Tissue Doppler Imaging Differentiates Physiological From Pathological Pressure-Overload Left Ventricular Hypertrophy in Rats

Geneviève Derumeaux, MD, PhD; Paul Mulder, PhD; Vincent Richard, PhD; Abdesselam Chagraoui, PhD; Catherine Nafeh, MD; Fabrice Bauer, MD; Jean-Paul Henry, BS; Christian Thuillez, MD, PhD

Background—The myocardial velocity gradient (MVG) is a recent index of regional myocardial function derived from endocardial and epicardial velocities obtained by tissue Doppler imaging (TDI). This index might be useful for discriminating between physiological and pathological left ventricular hypertrophy (LVH) and for documenting the early transition from compensated LVH to heart failure. We sought to compare MVG measured across the left ventricular posterior wall between normal rats and rats with physiological (exercise) and pathological (pressure-overload) LVH.

Methods and Results—Wistar rats were assigned to one of the following groups: sedentary, exercise (swimming), and 2-month or 9-month abdominal aortic banding. Compared with sedentary rats, exercise and 2-month banding led to similar and significant LVH. After 2-month banding, conventional parameters of systolic function (left ventricular fractional shortening and dP/dt max) were not affected. However, systolic and diastolic MVG were similar in exercise and sedentary rats but were significantly lower in rats with aortic banding. Aortic debanding after 2 months led to a full recovery of MVG, whereas MVG remained decreased when debanding was performed after 9 months.

Conclusions—Myocardial contraction and relaxation assessed by TDI were impaired in pressure-overload LVH but not in exercise LVH. Therefore, TDI is more sensitive than conventional echocardiography for assessing myocardial dysfunction in pressure-overload LVH and for predicting early recovery in myocardial function after loading conditions normalization. (Circulation. 2002;105:1602-1608.)

Key Words: hypertrophy ■ echocardiography ■ imaging

Concentric left ventricular hypertrophy (LVH) is initially an adaptive process that develops in response to a sustained pressure-overload to normalize LV wall stress.1,2 Exercise training also leads to concentric LVH, described as athlete’s heart, as demonstrated both in humans and in animals.3,4 In physiological LVH, the increase in ventricular mass is characterized by a normal organization of cardiac structure and no collagen increase.5 In contrast, in pathological LVH, structural changes and collagen accumulation accompany myocyte hypertrophy and may progressively lead to systolic and diastolic myocardial dysfunction.5–7

At present, conventional echocardiography is not sensitive enough to distinguish physiological from pathological LVH, to precisely assess systolic and diastolic functions in LVH, and to detect in its early stage the transition from compensated LVH to heart failure in pressure-overload LVH.8,9

Tissue Doppler imaging (TDI), an emergent ultrasound technique, provides new indexes of myocardial function such as the myocardial velocity gradient (MVG) measured between endocardial and epicardial myocardial velocities,10–13 which might accurately detect subtle changes in cardiac contractility otherwise undetectable by conventional echocardiography.

Therefore, we investigated whether TDI might help in differentiating physiological from pathological LVH. For this purpose, we used rat models of physiological (exercise) and pathological (aortic constriction) LVH and documented noninvasively the early transition from compensated LVH to heart failure in rats with pathological LVH.

Methods

All experiments performed in this study conformed to the Guiding Principles in the Care and Use of Animals approved by the American Physiological Society.

Animals

We included 3 groups of 3-month-old Wistar rats (Charles River, Saint-Aubin-Les-Elbeuf, France): 6 sedentary rats and 6 exercised rats. Physical training consisted of two 30-minute swimming periods
Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Exercise</th>
<th>2-Month Banding</th>
<th>9-Month Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>393±12</td>
<td>323±9</td>
<td>360±11*</td>
<td>373±15</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>156±7</td>
<td>155±7</td>
<td>249±13*</td>
<td>208±19*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>122±3</td>
<td>117±4</td>
<td>147±3*</td>
<td>153±5*</td>
</tr>
<tr>
<td>LVdP/dtmax, mm Hg/s</td>
<td>9667±865</td>
<td>10 917±820</td>
<td>10 000±447</td>
<td>5583±947*</td>
</tr>
<tr>
<td>LVdP/dtmin, mm Hg/s</td>
<td>−10 458±726</td>
<td>−13 000±347</td>
<td>−4667±543*</td>
<td>−4125±836*</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
*P<0.01 vs sedentary.

Results

Hemodynamic Measurements

As expected (Table 1), aortic systolic and diastolic blood pressures were significantly higher in banded than in sedentary and exercised rats, whereas LVdP/dtmax was significantly lower (P<0.01). LVdP/dtmin significantly decreased only in 9-month banded rats. Aortic systolic and diastolic pressures, LVdP/dtmax, and LVdP/dtmin were similar in sedentary and exercised rats.
Isolated Heart Studies

After 2-month banding, LVDp/dt max and LVDp/dt min were not altered compared with sedentary (4060±124 versus 4633±393 mm Hg/s and 2490±136 versus 2801±83 mm Hg/s, P=NS). In contrast, after 9-month banding, LVDp/dt max and LVDp/dt min were significantly decreased compared with both sedentary and 2-month banded rats (2143±558 and 1324±450 mm Hg/s, respectively, P<0.01).

Echocardiographic and Histological Measurements

Exercised and 2-month banded groups demonstrated similar concentric LVH compared with sedentary (P<0.01, Table 2), characterized by increased wall thickness with normal LV cavity dimensions (Figure 1). LV weight compared with sedentary (0.9±0.1 g) significantly increased in exercise (1.48±0.06 g) and in banded groups (1.58±0.29 g). LV systolic function assessed by LV fractional shortening was considered normal and was similar in the different groups. LV systolic wall stress was significantly higher in banded rats compared with the other groups (P<0.01).

Aortic-banded rats had a significantly higher LV collagen density (3.1±0.1%) after 2-month banding compared with sedentary (2±0.1%) and exercised rats (2.4±0.3%) (P<0.01) (Figure 1). After 9-month banding, LV collagen density significantly increased (5.1±0.1%, P<0.05 versus 2-month banding). Moreover, the increase in collagen was mostly

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**TABLE 2. Echocardiographic Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Exercise</th>
<th>2-Month Banding</th>
<th>9-Month Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWd, mm</td>
<td>1.7±0.1</td>
<td>2.5±0.1*</td>
<td>2.6±0.1*</td>
<td>2.7±0.9*</td>
</tr>
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<td>PWd, mm</td>
<td>1.7±0.2</td>
<td>2.2±0.1*</td>
<td>2.5±0.1*</td>
<td>2.6±0.7*</td>
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<td>LVD, mm</td>
<td>5.8±0.5</td>
<td>7.1±0.3</td>
<td>6.3±0.4</td>
<td>8.5±1.2*</td>
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<tr>
<td>LVs, mm</td>
<td>3.0±0.1</td>
<td>4.0±0.4</td>
<td>3.5±0.4</td>
<td>4.5±0.9*</td>
</tr>
<tr>
<td>LV FS %</td>
<td>46±8</td>
<td>44±5</td>
<td>45±3</td>
<td>45±7</td>
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<tr>
<td>LVM, g</td>
<td>0.6±0.1</td>
<td>1.3±0.1*</td>
<td>1.3±0.1*</td>
<td>1.9±0.3*</td>
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<tr>
<td>LV SWS, kdyne/cm²</td>
<td>26.5±2.2</td>
<td>27.4±2.9</td>
<td>53.0±5.5*</td>
<td>45±9.2*</td>
</tr>
</tbody>
</table>

Systolic velocities, cm/s

<table>
<thead>
<tr>
<th></th>
<th>Endocardium</th>
<th>Epicardium</th>
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</thead>
<tbody>
<tr>
<td>Echodcardium</td>
<td>5.2±0.3</td>
<td>4.8±0.3</td>
</tr>
<tr>
<td>Epicardium</td>
<td>2.4±0.3</td>
<td>2.6±0.2</td>
</tr>
<tr>
<td>SMVG, s⁻¹</td>
<td>2.8±0.1</td>
<td>2.2±0.1</td>
</tr>
</tbody>
</table>

Early diastolic velocities, cm/s

<table>
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<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardium</td>
<td>−6.1±0.5</td>
<td>−4.1±0.4</td>
</tr>
<tr>
<td>Epicardium</td>
<td>−3.5±0.4</td>
<td>−2.5±0.2</td>
</tr>
</tbody>
</table>

Atrial contraction velocities, cm/s

<table>
<thead>
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<th></th>
<th>Endocardium</th>
<th>Epicardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardium</td>
<td>−2.8±0.5</td>
<td>−3±0.4</td>
</tr>
<tr>
<td>Epicardium</td>
<td>−1.9±0.2</td>
<td>−2±0.2</td>
</tr>
<tr>
<td>EMVG/AMVG</td>
<td>1.4±0.2</td>
<td>2.3±0.1</td>
</tr>
</tbody>
</table>

LV FS indicates left ventricular fractional shortening; LVM, left ventricular mass; and LV SWS, left ventricular systolic wall stress.

*P<0.05 vs sedentary.

**Figure 1.** M-mode (left), TDI M-mode (middle), and LV collagen density (right) in the 3 groups. Note decrease in myocardial velocity in the banded group associated with increased collagen density.
localized in endomyocardial area after 2-month banding but was homogeneous throughout the myocardial wall after 9-month banding (Figure 2).

**Tissue Doppler Imaging**

As shown in Table 2, after 2-month banding, the systolic myocardial velocity gradient (SMVG) was significantly lower in the banded group than in sedentary and exercised animals \((P<0.001)\). This lower SMVG was related to lower endocardial velocities in the banded group, whereas epicardial velocities were similar in the 3 groups.

In early diastole (E), myocardial velocity gradient (EMVG) was also significantly lower in banded rats than in the other groups \((P<0.001)\). During atrial contraction (A), endocardial velocities were significantly higher in banded rats than in young and exercised rats. This resulted in diastolic abnormalities in the banded group, as shown by the EMVG/AMVG ratio, which was significantly lower than in the other groups. Despite similar LV mass, SMVG and EMVG could clearly differentiate the exercise group from the 2-month banded group, that is, physiological from pathological LVH (Figure 3). An SMVG cutoff value of 1 s\(^{-1}\) clearly separated rats from the banded group from the others. Thus, despite normal conventional indexes of systolic function (LV fractional shortening and \(LVdP/dt_{\text{max}}\)), TDI revealed abnormal systolic parameters in banded rats. Furthermore, the linear relation between SMVG and systolic wall stress suggests that increased wall stress contributed to the abnormal systolic data in the 2-month banded rats (Figure 4). Finally, the linear relation between EMVG/AMVG and \(LVdP/dt_{\text{min}}\) shows that TDI could accurately and noninvasively detect early diastolic dysfunction (Figure 5). Despite similar SMVG values, velocities in both endocardial and epicardial layers were lower 9 months than 2 months after banding \((P<0.05)\) (Figure 6).

![Figure 2](image1.png)

**Figure 2.** M-mode and LV collagen density in 2-month (left) and 9-month (right) banded rats. Note predominant increase in collagen density within endocardium after 2-month banding as opposed to homogeneous increase throughout the myocardium after 9-month banding.

![Figure 3](image2.png)

**Figure 3.** Left, Relation between SMVG (s\(^{-1}\)) and LV mass. Right, Relation between EMVG (s\(^{-1}\)) and LV mass. Despite similar LV mass, exercise and banded groups could be clearly distinguished by SMVG and EMVG, which were significantly lower in banded rats.
Effects of Aortic Debanding

When aortic debanding was performed early (2 months after banding), it resulted in significant and rapid increases in SMVG, EMVG, and AMVG that returned to normal values within 5 minutes after debanding and remained unchanged thereafter, despite persistent LVH. Conversely, when aortic debanding was performed 9 months after banding, SMVG, EMVG, and AMVG did not recover normal values after debanding and remained severely depressed (Figure 6).

Discussion

The main findings in this study are that (1) TDI provides sensitive indexes to differentiate physiological (ie, exercised group) from pathological (ie, aortic banding group) LVH, (2) in pressure-overload LVH, TDI could reveal early systolic and diastolic myocardial abnormalities despite normal usual indexes of systolic function, and (3) based on the respective decrease in endocardial only, or both epicardial and endocardial velocities, TDI could predict early recovery in regional myocardial function after normalization of afterload.

TDI is a relatively new modality, developed primarily to evaluate the direction and magnitude of myocardial motion. Myocardial velocities have been shown to be closely related to sonomicrometry measurements, a reference method for evaluation of myocardial function. Since TDI has been mainly evaluated in the setting of experimental and clinical ischemic cardiomyopathy, TDI has recently been shown to be very sensitive in the detection of hypertrophic cardiomyopathy in a transgenic rabbit model, irrespective of the presence or absence of LVH. Previous studies have also shown the ability of TDI to distinguish hypertrophic cardiomyopathy from athlete’s heart in humans.

The most important finding in this study is that we could accurately distinguish physiological from pressure-overload LVH by color M-mode TDI. Despite similar levels of LV mass, SMVG and EMVG/AMVG were significantly lower in the aortic-banded group than in exercised rats, whereas the conventional parameters of systolic function including LV fractional shortening and LVdP/dtmax were normal and similar in the 3 groups. At this very early stage of pressure overload (2 months), this finding is particularly interesting because the early state of concentric LVH is classically described as "compensated." It has been a matter of controversy whether the myocardium preserves normal systolic function in pressure-overload hypertrophy. Such a controversy results in part from the fact that most whole-heart studies incorporate endocardial measurements (eg, LV fractional shortening and ejection fraction) that reflect LV chamber function, whereas many in vitro studies use myocyte function. In fact, studies that use midwall circumferential stress-shortening relations to assess myocardial function in pressure-overload LVH demonstrate that myocardial contractile function is depressed despite the presence of a normal LV fractional shortening.

Our data suggest that SMVG might be an accurate marker of early systolic dysfunction in response to elevated LV afterload, as suggested by the negative linear relation with systolic wall stress observed at 2 months. At this time of banding, EMVG/AMVG ratio was also significantly lower than in the other groups. This alteration in diastolic function was correlated with LVdP/dtmin and could be explained both by LVH and by the moderate increase in ventricular collagen content.

It is noticeable that SMVG had similar values in sedentary and exercised rats. However, in clinical studies, systolic and diastolic MVG failed to distinguish normal patients and patients with LVH secondary to systemic hypertension. This discrepancy between clinical and experimental studies may be explained by the fact that MVG is influenced by aging.

There are various possible causes for the decrease in MVG in the rats with pathological LVH. Indeed, this decrease may reflect (1) early systolic and diastolic myocardial abnormalities that could not be detected by conventional echo methods, (2) structural alterations of the cardiac interstitium with increased content of myocardial collagen matrix, which has been demonstrated to be a major determinant of myocardial diastolic stiffness in hypertensive heart disease, whereas no sign of myocardial dysfunction has been reported in forms of LVH in which myocardial fibrosis is absent, for example,
athlete’s heart,31,32 (3) a decrease in myocardial β-adrenoceptor
density,33 and (4) an increase in afterload.33
Although all these parameters probably influence myocar-
dial velocity decrease in LVH, their impact varies with the
time course of the disease, as demonstrated by the difference
between early (2 months) or late (9 months) debanding. Early
debanding leads to an immediate recovery of normal velocity
and MVG, suggesting the main influence of afterload in-
crease on the observed myocardial dysfunction. This hypoth-
esis is supported by the fact that at that stage, both LVdP/dtmax
and LVdP/dtmin in isolated hearts (ie, at identical loading
conditions) are similar to control sedentary values. Further-
more, the fact that the increase in collagen content is limited
to the endocardial layer probably cannot by itself cause
myocardial dysfunction unless accompanied by an increased
afterload (as in the case of 2-month banding).
In contrast to debanding after 2 months, late (9-month)
debanding does not improve velocities and MVG. At that
stage of pressure-overload LVH, collagen content is mark-
edly increased throughout the myocardial wall. Moreover, the
studies in isolated hearts confirm the existence of severe alter-
ations in intrinsic myocardial contractility. This probably
explains the absence of recovery in myocardial function after
9-month banding.

Figure 6. Time course of changes in systolic endocardial (Endo) and epicardial (Epi) velocities (Vs) and in SMVG after aortic debanding
in two groups of rats (gray: 2-month banding; black: 9-month banding). After 9-month banding, debanding led to no improvement in
SMVG. Conversely, debanding after 2-month banding resulted in immediate recovery in SMVG.

Conclusions
Despite similar increase in LV mass in exercise and banded
rats, TDI revealed early systolic and diastolic dysfunction
only in pressure-overload LVH despite normal indexes of
systolic function. Therefore, TDI is an accurate method to
differentiate physiological from pathological (ie, pressure
overload) hypertrophy and to predict early recovery in re-

gional myocardial function after normalization of the loading
conditions.

Acknowledgments
We thank Françoise Lallemand for excellent technical expertise in
histology.

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Circulation. 2002;105:1602-1608; originally published online March 11, 2002;
doi: 10.1161/01.CIR.000012943.91101.D7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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