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Effects of incremental beta-blocker dosing on myocardial mechanics of the human left ventricle: MRI 3D-tagging insight into pharmacodynamics supports theory of inner antagonism


1Department of Congenital Heart Disease/Pediatric Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany; 2Department of Pediatric Cardiology, University of Nebraska Medical Center, Children’s Hospital and Medical Center, Omaha, Nebraska; 3Institute of Medical Genetics, Newcastle University, Newcastle upon Tyne, United Kingdom; and 4Department of Experimental Thoracic and Cardiovascular Surgery, University Hospital Münster, Münster, Germany

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Schmitt B, Li T, Kutty S, Khasheei A, Schmitt KR, Anderson RH, Lunkenheimer PP, Berger F, Kühne T, Peters B. Effects of incremental beta-blocker dosing on myocardial mechanics of the human left ventricle: MRI 3D-tagging insight into pharmacodynamics supports theory of inner antagonism. Am J Physiol Heart Circ Physiol 309: H45–H52, 2015. First published April 17, 2015; doi:10.1152/ajpheart.00746.2014.—Beta-blockers contribute to treatment of heart failure. Their mechanism of action, however, is incompletely understood. Gradients in beta-blocker sensitivity of helically aligned cardiomyocytes compared with counteracting transversely intruding cardiomyocytes seem crucial. We hypothesize that selective blockade of transversely intruding cardiomyocytes by low-dose beta-blockade unloads ventricular performance. Cardiac magnetic resonance imaging (MRI) 3D tagging delivers parameters of myocardial performance. We studied 13 healthy volunteers by MRI 3D tagging during escalated intravenous administration of esmolol. The circumferential, longitudinal, and radial myocardial shortening was determined for each dose. The curves were analyzed for peak value, time-to-peak, upslope, and area-under-the-curve. At low doses, from 5 to 25 \( \mu g \cdot kg^{-1} \cdot min^{-1} \), peak contraction increased while time-to-peak decreased yielding a steeper upslope. Combining the values revealed a left shift of the curves at low doses compared with baseline without esmolol. At doses of 50 to 150 \( \mu g \cdot kg^{-1} \cdot min^{-1} \), a right shift with flattening occurred. In healthy volunteers we found more pronounced myocardial shortening at low compared with clinical dosage of beta-blockers. In patients with ventricular hypertrophy and higher prevalence of transversely intruding cardiomyocytes selective low-dose beta-blockade could be even more effective. MRI 3D tagging could help to determine optimal individual beta-blocker dosing avoiding undesirable side effects.

left ventricular hypertrophy; beta-blockers; MRI

HEART FAILURE IS A MAJOR CAUSE of morbidity and mortality all over the world. Therapeutic beta-blockade is known to have long-term beneficial effects in patients suffering heart failure in terms of reduced hospitalization, improved left ventricular function, slowing of progression, and increased life expectancy (7). Such beta-blockade is now established as part of standard therapy, together with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Beta-blockade, nonetheless, requires careful monitoring, with appropriate titration of dosing to minimize adverse effects (3). A major goal of beta-blockade is reduction of heart rate to prolong myocardial rest at diastole. This desired negative chronotrophic effect often necessitates high doses and often comes with undesired negative inotropic and bathmotropic and side effects. Thus it is optimal to determine the appropriate individual dose at which better ventricular function is achieved, with avoidance of other effects, especially negative inotropy.

To quantify global and regional myocardial contraction, MRI 3D tagging can be used. This method uses the three-dimensional (3D) Complementary Spatial Modulation of Magnetization (CSPAMM) technique. It attaches demagnetization lines to the myocardium and virtually dissects it into cubes (see Fig. 1).

Histologically, within the ventricular mass, the cardiac myocytes are arranged in the form of a 3D meshwork, embedded in extracellular collagenous matrix formed by fibroblasts (see Fig. 2A) (2). The orientation of the long axis of each myocyte can be described using two angles and two planes (Fig. 2B). The first angle is the helical angle (\( \beta \)-angle; Fig. 2B, left), which describes the ascent or descent relative to the equatorial plane, this being the plane parallel to the base of the heart. The second is the angle of intrusion (\( \alpha \)-angle; Fig. 2B, right), which represents the deviation away from the tangential plane relative to the epicardial and endocardial surfaces.

In the healthy myocardium, the majority of cardiomyocytes are oriented tangentially with a small \( \alpha \)-angle. Within this population, those aligned in strictly circumferential fashion represent the driving force, well described by Krehl as “triebwerkzeug” (9) accounting for the systolic circumferential shortening. A smaller population of transversely intruding cardiomyocytes with a larger \( \alpha \)-angle provide auxotonic forces, which stabilize the shape of the left ventricle during...
The intruding component of the 3D mesh also serves to counteract to some extent the systolic mural thickening, thus providing for ventricular structure to function in an antagonistic fashion (10–12).

One of the features of myocardial hypertrophy is the realignment of mural architecture, with an increase in the intruding component of the mesh, both in terms of its amount and angulation (α-angle), along with a decrease in helical angulations (β-angle) (16). It is also now established that the intruding component is significantly more sensitive to beta-blockade compared with the dominant tangentially aligned population (10). After administration of beta-blockers, therefore, the tangentially aligned cardiomyocytes should be released from the antagonism provided by the intruding component and be able to act at full strength, producing enhanced longitudinal and circumferential shortening, and more pronounced systolic mural thickening. With this hypothesis in mind, we have now used MRI 3D tagging to monitor the effects of beta-blockade on global ventricular motion. Our ultimate aim is to define an optimal dose for each individual patient.

**METHODS**

**Study population.** This study was approved by the Ethics Committee of the Charité University Medicine Berlin and was performed in accordance with the institutional guidelines of the German Heart Institute Berlin. We included 13 healthy volunteers, 6 male and 7 female, with a...

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**Fig. 1.** MRI 3-dimensional (3D) tagging. Demagnetization lines are projected (tagged) on the myocardium in the 3 room directions for the duration of 1 heart cycle (see Methods, MRI data acquisition). It is shown how the tagging lines virtually cut the whole heart (left) into slices (middle) and further into cubes (right). The lines follow the myocardium through systole and diastole. Deformation of the lines reflects myocardial deformation. Deformation is differentiated in circumferential (red arrow), radial (blue arrow), and longitudinal shortening (purple arrow) and rotation (6, green angle). In an exemplary cube the myocyte aggregates can be arranged as depicted in Fig. 2A.

**Fig. 2.** Exemplary myocardial tagging block with arrangement of myocytes (A) and description of the helical and intruding angles within (B). A: predominant helical orientation of the myocyte aggregates. During systole (left) contraction of the helical myocyte aggregates leads to circumferential (red arrows) and longitudinal (pink arrows) shortening and to radial elongation which is wall thickening (blue arrows). In fact, during systole and early diastole the prolonged action potential of the small number of transversely intruding myocyte aggregates running in epicardial to endocardial direction evokes radial shortening and wall thinning (yellow arrows) thus counteracting circumferential and longitudinal shortening. This mechanism is referred to as “inner antagonism.” During diastole (right) relaxation of the helical myocytes leads to circumferential and longitudinal myocardial elongation (red and purple arrows) and consecutive myocardial wall thinning (blue arrows). Relaxation of the intruding myocytes slows down wall thinning after early diastole (yellow arrows). B: changes in concentric hypertrophy. The orientation of all myocytes, in summary called “Eigenvector,” changes from predominantly helical to a more intruding (α increases) and flatter (β diminishes) orientation (called “new Eigenvector”). This strengthens the inner antagonism and weakens systolic unloading of the left ventricle.
Accordingly, the total amount of fluid intake is summed. The values show that the total volume intake of

Volunteer pulse oximetry (SpO2) and five-lead electrocardiogram. Blood pressure would have prohibited an MRI examination. During the MRI imaging, health status of each volunteer to ensure absence of any adverse event that informed consent. We studied the past medical history and the current Beta-blocker doses (see Table 1). Each dose of esmolol was infused over a period of 13 min, with an initial interval of 4 min before starting the scanning. For each dose, we acquired a complete set of short axis views of the left ventricle, a 3D set of tagging data with a grid interspace of 7 mm and phase contrast measurements of flow in the ascending aorta.

**Data analysis.** Measurements of circumferential shortening, radial shortening, and longitudinal shortening were performed on the tagged MRI images using the software TagTrack (Versions 1.5.2 and 1.5.0; GyroTools, Zurich, Switzerland) (14). To enhance the accuracy, harmonic phase (HARP) analysis was applied, which allows for tracking of arbitrary tissue points with the help of their phase information. For short-axis derived circumferential and radial shortening analyses, we chose four representative slices between the apex and the cumulative end-diastolic images. The contours were then tracked automatically using the Analyse-it V2.22 (Analyse-it Software, Leeds, UK).

**RESULTS**

Esmolol was well tolerated by all volunteers. The hemodynamics and cardiac rhythm remained stable during the

<table>
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<tr>
<th>Volunteer</th>
<th>Age, yr</th>
<th>Body Weight, kg</th>
<th>5 μg·kg⁻¹·min⁻¹</th>
<th>10 μg·kg⁻¹·min⁻¹</th>
<th>25 μg·kg⁻¹·min⁻¹</th>
<th>50 μg·kg⁻¹·min⁻¹</th>
<th>100 μg·kg⁻¹·min⁻¹</th>
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<td>0.57</td>
<td>1.15</td>
<td>2.87</td>
<td>5.75</td>
<td>11.49</td>
<td>17.24</td>
<td>39.08</td>
<td>3.91</td>
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</table>

Duration for all doses is 12.5 min. Beta-blocker dose received by each volunteer during each incremental step and added up to the total amount of substance. Accordingly, the total amount of fluid intake is summed. The values show that the total volume intake of ~30 ml (0.34 ml·kg⁻¹·h⁻¹) is negligible and cannot be responsible for changes of contractile function due to preload changes.
acquisition of the images. The tagging measurements were successfully accomplished in all 13 volunteers. An average volume of 29.29 ± 3.91 ml (range 24.23–36.98 ml) was infused during the investigation (see Table 1). Systolic and diastolic blood pressure remained stable and heart rate stayed unchanged. Mean stroke volume decreased from 92.7 to 82.5 ml (see Table 2).

Changes in the circumferential shortening, radial shortening, and longitudinal shortening curves were observed at different doses of esmolol. Augmented peak, shortened time to peak, and resultant steeper upslope and smaller area under the curve were observed in the three curves of the patients at the three doses of 5, 10, and 25 μg·kg⁻¹·min⁻¹ as displayed for one exemplary volunteer (Fig. 4). This left shift of the curves indicates faster and stronger ventricular contraction. Circumferential and radial shortening peaks were more pronounced at these three doses. Moreover, total contraction time, represented by the width of the curve, was shortened, giving more time for diastolic recovery.

The decline of the shortening curves, which indicates the relaxation velocity, was shallow in curves with a steep upslope. Decline was steep in curves with a shallow upslope. At the higher doses of 50, 100, and 150 μg·kg⁻¹·min⁻¹, the times of systole and active diastolic relaxation became longer, with broadening of the width of the curve. The peak value decreased to levels lower than at baseline. The time to peak increased, the upslope flattened, and the area under the curve increased. These changes indicated a right shift of the curve, with weaker contraction and shortening of diastole (Fig. 4).

Peak values. We show the peak values for circumferential, radial, and longitudinal shortening at the different doses in Fig. 5A. Beginning from 5 up to 25 μg·kg⁻¹·min⁻¹, the medians and means for circumferential shortening and radial shortening were higher than at baseline without esmolol, while the peak values decreased at doses of 50 μg·kg⁻¹·min⁻¹ and above. For the longitudinal shortening, the peaks increased at the low doses of 10 and 25 μg·kg⁻¹·min⁻¹ and then dropped down to baseline. From these patterns, we concluded that dosing at the lower levels of 5, 10, and 25 μg·kg⁻¹·min⁻¹ in our volunteers in tendency leads to more extended myocardial shortening than does higher dosage.

Time to peak. The time to reach the peak of circumferential shortening, radial shortening, and longitudinal shortening curves became shorter during administration of low doses of esmolol (Fig. 5B). The means of time to peak were the shortest at 10 μg·kg⁻¹·min⁻¹. Beyond 25 μg·kg⁻¹·min⁻¹, increasing the dosage provoked time to peak extension in circumferential and radial shortening. The time to peak curve of longitudinal shortening fluctuated, but for all doses in all three dimensions, the medians and means were shorter than without esmolol.

Area under the curve. Figure 5C demonstrates that the AUC of circumferential shortening, radial shortening and longitudinal shortening was by trend larger at the three low doses. From doses of 50 up to 150 μg·kg⁻¹·min⁻¹, AUC became slightly smaller than at baseline.

Upslope. The upslope was sharply steeper from 5 to 25 μg·kg⁻¹·min⁻¹ in both circumferential shortening and radial shortening (Fig. 5D). It then slowed, although it remained higher with esmolol than without. As for time to peak, the trend of UPS was not obvious with longitudinal shortening. A trend toward elevated values, nonetheless, was noticeable with all doses of esmolol.

DISCUSSION

We have used MRI 3D tagging to measure the pharmacodynamic effects of increasing doses of esmolol on myocardial mechanics in normal hearts of human volunteers. We also measured variations in ventricular volumes and aortic flow under the effect of this second-generation beta-blocker.

We chose esmolol because of its cardio-selective beta₁-receptor blocking properties. It has no significant intrinsic sympathomimetic activity, nor vasodilatory or beta₂-effects, or membrane stabilizing activity. The drug has a rapid distribution half-life of 2 min, and a short duration of action, with an elimination half-life of ~9 min (1). The short half-life limited the time window for examination of each dose given in step-wise fashion to each volunteer. Thus it was easy to ensure the efficacy and safety of our chosen pharmacological tests.

CSPAMM tagging and HARP analysis. The MRI method used is based on the CSPAMM method to mark the myocardium. The transmural resolution of this technique allows for differentiating between the subendocardium, the mid-wall, and the subepicardium, and permits the detection of a

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**Table 2. Overview of the mean values of physiological data**

<table>
<thead>
<tr>
<th>Dose (μg·kg⁻¹·min⁻¹)</th>
<th>0 (Start)</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>100</th>
<th>150 (Stop)</th>
</tr>
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<tr>
<td>Systolic RR (± SD, mmHg)</td>
<td>109 ± 5</td>
<td>107 ± 8</td>
<td>109 ± 7</td>
<td>114 ± 4</td>
<td>106 ± 6</td>
<td>106 ± 7</td>
<td>108 ± 8</td>
</tr>
<tr>
<td>Diastolic RR (± SD, mmHg)</td>
<td>65 ± 6</td>
<td>65 ± 4</td>
<td>68 ± 4</td>
<td>70 ± 4</td>
<td>65 ± 7</td>
<td>64 ± 6</td>
<td>66 ± 9</td>
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<td>HF (± SD, l/min)</td>
<td>62 ± 6</td>
<td>60 ± 3</td>
<td>65 ± 5</td>
<td>60 ± 3</td>
<td>60 ± 6</td>
<td>59 ± 7</td>
<td>60 ± 6</td>
</tr>
<tr>
<td>QF stroke volume (± SD, ml)</td>
<td>92.7 ± 12.2</td>
<td>83.4 ± 1.5</td>
<td>84.0 ± 3.9</td>
<td>82.9 ± 2.1</td>
<td>87.5 ± 10.8</td>
<td>82.9 ± 12.9</td>
<td>82.5 ± 12.5</td>
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Fig. 4. Synopsis of one volunteer’s curves. Different doses of esmolol show different effects on circumferential, radial, and longitudinal shortening; displayed for 1 exemplary volunteer. Lower doses provoke a left shift of the circumferential and radial shortening curves while doses of 50 μg·kg⁻¹·min⁻¹ and above lead to a right shift and flattening compared with the curve without esmolol. For longitudinal shortening the lower doses yield a larger amplitude than the lower doses. AU, arbitrary units.
transmural strain gradient. Although the CSPAMM technique principally doubles the time required for acquisition, applying a segmented echoplanar imaging sequence allowed for acquisition of systolic and diastolic grid-tags within a single breath-hold (6, 15). This enabled us to cover the entirety of the left ventricle within three breath-holds, one for each chosen orientation, using the MRI navigator technique to ensure reproducible diaphragm position and stable lung volumes.

For the subsequent analysis, we used the HARP approach to detect small changes in myocardial strain, respectively, shortening, together with analysis of any regional abnormalities of mural motion (8). The technique allows for automated analysis of myocardial motion tracking, in particular

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**Fig. 5.** Descriptive analysis of all volunteers’ myocardial shortening values. Peak values (A) of myocardial shortening curves in all volunteers are displayed in the 3 dimensions: circumferential (CS PEAK), radial (RS PEAK) and longitudinal shortening (LS PEAK); Accordingly, B shows the time to peak (TTP) results, C depicts the rate of shortening (upslope), and in D the AUC as a measure of ventricular performance is shown. The results are shown as boxplots (black) with median and quartile width and as diamond blots (blue) with connected means and 95% confidence interval (CI). The red line indicates the respective mean value without esmolol.
on diastolic images. Systolic images may need manual refinement for accurately marking of midwall contours.

Our results demonstrate a dose-related enhancement in ventricular shrinkage both in terms of amount and velocity. Low doses of esmolol enhanced circumferential shortening and radial shortening. These effects can be used to optimize clinical use of beta-blockade at low doses. With the 3D-tagging method we can estimate the impact of the induced alterations on the measured variables, which are those generally measured in a clinical setting. For instance, Viskin et al. (17) found that nine-tenths of patients who were discharged from the hospital received doses of half or less than those shown to be effective in randomized clinical trials. Wikstrand (18) found that, during 3 mo of therapy, the heart rate was reduced to a similar degree with blockade at both high and low doses. During the titration phase, concentrations of the drugs in the plasma as measured at the 3-mo visit suggested that patients receiving low doses were more sensitive to beta-blockade than those in the high dose group. In this context, Bristow et al. (5) reported that low to moderate doses of metoprolol could restore downregulated beta1-receptors in the setting of dilated cardiomyopathy and might be preferable for restoring exercise responses. This was because during competitive exercise, beta-blockade at low doses could be overpowered by the evoked release of norepinephrine, thus allowing for full chronotropic and inotropic stimulation of the reconstituted beta-receptor pathway.

The mechanism we propose relates to the antagonistic potential of a particular arrangement in ventricular structure. This, in turn, permits us to speculate on a further potential beneficial effect of low dose beta-blockade on the hypertrophic ventricular mass.

**Myocardial functional architecture.** From a functional standpoint, the ventricular walls are largely made up of cardiomyocytes aligned in tangential fashion, with these cells aggregated to form subendocardial and subepicardial spiraling long chains, along with a core of circular cardiomyocytes in the centre of the ventricular walls. All together, these cardiomyocytes bring about ventricular constriction and shortening, while also causing mural thickening (Fig. 2A, left). According to direct force measurements, tangential netting components generate the unloading type of force signal, which slowly decays after having reached an early systolic peak (11). This signal proves to be relatively insensitive to negative inotropic therapy (10).

There is, however, also a second myocardial component, which is densely netted with the tangential compartment. The second population is more-or-less steeply inclined towards epicardium or endocardium and hence is aligned in a transverse and intruding direction. Part of its activity is to counteract systolic mural thickening, and hence it acts in an antagonistic sense relative to the tangential compartment (Fig. 2A, right). It generates an auxotonic signal, which, after having reached a first early systolic peak, keeps rising more-or-less steeply over the period of ejection to reach a second late systolic peak. Its active state outlasts that in the tangential compartment for some milliseconds, because it is hindered to shorten by the stronger tangential compartment. This oppositional action of helical and intruding aggregates, the inner antagonism, in healthy hearts is thought to stabilize the conical shape of the heart but in diseased hearts with an unbalanced high content of intruding aggregates causes diminished helical contraction and thus reduced emptying of the heart. The cardiomyocytes that make up the transverse intruding netting component have been shown to be significantly more sensitive to beta-blockade than the tangential spiraling compartment (10).

It is tempting to speculate that the marked differences in sensitivity to negative inotropic therapy are related to gradients in distribution of beta-receptors between the two compartments.

We infer that, in our healthy volunteers, the enhancement in ventricular systolic constriction induced by a weakening of the transverse intruding netting component is due to a structure-related heterogeneous distribution of beta1- and beta2-receptors. This would explain the difference in sensitivity to esmolol, although this has to be confirmed.

It is well known that calcium homeostasis and activation of cardiomyocytes are regulated by beta-receptors (13). Beta-receptor blockade will thus affect cells with high calcium demand most. Due to the prolonged activation state during auxotonic contraction, the intruding cardiomyocytes will consume more calcium than the spiraling cardiomyocytes, which contract in a shorter unloading fashion. For the same reason of a higher calcium demand intruding myocytes might express more beta-receptors than helically oriented cells.

Accordingly in failing hearts in patients with ischemic or idiopathic dilated cardiomyopathy, there is known to be spatial heterogeneity in the transmural distribution of beta-receptors (4). Beta1-receptors in the subendocardium are downregulated to nearly half that of the beta1-receptor density near the epicardium, which remains normal. The extent to which this layered heterogeneity in alteration in beta-receptor activity in the diseased heart coincides with the prevalence of tangential or transverse netting components in corresponding depths of the ventricular wall has yet to be determined.

We suggest, nonetheless, that presence of greater numbers of beta1-receptors within the oblique intruding cardiomyocytes generate the unloading type of force signal, which, after having reached a first early systolic peak, keeps rising more-or-less steeply over the period of ejection to reach a second late systolic peak. Its active state outlasts that in the tangential compartment for some milliseconds, because it is hindered to shorten by the stronger tangential compartment. This oppositional action of helical and intruding aggregates, the inner antagonism, in healthy hearts is thought to stabilize the conical shape of the heart but in diseased hearts with an unbalanced high content of intruding aggregates causes diminished helical contraction and thus reduced emptying of the heart. The cardiomyocytes that make up the transverse intruding netting component have been shown to be significantly more sensitive to beta-blockade than the tangential spiraling compartment (10).

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We suggest, nonetheless, that presence of greater numbers of beta1-receptors within the oblique intruding cardiomyocytes...
would make them more sensitive to esmolol. In this way, blockade at low doses could exert an instantaneous selective action on the intruding cardiomyocytes.

Irrespective of such niceties, selective blockade of the transverse intruding netting component has now been shown to reduce its antagonistic activity, hence shifting the balance between constricting and dilating forces in favor of the former. As a result, ventricular constriction is enhanced. On the other hand, elastic forces normally stored during systolic mural thickening by forceful auxotonic contraction are smaller, such that early diastolic ventricular filling is measurably slowed down.

Indeed, in our volunteers we found a flattened and prolonged decline of the longitudinal shortening curve at low beta-blocker doses and a faster decline at higher doses. We have also shown that the upslope and decline of the longitudinal shortening curve run in opposite ways (see Fig. 6).

**Limitations.** Our results, obtained in healthy young volunteers, can hardly be translated to assess the potential of beta-blockade within the wide range of cardiac diseases. Since we used the short-acting esmolol, our results also should not be extrapolated to infer the effect of beta-blockers typically used for the treatment of heart failure in the clinical setting, such as metoprolol and bisoprolol. Moreover, age, gender, physical training, and undefined individual properties play roles in the distribution of beta-receptors within the cardiomyocytes. We did not take these variables into consideration in our study, although we acknowledge that they might have contributed to the observed variability in our results.

**Conclusion.** We have demonstrated that MRI 3D tagging has the potential for detection of myocardial motion to provide detailed information regarding the impact of beta-blockade on cardiodynamic variables. Intravenous esmolol given at low doses to young healthy people enhances ventricular constriction, both in its amount and its velocity. At low doses, we failed to observe indicators of global ventricular negative inotropism. The results are in compliance with the assumption that the myocardium is organized in terms of an antagonistic system, which is prone to becoming derailed in the setting of myocardial hypertrophy. In consequence, it is tempting to speculate that beta-blockade at low dosage may be particularly beneficial for patients suffering from ventricular hypertrophy. In contrast, our data provide no conclusive answer to the question of any potential effect of beta-blockade in patients with genuine myocardial disease. Our study, nonetheless, provides an initial insight into the potential of MRI 3D tagging for the quantification of pharmacodynamic effects.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**