Application of three-dimensional speckle tracking echocardiography to assess left ventricular regional work using wall tension-regional area loop

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Hioki A, Masuda K, Asanuma T, Goto Y, Nakatani S. Application of three-dimensional speckle tracking echocardiography to assess left ventricular regional work using wall tension-regional area loop. Am J Physiol Heart Circ Physiol 308: H1258–H1264, 2015. First published March 13, 2015; doi:10.1152/ajpheart.00932.2014.—Three-dimensional (3-D) speckle tracking echocardiography allows us to track a change in regional endocardial surface area. The change of regional area during a cardiac cycle should be useful for assessing left ventricular regional work. We investigated the feasibility of assessing regional work, calculated as the area within the wall tension-regional area (T-A) loop using 3-D echocardiography. Three-dimensional full-volume images were acquired using 3-D echocardiography (Artida, Toshiba) at baseline and during brief occlusion of the left circumflex coronary artery in eight dogs. Wall tension was calculated according to Laplace’s law for a spherical model. Area change ratio (in %) determined by area tracking was transformed into a change of regional area (in cm²) by a custom software. We calculated the area within the T-A loop (TAA) in the area under transient ischemia (risk area) and the remote area as regional work and validated the T-A loop method by comparing the global integral of TAA with the total work assessed by the pressure-volume loop. During coronary occlusion, regional work for the risk area significantly decreased (baseline vs. method, 10.2 ± 0.3 vs. 7.8 ± 0.4 mmHg·cm³; P < 0.001). The wall T-A loop reflected regional dysfunction caused by myocardial ischemia. This analysis using 3-D speckle tracking echocardiography might be useful to quantify left ventricular regional work.

Three-dimensional speckle tracking echocardiography; pressure-volume loop; cardiac function; ventricular work

LEFT VENTRICULAR (LV) systolic function is commonly assessed with ejection fraction or fractional shortening in clinical practice. However, they are only a global index, and there is a systemic need of assessing regional function such as in myocardial ischemia and LV dyssynchrony (18). Heterogeneous contraction of the LV even in a healthy subject also prompted us to assess regional function in a quantitative manner (12, 29). LV regional function can be noninvasively evaluated by measuring myocardial strain and strain rate using both tissue-Doppler imaging and speckle tracking echocardiography (1, 6, 11). Strain and strain rate depend on interactions among contractile force, extrinsic loading conditions, LV geometry, and the elastic properties of the tissues (2, 25).

The area within LV pressure-length loop or pressure-strain loop has been demonstrated to be useful for analyzing LV regional dysfunction (17, 19, 22, 27). However, their method may not be appropriate as a direct measure of LV regional work, because it is only a unidirectional measurement (8). LV regional work can be reasonably assessed from the integral of wall tension with respect to the area of each region, i.e., area within a wall tension-regional area (T-A) loop (7, 9, 24). A previous study determined regional areas by pairs of orthogonal sonomicrometers placed on the LV endocardial surface in dogs (8). The problem is a lack of a clinically applicable method to measure LV regional area.

Recently, developed three-dimensional (3-D) speckle tracking echocardiography allows us not only to quantify regional myocardial deformation (20) but also to track changes in regional endocardial surface area (21). Thus, first, we investigated the feasibility of assessing LV regional work calculated as the area within the wall T-A loop derived from 3-D speckle tracking echocardiography. Second, to validate the T-A loop method, we compared the global integral of regional work assessed by the T-A loop with the total work assessed by the LV pressure-volume (P-V) loop (8).

METHODS

Animal Preparation

All animal studies were approved by our Ethics Review Board and performed in accordance with our institutional guidelines for the care and use of laboratory animals as well as the “Guide for the Care and Use of Laboratory Animals,” published by the National Institutes of Health (NIH Publication, 8th ed., 2011). Eight open-chest dogs (14.9 ± 0.8 kg) were anesthetized with intravenous pentobarbital sodium (35 mg/kg), intubated, and ventilated with room air using a respirator. Arterial oxygen saturation was monitored via a pulse oximeter. Anesthesia was maintained throughout the experiment with pentobarbital sodium (6 to 8 mg·kg⁻¹·h⁻¹). Adequacy of anesthesia was confirmed by the loss of light reflex during experiments. A 5-Fr, micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted via the femoral artery for continuous monitoring of LV pressure. Heart rate was measured by electrocardiogram.

Dogs were placed in the right recumbent position. A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. The proximal portion of the left circumflex coronary artery (LCx) was dissected free from surrounding tissues and replaced with a vascular occluder. A perivascular ultrasound flow probe (Transonic Systems, Ithaca, NY) was placed at the distal site of the occluder and connected to a digital flowmeter. At the termination of the study, the dogs were euthanized with KCl.

3-D Speckle Tracking Echocardiography

Echocardiographic examinations were performed using an Aplio Artida SSH-880CV ultrasound system with a PST-25PX transducer (Toshiba Medical Systems, Otawara, Japan). The frequency was 2 MHz on transmit and 4 MHz on receive. The frame rate was set at 1000 frames/s.
LV REGIONAL WORK USING 3-D ECHO

where $A_n$ is the area at frame $n$, and $A_1$ is the corresponding area at the peak of the R-wave of the electrocardiogram. Area change ratio, which is a parameter of systolic area change in a LV segment, was calculated offline as an average value of all unit segment values in each LV segment. T-A and P-V loops. The 3-D data sets by 3-D speckle tracking echocardiography and LV pressure data sets were exported to a custom software (Toshiba Medical Systems) (Fig. 3). LV pressures were interpolated at 30 Hz equally to the sampling frequency of 3-D speckle tracking echocardiography.

Three-dimensional echo analysis allowed us to calculate area change ratio (in %) automatically. By the custom software, information on LV regional endocardial surface area (in cm$^2$) in a unit segment was extracted. Each LV short-axis diameter at base, mid-, and apical levels was obtained from 3-D data sets. Wall tension was calculated according to Laplace’s law for a thin-wall and sphere geometric model, assuming that LV contractile force is solely supported by LV endocardial layer. Namely,

\[ T(t) = \frac{D(t)P(t)}{4}, \]

where $T(t)$ is wall tension (in mmHg·cm), $D(t)$ is LV short-axis diameter (in cm), and $P(t)$ is LV pressure (in mmHg) at time $t$. T-A loops were then automatically constructed, and regional work (in mmHg·cm$^3$) was calculated as the area within the T-A loop (TAA) (7, 24).

The LV volume was obtained by 3-D data sets, and P-V loops were automatically constructed by the custom software.

Statistics

Data are expressed as means ± SD. Hemodynamics were compared using a paired t-test. The regional works of remote and risk areas were compared between at baseline and during coronary occlusion using the Wilcoxon signed-rank test. Bland-Altman analysis was performed to compare global integral of TAA and total work using P-V loop. Inter-observer and intraobserver variabilities for area change ratio were analyzed from the risk and remote areas of a total of 10 clips using Bland-Altman analysis. Values of $P < 0.05$ were considered statistically significant.

Experimental Protocol

Three-dimensional data sets were acquired at baseline and during the occlusion of the LCx for 2 min, and LV pressure data were simultaneously obtained. The mechanical ventilator was stopped for a maximum of 10 s to minimize the effects of variation in heart position caused by

![Fig. 1. Three-dimensional (3-D) speckle tracking of the left ventricle (LV) at end diastole. Multiplanar reconstruction images correspond to the 2-chamber (right: B) and 4-chamber views (middle: A) and 3 short-axis views at different levels (left: C3, C5, C7). Full-volume, electrocardiography-gated, 3-D data sets were acquired from left lateral window because of the left lateral thoracotomy.](http://ajpheart.physiology.org/)

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breathing while acquiring the 3-D data sets because tracking quality can be affected by stitching artifacts appearing at the sector borders.

First, we assessed the regional work of a segment within the risk area, identified by myocardial contrast echocardiography and an opposite segment within the remote area at baseline and during the occlusion of LCx. Second, we analyzed correlations between the global integral of regional work assessed by T-A loops and the total work assessed by P-V loops at baseline and during coronary occlusion.

RESULTS

Coronary Flow and Hemodynamics

During coronary occlusion, LCx flow decreased from 21 ± 6 to 0 ± 0 ml/min (P < 0.05). Heart rate, LV systolic/end-diastolic pressures, and −dP/dt also significantly changed (Table 1).

Effect of Coronary Occlusion on Regional Work

Figure 4A shows a representative example of T-A loops in remote and risk areas obtained at baseline and during coronary occlusion. Directions of T-A loop rotation are all counterclockwise. During coronary occlusion, the cardiac cavity expanded and regional endocardial surface area for the remote and risk areas increased. Thus T-A loops shifted rightward for both areas. In addition, the change of regional endocardial surface area in a cardiac cycle for the risk area decreased, whereas that for the remote area increased.
Figure 4 summarizes regional work in remote and risk areas at baseline and during coronary occlusion. The TAA for the risk area significantly decreased from 26.8 ± 10.7 to 18.4 ± 7.8 mmHg·cm³ (P = 0.04) during coronary occlusion, whereas that for the remote area did not change.

Relationship Between Global Integral of TAA and Total Work-Derived P-V Loop

Figure 5 shows a representative example of a global integral of the T-A loop and the P-V loop obtained at baseline and during coronary occlusion. The global integral of the T-A loop shifted rightward during coronary occlusion because the LV endocardial surface area increased. The systolic excursion during coronary occlusion became smaller compared with that at baseline so that the area within the global integral of the T-A loop decreased. The P-V loop shifted rightward during coronary occlusion because LV volume increased. The LV systolic pressure concomitantly reduced so that the area within the P-V loop decreased. In all dogs, both global integral of TAA and total work derived from P-V loop significantly decreased during coronary occlusion (from 653.8 ± 176.3 to 484.6 ± 154.6 mmHg·cm³, P = 0.001 for global integral of TAA; and from 909.6 ± 249.9 to 713.9 ± 182.1 mmHg·cm³ for total work, P = 0.002).

Figure 6 shows a relationship between the global integral of TAA and total work obtained as the area within the P-V loop and Bland-Altman plots. The data are obtained from all dogs before and after coronary occlusion. The global integral of TAA had an excellent correlation with the total work obtained by the P-V loop, although it tended to underestimate (about 30%) the total work.

Mean difference and limits of agreement (+1.96 SD) of interobserver and intraobserver variabilities for area change ratio were -2.9 ± 9.1 and 0.5 ± 11.6%, respectively.

DISCUSSION

The present study demonstrated using 3-D speckle tracking echocardiography that regional work for the risk area (ischemic area) markedly decreased during coronary occlusion, whereas that for the remote area did not change and that the global integral of regional work obtained from T-A loops closely correlated with total work obtained from P-V loops both at baseline and during coronary occlusion. These findings indi-

Table 1. Hemodynamics

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Occlusion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>138 ± 22</td>
<td>142 ± 24</td>
<td>0.041</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>107 ± 11</td>
<td>100 ± 15</td>
<td>0.042</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>7 ± 2</td>
<td>11 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>+dP/dt, mmHg/s</td>
<td>1.625 ± 194</td>
<td>1,482 ± 250</td>
<td>0.060</td>
</tr>
<tr>
<td>−dP/dt, mmHg/s</td>
<td>−1,634 ± 289</td>
<td>−1,350 ± 426</td>
<td>0.002</td>
</tr>
<tr>
<td>LCx flow, ml/min</td>
<td>21 ± 6</td>
<td>0 ± 0</td>
<td>&lt;0.001</td>
</tr>
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Values are means ± SD. LVSP, left ventricular (LV) systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt, first derivative of LV pressure; LCx, left circumflex coronary artery. P values are for comparison with baseline values.
cate that 3-D speckle tracking echocardiography is useful to assess regional work based on T-A loops.

Regional Work Using T-A Loop

Goto et al. (8) assessed LV regional work in an experimental model from a wall tension-area loop obtained by sonomicrometry. Their findings formed the rationale of our study, but their method was too invasive to apply to humans. We assessed the work less invasively using echocardiography. They demonstrated that regional work for remote and risk areas decreased during coronary occlusion under a condition of fixed LV end-diastolic and end-systolic volumes using the excised, cross-circulated canine LV connected to a volume servo pump. They observed that regional work became negative for the risk area when LV end-diastolic volume was increased to a volume at which LV stroke work regained the control value. In contrast, we found that regional work for the risk area significantly decreased during coronary occlusion, whereas that for the remote area did not change in in vivo experiments where preload, afterload, and sympathetic activity were not artificially controlled. We did not observe negative regional work for the risk area probably because of a different degree of myocardial ischemia and different experimental setting. In their study, regional work for the remote area moderately decreased because LV end-systolic pressure reduced and end-systolic wall tension decreased. In the other study where LV end-diastolic volume increased to keep a stroke volume constant, they found regional work for the remote area increased (9). In our study, regional work for the remote area did not change because the change of regional endocardial surface area during a cardiac cycle for the remote area increased because of hypercontraction despite the decrease in LV pressure and wall tension at end systole. If we performed measurements when hypercontractile state was over, regional work for the remote area could have decreased.

Regional nonuniformity of wall dynamics in the normal LV has been reported by several investigators. Motoki et al. (12) demonstrated that the septum mainly contracted circumferentially and the free wall mainly contracted radially. In the present study, regional work for the risk area including free walls was less than that for the remote area including the septum even at baseline (26.8 ± 10.7 mmHg·cm³ vs. 45.2 ± 17.2 mmHg·cm³). Thus circumferential or radial strain cannot be a substitute for regional work.

Global Integral of T-A Loop Versus P-V Loop

We validated the T-A loop method by comparing the global integral of TAA with the total work assessed by the P-V loop as in the study by Goto et al. (8). Nesser et al. (14) validated 3-D speckle tracking echocardiography technique for LV volume measurements and demonstrated its superior accuracy and reproducibility over previously used, two-dimensional, speckle tracking echocardiography technique.

The present study underestimated (about 30%) the global integral of regional work by the T-A loop compared with the total work by the P-V loop as shown in the previous investi-
T-A loop (in mmHg·cm³) is equal to that of energy. Rectly reflect regional work. In contrast, the dimension of the areas of pressure-length and pressure-strain loops cannot di-
tively) differ from those of work or energy (in J). Thus the pressure-strain loops (in mmHg·cm and mmHg·%, respec-
ting may not reflect the overall performance of the region. First, since myocardial fibers are variously oriented within the LV (3, 4), a unidirectional measurement of segmental shorten-
ing may not reflect the overall performance of the region. Second, the dimensions of the areas within pressure-length and pressure-strain loops (in mmHg·cm and mmHg·%, respec-
tively) differ from those of work or energy (in J). Thus the areas of pressure-length and pressure-strain loops cannot di-
rectly reflect regional work. In contrast, the dimension of the T-A loop (in mmHg·cm³) is equal to that of energy.

Goto et al. (7–9) analyzed wall tension-area loops to evaluate quantitatively LV regional work. Their results demonstrated that this measurement of regional work was valid during dobutamine stress and global and regional ischemia. However, they acquired LV regional areas using pairs of orthogonal sono-
micrometers. Three-dimensional speckle tracking echocardiogra-
phy allows us to track a change in regional endocardial surface area noninvasively. The T-A loop obtained by 3-D speckle tracking echocardiography should be useful in clinical practice such as in the catheterization laboratory where LV pressure measurement is capable. Thus Goto et al. established the concept, and we exemplified it for the clinical application.

Three-dimensional speckle tracking echocardiography has been prevailing recently, but there are few clinical applications of this technology for assessing cardiac function (26). Our method could be a preface to bring this new technology down to the clinical practice.

Limitations

Heart rates were relatively high in this canine experimental study, and the relatively low frame rate of 31.6 Hz may be a problem. However, global assessment such as comparison of TAA may be possible with the present frame rate. Advancement of 3-D echocardiography or some other techniques such as frame reordering, which has been reported recently, would enhance the clinical value (15).

The concept of T-A loop is not new (7–9, 24). The significance of our study is that we demonstrated the feasibility of 3-D speckle tracking echocardiography to determine regional work for the first time. Our work will be helpful to apply the concept clinically. Urheim et al. (27) and Russell et al. (17) estimated regional work using pressure-strain loop. However, theoretically, regional work should be determined by pressure-
dimension loop or pressure-area loop as we did in the present study.

Invasive P-V loops should be obtained using a conductance catheter as a gold standard. However, because of a lack of the equipment, we measured LV volume by 3-D echocardiogra-
phy. The accuracy of LV volume by 3-D echocardiography has been validated, and it would be reasonable to construct P-V loops using it (10). We demonstrate that a conductance catheter is not always necessary to evaluate ventricular work. More-
over, with the present method, we can assess not only global but also regional work.

We should be careful to compare regional work from hearts of differing size (13). The value of regional work should be normalized to the unit volume of myocardium because the value of regional area depends on heart size.

We used Laplace’s law to assess wall tension. We know this is an oversimplification of the complicated LV structure, but we also know this has been frequently used in various research and clinical settings. However, we have to admit that this simple method may cause some errors.

We did not measure τ or other parameters of diastolic function using a catheter. Although assessment of diastolic functional changes in ischemic areas is of interest, it may be a subject of another study.

Clinical Implications

Because T-A loop analysis requires invasive pressure mea-
surement, its potential role would be to serve as a supplemen-
tary modality during LV catheterization. There are a lot of situations where measurement of not only total but also re-
gional work is desired. For example, T-A loop analysis might give us insight into how different therapeutic principles including medications modify myocardial function and how inter-
ventions like ventricular pacing change regional work at the pacing site (5, 16, 18). In a patient with left bundle branch block, the early activated segments produce little or negative work, whereas the late-activated segments produce more work than normal segments. This difference could lead to LV re-
modeling, which can be treated with cardiac resynchronization therapy (16–18, 26). Therefore, the present method could be useful when evaluating patients who are candidates for cardiac resynchronization therapy. Moreover, Russell et al. (17) sug-
gested regional work reflected myocardial glucose metabolism as well as oxygen consumption. This could be another area of interest to evaluate a disease state such as myocardial ischemia. A recent investigation has suggested that the contribution of regional kinetic energy at the base to overall LV work is different from that at the apex, which changes during exercise (23). Thus analysis of regional work during exercise would be of interest.

The direction of loop rotation provides information regarding active and passive contributions to regional myocardial deformation and motion (22). A hallmark of the actively contracting myocardium is that the segment shortens during systole when LV pressure is rising, whereas the passive myo-
cardium lengthens when LV pressure is rising. Furthermore, the passive myocardium shortens during isovolumic relaxation when LV pressure is falling. Because the demonstration of active contraction implies viable myocardium (27), the T-A loop might have the potential to differentiate between viable and nonviable myocardium.
In conclusion, the wall T-A loop accurately reflected regional dysfunction caused by myocardial ischemia. This analysis using 3-D speckle tracking echocardiography might be useful to quantify LV regional work.

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