

# Experimental Impact of Mucopolysaccharidosis on Right Atrial Contractile Capacity of Skinned Fibers

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## Abstract

**Objective:** Mucopolysaccharidosis is a group of inherited lysosomal storage disorders caused by the absence of an enzyme, contributing to the degradation of the Glycosaminoglycans (GAG). To evaluate if storage of GAGs affects the contractile capacity, we compared the contractile performance of patients with and without MPS in a skinned fiber model.

**Methods:** Right auricle tissue from 12 patients (4 MPS, 8 Non-MPS) undergoing cardiac operation for Mitral Valve Stenosis (MS) or Mitral Valve Regurgitation (MR) was harvested prior to implementation of extracorporeal Circulation (ECC). The trabeculae are resected from the right auricle; the tissue was dissected down to small bundles of fibers. They were chemically skinned by removal of cell membrane-dependent properties to gain the actin-myosin-formation. These bundles are dissected in single fiber stripes. The fibers were exposed to a gradual increase of calcium concentration (pCa) and the corresponding force was measured and recorded.

**Results:** 1.) pCa-force development was significant lower in fibers with MPS (p max  $2.2 \pm 0.1$  mN) than in fibers with MS ( $3.4 \pm 0.7$  mN, p 0.03) or MR ( $4.6 \pm 0.9$  mN, p 0.04). 2.) The pCa-force values of fibers with mitral valve stenosis and regurgitation did not differ significantly at single steps of calcium concentration among each other (p 0.3). 3.) Fibers with MR developed significant more force at almost all steps of calcium concentration than those with MPS (p 0.02) 4.) Fibers with MS developed only once significant more force compared to MPS fibers: pCa 5.5: 1.6 mN vs. 0.3 mN, p 0.02. 5.) Calcium sensitivity is similar in patients with MPS and MR (pCa 4.5), but different in patients with MS (pCa 5).

**Conclusion:** Patients with MPS develop significantly less force at similar calcium concentrations compared to patients with a mitral valve stenosis or regurgitation. We suggest that impairment of the contractile apparatus due to the accumulation of GAGs leads to early onset left ventricular hypertrophy and diastolic dysfunction limiting the ventricular filling. This stands in opposition to patients with mitral valve regurgitation with volume overload due to incomplete valve closure.

**Keywords:** Skinned fiber; Calcium sensitivity; Mucopolysaccharidosis; pCa-force-development; Mitral valve stenosis; Mitral valve regurgitation

## Introduction

Because of poor survival rate the role of right ventricular systolic dysfunction in patients with mitral valve disease is increasingly recognized. Right ventricular impairment or failure remains a challenge especially in postoperative intensive care unit. The importance of this issue can be seen in the observation, that a dysfunctional preoperative right ventricular function is associated with postoperative regurgitation, requirement of more blood transfusion, longer intensive care unit stays and hospital stays [1]. An early involvement of right ventricular function in mitral valve stenosis is shown by Tayyareci, who performed a study to detect early signs of right ventricular dysfunction in patients with MS [2]. He found some evidence for an early systolic dysfunction in patients without signs of systemic venous congestion. Le Tourneau estimates the incidence of right ventricular impairment in patients with mitral valve regurgitation at 30% and underlines that the dysfunction mainly depends on left ventricular remodeling and septal function [3]. Furthermore he emphasizes the impact of RV function as a predictor for postoperative cardiovascular survival.

Concerning mitral valve regurgitation McGinley shows that even in patients with preserved ejection fraction isolated left ventricular trabeculae show a significant reduction of contractile function and hence assumed that the impairment is not load-dependent but caused by a defect in calcium cycle [4]. Sade makes a similar observation, regarding a parallelism of severity of valve stenosis and right ventricular

contractile reserve [5]. This could also be seen for the left ventricular function regardless of the severity of disease [6]. But we assume that different valvular pathologies like stenosis or regurgitation depending on the degree of the disease may change the hemodynamic state of the myocardium.

In patients with mucopolysaccharidosis (MPS) we often find combined valve pathology. The macroscopic findings of the cardiac involvement in MPS include valve thickening, short chordae and hypertrophic papillary muscle secondary to glycosaminoglycan (GAG) accumulation, resulting in fibrosis and nodular deformation. This pathology mainly affects the left-sided valves. This valve degradation can lead to regurgitation as well as stenosis and most common the mitral valve is affected [7]. These diseases are a heterogeneous group of lysosomal storage disorders, which are caused by the absence of specific lysosomal enzymes having an incidence of 1:5000 live births [7,8]. As a result of the missing lysosomal enzymes the glycosaminoglycans

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(GAGs) accumulate in the enlarged lysosomes and are stored in several tissues, like the myocardium or the heart valves, but of course affect multiple organ systems [9]. Cardiac involvement is described in all MPS syndromes, but is highly associated with the dermatan sulfate storing types of MPS, i.e. MPS I, II und VI and is a common and early feature, emerging silently, and contributes to early mortality and can be found in 60-90% of all patients with MPS [7].

Considering that patients with chronic MR may stay asymptomatic for a long time and regarding the reversibility of disease progress and contractile reserve after cardiac surgery we wanted to objectify this impact on 3 different groups of patients with different mitral valve disease [10].

## Materials and Methods

### Origin of samples

Appendages of the right atria from the patients were obtained in the operation room. The tissue samples were resected routinely prior to right atrial cannulation and immediately stored in an oxygenated cardioplegic solution. All patients were informed and gave written consent before surgery. All fibers were exposed to gradual increase of calcium concentration (starting at 6.5 until 4.0). The calcium concentration is given as pCa and without any unit (negative decadic logarithm of calcium concentration). Every group consisted of 4 patients. We took 3 fibers from each patient. Consequently there are 6 steps of concentration.

### Details of ethics approval

According to § (§-describes the approval to use tissue of patients, who gave their written consent) 14 AVB, Absatz 3: patients, who will be admitted to the University Hospital will be informed and asked, if they agree to use tissue, that will be withdrawn within the operation, for research work. This tissue can be used without making further applications at the ethical review committee. (See: www.laek-rlp.de)

§ check

### Patients

#### The MPS group

This group consists of two female and two male patients. The average age of the patients was 35 years. Both male patients had MPS II (Hunter's disease) whereas both female patients were diagnosed with MPS I (Scheie's disease). The mean echocardiographic estimated ejection fraction 65%. One male patient underwent replacement of aortic and mitral valve, whereas the other three patients underwent mitral valve replacement. All patients had dilated left atrium and a left ventricular hypertrophy.

#### The MR group

Three patients of this group underwent mitral valve replacement and one patient mitral valve repair and consisted of one male and three female patients. The mean age was 72 years. The mean ejection fraction was 55%. All patients showed a higher degree mitral valve insufficiency, two of them had also a combined valve disease with stenotic parts. One patient had a prolapse of P2. No patient had a ring dilatation or dilatation of left atrium or ventricle. No patient had heart rhythm disturbances.

#### The MS group

The group consisted of two male and two female patients with a

mean age of 69 years. The mean EF was 55%. All patients underwent mitral valve replacement because of a higher degree valve stenosis. One patient had an atrial dilatation. No patient had heart rhythm disturbances.

The operation and the further stay on Intensive care unit proceeded without interference in all groups. The histological examination of the tissue was performed in all patients: the MPS patients showed a myxomatous degeneration of the valve tissue and accumulation of glycosaminoglycans, whereas the Non MPS fibers showed a degenerative transformation with endocardial fibrosis.

### Muscle preparation

We treated the tissue with an oxygenated cardioplegic solution using BDM (Butanedione-Monoxim, 30 mM) as an ATP-sensitive potassium canal inhibitor. A special solution containing 50% glycerol (Contents [mM]: Imidazole 20; Sodium azide 10; EGTA 4; Dithioerythriol 2; Magnesium chloride 5; ATP 5; ph 7) was used to prime the fibers for the experimental set up. We first resected the single trabeculae out of the papillary muscle and kept the fibers in the same solution, containing 1% Triton-X-100 in addition, for 24 hours at 4°C. For the experiments we skinned the fibers and cut muscle stripes with a size of 2-2.5 mm x 0.3 mm and mounted them on a force transducer (Figure 1).

We started the experimental cycle by bathing the fibers in relaxing solution (pCa 6.5) and then started with the activating solution. Both solutions had the same composition (Contents [mM]: Imidazole 20, Phosphocreatine 10; Sodium azide 10; EGTA 10; Magnesium chloride 25; Dithioerythriol 2; ATP 20) and 400 U/ml creatine kinase. In the contraction solution EGTA was substituted by CaEGTA. The free calcium concentration was obtained by mixing the relaxation and contraction solution in appropriate proportions. The desired calcium concentrations were calculated by a computer program, following the equation of Fabiato & Fabiato and given as pCa (-log of free  $Ca_2^{++}$ ). As mentioned we started the cycle with relaxation solution and prestretching the fibers to 20 mg (sarcomere length, 2  $\mu$ m). Then the concentration of calcium was stepwise increased by adding a calculated amount of contraction solution to the mixing chamber. The fibers started at a pCa of 6.5 (lowest calcium concentration) until the final calcium concentration of 4.0 (highest concentration) was achieved. The rising calcium concentration and force development were simultaneously

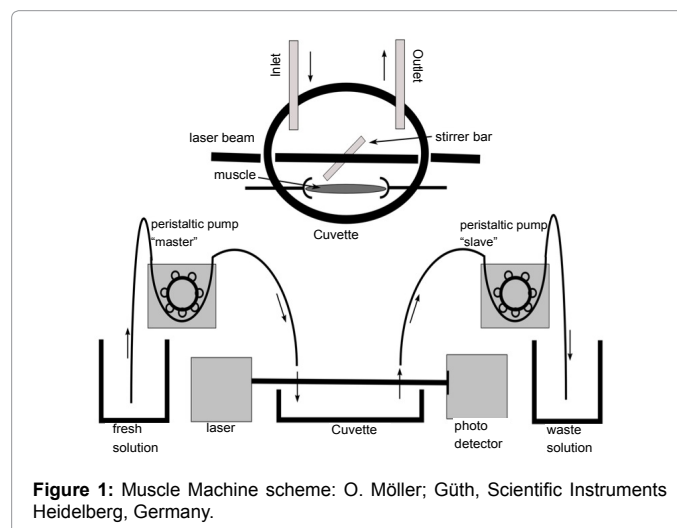


Figure 1: Muscle Machine scheme: O. Möller; Güth, Scientific Instruments Heidelberg, Germany.

recorded and sampled on a computer. The experimental setup and computer controlled feedback circuit were purchased from Scientific Instruments, Heidelberg, Germany.

### Statistical analysis

We used the Wilcoxon rang sum Test for evaluating the statistical significance and kept a significance level of 5%.

### Results

Fibers of patients with mucopolysaccharidosis behave different from those fibers, deriving from patients with mitral valve stenosis or regurgitation (Table 1). The fibers of the patients with mucopolysaccharidosis developed  $2.2 \pm 0.2$  mN at the highest step of calcium concentration and  $0.08 \pm 0.04$  mN at the lowest step of calcium concentration. The patients without MPS achieve  $4.1$  mN  $\pm$   $0.8$  mN at the top and  $0.3$  mN  $\pm$   $0.05$  mN at the lowest step (Figure 2).

The fibers of patients with mitral valve regurgitation achieved  $4.6 \pm 0.9$  mN at pCa 4.0. Fibers deriving from patients suffering from mitral valve stenosis generate  $3.4 \pm 0.9$  mN at pCa 4.0. The calcium sensitivity is at pCa 4.5 for the MPS fibers and the fibers of patients with MI at pCa 5.0 for the mitral stenosis. Fibers of MPS need more calcium to achieve half maximal activation (i.e. definition for calcium sensitivity).

Comparing the force values we find that fibers of MPS patients increase almost thirty fold their force values when starting at pCa 6.5 whereas fibers from MS increase fifteen fold and fibers from MR multiply force values at almost nine fold. The force development in the mitral regurgitation group developed the highest values, but do not have the highest affinity to calcium, the same can be found in the mitral stenosis group, which shows a higher affinity to calcium (pCa 5.5) but does not achieve higher values.

Comparing the force values at the different steps of calcium concentration, the MPS fibers differ significantly at almost all steps of calcium concentration from those fibers with mitral valve regurgitation: pCa 4.0: p 0.2; pCa 4.5 p 0.05; pCa 5.0 p 0.02; pCa 5.5 p 0.02; pCa 6.0 p 0.02; pCa 6.5 p 0.02. The fibers of patients with mitral valve stenosis only differ significantly at one calcium concentration (pCa 5.5) compared to those with mucopolysaccharidosis (p 0.02). The fibers of patients with mitral valve regurgitation and mitral valve stenosis did not differ significantly among each other.

The age seems to be a significant influencing factor: the younger age of the patients with mucopolysaccharidosis differed significantly from the other groups (p: 0.02 for MS and MR).

### Discussion

We observed clear differences of force development between patients with MPS and those without: patients with mucopolysaccharidosis

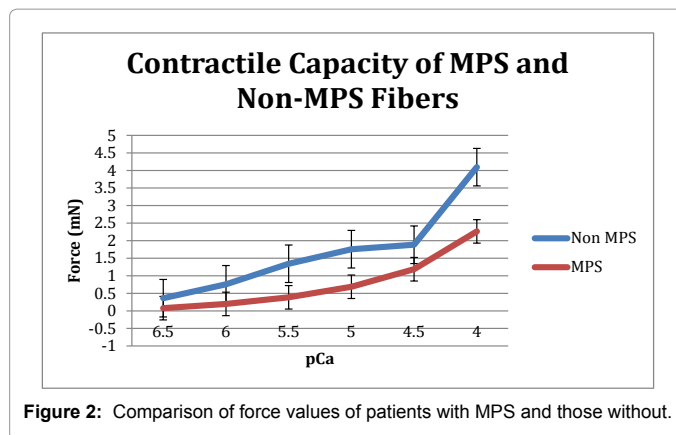


Figure 2: Comparison of force values of patients with MPS and those without.

achieve clearly less force than patients without MPS. Considering that lysosomal storage diseases deposit the incompletely degraded GAGs in several tissues, it might be conclusive that GAGs not only store in the thickened valves but also in the myocardium and the papillary muscle. But studies with this issue are missing until now. Furthermore the fibers of patients with MPS need more calcium to achieve half maximal activation. Braunlin describes that besides the valve thickening, the subvalvular apparatus presents shortened chordae tendineae and thick papillary muscle with dysmorphic leaflets [7]. Other retrospective studies show that left ventricular hypertrophy (LVH) and diastolic dysfunction emerges at an early state whereas ventricular dilatation and systolic dysfunction occurs later [11]. But studies about loss of contractility in these patients are lacking. The reason might be that most patients present a good ejection fraction with mild clinical symptoms, which are thought to be associated with the valve pathology. But however all our patients presented already atrial and/or ventricular dilatation and hypertrophy and therefore changes of the subvalvular apparatus and the myocardial apparatus cannot be excluded. Regarding the issue of atrial and/or ventricular contractility in MPS less is known. Beside the described changes of valvular morphology, single studies describe coronary artery narrowing and occlusion because of intimal proliferation from GAG deposition rather in coronary arterioles than in the large epicardial arteries. This might lead to changes in contractility because of different perfusion and supply, but is not described until now. Furthermore other vascular changes like wall thickness in great vessels like dilatation of ascending aorta and conduction abnormalities are described. Braunlin assumes that accumulation of GAGs influences the assembly of tropo-elastin. Hinek and Wilson show that this affects the structure and function of elastin [7,12]. These observations might influence cardiac atrial as well as ventricular contractility. But as mentioned studies are missing and these conclusions remain assumptions. Experimental examinations concerning cardiac contractile capacity in MPS-mice revealed significant contractile deficiencies indicated by decreases in end-systolic pressures when dobutamine was infused in MPS-mice [9]. Palant concludes that cardiac remodeling in animals with MPS leads to heightened adrenergic tone at the expense of cardiac reserve. All these studies allow assumptions, derived from these observation, but concrete analysis of atrial contractility in patients with MPS are missing. The importance of MPS for cardiac contractility can be seen in a study of Chen, who examined 27 boys (age 2-11 years) with Hunter syndrome: only 5 patients had normal echocardiographic and/or autopsy results, 19 had changes in mitral valve, 5 had changes in aortic valve and 10 patients had already signs of heart disease [13]. So MPS does not only affect cardiac heart valves, but also the whole cardiac

Diagnosis	MPS vs.MI	MPS vs.MS	MS vs.MI
pCa			
6.5	0.021	n.s.	n.s.
6.0	0.028	n.s.	n.s.
5.5	0.025	0.028	n.s.
5.0	0.024	n.s.	n.s.
4.5	n.s.	n.s.	n.s.
4.0	n.s.	n.s.	n.s.

Table 1: Overview of significant p-values (referring to the force values) at the correlating calcium concentrations (pCa). The force value for every step of calcium concentration was compared among the groups and tested for significance.

contractility. And of course deposition of GAGs also takes place in the ventricles as well as in the atria. The importance of atrial function to the global ejection fraction can be seen in atrial fibrillation. 15% of the ejection fraction is lost in patients with AF. This value correlates with the part of the atria to the global cardiac ejection fraction and might image the deficit of ventricular force in patients with MPS.

The fibers of patients with mitral valve regurgitation presented the highest force values; despite that calcium sensitivity was similar to the MPS fibers (at pCa 4.5). This is according to the clinical observation of being asymptomatic for a long time. Zile shows that LV remodeling is already observed in asymptomatic patients and may be a compensatory mechanism for volume overload. This might be an explanation for the clearly higher values in this group [14].

In patients with mitral valve stenosis we observed lower force values than in patients with MR. Referring to studies about contractility of right atrial appendage in patients with MS, contractile dysfunction can already be seen in patients with MS and sinus rhythm [15]. The decrease was related to increase in atrial afterload. Our patients however did not present Pulmonary Arterial Hypertension (PAH), nevertheless the force values were reduced and EF was described to be normal. But a decrease of EF with signs of systolic impairment is seen at later stages in mitral valve regurgitation as well as in MPS. Furthermore the right ventricle and atrium might not yet be affected of the MS by missing atrial afterload so far. Another explanation give Urabe and Cooper, who suggest that the right ventricle tend s to tolerate volume overload well and pressure overload poorly, whereas the left ventricle tends to tolerate volume overload poorly and pressure overload well [16,17]. But nevertheless the correlation of "normal" left ventricular function (in our cases EF > 50%) and contractility of atrial fibers is not sufficiently examined in literature. We observed a reduced force capacity in all patients with MPS although the EF was described to be normal. Willot described in his study of troponin mutation in different cardiomyopathies an increased calcium sensitivity and force development in hypertrophic cardiomyopathies and restrictive cardiomyopathies, whereas fibers of patients with dilated cardiomyopathy showed a decreased calcium sensitivity and force development [18]. And our MPS patients already had signs of atrial and ventricle dilatation that could also explain the lowered force. So we assume that cellular changes on level of the contractile apparatus already occurred.

But despite this assumption there is less information about the contractility of different cardiac cell types. So of course it is difficult to translate our observed results into vivo. Concerning the human skinned fibers, we know that calcium sensitivity is not only species-dependent as well as different in the atrium and ventricle. This corresponds with the fact of different myosin heavy chain and light chains in the atrium and ventricle. Morano shows that ventricle fibers are more sensitive to calcium [19]. Furthermore some studies show increased calcium sensitivity of hypertrophied human atria since in the hypertrophied human atrium ventricle-specific myosin heavy chains and myosin light chains appear [20]. But literature presents ambivalently referring to this issue: Vannier examined the characteristics of myofibrils in cardiac muscle from atria and ventricle and made an interesting finding: the adult atrial tissue shows the same contractile properties than ventricular tissue, but differs mainly in metabolic properties [20]. In opposite to that, Wankerl made an interesting observation when examining the calcium sensitivity in various kinds of cardiac disease: the calcium sensitivity from ventricle was higher in all patients at about 0.14 pCa Units, but was the same among the different heart diseases, whereas atrial fibers differed among the different cardiac diseases [21]. This

is probably an evidence for the assumption that cardiac pathologies can be better imaged in atrial tissue than in ventricle tissue maybe because of adaption to elevated pressure conditions of the ventricular fibers. Considering the different pressure and volume relations in the human ventricle and atrium, it is assumable, that calcium sensitivity and contractile proteins may differ. But nevertheless cardiac pathology in the different diseases will not exclusively affect the left heart side and differences of calcium sensitivity of atrial tissue in various cardiac diseases are already described and might give some evidence to the contractile status [22].

Referring to the valve disease in patients with mucopolysaccharidosis it is in general difficult to refer to literature because there is very little information about the myofilament performance in patients with MPS, so a discussion of these results is challenging because of the limited number and missing literature.

Beside the macroscopic findings of thickening of mitral and aortic valves, shortened chordae and hypertrophic papillary muscle cellular alterations were found like myxomatous degeneration and vacuolated and enlarged fibroblasts and histiocytes with glycosaminoglycan-laden cells (so called clear cells) [7,23]. But the cardiac involvement in MPS includes more: these clear cells also appear in coronary arteries, the aorta and the conduction system. So the affection of the cardiac system occurs in several ways and the impairment of the global contractile function in these patients occurs earlier than the valve pathology starts to cause symptoms [7,24]. This could explain the significant lower forces and calcium sensitivity in these patients and might be the histologic correlation to the echocardiographic findings of left atrial/ventricular volume overload and dilatation resulting in systolic as well as diastolic dysfunction [7]. Palpat showed in his study on MPS mice that differences in venous return is one of the fundamental deficiency of cardiac disease in MPS mice and that systolic and diastolic dysfunction might be decreased because of reduced preload [9]. He concludes that based on the Frank-Starling mechanism (increasing preload enhances contractility) reduced preload leads to reduced end diastolic volume and left ventricular pressure. So the changed anatomy in patients with MPS (short papillary muscle, thickened and stiff tissue, rigid myofilaments) might cause the restrictive myofilament function and lead to decreased force development and it can be assumed, that it will be found in all MPS patients presenting with cardiac involvement.

This study is a first experimental attempt to compare and describe contractile behavior of patients with and without this rare metabolic disorder. Of course further investigations with a higher number of individuals are needed to prove the observed differences but will remain a problem in rare diseases like mucopolysaccharidosis.

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