sarcomeric, cytoskeletal or mitochondrial proteins can result in myocardial incompetence to meet output demands. As reviewed previously [4], LVH was conventionally conceptualized to be required to maintain LV function by normalizing wall stress, as dictated by the law of Laplace [5]. With disease progression, LVH would in some cases progress to maladaptive LVH, characterized by increased fibrosis, which leads the way to HF [6]. The concept of adaptive and maladaptive LVH is now being challenged by data from animal experimental research, suggesting that any degree of LVH is detrimental for LV function and survival. In addition, observational studies have demonstrated that increased LV mass is associated with reduced LV function, and that LV dysfunction ameliorates upon LVH regression.

*Address correspondence to this author at the Department of Cardiology, Room E03.406, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; Fax: 0031-30-2581098; E-mail: p.doevendans@umcutrecht.nl

## EPIDEMIOLOGICAL EVIDENCE

### LVH: a Risk Factor for Cardiovascular Disease

The Framingham study was the first large-scale population based study to provide evidence that LVH confers increased cardiovascular risk [7]. After 30-years of follow-up in a representative sample of over 5,000 Framingham residents, electrocardiographic (ECG) patterns of LVH (ECG-LVH) were found to be associated with an increased development of various cardiovascular diseases (CVD), most notably HF, MI and stroke. ECG-LVH was related to an over 3 times increased risk for the incidence of coronary heart disease. However, ECG-LVH increased the risk of HF 17 times in subjects under the age of 65 years, and over 6 times in subjects over 65 years of age. Similarly, in the Second National Health And Nutrition Examination Survey Epidemiological Follow-up Study (NHANES-II), which studied a representative sample of the United States general population, ECG-LVH was associated with a two-fold increase in CVD development and CVD related death. Importantly, this risk was similar for normotensive when compared to hypertensive subjects. In a nested case-control study, Bots *et al.* observed that ECG-LVH was associated with a twofold increase in the risk of stroke (95% confidence interval 1.3 - 3.5) [8].

Compared to echocardiography, the sensitivity of ECG for the detection of LVH is low [9]. Therefore, more recent studies have used echocardiography instead. In a Framingham sub-study in more than 3,000 subjects of at least 40 years of age, and free of clinically apparent CVD, LVH was echocardiographically diagnosed in 15% of men and 21% of women [10]. LVH was strongly related to the incidence of CVD, CVD mortality, and all-cause mortality. After adjustment for age, classical risk factors and ECG-LVH, the relative risk of CVD for each increment of 50 g myocardium per meter height was 1.5 in both genders. The Heart Outcomes Prevention Evaluation (HOPE) study focused on high-risk subjects, defined as persons over 55

**0929-8673/07 $50.00+.00** 

years of age, with either a history of CVD, or diabetes mellitus plus one other cardiovascular risk factor [11]. Patients were not eligible if they had a history of HF, had a known ejection fraction (EF) below 40%, or had uncontrolled hypertension or overt nephropathy. Also in this high-risk population, LVH was a strong, independent risk factor for the development of HF, with a relative risk of 1.5. Also over shorter periods of time, LVH appears to confer an increased risk of LV dysfunction development. Rame *et al*. reported that during a 4-year follow-up period, 18% of 159 predominantly hypertensive black patients with LVH and a normal EF, developed reduced EF [12]. Similarly, in the population-based Cardiovascular Health Study, 14% of subjects in the highest LV mass quartile developed LV dysfunction over a 5 year observation period [13].

LVH can have a concentric morphology, i.e. increased mass in the absence of dilation, and thus increased relative wall thickness, or an eccentric morphology, i.e. increased mass with dilation, and thus normal relative wall thickness [4]. In Framingham subjects, concentric LVH conveyed increased cardiovascular risk when compared to eccentric LVH [14]. However, after adjustment for LV mass, the increase in risk associated with LV geometry was only modest. Likewise, concentric and eccentric LVH in hypertensive subjects was associated with similar cardiovascular risk in a study in 274 hypertensives with LVH [15]. In contrast, eccentric LVH was found to be a stronger predictor of adverse cardiovascular events than concentric LVH in a population-based sample of hypertensive patients [16]. Findings in the Losartan Intervention For Endpoint (LIFE) study also demonstrated differences in wall mechanics associated with variations in LV geometry in hypertensive patients. Impaired endocardial fractional shortening was most prevalent in eccentric LVH, whereas impaired midwall shortening was most prevalent with concentric LVH [17].

## LVH Regression

Pharmacological treatment can induce LVH regression. In a meta-analysis of 109 studies on blood-pressure lowering, Dahlöf and co-workers showed that angiotensin converting enzyme inhibitors (ACE-I), β-blockers, and calcium-antagonists all reduce LV mass, and that this effect is most pronounced with ACE-I [18]. In this meta-analysis diuretics reduced ventricular diameter, but not ventricular mass. More recently, the HOPE study demonstrated in high-risk patients that the ACE-I ramipril decreased the development and induced regression of ECG-LVH independent of blood pressure reduction [19]. These effects were significantly associated with reduced incidence of the composite end-point of cardiovascular death, MI or stroke (12.3% versus 15,8%) and of HF (9.3% versus 15.4%). Also in the LIFE study LVH regression was associated with reduced CVD incidence [20;21]. Using echocardiography it was found that regression of LV mass during antihypertensive treatment was significantly associated with lower cardiovascular death (hazard ratio (HR) 0.62), MI (HR 0.85), stroke (HR 0.76), and all-cause mortality (HR 0.72) [20]. Also, less-severe ECG-LVH was significantly associated with lower risks of cardiovascular death (HR 0.78), MI (HR 0.90) and stroke (HR 0.90). Furthermore, the LIFE study demonstrated superiority of the Angiotensin-II receptor type 2 ($AT_2$) antagonist losartan over the β-blocker atenolol in LVH reduction [22]. In a relatively small study, Light *et al*. demonstrated that postmenopausal estrogen replacement therapy, with or without progestins, can reduce vascular resistance and blood pressure, and reduce LV mass [23]. These effects were more pronounced in hypertensive than in normotensive women.

## LVH: a Response to Increased Wall Stress, or Not?

As mentioned above, LVH was originally postulated to be a compensatory, beneficial response to normalize wall stress. Yet, in patients with aortic stenosis, higher LV mass predicted LV dysfunction more strongly than wall stress [24;25]. This relation persisted in patients in whom LVH had normalized wall stress. The HyperGEN study population, which consisted of over 2,100 persons, in whom hypertension had been diagnosed before the age of 60 years, and who had at least one hypertensive sibling, reported similar findings [26]. Subjects who had a greater LV mass than to be expected from stroke work, gender and height, were demonstrated more frequently to have LV diastolic and systolic dysfunction. In addition, regression of concentric LVH upon treatment with the ACE-I lisinopril was associated with an improvement of midwall fractional shortening, which was more strongly dependent on LV mass reduction than on the reduction of circumferential end-systolic wall stress [27].

## Exercise-Induced LVH

LVH can also originate from prolonged physical exercise. In contrast to young patients with mild hypertension in whom LVH was associated with reduced LV diastolic function, exercise induced LVH in professional runners was associated with improved LV systolic and diastolic function [28]. Also in cyclists, LVH was not associated with significant abnormalities of cardiac function or metabolism as demonstrated by MRI and spectroscopy [29]. However, these studies provide no estimate of the long term cardiovascular risk. In addition, in athletes structural heart disease of the left ventricle is associated with an increased risk of sudden death due to arrhythmias [30].

## Genetics of LVH

The increased knowledge about the human genome and the technological advances in genotyping made it possible to study the association of genetic variations with disease, e.g. LVH. The most common variation is the single-nucleotide polymorphism (SNP), a DNA sequence variation occurring when a single nucleotide is replaced with another. A variation must occur in at least 1% of the population to be considered a SNP [31]. SNP analysis allows for the extrapolation of data from animal research to humans. In addition, it may point to a possible role for other genes, which have not yet been studied. Furthermore, in the future the genetic profile may be used to estimate the risk of disease, e.g. LVH, for the individual patient. Several studies reported an association between a SNP and increased LV mass. All associations discussed below were independent of

blood pressure and other confounding variables, except for the study by Poirier *et al*. [32], who did not report this information.

Several SNPs in the Ang-II gene were found to be associated with increased LV mass (e.g. [33;34]). Furthermore, Ang-II and $AT_1$-receptor polymorphisms were associated with the degree of LV mass regression during antihypertensive treatment [35]. Similarly, SNPs in calcineurin [32;36], an important protein in hypertrophic signaling, and in α-adducin [37], a cytoskeletal protein, were found to be associated with increased LV mass.

The most frequently employed animal pressure-overload model is aortic constriction (see Table **1**). Constricting the aorta at the level of the ascending aorta (AsAC) or transverse aorta (TAC) creates a high degree of LV pressure overload [41]. Abdominal aortic constriction (AbAC) results in less severe hypertension, and exerts its effects mainly by means of activating the Renin Aldosterone Angiotensin System (RAAS) by inducing renal hypotension [42].

The observational data outlined above have clearly linked LVH, with the exception of exercise-induced LVH, to an increased risk of the development of LV dysfunction and coronary heart disease, stroke and HF. Furthermore, LVH is also associated with an increased risk of death. Evidence from randomised controlled trials have shown that blood pressure lowering treatment can lead to regression of LVH. Importantly, LVH regression is related to improved LV function and a better prognosis.

## ANIMAL EXPERIMENTAL INVESTIGATIONS

LVH develops in order to normalize wall stress, as outlined above. The increase in LV mass originates from an increase in cell size (hypertrophy) of myocytes and from proliferation (hyperplasia) of non-muscle cells, most notably fibroblasts. In advanced stages of LVH, myocardial fibrosis is increased, resulting in decreased myocardial viscoelasticity which can lead to LV diastolic dysfunction [38]. Increased apoptosis is found in highly hypertrophic hearts and in failing hearts [4]. Many extrinsic and intrinsic molecular growth signals mediate hypertrophy, by activating various molecular pathways resulting in the expression of pro-hypertrophic genes. LVH development is associated with the induction of fetal-like gene re-programming and the induction of an immediate-early response genetic program [4]. The molecular background of hypertrophy has been

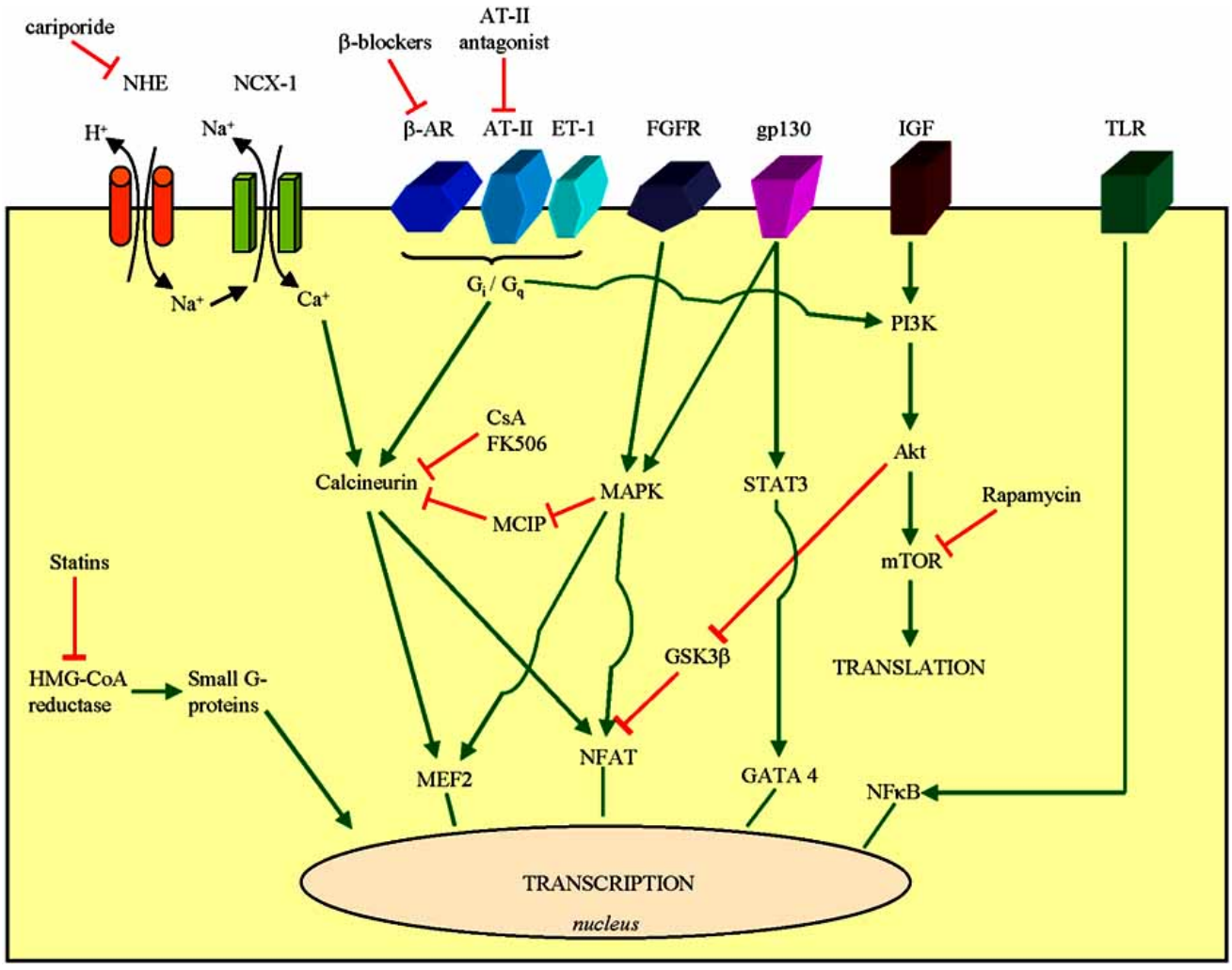


**Fig. (1).**

**Table 1. This Table Summarizes the Effect on LV Function of the Inhibition of LVH in a Situation of Pressure-Overload**

| Ref | Year | Pathway | Species | Model | LVH inhibition method | LVH response | Myofiber hypertrophy | LV dilation | Functional response | LV wall stress | Survival |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [47] | 1999 | Cn | mouse | TAC | CsA | inhibited | not reported | not reported | decreased | no change | decreased |
| [48] | 2000 | Cn | mouse | TAC | CsA | abolished | abolished | no change | no change (normal) | not reported | no change |
| [49] | 2002 | Cn | mouse | TAC | cardiac-specific hMCIP1-overexpression. | inhibited | not reported | inhibited | improved | not reported | no change |
| [50] | 2003 | Cn | mouse | TAC | MCIP1 -/- | inhibited | not reported | no change | no change (normal) | not reported | not reported |
| [51] | 2002 | Fas/ GSK3b | mouse | AbAC | Lpr | inhibited | not reported | increased | decreased, HF | not reported | reduced |
| [52] | 1999 | Cn | rat | AbAC | FK506 | abolished | not reported | not reported | no change (normal) | not reported | not reported |
| [53] | 2000 | Cn | rat | HBP (Dahl salt-sensitive rats) | FK506 (administration to young and older animals) | young: inhibited older: no change | not reported | no change | young: enhanced late: no change (normal) | young: no change older: increased | not reported |
| [54] | 2000 | Cn | rat | HBP (Dahl salt-sensitive rats) | FK506 (young and older; high and low dose) | young: high and low dose: inhibited older: high, but not low dose induced regression | young: high and low dose: inhibited older: high, but not low dose induced regression | no change | no change (normal) | not reported | young and older: no change |
| [59] | 2002 | NCX1 | mouse | NCX1-o.e *and* TAC | CsA | inhibited | not reported | decreased | improved (normalized) | not reported | not reported |
| [60] | *2000* | *Inhibition of protein synthesis* | rat | HBP (L-NAME) | L-NAME | abolished | abolished | reduced | no change (normal) | increased | not reported |
| [64] | 2004 | β-AR / eNOS | mouse | TAC | celiprolol | inhibited | inhibited | reduced | improved | not reported | not reported |
| [65] | 2005 | $Ca^{2+}$-channel | mouse | TAC | benedipine | inhibited | inhibited | reduced | improved | not reported | not reported |
| [67] | 2004 | Estrogen | mouse | TAC | raloxifene (selective estrogen receptor modulator) | inhibited | inhibited | no change | improved | not reported | not reported |
| [71] | 2001 | Various mechanisms, see text | mouse | TAC | simvastatin | inhibited | inhibited | reduced | improved | not reported | not reported |
| [75] | 1999 | Various mechanisms, see text | rat | AbAC | simvastatin or captopril | inhibited (simvastatin > captopril) | inhibited (simvastatin > captopril) | not reported | improved (simvastatin > captopril) | not reported | not reported |
| [76] | 2000 | Ang-II | mouse | AbAC | AT2 -/- | inhibited | inhibited | no change | no change (normal) | not reported | not reported |
| [85] | 2005 | ANP/ NHE | mouse | GC-A -/- | cariporide | inhibited | inhibited | no change | no change (normal) | not reported | not reported |

**(Table 1). contd.....**

| Ref | Year | Pathway | Species | Model | LVH inhibition method | LVH response | Myofiber hypertrophy | LV dilation | Functional response | LV wall stress | Survival |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [88] | 1999 | SAPK | rat | AsAC | viral transfer of SEK1(KR) | inhibited | inhibited | enhanced | no change (normal) | increased (not significant) | not reported |
| [89] | 2001 | p38 | rat | HBP (SP-SFD) | SB239063 | inhibited | not reported | enhanced | improved | not reported | increased |
| [90] | 1999 | gp130 | mouse | TAC | cardiac-specific gp130 -/- | inhibited | not reported | strongly enhanced | strongly decreased | not reported | strongly reduced |
| [91] | 2001 | gp130 | mouse | AbAC | cardiac-specific dominant negative gp130 TG | inhibited | inhibited | no change | no change (normal) | not reported | not reported |
| [92] | 2003 | Melusin | mouse | TAC | melusin -/- | inhibited | inhibited | enhanced | decreased | not reported | reduced |
| [94] | 1999 | FGF-2 | mouse | TAC | FGF2 -/- | inhibited | inhibited | no change | no change (normal) | not reported | not reported |
| [96] | 1999 | GPCR | mouse | TAC (loose and tight) | RGS4 | tight and loose TAC: inhibited | tight & loose TAC: inhibited | tight TAC: increased loose TAC: normal | tight TAC: decreased loose TAC: no change (normal) | not reported | tight & loose TAC: reduced |
| [98] | 2001 | GPCR | mouse | AbAC | Cardiac-specific ($G\alpha_q$- and $G\alpha_{11}$) -/- | inhibited | inhibited | no dilation in WT nor TG | improved (decrease diastolic function prevented) | not reported | not reported |
| [99] | 2002 | GPCR | mouse | TAC | 1) cardiac-specific inhibition of $G\alpha_q$ 2) β-hydroxylase -/- | inhibited | not reported | 1) inhibited 2) inhibited | 1) improved 2) improved | WT: normalized both TG: increased | not reported |
| [100] | 2002 | GPCR | mouse | TAC | KB-R7785 | inhibited | inhibited | reduced | improved | not reported | not reported |
| [103] | 2003 | mTOR | mouse | AsAC | rapamycin | inhibited | inhibited | reduced | no change (normal) | not reported | not reported |
| [108] | 2005 | MyD88 | rat | AsAC | dominant negative MyD88 transfection into heart | inhibited | inhibited | reduced | improved | not reported | not reported |
| [110] | 2003 | Adenosine | mouse | TAC | CADO | inhibited | inhibited (in vitro) | reduced | improved | not reported | not reported |
| [112] | 2002 | MMPs | mouse | volume overload | PD 166793 | inhibited | not reported | abolished | Improved (normalized) | not reported | not reported |

*Abbreviations:*

-/- = knock-out; AbAC = abdominal aortic constriction; Ang-II = Angiotensin-II; ANP = Atrial Natriuretic Peptide; AT2 = Angiotensin-II receptor type 2; β-AR = β-Adrenergic Receptor; CADO = 2-chloroadenosine; Cn = Calcineurin; CsA = Cyclosporin A; FGF-2 = Fibroblast Growth Factor 2; FK506 = Tacrolimus; $G\alpha_q$ *and* $G\alpha_{11}$ = G-proteins; GC-A = Guanylyl Cyclase-A receptor; gp130 = gp130 cytokine receptor; GPCR = G-Protein Coupled Receptor; GSK3β = Glycogen Synthase Kinase 3β; HBP = high blood pressure; hMCIP1 = human Modulatory Calcineurin Interacting Proteins; KB-R7785 = Disintegrin and Metalloprotease 12 inhibitor; L-NAME = $N^G$-nitro-L-Arginine Methyl Ester; Lpr = lymphoproliferative disease mice; MMPs = Matrix Metalloproteinases; mTOR = mammalian Target of Rapamycin; MyD88 = Myeloid Differentiation Factor 88; NCX1 = $Na^+/Ca^{2+}$-exchanger; NHE = $Na^+/H^+$ exchanger; NPPA = Pro-Atrial Natriuretic Peptide; p38 = p38-Mitogen Activity Protein Kinase; PD 166793 = MMP inhibitor; RGS4 = Regulator of G-protein Signaling sub-type 4; SAPK = Stress-Actived Protein Kinases; SB239063 = p38-inhibitor; SEK-1(KR) = SAPK inhibitor; SP-SFD = spontaneously hypertensive stroke-prone rats on a high salt high fat diet; TAC = transverse aortic constriction; TG = transgenic

described in detail elsewhere [4;39;40]. In this paper, the focus is on those animal experiments that reported the effect of inhibiting LVH on LV function.

Therefore, we have only discussed the pathways relevant to these articles (see Fig **1**).

## Calcineurin and Related Pathways

The most extensively studied pathway in pressure-overload is the calcineurin pathway. This pathway is activated by prolonged increases in cytosolic $Ca^{2+}$, which leads calcineurin to dephosphorylate the transcription factor Nuclear Factor of Activated T cells (NFAT), which then translocates to the nucleus [43]. In addition, calcineurin can directly and indirectly activate the transcription factor Myocyte Enhancer Factor 2 (MEF2). Calcineurin has an important role in LVH [44]. Mice with cardiac-specific over-expression of calcineurin display LVH. More conclusive genetic confirmation of the involvement of calcineurin in LVH development included pressure overload studies by Bueno and colleagues [45]. In this study it was demonstrated that mice harbouring disruption of the calcineurin A-beta, a gene encoding an important component of the catalytic site of calcineurin, were resistant to pressure-overload and agonist-induced LVH.

Calcineurin can be inhibited by cyclosporine A (CsA) and tacrolimus (FK506), which are used clinically as immunosuppressive agents. CsA and FK506 form a complex with endogenous immunophilin proteins, that interact with and inhibit calcineurin. Endogenous inhibition of calcineurin is mediated by modulatory calcineurin interacting proteins (MCIP). In addition, in unstimulated cells glycogen synthase kinase 3β (GSK3β) is unphos-phorylated. In this active state, GSK3β phosphorylates NFAT, thereby inactivating the calcineurin – NFAT signaling pathway. As reviewed by Bueno *et al*. and by Wilkins *et al*. [43;46], calcineurin inhibition resulted in reduced LVH in most, but not all, studies employing various animal models of LVH. Of note, studies on CsA or FK506 treatment are difficult to interpret, since these agents display systemic toxicity and significant non-calcineurin dependent effects. Meguro *et al*. used CsA to inhibit LVH after TAC, and reported decreased LV function and survival [47] (see Table **1**). However, the very high post-operative mortality rate in this study (43% in untreated and 72% in CsA-treated animals 3 weeks after TAC) makes valid interpretation of these results difficult. In the same experimental setting, Hill *et al*. managed to keep 5-week mortality in untreated mice down to 10% [48]. CsA abolished LVH, which did not influence LV dilation, LV function nor survival after pressure-overload. In a later experiment, the same group used TG mice with myocardial over-expression of the gene product of Down's Syndrome Critical Region 1 (DSCR1) or myocyte-enriched calcineurin interacting protein 1 (MCIP-1), an endogenous inhibitor, which, once overexpressed, results in cardiac-specific calcineurin inhibition [49]. Also in these mice, TAC-induced LVH was attenuated, yet LV dilation was inhibited, and cardiac function was improved compared to WT animals [49]. Paradoxically however, Vega *et al*. observed that MCIP-1 KO mice displayed less LVH in response to TAC than WT animals [50]. Again, LV dilation and cardiac function were not affected. These findings suggest that MCIP1 can facilitate or suppress cardiac calcineurin signaling in response to TAC.

The calcineurin pathway is closely involved with other signaling pathways. Of these, the Fas receptor signaling pathway and the $Na^+/Ca^{2+}$-exchanger pathway will be discussed below.

Fas receptor signaling has pro-apoptotic consequences in most cell-types. In cardiomyocytes however, prohypertrophic effects are more pronounced. Lymphoprolif-erative disease (lpr) mice lack a functional Fas receptor, and do not develop LVH after AbAC by a failure to inhibit GSK3β activity. In this study WT animals developed concentric LVH after AbAC, while cardiac function was not reduced. In contrast, lpr-mice developed LV dilation and HF, resulting in increased mortality. Importantly, no difference in apoptosis was observed [51]. In a rat study, abolishing AbAC-induced LVH with the calcineurin inhibitor FK506 did not result in functional deterioration or lower survival [52]. The Dahl salt-sensitive rat on a high salt diet develops hypertension from 7 weeks of age, accompanied by progressive LVH, eventually resulting in HF. Sakata *et al*. and Shimoyama *et al*. administered FK506 to these rats either early or late in the disease process [53] ;[54]. Early in the disease process, a low dose FK506 already proved sufficient to prevent LVH. Regression of LVH in older animals proved possible, but required a higher dose of FK506. Sakata *et al*. reported that early FK506-induced LVH attenuation prevented HF, whereas later treatment did not. Shimoyama *et al*. observed no compromised LV function in either untreated or treated rats. Sakata *et al*. did not report mortality rate, whereas Shimoyama *et al*. observed high mortality in treated animals, due to pulmonary infection as a consequence of impaired immunity.

At the onset of diastole, the sarcolemmal $Na^+/Ca^{2+}$-exchanger (NCX1) starts extruding cytosolic $Ca^{2+}$ in exchange for extracellular $Na^+$ (for review see [55]). In the failing heart, increased diastolic $Ca^{2+}$ concentrations have been observed [56]. NCX1 expression levels and activity are increased in animal models of pressure-overload and of HF (for review see [57], presumably in an attempt to maintain $Ca^{2+}$ homeostasis. The NCX1 promoter is dependent on GATA4 [58], a transcription factor with an important role in LVH [44]. In addition, increased NCX-1 protein levels were observed in the hearts of TG mice overexpressing a constitutively active form of calcineurin [59]. These findings suggest that NCX-1 expression is under control of a calcineurin dependent pathway. In addition, it was observed that CsA inhibited NCX-1 promoter activity *in vitro* [59]. NCX1-overexpressing TG animals develop LVH in response to cardiovascular stress during pregnancy, and die of HF. These animals also develop LVH when subjected to TAC [59]. In this setting, CsA treatment resulted in attenuated LVH and normalized cardiac function [59]. However, no WT animals were examined. Additionally, calcineurin levels were not measured.

The results reviewed above suggest that LVH attenuation by calcineurin inhibition, especially when obtained in a cardiac-specific manner, is associated with improved cardiac function and survival. This forms a strong motivation for further research on the calcineurin pathway. Below we will discuss studies reporting similar findings on cardiac function

and survival after interference with other pathways in LVH development.

### Nitric Oxide

$N^G$-nitro-L-arginine methyl ester (L-NAME) causes severe hypertension by vasoconstriction due to the inhibition of nitric oxide (NO) synthesis. However, L-NAME also inhibits cardiomyocyte protein synthesis. Bartunek *et al*. treated rats with L-NAME for 6 weeks [60]. Blood pressure in the ascending aorta rose to similar levels as untreated animals which were subjected to TAC. Whereas the animals subjected to TAC displayed LVH, LV wall mass remained unchanged in the L-NAME treated animals. LV systolic wall stress was elevated and comparable between L-NAME treated and animals that underwent TAC. Cardiac function remained normal in the TAC group, and, surprisingly, also in the L-NAME treated group. These observations could be explained, at least in part, by a decrease in LV diameter in the L-NAME group compared to the control and TAC groups; and by the observed increased myocardial contractility. Again, these findings suggest that LVH is not essential to maintain cardiac function.

Pharmacologically increased endothelial NO synthase (eNOS) signaling has been shown to exert anti-hypertrophic effects, also in a blood-pressure independent manner (for review see [61]). NO also has positive inotropic effects on cardiomyocytes, decreases myocardial fibrosis, and promotes angiogenesis (for review see [62]). NO seems to have an important role in LVH inhibition by β-blockers. Beta-blockers have been demonstrated clinically to reduce LVH [63]. In mice subjected to TAC, the selective $\beta_1$-blocker, celiprolol, attenuated LV hypertrophy and dilation, and reduced myocardial fibrosis [64]. Celiprolol improved fractional shortening, and prevented HF development. Interestingly, all salutary effects of celiprolol were blunted by the NO-inhibitor L-NAME, and celiprol increased myocardial eNOS protein levels and activity. These findings suggest that celiprolol exerts its effects via a NO-dependent pathway. In the same animal model, it was also observed that benedipine, a long-acting $Ca^{2+}$ -channel blocker, strongly attenuated LV hypertrophy and dilation, and prevented HF [65]. *In vitro*, co-administration of L-NAME prevented benedipine induced inhibition of protein synthesis in cardiomyocytes, again suggesting NO dependence. Interestingly, NO also seems to have an important role in LVH inhibition by 17β-estradiol. Treatment with 17β-estradiol prevents LVH after TAC [66]. Ogita *et al*. observed that the selective estrogen receptor modulator (SERM) raloxifene attenuated TAC-induced LVH, and prevented LV dysfunction [67]. The effects of raloxifene were partially counteracted by co-treatment with L-NAME, again indicating an important role for NO. As described below, LVH reducing effects of Hydroxy-3-MethylGlutaryl Coenzyme A (HMG-CoA) reductase inhibitors, or statins, may also operate partially through NO.

### Statins

Statins are widely used in clinical practice to lower serum cholesterol levels. In recent years, experimental research has focused on non-cholesterol mediated effects of statins on LVH. The molecular mechanisms behind these effects are complex and diverse. Firstly, statins inhibit mevalonate (MVA) synthesis [68]. MVA, which is synthesized by HMG-CoA reductase, is required for DNA replication and cell cycle progression, and thus for cell growth [69]. Secondly, statins interfere with small G protein signaling. Small G proteins are important in myocyte hypertrophy, and also in changes in sarcomeric and cytoskeletal organization characteristic for LVH (for review see [70]). Statins inhibit small G-protein mRNA and protein expression, and additionally, reduce their membrane-translocation and GTP-binding activity by inhibiting their isoprenylation [71]. Thirdly, statins have anti-oxidant mechanisms [71]. Fourthly, the anti-inflammatory properties of statins may also contribute to preservation of LV function [72]. Lastly, statins induce an upregulation of eNOS [73], and statins inhibit Matrix Metalloproteinases (MMPs) [74]. These latter two possible mechanisms of action are discussed in more detail in the section on LVH after MI. Luo observed that simvastatin attenuated AbAC-induced hypertrophy of the LV and individual myocytes, and that it did so to a greater extent than the ACE-I captopril [75]. The blunted hypertrophic response was associated with improved LV function, again most notably so in statin treated animals. This study did not provide evidence for the mechanism of action of statins. Takemoto confirmed these findings in a TAC-mouse-model. Interestingly, Takemoto observed decreased myocardial activity of small G proteins Rac1 and Rho and decreased superoxide anion ($O_2^-$) production. [71] Furthermore, in *in vitro* experiments, the addition of L-mevalonate could reverse angiotensin II (Ang II) induced myocyte hypertrophy [71].

### Angiotensin II and Atrial Natriuretic Peptide

AngII is a strong pro-hypertrophic stimulus. Compared to WT animals, AngII-KO mice displayed reduced LVH and myocardial fibrosis in response to AbAC, while LV dimensions and function were similar [76]. During LVH development, atrial natriuretic peptide (ANP) is upregulated, which acts as an intrinsic inhibitor of LVH both by downregulating blood pressure, but also by direct anti-hypertrophic effects [77]. Franco *et al*. demonstrated that proatrial natriuretic peptide (NPPA) null or hemizygous mice, display increased LVH after TAC compared to WT animals [78]. In the KO animals, the enhanced LVH was associated with increased dilation and reduced LV function. ANP is known to exert its effects on BP and LVH through its guanylyl cyclase-A receptor (GC-A) [79]. Mice with a global deficieny of GC-A display hypertension and LVH, which is disproportionate to the level of hypertension [80]. Additional evidence of a direct anti-hypertrophic effect on the myocardium is derived from the observation that cardiomyocyte-restricted GC-A deficient mice demonstrate LVH despite normotension [81]. Furthermore, when compared to WT animals, LVH and LV dysfunction in response to TAC were exacerbated. Interestingly, it was demonstrated that 17β-estradiol exerts its anti-hypertrophic effects, at least partly, through the induction of ANP [82].

### The Sodium/ Hydrogen Exchanger

The sodium/ hydrogen exchanger (NHE) is activated early in the hypertrophic response [83]. Enhanced NHE

activity results in an augmented $Na_i^+$-concentration, and eventually through $Na^+/Ca^{2+}$- exchange in an augmented $Ca^{2+}$-influx [84]. As discussed above, increased intracellular $Ca^{2+}$ levels can initiate LVH. After observing that LVH in global GC-A KO mice is associated with increased myocardial activity of the $Na^+/H^+$ exchanger NHE, Kilic *et al*. demonstrated that the NHE inhibitor cariporide attenuated LVH and myocardial fibrosis despite persistent hypertension [85]. Also in this study, reducing LVH did not negatively effect LV dilation and function.

### Mitogen Activity Protein Kinases

The Mitogen Activity Protein Kinase (MAPK) signaling pathway is important in the development of LVH (for review see [86;87]). The MAPK-family consists of p38 MAPKs, extracellular signal-regulated kinases (ERKs), and c-Jun N-terminal kinases (JNKs). The latter two groups are also known as stress-actived protein kinases (SAPKs). In severe hypertension induced by ascending aortic constriction (AsAC), inhibiting SAPK signaling by viral transfer of the SAPK inhibitor, SEK-1(KR), resulted in decreased hypertrophy of the LV and individual cardiomyocytes [88]. LV function was not deteriorated, but dilation was increased. Spontaneously hypertensive stroke-prone rats develop hypertension and LVH when on a high salt high fat diet. In this rat model, long-term inhibition of p38-MAPK by SB239063, resulted in attenuated LVH, and increased dilation [89]. However, LV function and survival were increased.

Interleukin-6 (IL-6) and several other pro-hypertrophic cytokines mediate their effects via the gp130 cytokine receptor, followed down-stream by activation of the MAPKs and the transcription factor Signal Transducer and Activator of Transcription 3 (STAT3). After TAC, cardiac-specific gp130-deficient mice displayed attenuated LVH, associated with the rapid onset of dilated cardiomyopathy, which resulted in reduced survival [90]. However, this may be due to the observed induction of massive apoptosis, rather than to the reduction in LVH. In contrast, Uozumi did not observe increased apoptosis in a similar setting [91]. In this study, the cardiac-selective expression of a dominant negative mutant of gp130 attenuated pressure-overload induced LVH in the mouse, but was not associated with changes in LV dilation or function.

### Melusin

Melusin interacts with the integrin $\beta_1$ cytoplasmic domain in pressure overload induced LVH. After TAC, Melusin-deficient mice displayed reduced LVH and increased dilation. LV function and survival were decreased [92]. After TAC, KO mice displayed increased GSK-3β phosphorylation, and, thus, more inhibition of NFAT, when compared to WT animals. In contrast, when compared to WT mice, KO mice developed a similar degree of LVH in response to chronic administration of AngII or phenylephrine, suggesting that melusin only plays a role in LVH induced by biomechanical stress. In line with these results, cardiac-specific overexpression of melusin resulted in concentric LVH after pressure-overload, in contrast to WT animals that displayed eccentric LVH culminating in HF [93]. While WT animals developed HF, this was prevented in TG mice. These findings suggest that melusin is required for the maintenance of cardiac function in the face of long-standing LVH.

### Fibroblast Growth Factor 2

Schultz *et al*. observed a blunted hypertrophic response after TAC in fibroblast growth factor 2 (FGF-2) KO mice [94]. No excess LV dilation was observed, and LV function maintained normal in both WT and TG animals.

### G-proteins

G-proteins mediate signal transduction immediately down-stream to the 7-transmembrane receptors for endothelin ($G_q$), ang-II ($G_q$) and norepinephrine ($G_q$ and $G_i$) (for review, see Rockman *et al.* [95]). In unstimulated cells, the α, β and γ-sub-units of heterotrimeric G-proteins form a complex. After activation by 7-transmembrane receptors, guanosine triphosphate (GTP) binds to the α-subunit, followed by the dissociation of the β and γ-sub-units. Due to GTPase activity, GTP eventually dissociates from the $G_\alpha$-subunit again, leading to the reformation of heterotrimers. GTPase-activating proteins (GAPs) promote the deactivation of $G_\alpha$-GTP-complexes, which have only weak intrinsic GTP hydrolysis activity. Rogers *et al*. engineered transgenic mice cardiac-specifically overexpressing Regulator of G-protein Signaling sub-type 4 (RGS4), a GAP which deactivates $G_{\alpha i}$ and $G_{\alpha q}$ proteins [96]. First, these mice were subjected to tight TAC, i.e. 60-70% stenosis of the transverse aorta. Whereas 80% of non-transgenic mice survived for at least 1 week post-operatively, most RGS4-TG mice died within 2 hours after tight TAC. One-week survival was as low as 11% in the RGS4-TG animals. Interestingly, 1 week after surgery, most WT animals developed significant LVH. In contrast, two days post surgery, surviving RGS4-TG animals demonstrated LV dilation, wall thinning and depressed LV function, in the absence of significant LVH. To increase post-operative survival, mice were subjected to loose TAC, i.e. 40-50% stenosis of the transverse aorta. 75% of WT animals survived until 1 week after loose TAC, as compared to only 33% of RGS4-mice. LVH was significantly blunted in TG-mice, but LV function and LV volume remained at base-line levels, similarly to WT animals. Whereas WT animals displayed fibrosis and myofibrillar disarray, TG-mice did not. TG animals exhibited a decreased myocardial contractility early after surgery, which may explain the marked reduction in short-term survival. It is tempting to speculate that in the long term surviving TG animals might actually fare better than WT mice, since the former did not display LV dysfunction, nor histological abnormalities 1 week after surgery. A question which could not be answered from these data. Interestingly, mice with cardiac specific over-expression of a peptide inhibiting $G_{\alpha q}$, but not $G_{\alpha i}$, also demonstrated a reduced hypertrophic response to TAC, but had no reduction in survival [97]. Unfortunately, LV function was not reported in this study. Wettschureck *et al*. constructed mice lacking both $G_{\alpha q}$ and $G_{\alpha i}$ in the heart [98]. The hypertrophic

response to TAC was completely abrogated in these mice. Whereas neither WT nor TG animals displayed LV dilation or LV systolic dysfunction, diastolic LV function was preserved only in TG animals. In a landmark paper, Esposito *et al*. reported on TG mice with cardiac-specific overexpression of a carboxyl terminal peptide of $G_{\alpha_q}$ that specifically inhibits $G_{\alpha_q}$ mediated signaling [99]. The same study also employed animals deficient in dopamine β-hydroxylase, an enzyme essential in the production of norepinephrine and epinephrine. Both strains demonstrated a blunted hypertrophic response after TAC. Seven days after TAC, wall stress was normal in wild-type animals, but significantly elevated in both transgenic strains, as demonstrated by sonomicrometry. During a post-surgical period of 8 weeks, echocardiography demonstrated progressive LV dilation and dysfunction in WT mice but not in either TG strain, which retained normal values. Thus, while blunting LVH resulted in failure to normalize wall stress after TAC, the LV dysfunction as observed in wild-type mice was prevented in this study.

G-protein coupled receptor signaling involves transactivation of the epidermal growth factor receptor (EGFR) [100]. This is mediated by the EGRF ligand truncated heparin-binding EGF (HB-EGF). Disintegrin and metalloprotease 12 (ADAM12) is required for truncating membrane-bound pro-HB-EGF. After TAC, ADAM12-inhibition by KB-R7785 prevented HB-EFG shedding, which was associated with reduced LVH and improved LV function [100].

### Mammalian Target of Rapamycin

The mammalian target of rapamycin (mTOR) is an important component of the phosphoinositide 3-kinase (PI3K) pathway, which plays an important role in LVH development [101]. Activation of the PI3K enzymes by G protein coupled receptors or by the insulin growth factor-1 (IGF-1) receptor, results in activation of the kinase Akt. Akt in turn activates mTOR and inhibits GSK3β. Upon activation by Akt, mTOR promotes translation via its effectors p70 ribosomal S6 kinase (p70S6K) and eIF4E. After forming an inhibitory complex with FK506-binding protein (FKBP12), rapamycin binds to mTOR and inhibits activation of the targets of mTOR [102]. This way, rapamycin inhibits hypertrophic cell growth. Shioi *et al*. observed attenuated hypertrophy of the LV and individual myocytes and attenuated LV dilation and myocardial fibrosis in mice after TAC upon pre-treatment with rapamycin [103]. Cardiac function remained normal in both treated and untreated mice. No adverse rapamycin side effects were observed. In a later study the same group reported LVH regression when rapamycin therapy was started 1 week after TAC [104]. At that point in time, LVH development in some animals was associated with normal LV function, whereas others displayed LV dysfunction and dilation. Rapamycin induced LV mass regression in both groups. In addition, in decompensated animals, LV dilation and LV dysfunction were also partially reversed. The degree of LVH regression after rapamycin was greater in mice with normal cardiac function, suggesting that the mTOR-dependent pathway is of greater importance in the initial stages of LVH than after the onset of LV dysfunction.

### Nuclear Factor kappa B

Nuclear Factor kappa B (NFκB) is a transcription factor which is important in many processes, most notably apoptosis, immunity and cell growth (for review see [105]). NFκB can be activated by a number of signaling pathways, e.g. via the Toll like receptor (TLR). TLRs were demonstrated to have an important role in innate immunity and CVD (for review see [106]). TLRs activate NFκB upon binding pathogen associated molecular patterns (PAMPS) and endogenous ligands. Interestingly, also other pathways are known to activate NFκB. Most of these, such PI3K, NFAT, Ras, gp130 and JAK/STAT signaling, were also demonstrated to be important in LVH development. Indeed, Li *et al*. demonstrated that inhibiting NFκB resulted in attenuated LVH after aortic banding [107]. The same group demonstrated that Toll-like receptor 4 (TLR4)-deficient mice demonstrate reduced LVH after pressure-overload [108]. An important signaling molecule involved in the TLR4 pathway leading to NFκB activation is myeloid differentiation factor 88 (MyD88) [106]. Viral transfection of dominant negative MyD88 reduced LVH and myocardial fibrosis, and improved cardiac function after AsAC [109]. Furthermore, blocking MyD88 was associated with a decrease in myocardial apoptosis. After TAC, treatment with the adenosine analogue 2-chloroadenosine (CADO) resulted in a reduction of LV hypertrophy, dilation and fibrosis, and cardiac function was enhanced [110]. Adenosine may exert its anti-hypertrophic effects by anti-adrenergic effects, as plasma NE levels were decreased in this study. In addition, myocardial expression of RGS4 was found to be upregulated.

Cardiac remodeling is preceded by partial degradation of the extracellular matrix by Matrix Metalloproteinases (MMPs) [111]. By creating intrarenal abdominal aortocaval fistula, Chancey exposed mice to chronic biventricular volume overload, resulting in LVH and LV dilation, and LV dysfunction [112]. The MMP inhibitor PD 166793 abolished LV dilation and reduced LVH, resulting in the preservation of LV function. In line with these findings, a cross-sectional study in Framingham participants demonstrated that plasma MMP-9 was detectable in 20% of individuals [113]. Detectable plasma MMP-9 levels were associated with increased LV end-diastolic dimensions and increased wall thickness in men, but not in women.

### Genetic Re-Programming

Consistently, the attenuation of LVH after pressure-overload was associated with inhibition of the induction of the fetal gene re-programming and the immediate-early response genetic program associated with LVH development.

## LVH AFTER MYOCARDIAL INFARCTION

### Angiotensin II

Several studies focused on the effect on LV-function of blocking or antagonizing Ang-II after MI (see Table **2**). Harada *et al*. induced MI by ligating the left coronary artery (LCA) in Ang-II receptor type-1a (AT1a)-KO mice [114]. Compared to WT animals, KO mice displayed less LVH, LV dilation, and LV fibrosis after MI. Importantly, despite

**Table 2. LVH After myocardial Infarction**

| Ref | Year | Pathway | Species | Model: LCA ligation +: | LVH response | Myofiber hypertrophy | LV dilation | Functional response | Survival |
|---|---|---|---|---|---|---|---|---|---|
| [114] | 1999 | Ang-II | mouse | AT1a -/- | inhibited | not reported | inhibited | improved | increased |
| [115] | 2005 | Ang-II | mouse | AT1a -/- | female -/-: inhibited, male -/-: no change | female -/-: inhibited, male -/-: no change | no change | male -/-: no change female -/-: enhanced (normal) | no change |
| [116] | 1999 | Ang-II | rat | irbesartan | inhibited | not reported | inhibited | improved | not reported |
| [117] | 2000 | Ang-II | rat | lisinopril *or* losartan *or* lisonopril + losartan | inhibited, especially in combination therapy | not reported | inhibited | no change | increased, especially in combination therapy |
| [118] | 2000 | Cn | rat | CsA | inhibited | not reported | enhanced | inhibited | not reported |
| [119] | 2002 | Cn | rat | CsA | inhibited | not reported | enhanced | inhibited | not reported |
| [120] | 2001 | Cn | rat | CsA | inhibited | not reported | enhanced | enhanced diastolic function | no change |
| [121] | 2004 | Cn | mouse | cardiac-specific MCIP1 overexpression | inhibited | inhibited | inhibited | improved | increased |
| [73] | 2002 | *various mechanisms, see text* | rat | cerivastatin | inhibited | not reported | no change | improved | no change |
| [74] | 2002 | *various mechanisms, see text* | mouse | fluvastatin | inhibited | inhibited | inhibited | improved | increased |
| [122] | 2003 | MCP-1 | mouse | 7ND-transfection | inhibited | inhibited | inhibited | improved | increased |
| [123] | 2004 | NOS3 | mouse | cardiac-specific NOS3 overexpression | inhibited | inhibited | inhibited | improved | no change |
| [124] | 2005 | S100B | mouse | S100B overexpression | inhibited | not reported | no change | no change | decreased |
| [125] | 2001 | NHE | rat | cariporide | inhibited | abolished | inhibited | improved | not reported |
| [126] | 2000 | NHE | rat | cariporide | inhibited | abolished | no change | improved | not reported |

Abbreviations:
-/- = knock-out; 7ND = MCP-1 mutant; Ang-II = Angiotensin-II; AT1a = Angiotensin-II receptor type 1a; Cn = Calcineurin; CsA = Cyclosporin A; MCP-1 = Monocyte Chemoattractant Protein-1; MCIP1 = Modulatory Calcineurin Interacting Proteins; NHE = $Na^+/H^+$-exchanger; S100B = intrinsic LVH inhibitor.

the blunted hypertrophic response, LV function was preserved and survival increased. Interestingly, female, but not male, AT1a-KO mice displayed significantly less LVH after MI [115]. LV function was preserved only in female KO mice. These results suggest that the pro-hypertrophic effects of Ang-II are mediated by the AT1a-receptor in female mice, while the AT1a receptor is less crucial in male. However, the finding that systolic BP was significantly lower in KO's than in WT animals confounds these results. Selective pharmaceutical antagonism of the AT1-receptor by irbesartan after LCA-ligation in rats resulted in an attenuated hypertrophic response, less dilation, and a better preservation of LV function [116]. The addition of an ACE-I (lisinopril) to an AT1-antagonist (losartan) resulted in enhanced blunting of LVH and LV dilation, and better preserved LV function compared to either the ACE-I or the AT1-antagonist individually [117].

### Calcineurin

Results of inhibiting the calcineurin pathway after MI may seem contradictive at first glance. In studies by Oie *et al*. and by Youn *et al*., blunting the hypertrophic response after MI by calcineurin-inhibition with CsA resulted in increased dilation, and reduced LV-function [118], [119]. In the former study, CsA-treated rats also demonstrated diminished survival. In another study however, diminished LVH by CsA-treatment resulted in better preservation of LV-function, and survival was similar to untreated rats [120]. As discussed above, studies using CsA must be interpreted with caution. Van Rooij and co-workers used a more elegant method to inhibit calcineurin [121]. They engineered TG mice carrying MCIP1 under control of the α-myosin heavy chain promoter. This cardiomyocyte restricted MCIP1 over-expression resulted in decreased calcineurin activity, decreased hypertrophy of the LV and of individual myocytes after MI, and increased LV dilation. Importantly, cardiac function was better preserved and survival was higher in TG animals. These studies suggest that blunting LVH after MI by interference with calcineurin can be beneficial for preserving LV function and survival, provided that systemic side effects are avoided.

### Statins

As was also discussed in the section on pressure overload, statins were found to have anti-hypertrophic properties. After MI, cerivastatin resulted in reduced LVH without increased dilation. LV function and survival were similar to untreated rats [73]. Interestingly, NOS-inhibition by L-NAME abolished these salutary effects, suggesting that cerivastatin exerts its anti-hypertrophic effect by increasing NOS. Hayashadani *et al*. observed that fluvastatin-treated mice demonstrated reduced post-infarction LVH and LV dilation, while cardiac function was improved [74]. The increase in interstitial fibrosis, and LV MMP-2 and MMP-13 activity after infarction were attenuated by fluvastatin. Importantly, cholesterol levels did not differ between treated and untreated animals.

### Various Other Pathways

Transfecting an N-terminal deletion mutant of monocyte chemoattractant protein-1 (MCP-1), which acts to inhibit endogenous MCP-1, resulted in less hypertrophy of the LV and individual myocytes, and less LV dilation and fibrosis afer MI [122]. LV function was better preserved and survival was increased. Cardiomyocyte-specific over-expression of nitric oxide synthase 3 (NOS-3) gave similar results [123]. Tsoporis *et al*. found that transgenic mice over-expressing S100B, an intrinsic negative regulator of LVH, demonstrate attenuated LVH after MI at similar dilation and LV function compared to WT animals [124]. Similar to the findings of Kilic *et al*. in pressure-overload, Kusumoto *et al*. and Yoshida *et al*. observed that the administration of the NHE-inhibitor cariporide before or immediately after LCA ligation resulted in attenuated LVH, which was associated with improved cardiac function [125;126].

### Wall Stress

Unfortunately, since LV systolic wall stress was not reported, it is not known whether blunted post-myocardial LVH indeed resulted in increased wall stress in the studies reviewed in this section.

### Apoptosis

Regrettably, only Oie *et al*. and Tsoporis *et al*. studied the effect of the intervention on post-MI apoptosis [118;124]. Oie *et al*. found that apoptosis was very rare, and concluded that the observed changes in LVH, LV dilation or LV function could therefore not be accounted for by a change in apoptosis [118]. In contrast, Tsoporis *et al*. found that over-expression of S100B was associated with increased apoptosis. As reviewed previously [127], LVH and apoptosis are a 'balancing act'. Interventions that reduce LVH, may increase apoptosis. Highly increased apoptosis may eventually result in HF, due to detrimental effects on LV geometry and function [128]. However, the results of Tsoporis suggest that in the post-MI setting the beneficial effect of blunting LVH may outweigh possible adverse effects of an increase in apoptosis.

### Genetic Re-Programming

Similar to the animal studies on pressure overload, the attenuation of LVH after MI was associated with inhibition of induction of the fetal gene re-programming and immediate/early response-genetic program.

## PERSPECTIVE

The accumulating evidence from obversational and animal-experimental studies suggests that, in pressure overload or after MI, hypertrophy is not required to maintain cardiac function. This is in contrast to conventional conceptualization. Therefore, in future experiments investigators should focus on cardiac function, not on morphology. However, most of the data reviewed above originate from experimental studies in rodents with only a short follow-up period. Longer studies are required to clarify whether an attenuated hypertrophic response to MI or pressure-overload remains beneficial in the long-run. In addition, experimental research in larger animals should be

performed. Furthermore, longer term follow-up studies in patients with hypertension and after MI should be conducted. Such studies should employ MRI. When compared to echocardiography, cardiac MRI is much more accurate in determining LV geometry and function, especially in subjects with LV pathology [129]. Gadolineum contrast enhances the visualization of myocardial scar tissue, thus enabling the distinction between infarcted and non-infarcted myocardium [130], and the differentiation between various forms of non-ischaemic LVH [131]. Additionally, MRI is highly suitable for regional wall motion analysis [132]. The ongoing technological and statistical advances in the field of SNP analysis will enable increasingly detailed and increasingly extensive investigation of the genetic background of LVH and LVH regression.

If such studies confirm that any degree of LVH is detrimental, clinicians should focus on LVH prevention and regression. In patients with hypertension, blood pressure should be treated assertively.

As discussed in this review, molecular cardiological research has provided ample possibilities for the development of more cardiac-specific pharmaceutical interventions, which should be tailor-made to the pathology and genetic make-up of the individual patient. The efficacy of such an approach should be evaluated in the near future.

## ABBREVIATIONS

-/- = knock-out

7ND = MCP-1 mutant

AbAC = abdominal aortic constriction

ACE-I = Angiotensin Converting Enzyme Inhibitor

ADAM12 = Disintegrin and Metalloprotease 12

Ang-II = Angiotensin-II

ANP = Atrial Natriuretic Peptide

AT1a = Angiotensin-II Receptor type 1a

AT2 = Angiotensin-II Receptor type 2

β-AR = β-Adrenergic Receptor

CADO = 2-chloroadenosine

Cn = Calcineurin

CsA = Cyclosporin A

DSCR1 = Down's Syndrome Critical Region 1 (=MCIP1)

ECG = electrocardiography

ECG-LVH = ECG pattern of LVH

EF = ejection fraction

EGFR = Epidermal Growth Factor Receptor

eNOS = endothelial NO Synthase

ERKs = Extracellular Signal-Regulated Kinases

FGF-2 = Fibroblast Growth Factor 2

FK506 = Tacrolimus

$G\alpha_q$ *and* $G\alpha_{11}$ = G-proteins

GC-A = Guanylyl Cyclase-A receptor

gp130 = gp130 cytokine receptor

GPCR = G-Protein Coupled Receptor

GSK3β = Glycogen Synthase Kinase 3β

HBP = high blood pressure

HB-EGF = Heparin-Binding EGF

HF = heart failure

HMG-CoA = Hydroxy-3-MethylGlutaryl Coenzyme A

(h)MCIP1 = (human) Modulatory Calcineurin Interacting Proteins (=DSCR1)

HR = hazard ratio

IGF-1 = Insulin Growth Factor-1

JNKs = c-Jun N-terminal kinases

KB-R7785 = Disintegrin and Metalloprotease 12 inhibitor

L-NAME = $N^G$-nitro-L-Arginine Methyl Ester

LCA = left coronary artery

Lpr = lymphoproliferative disease mice

LVH = left ventricular hypertrophy

MAPK = Mitogen Activity Protein Kinase

MCIP1 = *see* (h)MCIP

MCP-1 = Monocyte Chemoattractant Protein-1

MEF2 = Myocyte Enhancer Factor 2

MI = myocardial infarction

MMPs = Matrix Metalloproteinases

MRI = magnetic resonance imaging

mTOR = mammalian Target Of Rapamycin

MVA = mevalonate

MyD88 = Myeloid Differentiation Factor 88

NCX1 = $Na^+/Ca^{2+}$-exchanger

NFAT = Nuclear Factor of Activated T cells

NFκB = Nuclear Factor kappa B

NHE = $Na^+/H^+$-exchanger

NPPA = Pro-Atrial Natriuretic Peptide

p38 = p38-Mitogen Activity Protein Kinase

p70S6K = p70 ribosomal S6 kinase

PD 166793 = MMP-inhibitor

PI3K = phosphoinositide 3-kinase

RGS4 = Regulator of G-protein Signaling sub-type 4

S100B = intrinsic LVH inhibitor

SAPK = Stress-Actived Protein Kinases

SB239063 = p38-inhibitor

SEK-1(KR) = SAPK inhibitor

SNPs = single nucleotide polymorphisms

SP-SFD = spontaneously hypertensive stroke-prone rats on a high salt high fat diet

STAT3 = Signal Transducer and Activator of Transcription 3

TAC = transverse aortic constriction

TG = transgenic

TLR4 = Toll-like Receptor 4

## REFERENCE


[1] Kannel, W. B. *Heart Fail. Rev.* **2000,** *5*, 167-173.

[2] Levy, D.; Larson, M. G.; Vasan, R. S.; Kannel, W. B.; Ho, K. K. *JAMA* **1996,** *275*, 1557-1562.

[3] He, J.; Ogden, L. G.; Bazzano, L. A.; Vupputuri, S.; Loria, C.; Whelton, P. K. *Arch. Intern. Med.* **2001,** *161*, 996-1002.

[4] Lips, D. J.; De Windt, L. J.; van Kraaij, D. J.; Doevendans, P. A. *Eur. Heart J.* **2003,** *24*, 883-896.

[5] Grossman, W.; Jones, D.; McLaurin, L. P. *J. Clin. Invest.* **1975,** *56*, 56-64.

[6] James, M. A.; Saadeh, A. M.; Jones, J. V. *J. Cardiovasc. Risk* **2000,** *7*, 187-190.

[7] Kannel, W. B.; Levy, D.; Cupples, L. A. *J. Cardiovasc. Pharmacol.* **1987,** *10 Suppl 6*, S135-S140.

[8] Bots, M. L.; Nikitin, Y.; Salonen, J. T.; Elwood, P. C.; Malyutina, S.; Freire de, C. A.; Sivenius, J.; Di, C. A.; Lagiou, P.; Tuomilehto, J.; Koudstaal, P. J.; Grobbee, D. E. *J. Epidemiol. Community Health.* **2002,** *56 Suppl 1:i8-13.*, i8-13.

[9] Crow, R. S.; Prineas, R. J.; Rautaharju, P.; Hannan, P.; Liebson, P. R. *Am. J. Cardiol.* **1995,** *75*, 1233-1238.

[10] Levy, D.; Garrison, R. J.; Savage, D. D.; Kannel, W. B.; Castelli, W. P. *N. Engl. J. Med.* **1990,** *322*, 1561-1566.

[11] Arnold, J. M.; Yusuf, S.; Young, J.; Mathew, J.; Johnstone, D.; Avezum, A.; Lonn, E.; Pogue, J.; Bosch, J. *Circulation* **2003,** *107*, 1284-1290.

[12] Rame, J. E.; Ramilo, M.; Spencer, N.; Blewett, C.; Mehta, S. K.; Dries, D. L.; Drazner, M. H. *Am. J. Cardiol.* **2004,** *93*, 234-237.

[13] Drazner, M. H.; Rame, J. E.; Marino, E. K.; Gottdiener, J. S.; Kitzman, D. W.; Gardin, J. M.; Manolio, T. A.; Dries, D. L.; Siscovick, D. S. *J. Am. Coll. Cardiol.* **2004,** *43*, 2207-2215.

[14] Krumholz, H. M.; Larson, M.; Levy, D. *J. Am. Coll. Cardiol.* **1995,** *25*, 879-884.

[15] Verdecchia, P.; Schillaci, G.; Borgioni, C.; Ciucci, A.; Gattobigio, R.; Zampi, I.; Santucci, A.; Santucci, C.; Reboldi, G.; Porcellati, C. *Am. J. Cardiol.* **1996,** *78*, 197-202.

[16] Devereux, R. B.; Bella, J. N.; Palmieri, V.; Oberman, A.; Kitzman, D. W.; Hopkins, P. N.; Rao, D. C.; Morgan, D.; Paranicas, M.; Fishman, D.; Arnett, D. K. *Hypertension* **2001,** *38*, 417-423.

[17] Wachtell, K.; Rokkedal, J.; Bella, J. N.; Aalto, T.; Dahlof, B.; Smith, G.; Roman, M. J.; Ibsen, H.; Aurigemma, G. P.; Devereux, R. B. *Am. J. Cardiol.* **2001,** *87*, 54-60.

[18] Dahlof, B.; Pennert, K.; Hansson, L. *Am. J. Hypertens.* **1992,** *5*, 95-110.

[19] Mathew, J.; Sleight, P.; Lonn, E.; Johnstone, D.; Pogue, J.; Yi, Q.; Bosch, J.; Sussex, B.; Probstfield, J.; Yusuf, S. *Circulation* **2001,** *104*, 1615-1621.

[20] Devereux, R. B.; Wachtell, K.; Gerdts, E.; Boman, K.; Nieminen, M. S.; Papademetriou, V.; Rokkedal, J.; Harris, K.; Aurup, P.; Dahlof, B. *JAMA* **2004,** *292*, 2350-2356.

[21] Okin, P. M.; Devereux, R. B.; Jern, S.; Kjeldsen, S. E.; Julius, S.; Nieminen, M. S.; Snapinn, S.; Harris, K. E.; Aurup, P.; Edelman, J. M.; Wedel, H.; Lindholm, L. H.; Dahlof, B. *JAMA* **2004,** *292*, 2343-2349.

[22] Devereux, R. B.; Dahlof, B.; Gerdts, E.; Boman, K.; Nieminen, M. S.; Papademetriou, V.; Rokkedal, J.; Harris, K. E.; Edelman, J. M.; Wachtell, K. *Circulation* **2004,** *110*, 1456-1462.

[23] Light, K. C.; Hinderliter, A. L.; West, S. G.; Grewen, K. M.; Steege, J. F.; Sherwood, A.; Girdler, S. S. *J. Hypertens.* **2001,** *19*, 269-278.

[24] Huber, D.; Grimm, J.; Koch, R.; Krayenbuehl, H. P. *Circulation* **1981,** *64*, 126-134.

[25] Krayenbuehl, H. P.; Hess, O. M.; Ritter, M.; Monrad, E. S.; Hoppeler, H. *Eur. Heart J.* **1988,** *9 Suppl E*, 19-23.

[26] de Simone, G.; Kitzman, D. W.; Palmieri, V.; Liu, J. E.; Oberman, A.; Hopkins, P. N.; Bella, J. N.; Rao, D. C.; Arnett, D. K.; Devereux, R. B. *Am. J. Hypertens.* **2004,** *17*, 828-833.

[27] Perlini, S.; Muiesan, M. L.; Cuspidi, C.; Sampieri, L.; Trimarco, B.; Aurigemma, G. P.; gabiti-Rosei, E.; Mancia, G. *Circulation* **2001,** *103*, 678-683.

[28] Palazzuoli, A.; Gennari, L.; Calabria, P.; Nami, R.; Martini, G.; Palazzuoli, V.; Nuti, R. *Blood Press* **2004,** *13*, 14-19.

[29] Pluim, B. M.; Lamb, H. J.; Kayser, H. W.; Leujes, F.; Beyerbacht, H. P.; Zwinderman, A. H.; van der Laarse A.; Vliegen, H. W.; de Roos A.; van der Wall, E. E. *Circulation* **1998,** *97*, 666-672.

[30] Link, M. S.; Homoud, M. K.; Wang, P. J.; Estes, N. A., III *Cardiol. Rev.* **2001,** *9*, 21-30.

[31] Crawford, D. C.; Nickerson, D. A. *Annu. Rev. Med.* **2005,** *56.*, 303-320.

[32] Poirier, O.; Nicaud, V.; McDonagh, T.; Dargie, H. J.; Desnos, M.; Dorent, R.; Roizes, G.; Schwartz, K.; Tiret, L.; Komajda, M.; Cambien, F. *Eur. J. Hum. Genet.* **2003,** *11*, 659-664.

[33] Gharavi, A. G.; Lipkowitz, M. S.; Diamond, J. A.; Jhang, J. S.; Phillips, R. A. *Am. J. Cardiol.* **1996,** *77*, 1315-1319.

[34] Jeng, J. R. *Am. J. Hypertens.* **1999,** *12*, 443-450.

[35] Kurland, L.; Melhus, H.; Karlsson, J.; Kahan, T.; Malmqvist, K.; Ohman, P.; Nystrom, F.; Hagg, A.; Lind, L. *J. Hypertens.* **2002,** *20*, 657-663.

[36] Tang, W.; Arnett, D. K.; Devereux, R. B.; Panagiotou, D.; Province, M. A.; Miller, M. B.; de, S. G.; Gu, C.; Ferrell, R. E. *Am. Heart J.* **2005,** *150*, 845-851.

[37] Winnicki, M.; Somers, V. K.; Accurso, V.; Hoffmann, M.; Pawlowski, R.; Frigo, G.; Visentin, P.; Palatini, P. *J. Hypertens.* **2002,** *20*, 1771-1777.

[38] Burlew, B. S.; Weber, K. T. *Herz* **2002,** *27*, 92-98.

[39] Frey, N.; Olson, E. N. *Annu. Rev. Physiol.* **2003,** *65*, 45-79.

[40] Frey, N.; Katus, H. A.; Olson, E. N.; Hill, J. A. *Circulation* **2004,** *109*, 1580-1589.

[41] Rockman, H. A.; Ross, R. S.; Harris, A. N.; Knowlton, K. U.; Steinhelper, M. E.; Field, L. J.; Ross, J., Jr.; Chien, K. R. *Proc. Natl. Acad. Sci. USA* **1991,** *88*, 8277-8281.

[42] Komuro, I.; Kurabayashi, M.; Takaku, F.; Yazaki, Y. *Circ. Res.* **1988,** *62*, 1075-1079.

[43] Wilkins, B. J.; Molkentin, J. D. *Biochem. Biophys. Res. Commun.* **2004,** *322*, 1178-1191.

[44] Molkentin, J. D.; Lu, J. R.; Antos, C. L.; Markham, B.; Richardson, J.; Robbins, J.; Grant, S. R.; Olson, E. N. *Cell* **1998,** *93*, 215-228.

[45] Bueno, O. F.; Wilkins, B. J.; Tymitz, K. M.; Glascock, B. J.; Kimball, T. F.; Lorenz, J. N.; Molkentin, J. D. *Proc. Natl. Acad. Sci. USA* **2002,** *99*, 4586-4591.

[46] Bueno, O. F.; van, R. E.; Molkentin, J. D.; Doevendans, P. A.; De Windt, L. J. *Cardiovasc. Res.* **2002,** *53*, 806-821.

[47] Meguro, T.; Hong, C.; Asai, K.; Takagi, G.; McKinsey, T. A.; Olson, E. N.; Vatner, S. F. *Circ. Res.* **1999,** *84*, 735-740.

[48] Hill, J. A.; Karimi, M.; Kutschke, W.; Davisson, R. L.; Zimmerman, K.; Wang, Z.; Kerber, R. E.; Weiss, R. M. *Circulation* **2000,** *101*, 2863-2869.

[49] Hill, J. A.; Rothermel, B.; Yoo, K. D.; Cabuay, B.; Demetroulis, E.; Weiss, R. M.; Kutschke, W.; Bassel-Duby, R.; Williams, R. S. *J. Biol. Chem.* **2002,** *277*, 10251-10255.

[50] Vega, R. B.; Rothermel, B. A.; Weinheimer, C. J.; Kovacs, A.; Naseem, R. H.; Bassel-Duby, R.; Williams, R. S.; Olson, E. N. *Proc. Natl. Acad. Sci. USA* **2003,** *100*, 669-674.

[51] Badorff, C.; Ruetten, H.; Mueller, S.; Stahmer, M.; Gehring, D.; Jung, F.; Ihling, C.; Zeiher, A. M.; Dimmeler, S. *J. Clin. Invest.* **2002,** *109*, 373-381.

[52] Shimoyama, M.; Hayashi, D.; Takimoto, E.; Zou, Y.; Oka, T.; Uozumi, H.; Kudoh, S.; Shibasaki, F.; Yazaki, Y.; Nagai, R.; Komuro, I. *Circulation* **1999,** *100*, 2449-2454.

[53] Sakata, Y.; Masuyama, T.; Yamamoto, K.; Nishikawa, N.; Yamamoto, H.; Kondo, H.; Ono, K.; Otsu, K.; Kuzuya, T.; Miwa, T.; Takeda, H.; Miyamoto, E.; Hori, M. *Circulation* **2000,** *102*, 2269-2275.

[54] Shimoyama, M.; Hayashi, D.; Zou, Y.; Takimoto, E.; Mizukami, M.; Monzen, K.; Kudoh, S.; Hiroi, Y.; Yazaki, Y.; Nagai, R.; Komuro, I. *Circulation* **2000,** *102*, 1996-2004.

[55] Sipido, K. R.; Volders, P. G.; Vos, M. A.; Verdonck, F. *Cardiovasc. Res.* **2002,** *53*, 782-805.

[56] Balke, C. W.; Shorofsky, S. R. *Cardiovasc. Res.* **1998,** *37*, 290-299.

[57] Studer, R.; Reinecke, H.; Vetter, R.; Holtz, J.; Drexler, H. *Basic Res. Cardiol.* **1997,** *92 Suppl 1*, 53-58.

[58] Cheng, G.; Hagen, T. P.; Dawson, M. L.; Barnes, K. V.; Menick, D. R. *J. Biol. Chem.* **1999,** *274*, 12819-12826.

[59] Jordan, M. C.; Quednau, B. D.; Roos, K. P.; Ross, R. S.; Philipson, K. D.; Nicholas, S. B. *Ann. N. Y. Acad. Sci.* **2002,** *976*, 259-267.

[60] Bartunek, J.; Weinberg, E. O.; Tajima, M.; Rohrbach, S.; Katz, S. E.; Douglas, P. S.; Lorell, B. H. *Circulation* **2000,** *101*, 423-429.

[61] Kempf, T.; Wollert, K. C. *Bioessays* **2004,** *26*, 608-615.

[62] Bloch, K. D.; Janssens, S. *Trends Cardiovasc. Med.* **2005,** *15*, 249-253.

[63] Gottdiener, J. S.; Reda, D. J.; Massie, B. M.; Materson, B. J.; Williams, D. W.; Anderson, R. J. *Circulation* **1997,** *95*, 2007-2014.

[64] Liao, Y.; Asakura, M.; Takashima, S.; Ogai, A.; Asano, Y.; Shintani, Y.; Minamino, T.; Asanuma, H.; Sanada, S.; Kim, J.; Kitamura, S.; Tomoike, H.; Hori, M.; Kitakaze, M. *Circulation* **2004,** *110*, 692-699.

[65] Liao, Y.; Asakura, M.; Takashima, S.; Ogai, A.; Asano, Y.; Asanuma, H.; Minamino, T.; Tomoike, H.; Hori, M.; Kitakaze, M. *Cardiovasc. Res.* **2005,** *65* (4), 879-888.

[66] van Eickels, M.; Grohe, C.; Cleutjens, J. P.; Janssen, B. J.; Wellens, H. J.; Doevendans, P. A. *Circulation* **2001,** *104*, 1419-1423.

[67] Ogita, H.; Node, K.; Liao, Y.; Ishikura, F.; Beppu, S.; Asanuma, H.; Sanada, S.; Takashima, S.; Minamino, T.; Hori, M.; Kitakaze, M. *Hypertension* **2004,** *43*, 237-242.

[68] Goldstein, J. L.; Brown, M. S. *Nature* **1990,** *343*, 425-430.

[69] Habenicht, A. J.; Glomset, J. A.; Ross, R. *J. Biol. Chem.* **1980,** *255*, 5134-5140.

[70] Clerk, A.; Sugden, P. H. *Circ. Res.* **2000,** *86*, 1019-1023.

[71] Takemoto, M.; Node, K.; Nakagami, H.; Liao, Y.; Grimm, M.; Takemoto, Y.; Kitakaze, M.; Liao, J. K. *J. Clin. Invest.* **2001,** *108*, 1429-1437.

[72] Pruefer, D.; Scalia, R.; Lefer, A. M. *Arterioscler. Thromb. Vasc. Biol.* **1999,** *19*, 2894-2900.

[73] Nahrendorf, M.; Hu, K.; Hiller, K. H.; Galuppo, P.; Fraccarollo, D.; Schweizer, G.; Haase, A.; Ertl, G.; Bauer, W. R.; Bauersachs, J. *J. Am. Coll. Cardiol.* **2002,** *40*, 1695-1700.

[74] Hayashidani, S.; Tsutsui, H.; Shiomi, T.; Suematsu, N.; Kinugawa, S.; Ide, T.; Wen, J.; Takeshita, A. *Circulation* **2002,** *105*, 868-873.

[75] Luo, J. D.; Zhang, W. W.; Zhang, G. P.; Guan, J. X.; Chen, X. *Clin. Exp. Pharmacol. Physiol.* **1999,** *26*, 903-908.

[76] Senbonmatsu, T.; Ichihara, S.; Price E Jr; Gaffney, F. A.; Inagami, T. *J. Clin. Invest.* **2000,** *106*, R25-R29.

[77] de Bold, A. J.; Borenstein, H. B.; Veress, A. T.; Sonnenberg, H. *Life Sci.* **1981,** *28*, 89-94.

[78] Franco, V.; Chen, Y. F.; Oparil, S.; Feng, J. A.; Wang, D.; Hage, F.; Perry, G. *Hypertension* **2004,** *44*, 746-750.

[79] Drewett, J. G.; Garbers, D. L. *Endocr. Rev.* **1994,** *15*, 135-162.

[80] Lopez, M. J.; Wong, S. K.; Kishimoto, I.; Dubois, S.; Mach, V.; Friesen, J.; Garbers, D. L.; Beuve, A. *Nature* **1995,** *378*, 65-68.

[81] Holtwick, R.; van, E. M.; Skryabin, B. V.; Baba, H. A.; Bubikat, A.; Begrow, F.; Schneider, M. D.; Garbers, D. L.; Kuhn, M. *J. Clin. Invest.* **2003,** *111*, 1399-1407.

[82] Babiker, F. A.; De Windt, L. J.; van, E. M.; Thijssen, V.; Bronsaer, R. J.; Grohe, C.; van, B. M.; Doevendans, P. A. *Circulation* **2004,** *109*, 269-276.

[83] Cingolani, H. E.; Alvarez, B. V.; Ennis, I. L.; Camilion de Hurtado, M. C. *Circ. Res.* **1998,** *83*, 775-780.

[84] Cingolani, H. E.; Camilion de Hurtado, M. C. *Circ. Res.* **2002,** *90*, 751-753.

[85] Kilic, A.; Velic, A.; De Windt, L. J.; Fabritz, L.; Voss, M.; Mitko, D.; Zwiener, M.; Baba, H. A.; van, E. M.; Schlatter, E.; Kuhn, M. *Circulation* **2005,** *112*, 2307-2317.

[86] Petrich, B. G.; Wang, Y. *Trends Cardiovasc. Med.* **2004,** *14*, 50-55.

[87] Liang, Q.; Molkentin, J. D. *J. Mol. Cell Cardiol.* **2003,** *35*, 1385-1394.

[88] Choukroun, G.; Hajjar, R.; Fry, S.; del, M. F.; Haq, S.; Guerrero, J. L.; Picard, M.; Rosenzweig, A.; Force, T. *J. Clin. Invest.* **1999,** *104*, 391-398.

[89] Behr, T. M.; Nerurkar, S. S.; Nelson, A. H.; Coatney, R. W.; Woods, T. N.; Sulpizio, A.; Chandra, S.; Brooks, D. P.; Kumar, S.; Lee, J. C.; Ohlstein, E. H.; Angermann, C. E.; Adams, J. L.; Sisko, J.; Sackner-Bernstein, J. D.; Willette, R. N. *Circulation* **2001,** *104*, 1292-1298.

[90] Hirota, H.; Chen, J.; Betz, U. A.; Rajewsky, K.; Gu, Y.; Ross, J., Jr.; Muller, W.; Chien, K. R. *Cell* **1999,** *97*, 189-198.

[91] Uozumi, H.; Hiroi, Y.; Zou, Y.; Takimoto, E.; Toko, H.; Niu, P.; Shimoyama, M.; Yazaki, Y.; Nagai, R.; Komuro, I. *J. Biol. Chem.* **2001,** *276*, 23115-23119.

[92] Brancaccio, M.; Fratta, L.; Notte, A.; Hirsch, E.; Poulet, R.; Guazzone, S.; De, A. M.; Vecchione, C.; Marino, G.; Altruda, F.; Silengo, L.; Tarone, G.; Lembo, G. *Nat. Med.* **2003,** *9*, 68-75.

[93] De Acetis, M.; Notte, A.; Accornero, F.; Selvetella, G.; Brancaccio, M.; Vecchione, C.; Sbroggio, M.; Collino, F.; Pacchioni, B.; Lanfranchi, G.; Aretini, A.; Ferretti, R.; Maffei, A.; Altruda, F.; Silengo, L.; Tarone, G.; Lembo, G. *Circ. Res.* **2005,** *96*, 1087-1094.

[94] Schultz, J. E.; Witt, S. A.; Nieman, M. L.; Reiser, P. J.; Engle, S. J.; Zhou, M.; Pawlowski, S. A.; Lorenz, J. N.; Kimball, T. R.; Doetschman, T. *J. Clin. Invest.* **1999,** *104*, 709-719.

[95] Rockman, H. A.; Koch, W. J.; Lefkowitz, R. J. *Nature* **2002,** *415*, 206-212.

[96] Rogers, J. H.; Tamirisa, P.; Kovacs, A.; Weinheimer, C.; Courtois, M.; Blumer, K. J.; Kelly, D. P.; Muslin, A. J. *J. Clin. Invest.* **1999,** *104*, 567-576.

[97] Akhter, S. A.; Luttrell, L. M.; Rockman, H. A.; Iaccarino, G.; Lefkowitz, R. J.; Koch, W. J. *Science* **1998,** *280*, 574-577.

[98] Wettschureck, N.; Rutten, H.; Zywietz, A.; Gehring, D.; Wilkie, T. M.; Chen, J.; Chien, K. R.; Offermanns, S. *Nat. Med.* **2001,** *7*, 1236-1240.

[99] Esposito, G.; Rapacciuolo, A.; Naga Prasad, S. V.; Takaoka, H.; Thomas, S. A.; Koch, W. J.; Rockman, H. A. *Circulation* **2002,** *105*, 85-92.

[100] Asakura, M.; Kitakaze, M.; Takashima, S.; Liao, Y.; Ishikura, F.; Yoshinaka, T.; Ohmoto, H.; Node, K.; Yoshino, K.; Ishiguro, H.; Asanuma, H.; Sanada, S.; Matsumura, Y.; Takeda, H.; Beppu, S.; Tada, M.; Hori, M.; Higashiyama, S. *Nat. Med.* **2002,** *8*, 35-40.

[101] Proud, C. *Cardiovasc. Res.* **2004,** *63*, 403-413.

[102] Schmelzle, T.; Hall, M. N. *Cell* **2000,** *103*, 253-262.

[103] Shioi, T.; McMullen, J. R.; Tarnavski, O.; Converso, K.; Sherwood, M. C.; Manning, W. J.; Izumo, S. *Circulation* **2003,** *107*, 1664-1670.

[104] McMullen, J. R.; Sherwood, M. C.; Tarnavski, O.; Zhang, L.; Dorfman, A. L.; Shioi, T.; Izumo, S. *Circulation* **2004,** *109*, 3050-3055.

[105] Baldwin, A. S. Jr. *Annu. Rev. Immunol.* **1996,** *14*, 649-683.

[106] Pasterkamp, G.; Van Keulen, J. K.; De Kleijn, D. P. Role of Toll-like receptor 4 in the initiation and progression of atherosclerotic disease. *Eur. J. Clin. Invest.* **2004,** *34*, 328-334.

[107] Li, Y.; Ha, T.; Gao, X.; Kelley, J.; Williams, D. L.; Browder, I. W.; Kao, R. L.; Li, C. *Am. J. Physiol Heart Circ. Physiol.* **2004,** *287*, H1712-H1720.

[108] Ha, T.; Li, Y.; Hua, F.; Ma, J.; Gao, X.; Kelley, J.; Zhao, A.; Haddad, G. E.; Williams, D. L.; William, B., I; Kao, R. L.; Li, C. *Cardiovasc. Res.* **2005,** *68*, 224-234.

[109] Ha, T.; Hua, F.; Li, Y.; Ma, J.; Gao, X.; Kelley, J.; Zhao, A.; Haddad, G. E.; Williams, D. L.; Browder, I. W.; Kao, R. L.; Li, C. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *400*, 69-74.

[110] Liao, Y.; Takashima, S.; Asano, Y.; Asakura, M.; Ogai, A.; Shintani, Y.; Minamino, T.; Asanuma, H.; Sanada, S.; Kim, J.; Ogita, H.; Tomoike, H.; Hori, M.; Kitakaze, M. *Circ. Res.* **2003,** *93*, 759-766.

[111] Janicki, J. S.; Brower, G. L.; Gardner, J. D.; Chancey, A. L.; Stewart, J. A., Jr. *Heart Fail. Rev.* **2004,** *9*, 33-42.

[112] Chancey, A. L.; Brower, G. L.; Peterson, J. T.; Janicki, J. S. *Circulation* **2002,** *105*, 1983-1988.

[113] Sundstrom, J.; Evans, J. C.; Benjamin, E. J.; Levy, D.; Larson, M. G.; Sawyer, D. B.; Siwik, D. A.; Colucci, W. S.; Sutherland, P.; Wilson, P. W.; Vasan, R. S. *Circulation* **2004,** *109*, 2850-2856.

[114] Harada, K.; Sugaya, T.; Murakami, K.; Yazaki, Y.; Komuro, I. *Circulation* **1999,** *100*, 2093-2099.

[115] Bridgman, P.; Aronovitz, M. A.; Kakkar, R.; Oliverio, M. I.; Coffman, T. M.; Rand, W. M.; Konstam, M. A.; Mendelsohn, M. E.; Patten, R. D. *Am. J. Physiol. Heart Circ. Physiol.* **2005,** *289*, H586-H592.

[116] Ambrose, J.; Pribnow, D. G.; Giraud, G. D.; Perkins, K. D.; Muldoon, L.; Greenberg, B. H. *J. Cardiovasc. Pharmacol.* **1999,** *33*, 433-439.

[117] Zornoff, L. A.; Paiva, S. A.; Matsubara, B. B.; Matsubara, L. S.; Spadaro, J. *J. Cardiovasc. Pharmacol. Ther.* **2000,** *5*, 203-209.
[118] Oie, E.; Bjornerheim, R.; Clausen, O. P.; Attramadal, H. *Am. J. Physiol. Heart Circ. Physiol.* **2000,** *278*, H2115-H2123.
[119] Youn, T. J.; Piao, H.; Kwon, J. S.; Choi, S. Y.; Kim, H. S.; Park, D. G.; Kim, D. W.; Kim, Y. G.; Cho, M. C. *Eur. J. Heart Fail.* **2002,** *4*, 713-718.
[120] Deng, L.; Huang, B.; Qin, D.; Ganguly, K.; El-Sherif, N. *J. Cardiovasc. Electrophysiol.* **2001,** *12*, 1055-1061.
[121] van Rooij, E.; Doevendans, P. A.; Crijns, H. J.; Heeneman, S.; Lips, D. J.; van, B. M.; Williams, R. S.; Olson, E. N.; Bassel-Duby, R.; Rothermel, B. A.; De Windt, L. J. *Circ. Res.* **2004,** *94*, e18-e26.
[122] Hayashidani, S.; Tsutsui, H.; Shiomi, T.; Ikeuchi, M.; Matsusaka, H.; Suematsu, N.; Wen, J.; Egashira, K.; Takeshita, A. *Circulation* **2003,** *108*, 2134-2140.
[123] Janssens, S.; Pokreisz, P.; Schoonjans, L.; Pellens, M.; Vermeersch, P.; Tjwa, M.; Jans, P.; Scherrer-Crosbie, M.; Picard, M. H.; Szelid, Z.; Gillijns, H.; Van de, W. F.; Collen, D.; Bloch, K. D. *Circ. Res.* **2004,** *94*, 1256-1262.
[124] Tsoporis, J. N.; Marks, A.; Haddad, A.; Dawood, F.; Liu, P. P.; Parker, T. G. *Circulation* **2005,** *111*, 598-606.
[125] Kusumoto, K.; Haist, J. V.; Karmazyn, M. *Am. J. Physiol. Heart Circ. Physiol.* **2001,** *280*, H738-H745.
[126] Yoshida, H.; Karmazyn, M. *Am. J. Physiol. Heart Circ. Physiol.* **2000,** *278*, H300-H304.
[127] Van Empel, V.; De Windt, L. J. *Cardiovasc. Res.* **2004,** *63*, 487-499.
[128] Van Empel, V.; Bertrand, A. T.; Hofstra, L.; Crijns, H. J.; Doevendans, P. A.; De Windt, L. J. *Cardiovasc. Res.* **2005,** *67*, 21-29.
[129] Grothues, F.; Smith, G. C.; Moon, J. C.; Bellenger, N. G.; Collins, P.; Klein, H. U.; Pennell, D. J. *Am. J. Cardiol.* **2002,** *90*, 29-34.
[130] Judd, R. M.; Wagner, A.; Rehwald, W. G.; Albert, T.; Kim, R. J. *Nat. Clin. Pract. Cardiovasc. Med.* **2005,** *2*, 150-158.
[131] Mahrholdt, H.; Wagner, A.; Judd, R. M.; Sechtem, U.; Kim, R. J. *Eur. Heart J.* **2005,** *26*, 1461-1474.
[132] O'Dell, W. G.; McCulloch, A. D. *Annu. Rev. Biomed. Eng.* **2000,** *2*, 431-456.

**Received: June 12, 2006 Revised: September 30, 2006 Accepted: September 30, 2006**