The Slope of the Segmental Stretch-Strain Relationship as a Noninvasive Index of LV Inotropy

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OBJECTIVES The aim of this study was to test the hypothesis that the noninvasively constructed slope of the relationship between left ventricular (LV) regional systolic strain and stretch during atrial contraction represents LV inotropic state.

BACKGROUND LV systolic response to a changing preload depends on its inotropic state. Changing the preload has allowed constructing the slope of the end-systolic pressure-volume relationship that is used as an invasive measurement of LV inotropy. We assumed that the slope of the relationship between regional systolic LV strain (total_S) and stretch during atrial contraction (preS) depends on the LV inotropic state as well and can thus be used as a LV inotropy index.

METHODS Strain curves (tissue Doppler) were extracted from 27 healthy individuals to determine the normal stretch-strain relationship at rest, during a low-dose dobutamine (LD) challenge and during passive leg-lift (LL). The method was also applied in 7 patients with breast cancer before and after chemotherapy with anthracyclines.

RESULTS PreS and total_S correlated closely in all subjects ($r = 0.82$). Total_S values increased ($p < 0.05$) with LD (–20.44 ± 3.89% vs. –24.24 ± 5.55%) and LL (–19.65 ± 3.77% vs. –24.05 ± 3.67%), whereas preS increased only with LL (5.96 ± 1.72% vs. 8.61 ± 2.18%), but not with LD (6.83 ± 2.34% vs. 7.29 ± 2.24%). No changes of total_S or preS were observed after the exposure to chemotherapy (–21.23 ± 2.93% vs. –21.49 ± 2.89% and 8.11 ± 1.03% vs. 8.59 ± 1.73%, respectively). The slope of stretch-strain relationship got steeper with LD (–1.47 ± 0.36 vs. –2.34 ± 0.36, $p < 0.05$), declined after the chemotherapy (–1.68 ± 0.15 to –0.86 ± 0.23, $p < 0.05$) and did not change with LL (–1.39 ± 0.57 vs. –1.51 ± 0.38, $p = \text{NS}$).

CONCLUSIONS The slope of the regional stretch-strain relationship can be regarded as a noninvasive index of myocardial inotropic state. It gets steeper with increasing inotropy, does not change with preload induced changes of LV systolic function, and flattens after the exposure to a cardiotoxic drug. (J Am Coll Cardiol Img 2013;6:419–28) © 2013 by the American College of Cardiology Foundation.
notropy describes the intrinsic ability of myocardium to generate force independent of loading conditions. Clinically applicable measurements of notropy could be very useful in various clinical settings such as chronic heart failure and valvular heart disease. However, this remains a difficult task as noninvasive estimates of the left ventricular (LV) inotropic state are limited by their load dependency.

Currently, only invasive measurements, such as the end-systolic pressure-volume relationship and preload recruitable stroke work, give a good estimate of myocardial inotropy. They both use the Frank-Starling mechanism, which is known as a phenomenon where at a given inotropic state active force developed by the ventricle increases with increasing preload. As this systolic LV response to preload is also modulated by the inotropic state, varying preload and measuring the LV response to this intervention can be used to assess LV inotropy. Unfortunately, this approach towards an estimation of the cardiac inotropic state cannot be easily applied in the daily routine as it requires simultaneous invasive recordings of LV pressures and volumes under changing preload conditions. Moreover, varying preload and invasively measuring the LV pressure and volume response cannot be applied in heart failure patients that do not tolerate volume challenges.

A similar relationship between diastolic preload and systolic LV response may be present on a regional level as well. It is known that regional myocardial stretch during atrial contraction and systolic LV strain are inhomogeneous and related to each other (1). We therefore hypothesized that the slope of this intraventricular stretch–strain relationship could be measured by myocardial deformation imaging and used as an estimate of global LV inotropy in analogy to the invasive approaches.

**ABBR**

**E** = ejection fraction
**EDV** = end-diastolic volume
**EF** = ejection fraction
**ESV** = end-systolic volume
**FU** = follow-up
**LD** = low-dose dobutamine challenge
**LL** = passive leg lift
**MRI** = magnetic resonance imaging
**preS** = left ventricular stretch during atrial contraction
**S** = sphericity index
**TDI** = tissue Doppler imaging
**total S** = left ventricular systolic shortening
**WS** = wall stress

**METHODS**

**Study population.** Thirty-five healthy individuals and 7 patients with breast cancer undergoing chemotherapy with cardiotoxic anthracycline were recruited to the study. All study participants were free from cardiovascular disease. The baseline echocardiographic examination in those individuals showed a sinus rhythm, normal LV systolic and diastolic function, and ruled out any structural heart disease. Individuals with signs of myocardial infarction, arrhythmias, LV hypertrophy, or conduction disturbances on the electrocardiogram were also not included in the study. Other exclusion criteria were: significant (≥50%) coronary artery stenosis on angiography in the previous 4 years, signs of relevant ischemic heart disease on perfusion and delayed enhancement magnetic resonance imaging (MRI) or single-photon emission computed tomography, previous hospital admission with signs suggestive of myocardial ischemia or with elevated cardiac enzymes. All study subjects signed an informed consent before inclusion. The study complied with the Declaration of Helsinki and the local ethical committee approved the study protocol.

The study population of healthy subjects was split in 3 groups: 1) the normal stretch–strain relationship was defined in 19 individuals; 2) to test the effect of increased inotropy on the slope of the stretch–strain relationship LV inotropy was modulated pharmacologically in a subset of 8 individuals from this first group; and 3) the third group consisted of the remaining 16 subjects in whom an acute increase of LV preload was induced by passive leg lifting to test its effect on the stretch–strain relationship.

Finally, the effect of the decreasing contractility on the slope of stretch–strain relationship was tested in patients with breast cancer before and after 3 cycles of standard chemotherapy with anthracycline.

**Study protocol.** An echocardiographic examination was performed with an ultrasound scanner (GE Vingmed Ultrasound, Vivid 7 or E9, Horten, Norway), equipped with 2.5 MHz M3S and M5S transducers. B-mode acquisitions of 4-chamber and 2-chamber views, pulsed wave Doppler recordings of the LV outflow tract and the mitral valve inflow were acquired. In addition, the sector size was reduced in order to obtain narrow sector tissue Doppler imaging (TDI) acquisitions (frame rate [FR] 180 to 210 Hz) of properly aligned LV walls (infroseptal, anterolateral, anterior, inferior, inferolateral, and anteroseptal). This protocol was followed in the first group of healthy individuals and in the breast cancer patients, where it was used both at baseline (BL) (i.e., within 4 weeks before the start of a standard chemotherapy protocol with anthracycline) and at follow-up (FU) (i.e., within 7 to 14 days after the third chemotherapy cycle).
In the second group of healthy subjects B-mode acquisitions of 4-chamber, 2-chamber, and apical long-axis views with underlying TDI (FR 100 to 120 Hz) were acquired at rest (BL) and at the state of increased myocardial inotropy induced by a low-dose (10 μg/kg/min) dobutamine challenge (LD). Hereto, dobutamine infusion was started after the acquisition of the baseline images and continued for 3 min. After 3 min the LD stage images were recorded and the dobutamine infusion was stopped. Peripheral brachial artery blood pressure was measured at both stages using an electronic sphygmomanometer.

To investigate the influence of acute increase in LV preload, narrow sector TDI (FR 180 to 210 Hz) of the inferoseptal wall, pulsed wave Doppler of the mitral valve inflow and an additional apical triplane image of the LV were continuously recorded at rest and during subsequent passive leg lifts (LL) in the third study group of healthy subjects. Hereto, both legs of the supine individual were lifted to an angle of approximately 30° from a horizontal position and kept in that position for 30 s while continuously recording echocardiographic data. The 30 s time span was chosen as the preload effect of this maneuver is acute and rather short lived (2) and an acute increase of LV end-diastolic volume (EDV) as well as typical changes of mitral inflow pattern without a change in heart rate occur already after 15 s (3). After the legs are returned to the horizontal position all preload induced changes are known to disappear completely (2). Therefore, the LL could be performed repeatedly, and separate continuous acquisitions of inferoseptal wall, mitral inflow, and LV triplane view could be obtained.

The LV EDV measured from the triplane recordings was used to define the cardiac cycle with the largest preload (i.e., EDV). Peripheral blood pressure was continuously monitored during the passive LL with a commercially available Finometer system (Finapres Medical Systems, Amsterdam, the Netherlands).

Data analysis. Conventional echocardiographic data were analyzed using commercially available software (Echopac version 110.1.2; GE Vingmed Ultrasound). LV EDV and end-systolic volume (ESV), as well as LV ejection fraction (EF) were measured from apical 4- and 2-chamber views using Simpson biplane method. In subjects that underwent a leg-lift test, LV EDV, ESV, and EF were calculated continuously from the triplane LV volume acquisition.

The LV sphericity index (LV SI) at end-diastole, giving an estimate of global LV shape, was calculated by dividing the LV EDV by the volume of a sphere with the same long axis dimension. The latter parameter was calculated as 4/3 π × (long axis diameter at end-diastole/2)³ (4). Global LV end-systolic wall stress (WS) was calculated by the formula: $WS = \frac{(p \times r)}{2h}$, where $p$ is the peripheral systolic blood pressure, $r$ is the effective radius of the LV (calculated as $\sqrt[3]{(3/4 \times LV ESV \times \pi)}$), and $h$ is the LV wall thickness, measured as an average of mid segments of septal and lateral LV walls from parasternal long axis images.

Peak E-wave, peak-A wave velocities, and E wave deceleration time were measured from the pulsed wave Doppler recordings of the mitral inflow.

The same software was used for myocardial deformation analysis. Hereto, the onset of the P wave on the electrocardiography, indicating the beginning of atrial contraction, instead of the start of the QRS complex was chosen as a zero reference point for deformation. The timing of mitral valve closure, aortic valve opening, aortic valve closure and mitral valve opening were measured from the Doppler recordings. Three samples (size 12 × 6 mm) were distributed equally from the base to the apex of each LV wall and manually tracked through the cardiac cycle to ensure their position within the myocardial segment. Segments where the tracking was failing were excluded from further analysis. From the obtained segmental myocardial deformation curves lengthening or stretch (preS) of the LV during atrial contraction was measured as the peak positive strain (%) during the atrial contraction. The total systolic strain (total_S) was defined as a total shortening (%) of the segment (i.e., strain difference between the peak late diastolic strain and end-systolic strain values) (Fig. 1).

In patients that received a low-dose dobutamine challenge all the parameters were calculated at BL and LD stages. In case the passive leg-lift test was performed, all the parameters were measured at BL and during the peak preload increase, which was defined as the cardiac cycle with the highest increase of LV EDV during the passive LL. In this way we made sure that an acute LV response to the preload challenge was measured and that no reflex-mediated changes of inotropy were occurring. Finally, in the patients undergoing chemotherapy the same parameters were calculated at BL and at FU stages.

Stretch-strain relationship. To obtain the stretch-strain relationship within a ventricle linear regression lines were estimated through 18 segmental preS and
total_S values in every individual. For the subjects that underwent passive LL, regression lines were
drawn through 3 segmental values extracted from
basal, mid, and apical levels of the inferoseptal wall.
The obtained intercepts and slopes were averaged
per group and per stage to represent the mean
relation.

In order to test reproducibility of the regres-
sion equations 10 randomly chosen rest studies
from the first group of healthy subjects were
reanalyzed by the same observer blinded to the
initial results.

Statistical analysis. Statistical analysis was per-
formed with SPSS version 18.0 (SPSS, Inc., Chi-
cago, Illinois). Values are expressed as mean ± SD.
Variables were checked to be normally distributed
(visually from the appearance of the histograms)
and to have equal variances (Levene’s test of homo-
genity). Independent samples $t$ test was performed
to detect significant differences between the
groups. Significant changes of parameters at dif-
ferent stages were determined by paired samples $t$
test. A $p$ value <0.05 was considered statistically
significant. Intraobserver variability was calculated
as a mean error between 2 repeated measurements.
By study design, it was not possible to analyze the
echocardiographic images blinded with regard to
the inotropic or preload modulation.

RESULTS

The demographic information and echocardiographic
characteristics of the study population are summarized
in Table 1. A total of 27 healthy individuals and 7
patients with breast cancer undergoing treatment with
cardiotoxic anthracycline were included. Three individ-
uals from the first group and 5 from the LL group
of the healthy study population were excluded due to
suboptimal TDI image quality.

In the first group of subjects ($n = 16$) mean
segmental preS was $6.70 ± 2.49\%$, and mean
segmental total_S was $–20.15 ± 4.49\%$. As shown
in Figure 2, those 2 parameters correlated closely
among the LV segments in every patient ($r = 0.82$
range 0.69 to 0.95). The mean intercept of the
regression lines was $–10.52 ± 3.14$ (range $–5.05 to
–17.8$) with a mean slope of $–1.45 ± 0.28$ (range
$–1.01 to –1.9$). The same observer could reproduce
individual intercepts with a mean error of 19.7% and
slopes with a mean error of 12%.

Low-dose dobutamine infusion resulted in a de-
crease of LV ESV, an increase of LV stroke volume
(SV), and an increase of LV EF. LV WS and SI, on
the other hand, did not show any significant changes
in response to dobutamine (Table 1). Segmental
segmental total_S increased significantly ($–20.44 ± 3.89\% vs.
$–24.24 ± 5.55\%, p < 0.05$), while segmental preS
did not change ($6.83 ± 2.34\% vs. 7.29 ± 2.24\%, p = NS$) with dobutamine challenge (Table 2). A typical
example of stretch-strain relationship response to LD
is given in Figure 3A. The mean slope of the preS-
total_S regression lines increased significantly from
$–1.47 ± 0.36$ to $–2.34 ± 0.36$ ($p < 0.05$) and the
mean intercept decreased from $–10.17 ± 2.39$ to
$–6.5 ± 4.73$ ($p < 0.05$) (Table 2, Fig. 4A). This
response of the stretch–strain relationship was seen in every individual (Fig. 5A).

During the passive leg lift LV EDV, LV SV, LV EF, E-wave, and A-wave velocities increased significantly (Table 1), while LV SI, blood pressure, global LV WS, and heart rate did not change from the baseline (Table 1). Both preS and total_S increased significantly with LL (5.96 ± 1.72% vs. 8.61 ± 2.18%, p < 0.05; −19.65 ± 3.77% vs. −24.05 ± 3.67%, p < 0.05) (Table 2). No change of the mean slopes and intercepts of the regression lines between preS and total_S were observed (−1.39 ± 0.57 vs. 1.51 ± 0.38 and −11.29 ± 2.34 vs. −11.29 ± 4.04, respectively) (Table 2, Fig. 4B). Change of preS (Δ_preS) during the LL correlated significantly (r = 0.76) with the change of total_S (Δ_total_S) (Fig. 6).

All the breast cancer patients had normal LV systolic and diastolic function at baseline. After the treatment with anthracycline a significant increase of LV EDV and a decrease of LV EF was observed (Table 1), whereas LV SI and global LV WS did not change. Similarly, total_S and preS did not change significantly from baseline (−21.23 ± 2.93% vs. −21.49 ± 2.89%, p = NS, and 8.11 ± 1.03% vs. 8.59 ± 1.73%, p = NS, respectively) (Table 2). A typical example of the response of the stretch–strain relationship to the treatment with anthracycline is given in Figure 3B. The significant decrease of the slope of preS-total_S relationship after the chemotherapy was observed in 6 of 7 patients (Fig. 5B). The mean slope of the preS-total_S regression lines decreased significantly from −1.68 ± 0.15 to −0.86 ± 0.23 (p < 0.05) and the mean intercept increased from −7.76 ± 3.37 to −13.97 ± 2.66 (p < 0.05) (Table 2, Fig. 4C).

**DISCUSSION**

In this study we have related segmental systolic LV strain to segmental stretch of myocardin during atrial contraction to obtain a regional stretch–strain relationship. We have shown that the slope of this relationship gets steeper in response to a dobutamine challenge, does not change with preload induced increase of LV function and flattens after the exposure to a cardiotoxic drug. It may thus serve as an index of LV inotropy.

**Presence of regional stretch–strain relationship in the healthy LV.** As expected from Frank-Starling law, longitudinal myocardial systolic shortening was closely related to longitudinal stretch during atrial contraction in healthy individuals. The normal stretch–strain regression equation, obtained by echocardiography through 18 segmental values in our study (total_S = −10.52 − 1.45 × PreS) was nearly identical to the regression equation reported by Zwanenburg (1) for the circumferential defor-

**Table 1. General Characteristics and Echocardiographic Parameters of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>First Group* (n = 16)</th>
<th>Dobutamine Group (Subset [n = 8] of the First Group)</th>
<th>LL Group (n = 11)</th>
<th>Anthracycline Group† (n = 7)</th>
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<td></td>
<td>BL</td>
<td>LD</td>
<td>BL</td>
<td>BL</td>
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<tr>
<td>Mean age, yrs</td>
<td>56.1 ± 13.6</td>
<td>58.5 ± 10.8</td>
<td>52.9 ± 3.3</td>
<td>71.6 ± 3.1</td>
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<td>Male/female</td>
<td>9/7</td>
<td>6/2</td>
<td>6/5</td>
<td>0/8</td>
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<tr>
<td>BMI, kg/m²</td>
<td>26.06 ± 3.83</td>
<td>24.37 ± 3.58</td>
<td>24.6 ± 1.75</td>
<td>25.95 ± 4.77</td>
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<td>Heart rate, beats/min</td>
<td>59.57 ± 9.26</td>
<td>60.39 ± 8.71</td>
<td>67.98 ± 10.89‡</td>
<td>65.64 ± 9.10</td>
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<td>Systolic ABP, mm Hg</td>
<td>135.3 ± 17.14</td>
<td>135 ± 13.88</td>
<td>149 ± 17.58‡</td>
<td>138.94 ± 19.17</td>
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<td>Diastolic ABP, mm Hg</td>
<td>81.1 ± 10.03</td>
<td>83 ± 9.02</td>
<td>75.2 ± 8.44</td>
<td>71.74 ± 27.53</td>
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<tr>
<td>LV EDV, ml</td>
<td>91.44 ± 21.71</td>
<td>88.63 ± 19.12</td>
<td>88.13 ± 17.27</td>
<td>101.14 ± 14.97‡</td>
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<td>LV ESV, ml</td>
<td>36.19 ± 10.3</td>
<td>35.75 ± 9.82</td>
<td>30.88 ± 10.15‡</td>
<td>45.29 ± 11.08§</td>
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<td>LV EF, %</td>
<td>60.56 ± 6.00</td>
<td>60.13 ± 3.94</td>
<td>65.75 ± 4.98‡</td>
<td>57.43 ± 4.65§</td>
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<td>Sphericity index</td>
<td>0.33 ± 0.07</td>
<td>0.32 ± 0.04</td>
<td>0.33 ± 0.03</td>
<td>0.30 ± 0.04</td>
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<td>LV WS, mm Hg</td>
<td>214.85 ± 47.42</td>
<td>225.97 ± 52.5</td>
<td>215.55 ± 46.8§</td>
<td>226.06 ± 31.14</td>
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<td>E velocity, cm/s</td>
<td>0.69 ± 0.12</td>
<td>0.70 ± 0.13</td>
<td>—</td>
<td>0.67 ± 0.1</td>
</tr>
<tr>
<td>A velocity, cm/s</td>
<td>0.68 ± 0.18</td>
<td>0.67 ± 0.20</td>
<td>—</td>
<td>0.53 ± 0.13</td>
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<tr>
<td>E/A ratio</td>
<td>1.12 ± 0.35</td>
<td>1.13 ± 0.38</td>
<td>—</td>
<td>1.33 ± 0.36</td>
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<td>E wave DecT, ms</td>
<td>225.61 ± 50.60</td>
<td>203.49 ± 45.72</td>
<td>—</td>
<td>212.36 ± 15.45</td>
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</table>

Values are mean ± SD or n. Individuals used to define normal pre-stretch–strain relationship. † Patients with breast cancer undergoing treatment with cardiotoxic anthracycline. p < 0.05 against the baseline of the same group. ‡ Calculated from triplane acquisitions. ABP = arterial blood pressure; BL = baseline; BMI = body mass index; DecT = deceleration time; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; Fu = follow-up after 3 cycles of chemotherapy; LD = low-dose dobutamine; LL = passive leg lift; LV = left ventricular; SV = stroke volume; WS = wall stress.
The presence of such relationship in the LV suggests that the Frank-Starling mechanism should not be regarded only as a global phenomenon and that it truly applies on a regional level as well. This is also apparent from numerous experimental studies that have investigated and described the underlying cellular mechanisms of the Frank-Starling phenomenon. According to these studies, passive stretching of myocardial sarcomeres increases their sensitivity to Ca\(^{2+}\), which results in more force generated at a given Ca\(^{2+}\) concentration, that is, at a given inotropic state (5–7). In vivo regional differences of passive stretch and strain are naturally present, in spite of little variation between myocardial fiber mechanics in different LV walls (8). In fact, this heterogeneity of segmental passive stretch (9) and strain values (10) at a given global LV preload seems to result from the local differences in wall curvature and thickness as demonstrated in simulation studies on the interplay between myocardial mechanics and ventricular shape.

It should be noted that for the regional stretch-strain relationship, passive LV stretch during atrial contraction was used as a measure of preload therefore assuming that the myocardium is at its minimal stress state during diastasis (11). As such, the relative change of LV segmental length during atrial contraction was considered as a noninvasive equivalent for the passive stretch of the myocardial fibers measured in the experimental studies on the basic mechanisms of the Frank-Starling law (7).

**The slope of regional stretch-strain relationship as an estimate of myocardial inotropic state.** In vitro studies have shown that with increased inotropy the stretch-force relationship gets steeper (7). As such, the steepening of the stretch-strain relationship slope observed during the dobutamine challenge in our study was not unexpected. Moreover, these results are in agreement with the findings of the

<table>
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<th>Table 2. Myocardial Deformation Parameters of the Study Population</th>
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<td>**First Group(^{a}) (n = 16)</td>
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<td></td>
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<tr>
<td>PreS, %</td>
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<tr>
<td>Stretch-strain relationship</td>
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<tr>
<td>Slope</td>
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</table>

Values are mean ± SD. \(^{a}\)Individuals used to define normal pre-stretch-strain relationship. \(^{f}\)Patients with breast cancer undergoing treatment with cardiotoxic anthracycline. \(^{p} < 0.05\) against the baseline of the same group.

PreS = stretch of myocardial segment during the atrial contraction; Total_S = total systolic strain; other abbreviations as in Table 1.
in vivo study performed more than 20 years ago by Glower et al. (12). They were one of the first to report a close linear relationship between the end-diastolic length of myocardial segment and regional stroke work, the slope of which was getting steeper with increasing LV inotropy.

Of course, neither the isometric force measured in the in vitro experiments nor the regional stroke work measured in the in vivo setting can be directly replaced by the systolic strain that we used in our study. We presumed that the slope of stretch-strain relationship describes the changes of myocardial inotropic state the same way as end-diastolic length-regional stroke work relationship does.

On the other hand, LL induced preload increase did not change the slope of stretch-strain relation-

![DIAGRAM](A)

**Figure 3. An Example of Stretch-Strain Relationship Changes in Response to Increased and Decreased Inotropy**

Stretch-strain relationships and regression equations (A) at rest (blue line) and during the low-dose dobutamine challenge (green line) in 1 of the healthy study subjects, and (B) at the baseline (blue line) and after 3 cycles of chemotherapy with anthracycline (green line) in 1 of the patients with breast cancer. BL = rest; LD = low-dose dobutamine challenge; FU = follow-up after the treatment with anthracycline; other abbreviations as in Figure 1.

![DIAGRAM](B)

![DIAGRAM](C)

**Figure 4. Changes of Stretch-Strain Relationship in Response to Increased Inotropy, Increased Preload, and Decreased Inotropy**

Stretch-strain relationships and regression equations (A) at rest (green line) and during the low-dose dobutamine challenge (pink line), (B) at rest (green line) and during the passive leg lift (pink line), and (C) at baseline (green line) and after 3 cycles of treatment with anthracycline (pink line). The regression lines are obtained by averaging slopes and intercepts obtained per patient. For graphical display, they are shown together with the mean values that are represented by dots. Abbreviations as in Figure 1.
ship. The significant increase of global LV systolic function parameters, such as LV SV, LV EF, and segmental systolic strain values during the leg lift, was thus mainly determined by increased passive myocardial stretch during the atrial contraction, and not by changes of LV inotropy. This was confirmed by the significant correlation between the change of segmental preS and the change of total_S with the LL observed in this group (Fig. 5).

In contrast to the dobutamine challenge, the exposure to a cardiotoxic anthracycline resulted in a significant flattening of the slope of the stretch-strain relationship, suggesting its capability to detect the decreased LV intrinsic inotropic state. From experimental studies it is known that therapy with this drug induces myocyte death and disruption of the sarcomere structure (13,14). As such, any fall of systolic cardiac function in patients undergoing chemotherapy can likely be attributed to the impairment of LV inotropy, especially if no previously known cardiac pathology is present and if the loading conditions of the heart are normal and not changing with the treatment. This is consistent with the decrease of LV EF seen in this group of patients at follow-up, even though the latter remained within the limits of normality. This is not unexpected as early stages of anthracycline-induced cardiac damage are usually subclinical and not detectable with conventional echocardiographic tools (15). Nevertheless, even though in this small cohort of patients no change was seen in mean preS or total_S values, a significant decline of the stretch-strain relationship slope was observed in 6 of 7 patients. Thus, this method seems to be advantageous over conventional deformation analysis when subtle changes of LV inotropy have to be detected.

It should also be pointed out that in the patients with the breast cancer the slopes of stretch-strain relationship at the baseline were slightly steeper and LVEF slightly higher than in the other groups of healthy subjects in our study. This might indeed

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**Figure 5.** Individual Changes of the Slope of Stretch-Strain Relationship With Increased and Decreased Inotropy

Changes of the slope of stretch-strain relationship in individual patients (represented by colored lines) (A) during the low-dose dobutamine challenge and (B) after 3 cycles of chemotherapy. Abbreviations as in Figure 3.

**Figure 6.** Relationship Between ΔStretch and ΔStrain in the Passive Leg Lift Group

Dashed line represents 95% confidence interval of the regression line. Δ_preS = change of segmental stretch of myocardium during the atrial contraction with passive leg lift; Δ_total_S = change of total segmental systolic strain with passive leg lift.

Δ_Total_S = -1.38 – 1.14 × Δ_preS

R Linear = 0.76
indicate an enhanced inotropic state caused by increased sympathetic stimulation due to the malignant process. In fact, it would also explain higher heart rates seen in those patients already at baseline. On the other hand, higher LV EF might simply be a result of smaller LV volumes in this group of female patients. In any case, this should not change the interpretation of our results, as all the individual slopes of stretch-strain relationships in the breast cancer patients at baseline were within the range of normal values seen in the healthy volunteers in our study.

These results provide a strong argument for the hypothesis that the steepening of the stretch-strain relationship slope is specific to the increase of LV inotropic state, whereas the flattening of it is capable to detect the decrease of LV inotropy. All of this suggests that stretch-strain relationship can be regarded as a noninvasive measure of LV inotropic state.

**Potential clinical application of the stretch-strain relationship.** A noninvasive and easily applicable method for the estimation of myocardial inotropy is currently lacking in clinical practice, in particular due to the load dependency of conventional parameters of LV systolic function. The proposed stretch-strain relationship can be easily extracted from adapted myocardial strain curves obtained by any deformation imaging technique, such as TDI, 2D speckle tracking, or tagged MRI, which makes it an attractive tool to be used in the routine. This relationship can be obtained in any patient at rest. The interpretation of the results does not require any additional interventions, such as leg-lift, Valsalva maneuver, or pharmacological infusions.

The proposed stretch-strain relationship can potentially serve in clinical routine, when a detection of deteriorating intrinsic LV function is important. Our results suggest that it might be used to detect cardiotoxicity in patients undergoing chemotherapy. Besides that, it could possibly be applied for the follow up of patients with mitral or aortic valve regurgitation as in those patients early detection of decreasing myocardial inotropy is crucial for the correct timing of surgical intervention (16). Moreover, it might be a beneficial parameter to monitor the treatment of heart failure patients or to differentiate physiological forms of LV hypertrophy from the pathological ones. All of those potential implications of LV stretch-strain relationship remain the topics for future studies.

**Study limitations.** The gold standard to assess inotropic state (i.e., analysis of end-systolic pressure-volume relationship) could not be used as a reference method in this study because of its invasive nature. Therefore, an assumption had to be made that contractility was normal in all included individuals. Furthermore, we presumed that segmental myocardial inotropy was homogeneous within each ventricle, as the slopes of regional stretch-strain relationships had to give a measure of global intraventricular inotropic state. However, as only subjects without evidence of coronary heart disease were included to this study, regional inhomogeneities of LV function were unlikely.

Secondly, in this study we did not evaluate the effect of afterload on stretch-strain relationship because of the rapid positive inotropic response of the LV to an acute afterload increase (17). It should also be mentioned, that in the group of subjects who underwent the passive leg-lift the regression lines were drawn through only 3 segmental stretch and strain values, as obtaining all 18 segments in those individuals was not practical due to the short duration of the preload increasing effect of this maneuver. However, we still feel confident about the regression equations obtained in that study group, as individual intercepts and slopes were very close to the ones obtained in other study subjects through 18 segmental values.

Finally, this method cannot be used in patients with atrial arrhythmias or high heart rates with fusion of mitral inflow E and A waves, since a precise separation between active LV relaxation (early diastole) and passive LV stretch (late diastole) is required. The effect of increased filling pressures, decreased LV compliance and dysynchrony on the presence of passive LV stretch and on the applicability of stretch-strain relationship needs further detailed investigations as well.

**Conclusions**

The presence of a regional stretch-strain relationship in an individual ventricle shows that a major part of intraventricular variability of systolic strain can be explained by segmental differences in passive stretch during atrial contraction as a direct consequence of the Frank-Starling mechanism. The slope of this relationship gets steeper with increasing inotropy, does not change with preload induced changes of LV systolic function and flattens after the exposure to a cardiotoxic drug, suggesting that it
could serve as a noninvasive index of myocardial contractility.

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