

RAAS inhibitors should be avoided if possible in patients with obstructive HCM

Influence of RAAS inhibition on outflow tract obstruction in hypertrophic cardiomyopathy

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Summary

Background: Two-thirds of patients with hypertrophic cardiomyopathy (HCM) develop symptomatic dynamic left ventricular outflow tract (LVOT) obstruction. Renin angiotensin aldosterone system (RAAS) inhibitors are well-established antihypertensive drugs and have recently been reported to be safe even in patients with severe aortic stenosis. However, their effect in HCM patients with dynamic LVOT obstruction is not yet well investigated.

Methods: Fourteen HCM patients (age 68.5 ± 9.6 years; nine women) with symptomatic LVOT obstruction (>30 mm Hg) under RAAS inhibition therapy (seven ramipril, six candesartan, one losartan) were investigated. LVOT gradients and New York Heart Association (NYHA) class were assessed before and after withdrawal of RAAS inhibitors. Statistical analysis was performed using Wilcoxon paired signed rank tests.

Results: RAAS inhibitors were either not replaced (four patients), changed to alternative medication (eight patients) or the pre-existing β -blocker dose was adjusted (two patients). After RAAS withdrawal the LVOT gradient was significantly reduced from 94 ± 53 mm Hg to 36 ± 30 mm Hg ($p = 0.001$) associated with an improvement in NYHA class from 2.8 ± 0.5 to 2.1 ± 0.4 ($p = 0.001$).

Conclusion: In obstructive HCM withdrawal of RAAS inhibitors can cause a significant reduction of the LVOT gradient and an improvement of patients' symptoms. Thus, current data confirming the safety of RAAS inhibition in severe aortic stenosis cannot be transferred to HCM patients with dynamic obstruction. RAAS inhibitors should rather be avoided and if compulsory, monitored by regular assessment of the LVOT gradient.

Key words: ACE inhibitors; angiotensin receptor blocker

at rest or during exercise caused by hypertrophy associated with systolic anterior movement of the mitral valve [1, 2]. This is considered to be a predictor of progressive heart failure and cardiovascular death [3, 4]. As LVOT obstruction is one major cause for the development of severe symptoms, such as dyspnoea, chest pain, presyncope or syncope, reduction of the LVOT gradient is an important therapeutic target in symptomatic HCM patients. Although reduction of LVOT obstruction by surgical myectomy or interventional alcohol septum ablation has proved to be effective, invasive therapeutic options should be considered only if pharmacological treatment with negative inotropic agents such as β -blockers and nondihydropyridine calcium antagonists was unsuccessful [5].

Renin angiotensin aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are well-established antihypertensive drugs and have been reported to reduce mortality and morbidity in patients with impaired systolic function, with diabetic nephropathy, or at high risk of cardiovascular events [6–8]. They are also thought to reduce cardiac fibrosis in response to pressure overload [9] and attenuate progression of myocardial hypertrophy [10]. Due to their ability to reduce cardiac afterload, RAAS inhibitors have previously been regarded as contraindicated in patients with outflow tract obstruction caused by aortic stenosis [11] and consequently also in obstructive HCM. In contrast, recent data have demonstrated that ACEI and ARB therapy is relatively safe and generally well tolerated in patients even with severe aortic stenosis [12–14].

ACEIs play a pivotal role in systolic heart failure during the course of end-stage HCM and in the absence of LVOT obstruction [5], and seem to be beneficial in reducing myocardial mass and the development of fibrosis in these patients [15]. Still, very few data exist on the haemodynamic effects of RAAS inhibition in obstructive

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic inherited heart disease and, in most cases, characterised by asymmetrical left ventricular hypertrophy. Two-thirds of patients develop dynamic left ventricular outflow tract (LVOT) obstruction either

tive HCM [16, 17]. Accordingly, current guidelines recommend cautious use of RAAS inhibitors in these patients [18]. In contrast, recently published data suggest that the ARB losartan can be safely used in all HCM patients irrespective of LVOT obstruction [19].

To shed more light on the haemodynamic effects of RAAS inhibition in obstructive HCM, 14 symptomatic HCM patients with LVOT obstruction initially presenting with RAAS inhibition therapy in our outpatient clinic were systematically investigated, and clinical, laboratory and transthoracic echocardiography parameters were assessed before and after withdrawal of RAAS inhibitors.

Methods

Study population

The study cohort comprised 14 symptomatic adult patients with obstructive HCM (LVOT gradient >30 mm Hg) initially presenting with RAAS inhibitor therapy in the outpatient clinic at the University Heart Centre Hamburg between July 2011 and August 2014. Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle with a maximum wall thickness of ≥ 15 mm and without the presence of abnormal loading conditions or another cardiac or systemic disease that could produce the magnitude of hypertrophy evident. All patients with additional hypertension were diagnosed with HCM according to at least one of the following criteria: hypertension occurring years after the diagnosis of HCM ($n = 11$), detection of an HCM-causing gene mutation or family history of HCM ($n = 6$), maximum wall thickness exceeding the expected dimension caused by hypertension alone (i.e., ≥ 20 mm; $n = 9$), and/or presence of marked mitral leaflet elongation. The inclusion criteria for the study were: a significant LVOT gradient at rest, during a Valsalva manoeuvre or cycle ergometer exercise (peak gradient ≥ 30 mm Hg), normal systolic left ventricular (LV) function (ejection fraction $>50\%$), and concomitant treatment with an ACEI or ARB.

The study was in line with the principles outlined in the Declaration of Helsinki and approved by the local ethics committee of the "Ärztchamber Hamburg" (PV4056).

Clinical assessment

Before withdrawal of RAAS inhibition therapy and a median of 1 month afterwards, each patient was investigated by means of clinical assessment, echocardiography and laboratory tests. Clinical assessment included HCM-related symptoms such as dyspnoea,

angina, (pre-)syncope and palpitations. Dyspnoea was graded according to the New York Heart Association (NYHA) classification. Blood pressure measurements and a 12-lead ECG at rest were recorded.

Echocardiography

Two-dimensional transthoracic and Doppler echocardiography was performed using an iE33 Philips® ultrasound system to assess systolic and diastolic LV function, maximum LV wall thickness, mitral valve function and the peak LV outflow tract gradient. Images were obtained from standard apical, parasternal and subcostal views. Peak early (E wave) and late (A wave) transmitral filling velocities and deceleration time of E (DT of E wave) were measured with pulsed wave Doppler of transmitral flow in the apical four-chamber view. Tissue Doppler imaging was used in the colour-guided pulsed wave Doppler mode to assess peak early (E') mitral annulus velocities at the septal and lateral mitral valve annulus in the apical four-chamber view. Grading of diastolic dysfunction was determined according to current recommendations [20].

LVOT obstruction was identified from a peak outflow gradient ≥ 30 mm Hg measured by continuous- and pulsed-wave Doppler at rest and during a Valsalva manoeuvre. One patient, who was nonobstructive at rest and during Valsalva manoeuvre, underwent symptom-limited exercise echocardiography using a standard ergometer protocol with a 12-lead ECG, blood pressure and heart rate monitoring. Peak LVOT gradient was assessed before, during and immediately after exercise. All measurements were made in the morning in our outpatient clinic in a nonblinded fashion.

Laboratory values

Cardiac markers, such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high sensitive troponin T values, were obtained and a possible correlation with heart failure symptoms was assessed. Routine laboratory tests comprising blood count, creatinine, transaminases and C-reactive protein were undertaken to rule out either other diseases influencing the haemodynamic status or adverse effects due to the change of medication.

Statistical analysis

Data are reported as mean $\pm$ standard deviation (SD) and compared by Wilcoxon paired signed rank tests. A p-value <0.05 was considered statistically significant. All analyses were carried out using STATA 13 (Stata-Corp. 2013).

Results

Baseline characteristics of the study population are summarised in table 1. All patients presented with normal systolic LV function and symptomatic LVOT obstruction (>30 mm Hg) either at rest (11 patients), or during a Valsalva manoeuvre (two patients) or cycle ergometer exercise (one patient). Half of the patients received antihypertensive medication with the ACEI ramipril (seven patients) and the other half with an ARB (candesartan six patients, losartan one patient) in addition to a β -blocker or verapamil. In four patients RAAS inhibition was withdrawn without alternative antihypertensive medication, eight patients received alternative treatment with moxonidine, and in two patients the dose of the pre-existing β -blocker was adjusted.

Withdrawal of RAAS inhibitors reduces LVOT gradient

The withdrawal of RAAS inhibition and change to alternative antihypertensive medication in patients with symptomatic LVOT obstruction was well tolerated and no adverse events were reported. After drug withdrawal a significant reduction of the LVOT gradient from 94 ± 53 mm Hg to 36 ± 30 mm Hg was observed (fig. 1; $p = 0.001$; $n = 14$). There was no significant difference between patients initially taking ramipril and those taking candesartan or losartan as to the reduction of the LVOT gradient ($p = 0.37$).

Table 1: Baseline characteristics.

Age (yrs)	68 $\pm$ 9
male / female	5/9
NYHA functional class	2.8 $\pm$ 0.5
Septal wall (mm)	21 $\pm$ 3.9
Posterior wall (mm)	14 $\pm$ 3.9
LVEDD (mm)	41 $\pm$ 6.3
Peak LVOT gradient (mm Hg)	94 $\pm$ 53
SAM of the mitral valve (n)	14
Left atrial diameter (mm)	42 $\pm$ 6
E/A	0.8 $\pm$ 0.3
Concomitant medication, n (%)	14 (100)
Beta-blocker	12 (86)
Verapamil	1(7)
Diuretic	7 (50)
Dihydropyridine-like CCB	2 (14)

Values are given as total number or mean $\pm$ standard deviation. CCB = calcium channel blocker, LVEDD = left ventricular end-diastolic diameter, LVOT = left ventricular outflow tract, NYHA = New York Heart Association, SAM = systolic anterior movement.

Improvement of clinical symptoms by withdrawal of RAAS inhibitors

Patients' symptoms improved significantly after withdrawal of RAAS inhibitors as reflected by a significant reduction in the NYHA functional class from 2.8 ± 0.5 to 2.1 ± 0.4 (fig. 2; $p = 0.001$; $n = 14$). No significant difference between patients initially taking ramipril and those taking candesartan or losartan was observed ($p = 0.38$).

Effects of changes in medication on cardiac markers, vitality parameters, and diastolic dysfunction

Neither the systolic and diastolic blood pressure nor the mean heart rate were significantly altered after RAAS withdrawal. Also, no influence on NT-proBNP and high sensitive troponin T levels was observed after change of medication, as shown in table 2. Furthermore, RAAS withdrawal did not alter the grade of diastolic dysfunction or the magnitude of mitral valve regurgitation.

Discussion

This study demonstrates that withdrawal of RAAS inhibitors in HCM patients with symptomatic LVOT obstruction significantly reduces the LVOT gradient and improves symptoms reflected by a reduction of NYHA functional class.

At the time of initial presentation, 11 of the 14 patients with relevant LVOT obstruction were so severely symp-

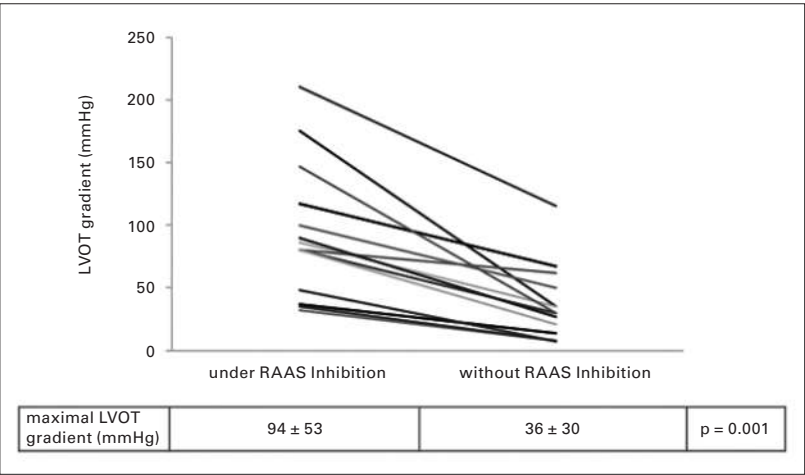


Figure 1: Maximal LVOT gradient at rest (n = 11), under Valsalva manoeuvre (n = 2) or exercise stress test (n = 1) in 14 obstructive HCM patients under RAAS inhibition and after withdrawal. Each patient is represented by a line connecting two gradient measurements. Values are given as mean $\pm$ standard deviation. HCM = hypertrophic cardiomyopathy, LVOT = left ventricular outflow tract, RAAS = renin-angiotensin-aldosterone system.

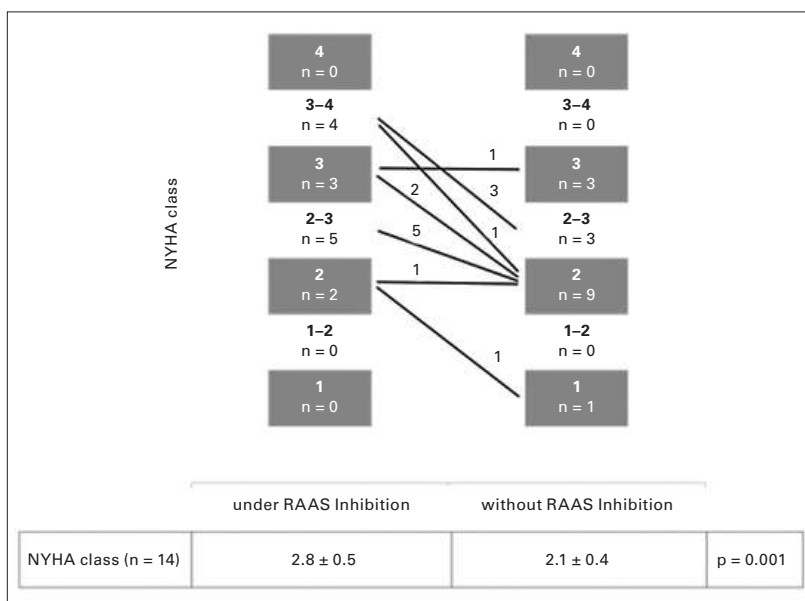


Figure 2: NYHA (New York Heart Association) functional class in 14 obstructive HCM patients under RAAS inhibition and after withdrawal. Values are given as mean ± standard deviation. The total number of patients are given in circles for each line connecting NYHA classes with and without RAAS inhibition. HCM = hypertrophic cardiomyopathy, RAAS = renin-angiotensin-aldosterone system.

tomatic that invasive septum reduction therapy was indicated. After ARB/ACEI withdrawal, only four patients still had an indication for surgical/interventional therapy. Two of these suffered from severe mitral valve insufficiency, which was still relevant after the change of medication even though the LVOT gradient was significantly reduced. The other two patients were still symptomatic with a maximum gradient of more than 50 mm Hg and were therefore referred for myectomy, although the gradient was significantly reduced after RAAS inhibitor withdrawal. In

our patients disopyramide was not added to the existing β -blocker medication as recommended by the European Guidelines since it is not authorised for sale in Germany.

Since no significant changes in blood pressure or heart rate were observed after the change of medication, the possibility that the reduction of the LVOT gradient after RAAS inhibitor withdrawal was based on insufficient antihypertensive treatment could be excluded in this cohort. Unexpectedly, the mean NT-proBNP level was not significantly reduced after reduction of the LVOT gradient. However, closer analysis of these data showed that, in the majority of patients, NT-proBNP concentrations were in fact lower after RAAS inhibitor withdrawal. In only three patients, with either severe mitral insufficiency or still significantly elevated gradients, were the NT-proBNP levels even increased after changing the medical therapy. The small number of patients in this cohort may explain why this trend did not reach statistical significance.

Previous trials have described a beneficial effect of RAAS inhibitors in nonobstructive HCM on systolic and diastolic LV function as well as on hypertrophy and myocardial fibrosis [21–24]. Therefore, in non-obstructive HCM patients with a reduced LV ejection fraction of less than 50%, the use of ACEI or ARB therapy is recommended, in line with the guidelines for chronic heart failure. However, there are no clear recommendations concerning the use of ACEIs or ARBs as antihypertensive medication in HCM patients with a preserved LV ejection fraction [5] and significant LVOT obstruction. In the past decades the cautious use of RAAS inhibition in obstructive diseases such as hypertrophic obstructive cardiomyopathy and aortic stenosis was based on the idea that an excessive reduction of the cardiac afterload and the inability to subsequently increase cardiac output might lead to a dangerous decrease in coronary or brain perfusion and might therefore cause exercise-related symptoms such as angina, syncope or even sudden cardiac death.

In a study from 1998 using an invasive approach of intracoronary application of enalaprilat followed by a systemic sublingual captopril dose in obstructive HCM patients, the authors observed a significant drop of the LVOT gradient and an increase in the coronary blood flow directly after intracoronary injection, whereas this was counteracted after systemic application of ACEI. Therefore, they concluded that only selective inhibition of the cardiac, but not circulatory, RAAS might be beneficial in obstructive HCM [16]. Based on this retrospective study, the current American guidelines for the treatment of HCM still suggest a cautious use of systemic RAAS inhibitors in patients with rest-

Table 2: Influence of RAAS inhibitors on cardiac marker, haemodynamic parameters and diastolic dysfunction.

	Under RAAS inhibition	Without RAAS inhibition	p-value
Troponin (ng/ml)	16 ± 9	19 ± 10	0.48
NT-proBNP (ng/l)	3733 ± 3722	3478 ± 3207	0.6
Creatinine (mg/dl)	1.6 ± 1.8	1.5 ± 1.7	0.06
SBP (mm Hg)	136 ± 17	139 ± 13	0.29
DBP (mm Hg)	74 ± 9	78 ± 7	0.09
HR (bpm)	71 ± 15	66 ± 9	0.17
Diastolic dysfunction, grade	1.4 ± 0.5	1.5 ± 0.5	0.32

Values are given as mean + standard deviation. DBP = diastolic blood pressure, HR = heart rate, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, RAAS = renin-angiotensin-aldosterone system, SBP = systolic blood pressure

ing or exacerbated LVOT obstruction, assuming aggravation of the outflow tract gradient due to a reduction in cardiac afterload by vasodilatation [12, 18, 25, 26]. In contrast, a very recently published prospective trial on 133 HCM patients stated the ARB losartan to be safe even in the presence of LVOT obstruction. However, only 12% of these patients presented with a LVOT gradient at rest of more than 30 mm Hg. Furthermore, according to the subgroup analysis precisely these patients showed a difference in favour of placebo. In our opinion, the haemodynamic effects of RAAS inhibition on LVOT obstruction are not sufficiently understood to be able to generally consider them safe in HCM.

Interestingly, recent studies also suggest that patients with valvular aortic stenosis may benefit from RAAS inhibitor therapy due to its beneficial effects on myocardial fibrosis as well as on systolic and diastolic function, while haemodynamic problems seemed to be negligible in these patients [12, 25, 26]. Apart from the aforementioned study [16], however, the effects of RAAS inhibition on dynamic LVOT obstruction in HCM patients have not yet been systematically investigated. Our data suggest that observations from patients with valvular aortic stenosis cannot be directly transferred to HCM patients with LVOT obstruction. This might be due to the dynamic nature of the outflow tract obstruction in HCM, which is described as a flow against a potentially abnormal mitral valve. The resulting drag forces provoke a movement of the mitral valve towards the LVOT causing a late-peaking systolic velocity [27, 28]. This systolic anterior motion-associated late-systolic gradient seems to follow different haemodynamic rules than the midsystolic peak velocity in aortic stenosis and may cause serious aggravation under certain circumstances by triggering itself. Furthermore it is well known that dynamic LVOT obstruction in HCM patients responds sensitively to

changes in myocardial contractility, ventricular volume and afterload [29]. Thus, in HCM drag forces causing the late-peaking velocity in the LVOT might be aggravated more severely by RAAS inhibitor-induced reduction of cardiac afterload than the more static obstruction in aortic stenosis.

Conclusions

These data provide evidence that, despite their positive effects on LV hypertrophy and cardiac fibrosis, RAAS inhibitors should be avoided in obstructive HCM patients and, if necessary, monitored by regular echocardiographic assessment of the LVOT gradient at rest as well as during exercise. Since RAAS inhibitor therapy is widely used in patients with cardiac diseases, its haemodynamic effects in patients with LVOT obstruction should be carefully considered after individual appraisal of its benefits and disadvantages.

Limitations

This observational study was not designed as a randomised trial and is limited by the small number of obstructive HCM patients presenting with an initial RAAS inhibitor therapy in our outpatient clinic. Also, the observation period was too short to draw any conclusions about long-term effects of the RAAS inhibitor withdrawal in these patients.

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References

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