New insights in the pathophysiology of mitral and aortic regurgitation in pediatric age: role of angiotensin-converting enzyme inhibitor therapy

Carlo Pisacane, Giuseppe Pacileo, Giuseppe Santoro, Berardo Sarubbi, Carola Iacono, Maria Giovanna Russo, Raffaele Calabrò

Division of Pediatric Cardiology, Second University of Naples, Naples, Italy

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This review has been focused on the new insights in the pathophysiology of mitral and aortic regurgitation and on the role of ACE-inhibitor therapy in children with chronic volume overload due to left-sided valvular lesions. Recent clinical studies show that these drugs have favorable effects when administered orally in chronic mitral and aortic regurgitation. Interestingly, the beneficial effects of ACE-inhibition regard the basic anatomic, hemodynamic and adaptive pathologic conditions related to volume overload, namely, the regurgitant orifice area and volume and ventricular remodeling. The heart is a plastic structure, constantly being altered in size, shape and composition in response to chronic volume overload. Thus, modulation of cardiac plasticity by ACE-inhibition raises the possibility of using new therapeutic strategies specifically designed to prevent and/or antagonize the mechanical disadvantages secondary to volume overload-induced cardiac remodeling. The beneficial effects of ACE-inhibition have also been observed in growing children with asymptomatic valvular regurgitation; thus, it appears that the unloading therapy has the potential of influencing the natural history of both mitral and aortic regurgitation and possibly delays surgical valve repair or replacement. These data justify early inhibition of the renin-angiotensin system in children with left ventricular volume overload due to mitral and aortic regurgitation.

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Address:

Dr. Carlo Pisacane

Via Lone, 4
84011 Amalfi (SA)
E-mail:
cpisacane@tiscalinet.it

Mitral and aortic valve regurgitation represents a significant management problem in pediatric patients. In fact, contrary to what is commonly thought, significant mitral or aortic valve regurgitation is a relatively frequent finding in children, consequent to acquired or congenital valve dysfunction or to interventional procedures[1,2] or cardiac surgery[3-5].

The management of this condition in pediatric age is rendered difficult by the fact that, unlike what is reported in adolescents and adults[6], no specific criteria to define the best timing for valve surgery are currently available. In addition, recent data indicate that, in children with severe chronic mitral regurgitation, delaying surgery until the appearance of clinical symptoms of insufficiency does not significantly increase the risk of left ventricular dysfunction in long-term postoperative follow-up[7]. Again, children with severe aortic valve regurgitation show prolonged functional stability due to compensatory hypertrophy, even in the presence of marked ventricular dilation[8]. Therefore, had the indication for surgery been based only on the size of the left ventricle or the severity of valve regurgitation, these patients would undergo surgery too early.

Despite the improvement in surgical techniques, mortality due to mitral or aortic valve surgery in pediatric age is not negligible[9-13]. Many problems in the postoperative long-term follow-up still remain, mainly progressive degeneration of the valve tissue, patient-prosthesis mismatch during growth and the difficulties of chronic anticoagulant therapy[14]. Therefore, it is widely agreed that, for children with severe mitral or aortic regurgitation, surgery should be delayed as long as possible[15-17]. However, such an approach requires that conservative management be directed to the prevention or, at least, the delay of progressive dilation of the left ventricular cavity in order to limit irreversible myocardial dysfunction secondary to chronic volume overload.

Recent clinical studies in adult patients with severe mitral[18] or aortic[19,20] regurgitation have shown that orally administered angiotensin-converting enzyme (ACE) inhibitors are particularly effective not only in reducing the magnitude of valve regurgitation but also in halting or, at least, slowing down the progression of the morphologic, geometric and functional changes in the left ventricle. These observations indicate that ACE blocking agents may favorably influence the natural history of mitral and aortic valve regurgitation, thus delaying the need for surgery[21].

As the problem of pharmacological treatment of mitral and aortic valve regurgitation has, in recent years, also arisen for children, the aim of this review was to summarize the current state of knowledge about the pathophysiologic aspects of mitral and aortic valve incompetence and the use of ACE-inhibitors in chronic left ventricular volume overload secondary to these valve disorders in pediatric age.

Rationale for ACE-inhibitor therapy in patients with mitral and aortic valve regurgitation

The rationale for ACE-inhibition in mitral and aortic valve regurgitation is essentially based on a thorough knowledge of the hemodynamic determinants of regurgitant flow and of the hemodynamic and neurohormonal mechanisms causing and self-maintaining "cardiac remodeling". This process consists of the modifications in the size, shape and composition of the cardiac chambers as well as in the thickness and composition of the walls in response to physical loads and/or receptor activation, whether caused by loss or overload of cardiac myocytes, or by the effects of external hormonal or chemical factors[22,23].

Determinants of valvular regurgitation. In mitral insufficiency, the regurgitant volume mainly depends on two factors, namely, the size of the regurgitant orifice and the systolic pressure gradient between the ventricle and the left atrium[24]. Experimental studies have shown that in acute mitral regurgitation the area of the regurgitant orifice strongly depends on changes in both the size and contractile status of the left ventricle[25]. In particular, as either the preload or the afterload rises or the myocardial contractility falls, the regurgitant orifice increases thus resulting in an increase in the magnitude of valve regurgitation[26]. This statement stresses the practical importance of reducing the left ventricular size and of modifying the loading conditions in order to reduce the regurgitant volume[27].

In general, the mitral regurgitant orifice is classified as dynamic or fixed, according to whether or not it changes in size during different loading (pressure and/or volume) conditions. It is considered fixed in patients with mitral regurgitation due to annulus calcification, infective endocarditis or rheumatic disease[28], and dynamic in those with valve prolapse, dilated cardiomyopathy and myocardial ischemia[28]. This distinction may have important clinical implications. It has been suggested that unloading therapy appears useless in fixed orifice mitral regurgitation[27,29,30]. However, recent studies have shown significant variability in mitral regurgitant orifice behavior in response to acute changes of loading conditions, regardless of the etiology of valve disease[31]. This indicates that, in each patient, the etiology of mitral regurgitation alone cannot accurately predict whether the regurgitant orifice is fixed or dynamic. As a consequence, in contrast to previous reports[27], unloading therapy should always be taken into consideration in moderate or severe mitral regurgitation, particularly in pediatric patients who more frequently show a dynamic regurgitant orifice.

The systolic pressure gradient across the mitral valve, which is a function of both the systemic vascular resistance and of the forward stroke volume, is the other determinant of the severity of mitral regurgitation. However, experimental[25,32] and clinical[33,34] data indicate that it is less important than the area of the regurgitant orifice in determining the severity of regurgitation. In fact, as the magnitude of mitral regurgitation is directly related to the dimensions of the regurgitant orifice but to the square route of the systolic pressure gradient between the left ventricle and atrium[27], any factor that modifies the regurgitant orifice size affects regurgitation more than systolic pressure gradient changes.

In aortic insufficiency, the regurgitant orifice size, the diastolic pressure gradient between the aorta and the left ventricle and the duration of diastole influence the regurgitant volume[35].

As for mitral regurgitation, the area of the aortic regurgitant orifice can show dynamic or fixed characteristics and may or may not change with loading conditions. In experimental aortic regurgitation[36], compared to baseline values the regurgitant orifice area increased by almost 40% after the administration of dopamine and dropped by 28% after the administration of nitroprusside. These changes resulted from different degrees of aortic valve cusp coaptation due to geometric changes in the aortic root consequent to modifications in the aortic pressure. In addition, it has been observed that, during diastole, the dimensions of the base of the aortic valve increase in parallel with the left ventricular diastolic pressure[37]. Therefore, it may be that the aortic annulus is over-stretched in the presence of higher left ventricular diastolic pressures resulting in an increase in the size of the regurgitant orifice.

Aortic root size changes are also evident during follow-up of patients with different degrees of chronic aortic regurgitation. In 127 patients older than 14 years and with chronic aortic regurgitation, Padial et al.[38] reported a progressive dilation of the aortic root, with a faster rate of changes at the level of the supra-aortic ridge (sinotubular junction) in those with more severe degrees of valvular dysfunction. The supra-aortic ridge,

which is the upper supporting structure of the annulus and cusps, is of vital importance for aortic valve competence. In fact, when its structural integrity is compromised, significant aortic regurgitation occurs[39] because of central defects that cannot be closed by the cusps. Moreover, it has been shown that even patients with chronic aortic regurgitation and aortic root enlargement involving the supra-aortic ridge and the proximal portion of the ascending aorta have a markedly hypertrophied and dilated left ventricle[39]. Therefore, it appears that aortic dilation may play a key role in progressive aortic regurgitation, with greater degrees of root dilation causing greater distortion of the structures supporting the aortic valve cusps, and, hence, further increases in valvular regurgitation. In turn, the resultant increase in stroke volume imposes more stress on the aortic root, which may dilate further. Moreover, the increased severity of aortic regurgitation and pulse pressure cause a further rise in the mean systemic blood pressure, resulting in higher aortic wall stress, progressive dilation and, consequently, more aortic regurgitation.

Therefore, whatever the involvement of these factors, the pharmacological reduction of the loading conditions might decrease the regurgitant volume with beneficial effects on the overloaded left ventricle. However, unloading interventions may be less effective in case of marked calcification of the cusps and aortic annulus[27,36], but this condition is rarely found in pediatric aortic regurgitation.

Loading conditions and left ventricular remodeling in chronic mitral and aortic regurgitation. Mitral and aortic regurgitation are both frequently classified as volume overload states. However, different loading conditions are present in patients with similar volume overload due to mitral versus aortic regurgitation[40].

It is generally held that, in mitral regurgitation, the low impedance pathway for ejection into the left atrium reduces left ventricular afterload. However, important concepts regarding the pathophysiology of chronic mitral regurgitation are too frequently misunderstood. In contrast to aortic regurgitation, mitral regurgitation is a "low-pressure" volume overload in which the regurgitant (excess) volume pumped is ejected into the low-pressure left atrium. This type of volume overload results in limited left ventricular hypertrophy and is therefore characterized by the highest radius to thickness ratio and lowest mass to volume ratio, setting the scene for inadequate hypertrophy. The reason for inadequate hypertrophy is that, in chronic mitral regurgitation, the peak systolic wall stress – the modulator of hypertrophy – is less elevated because ejection, and therefore reduction in volume, begins and progresses before the left ventricular pressure reaches the aortic pressure. Because of this early reduction in radius and increase in wall thickness at relatively low pressures, the peak systolic stress is lower than in other lesions with similar cavity dilation (e.g. chronic aortic regurgitation) and, as a consequence, results in only weak stimulation for hypertrophy. Using simultaneous left ventricular micromanometer and biplane cineangiography, Corin et al.[41] found normal values of left ventricular peak systolic pressure in patients with chronic mitral regurgitation. However, the peak systolic stress was increased as a result of the modification in the hemodynamic determinants of left ventricular wall stress: left ventricular pressure and wall thickness were within the normal range but the ventricular minor axis was significantly higher. More importantly, from aortic valve opening to closure (a period of normal ventricular pressure), an increase in the mean systolic stress was also found, suggesting that, in mitral regurgitation, even the normally functioning ventricle faces a significant and sustained increase in afterload during the period of aortic valve opening. Finally, the end-systolic wall stress was elevated in patients with mitral regurgitation and a lowered ejection fraction. Thus, in mitral regurgitation the situation is paradoxical because while the lesion itself tends to unload the left ventricle, the left ventricular geometry which develops actually places this cavity at a systolic mechanical disadvantage by causing "afterload excess"[42].

In aortic regurgitation, the extra volume is ejected into the high impedance systemic arterial circuit, which causes both volume and pressure overload on the left ventricle. The high systolic blood pressure due to an increase in pulse pressure, combined with an increased radius, increases the left ventricular systolic wall stress, which may be as high as that seen in aortic stenosis[43]. This higher stress results in a thicker left ventricle and a lower radius to thickness ratio than in mitral regurgitation. Although these geometric factors would tend to lower systolic wall stress, the higher systolic pressure offsets this adaptive response and thus the systolic wall stress usually increases[40,42].

Therefore, given the increased afterload both in mitral and aortic regurgitation, it is physiologically plausible that the pharmacologically-induced reduction in hemodynamic load might in part delay and possibly revert the progression of the remodeling process (i.e., ventricular dilation, change in the geometry of the ventricular chamber from the normal prolate ellipse to a more spherical shape, increased myocardial mass) by reducing left ventricular wall stress[27].

Cardiac remodeling due to volume overload (valvular regurgitation) is influenced not only by the hemodynamic load (physical forces producing initial ventricular dilation) but also by neurohormonal activation (renin-angiotensin system and sympathetic nervous system) and by other factors still under investigation (endothelin, cytokines – tumor necrosis factors and interleukins, nitric oxide production and oxidative stress)[23]. It has been demonstrated that the renin-angiotensin system is rapidly up-regulated in response to cardiac volume overload and seems to be a serious candidate for mediating part of the complex sequence of compensatory events that ultimately result in an adversely remodeled left ventricle[44-48].

The rationale for using ACE-inhibitors as an "anti-remodeling" strategy in children with volume overload due to valvular regurgitation is that these agents have multiple mechanisms of action involving both hemodynamic and neurohormonal factors as well as autocrine and paracrine mechanisms[49]. ACE-inhibitors reduce the production of angiotensin II which is a potent vasoconstrictor released not only by the juxtaglomerular apparatus but also by organs such as the heart and arterial walls[50,51]. It has been shown that angiotensin II acts as a growth factor for cardiac myocytes and vasculature by inducing multiple autocrine growth factors[52,53]. Moreover, it promotes myocyte death by necrosis or apoptosis[54-56] and causes perivascular, interstitial, and myocardial fibrosis[57]. These changes may play a relevant role in the overall development and progression of cardiac remodeling.

A model for left ventricular remodeling due to mitral or aortic regurgitation in which hemodynamic-neurohormonal coupling may be operative is reported in figure 1.

Clinical studies with ACE-inhibitors on mitral and aortic valve regurgitation in children

Mitral regurgitation. The first report about the positive acute effects of ACE-inhibition in children with moderate to severe asymptomatic chronic mitral regurgitation has recently been published by our group[58]. We found that a single oral dose (0.40 mg/kg, maximum dose 20 mg) of the ACE-inhibitor enalapril decreased the area of the effective regurgitant orifice, an index of the severity of mitral regurgitation, by 34%, thereby significantly reducing the regurgitant volume and fraction by 38 and 31% respectively (Fig. 2). Compared to controls, the end-systolic wall stress, an index of myocardial afterload, and the systemic vascular resistance also decreased by 16 and 18% respectively. As a result of the enalapril-induced fall in preload and afterload, the left ventricular end-diastolic and end-systolic volumes decreased by 6 and 17% respectively. Conversely, the forward stroke volume, which only reflects effective for-

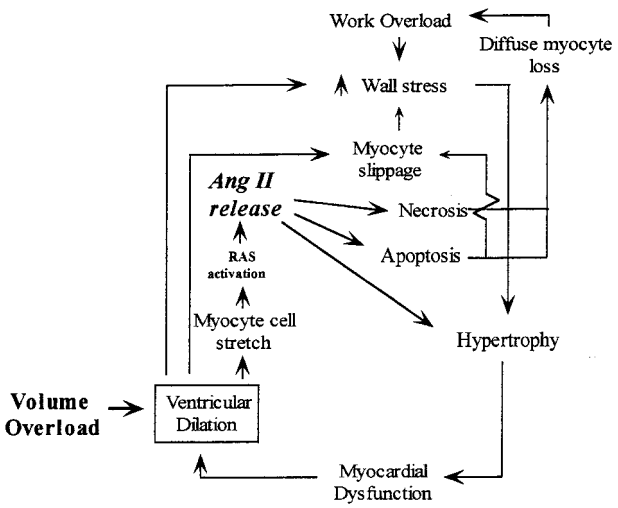

Figure 1. *Model for left ventricular remodeling due to mitral or aortic regurgitation. Added to the physical forces producing initial ventricular dilation (mechanical stress), is the activation of the renin-angiotensin system (RAS) induced by myocyte cell stretch. Chronic ventricular dilation is accomplished by side-to-side myocyte slippage and myocyte elongation through serial addition of sarcomeres. Angiotensin II (Ang II) release promotes not only reactive hypertrophy to sustain the load, but also myocyte death by necrosis and apoptosis which permits myocyte translocation and ventricular remodeling.*

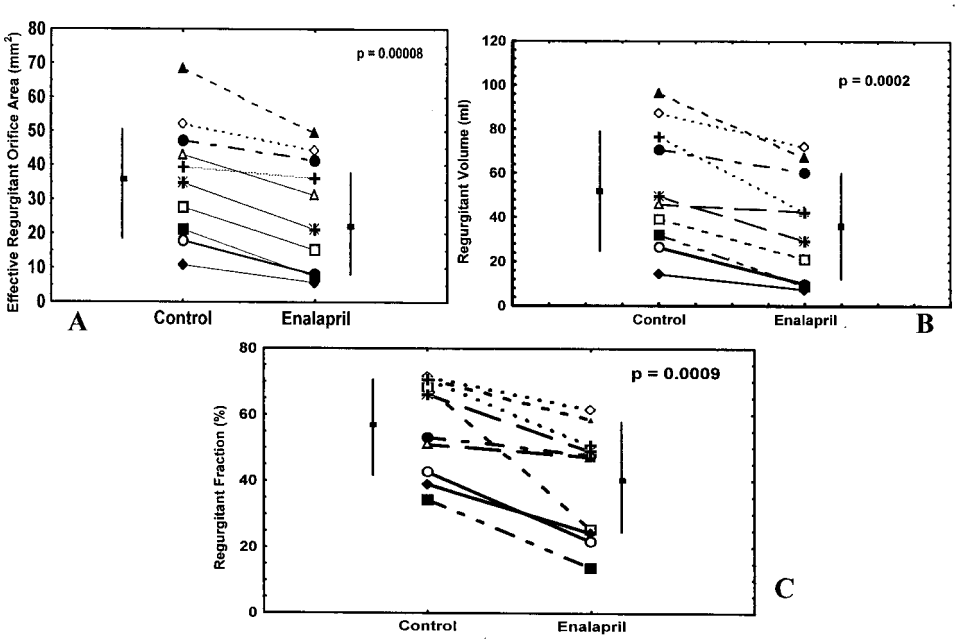

Figure 2. *The effects of one oral dose of enalapril on the effective regurgitant orifice area* (A), *volume* (B) *and fraction* (C) *in pediatric patients with chronic asymptomatic moderate to severe mitral regurgitation. From Calabrò et al.[58], modified.*

ward flow, increased by 5% and the total left ventricular ejection fraction by 6%. The stress-velocity index (an index which allows differentiation of changes in myocardial contractility due to alterations in ventricular loading conditions) did not change significantly after administration of enalapril.

On the whole, these data suggest that the preload and afterload changes after a single oral dose of enalapril effectively 1) reduce the severity of mitral regurgitation, 2) improve cardiac performance, and 3) partially revert the alterations in left ventricular geometry. Globally, these changes may counteract the mechanical disadvantages engendered by ventricular remodeling secondary to volume overload.

To date, only scant information about the long-term effects of ACE-inhibitors on left ventricular remodeling and function in children with moderate to severe mitral regurgitation is available, probably owing to the low incidence of isolated, significant, left valvular insufficiency in young children when only one institution is considered.

Seguchi et al.[48] showed a significant decrease in left ventricular end-diastolic dimensions and an increase in left ventricular fractional shortening after a relatively short period of enalapril treatment in pediatric patients with congestive heart failure following postoperative mitral regurgitation.

Even our preliminary results on this topic (unpublished data) are very promising. In fact, in a 6 month follow-up study, ACE-inhibitor therapy with enalapril reduced the severity of mitral regurgitation and favorably modified the remodeling process due to volume overload by reducing left ventricular volumes, myocardial mass and wall stress.

An example of the anti-remodeling properties of enalapril therapy on the left ventricle, overloaded because of moderate to severe mitral regurgitation in children, is reported in figure 3.

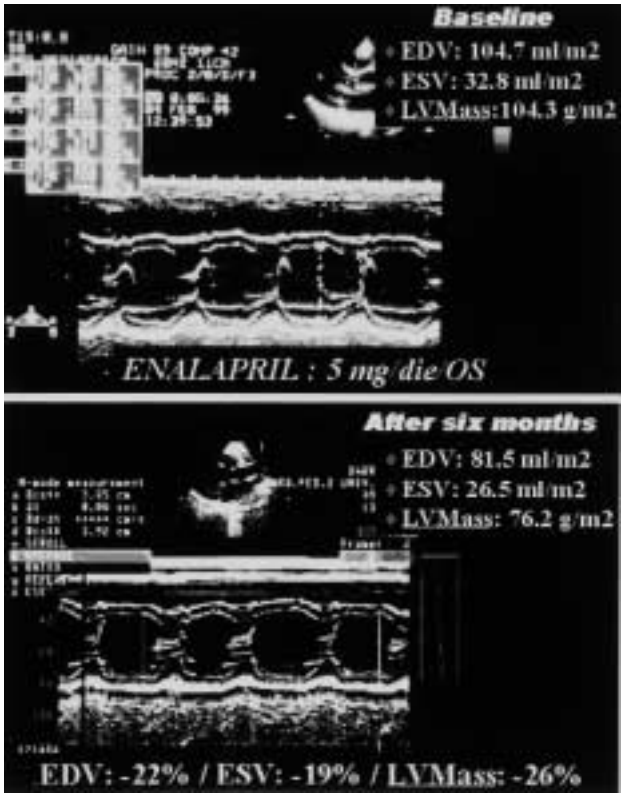

Figure 3. *An example of the anti-remodeling effects of the ACE-inhibitor enalapril (5 mg/day orally) in a 5-year-old female with chronic asymptomatic severe mitral regurgitation* (upper panel). *After 6 months of ACE-inhibition* (lower panel) *a marked reduction in left ventricular volumes and mass was observed. EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; OS = orally.*

Aortic regurgitation. The hemodynamic effects of a single oral dose of the ACE-inhibitor enalapril (0.40 mg/kg, maximal dose 20 mg) were evaluated in 7 asymptomatic pediatric patients (mean age 9.9 ± 3.7 years, range 6-16 years) with moderate to severe chronic aortic regurgitation[59]. Compared with baseline values, ACE-inhibition caused a marked reduction in the effective regurgitant orifice area with a consequent decrease of regurgitant volume and fraction. As a result, left ventricular end-diastolic and end-systolic volumes declined by 6 and 11% respectively. The peak-systolic and end-systolic wall stress also decreased by 12.5 and 6.5% respectively. Although the total stroke volume declined by 21%, neither the ejection fraction nor the stress velocity index (an index of myocardial contractility) was significantly influenced by enalapril.

These acute beneficial effects of ACE-inhibition were also maintained in long-term treatment. Alehan and Ozkutlu[60] studied the effect of captopril (1 to 1.5 mg/kg/day orally) in 20 children with moderate to severe asymptomatic chronic aortic regurgitation and normal left ventricular systolic function. After 12 months of therapy, the left ventricular end-diastolic and end-systolic diameters and the left ventricular end-diastolic and end-systolic volume indexes decreased significantly. Even the regurgitant fraction was significantly reduced (27.8%) with a 21% regression in myocardial mass index. Left ventricular meridional and circumferential wall stresses were both reduced significantly by captopril, whereas the ejection fraction remained unchanged.

On the whole, these short- and long-term clinical studies clearly demonstrate that, in pediatric patients with chronic aortic regurgitation, ACE-inhibitor therapy reduces the regurgitant orifice area and the regurgitant volume and fraction, and favorably modifies left ventricular volumes, hypertrophy and wall stress. Thus, it might significantly contribute to halt and/or reverse left ventricular remodeling due to volume overload.

The beneficial effects of ACE-inhibitor therapy have recently been confirmed by Mori et al.[61] in a randomized and placebo-controlled study. This study examined whether long-term (mean follow-up period 3.1 ± 1.7 years) therapy with an ACE-inhibitor (cilazapril 0.03 to 0.04 mg/kg/day, maximum dose 1.0 mg/day) or enalapril (0.15 to 0.4 mg/kg/day, maximum dose 5

mg/day) limits excessive increases in left ventricular mass and volume in growing children (mean age of subjects 5.0 ± 5.2 years) with aortic or mitral regurgitation. In the ACE-inhibitor group the left ventricular dimensions, wall thickness and mass decreased significantly from baseline to follow-up, whereas an increase was observed in the control group. This study suggests that long-term treatment with ACE-inhibitors is effective in reducing not only left ventricular volume but also left ventricular hypertrophy in the volume overloaded heart of growing children.

Conclusions

Although limited, the available data suggest that oral therapy with antagonists of the renin-angiotensin system may favorably affect the prognosis of children with left ventricular volume overload due to mitral and aortic regurgitation. The reported beneficial effects apparently concern the basic anatomic, hemodynamic and adaptive pathologic conditions related to the volume overload, namely, the regurgitant orifice area and volume and ventricular remodeling. Considering the heart as a plastic structure, constantly being altered in size, shape and composition in response to chronic hemodynamic overloading, modulation of this plasticity by ACE-inhibitors should be a primary therapeutic target both to prevent as well as to treat cardiac remodeling. As the beneficial effects of ACE-inhibition have also been obtained in growing children with asymptomatic valvular regurgitation, it appears that unloading therapy potentially influences the natural history of both mitral and aortic regurgitation and possibly delays surgical valve repair or replacement. Thus, these observations would justify inhibition of the renin-angiotensin system very early in the dynamic process of left ventricular remodeling due to valvular regurgitation. However, multicenter, randomized, double-blind studies are required to determine the definitive role of ACE-inhibitors in the long-term outcome of children with moderate to severe mitral and aortic regurgitation.

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