The interaction between left ventricular wall motion and intraventricular flow propagation in acute and chronic ischemia.

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Running head: The impact of LV dysfunction on flow propagation.

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Abstract

Myocardial ischemia has been associated with left ventricular (LV) post-systolic shortening. The combination of Tissue Doppler imaging (TDI) and high frame rate acquisition of 2-D color flow makes it possible to study the interaction between LV wall motion and intraventricular flow propagation. The aim of this study was in a clinical model to study the impact of acute myocardial ischemia and prior myocardial infarct might have on LV flow patterns, and to explain the underlying mechanisms from the tissue Doppler data. LV flow propagation and tissue velocities during early diastole were studied in 18 healthy individuals, 17 patients with prior anterior myocardial infarct and 16 patients before and during percutaneous coronary intervention (PCI) of the left anterior descending artery. Normal individuals had intraventricular flow propagation towards apex during isovolumic relaxation. During this early diastolic time phase, myocardial velocities measured at mid and apical septal segment were directed away from apex. Prior to PCI, patients without myocardial infarction had similar findings as in normals. In contrast, each patient with either prior myocardial infarction or PCI induced acute ischemia had flow propagation opposite to normals and tissue velocities reversed towards apex during early diastole. Reversal of early diastolic LV flow propagation in acute and chronic anterior myocardial ischemia reflects post-systolic shortening in the dyskinetic apical and septal myocardial segments.

Keywords: Tissue Doppler echocardiography, left ventricular function.
**Introduction**

Left ventricular (LV) regional wall motion abnormalities are a common finding in myocardial ischemia (18; 33; 35) and are also found in non-ischemic segments adjacent to areas of ischemia(17). Wall motion abnormalities in ischemia have been evaluated by many methods, including two-dimensional echocardiography, magnetic resonance imaging, radionuclide and angiography. Much attention has been focused on the wall motion abnormalities during systole, but ischemia might also have severe impact on wall motion during early diastole (8; 16; 27). An elastic recoil maneuver or delayed active shortening of the ischemic myocardium is occurring immediately before, during and after the isovolumic relaxation (IVR) period(26). Furthermore, recent studies have demonstrated reversal of intraventricular flow propagation during IVR in patients with anterior myocardial infarct(6) and in animals during acute ischemia (36). Since blood is incompressible, intraventricular blood flow must accompany regional wall motion during the cardiac cycle(9; 38). It is therefore reasonable to believe that alterations in regional myocardial contraction may have impact on intraventricular flow.

With the introduction of tissue Doppler imaging (TDI) we have got a fast and accurate method for noninvasive assessment of regional myocardial function(11; 12; 15; 19; 34). The combined use of LV color flow and TDI have made it feasible to study the interaction between regional wall motion abnormalities and intraventricular flow pattern.

The aim of the present study was thus to investigate how regional wall motion abnormalities in the ischemic myocardium interact with intraventricular flow pattern during IVR in a clinical model.
**Materials and Methods**

**Control group:** Eighteen healthy individuals were recruited from the hospital staff. None had prior history of cardiac disease. LV function was normal as evaluated from echocardiography.

**Myocardial infarct group:** Seventeen patients with prior anterior myocardial infarct were included. All had diameter stenosis more than 50% in the left anterior descending coronary artery (LAD) except for two patients that did not have significant stenosis. LV dysfunction corresponding to the LAD territory was present at rest as demonstrated by the ventriculogram or echocardiography. Normal myocardial function was found in the other LV regions.

**Acute ischemic group:** Sixteen patients with stable angina undergoing percutaneous coronary intervention (PCI) were included in this group. All had significant diameter stenosis (≥ 50%) of LAD without any LV dysfunction at rest. In addition, five patients had significant stenosis of the circumflex artery and eight had stenosis of the right coronary artery. The lesion in LAD was always treated first by angioplasty. Patients with significant collateral arteries were not studied in order to assure that PCI created significant myocardial ischemia. No patients had history or findings of valvular heart disease. All were in regular sinus rhythm. Clinical and hemodynamic characteristics of all study subjects are presented in Table 1. The regional ethical committee on human research approved the study. Written informed consent was given by all individuals.
**Cardiac catheterization**

Standard left heart catheterization with coronary angiography was performed in all angina patients and in those with prior anterior myocardial infarction. Left ventricular ejection fraction (LVEF) was calculated using a single plane ellipsoidal formula. PCI of the LAD stenosis was performed in those with angina pectoris using standard approach. The balloon inflations lasted 30 – 120 seconds. Coronary stenting was performed in 14 patients.

**Echocardiography**

Studies were performed with a System Five system (GE Vingmed Ultrasound, Horten, Norway). All echocardiographic images of the left ventricle were obtained from the apical 4-chamber view with visualization of aortic valve at rest and during the balloon inflation. This scanner enables visualization of low velocity 2-D blood flow and low velocity filter was set at 4 cm/s in order to obtain color flow maps during IVR(6). The duration of IVR (IVRT) was measured by standard pulsed Doppler methods. Color M-mode recordings of LV inflow were performed from the LV base to apex.

TDI measures were performed in the apical and mid segments of the septal and lateral walls. Myocardial longitudinal velocity vectors were displayed as color-coded images superimposed on the 2-D gray scale echocardiographic images in real time display as previously described(7). The color-coded tissue velocities were decoded to numeric values (Echopac, GE Vingmed). Image acquisitions in the acute ischemia group were performed before, during and after balloon inflation.
**Data analysis**

The IVR period in the 2-D color flow recordings was defined as the period between the closure of aortic valve with interrupted outflow and the mitral valve opening associated with the start of inflow velocities. The image frames from the start to the end of IVR were examined for the extent and direction of intraventricular flow. The largest unidirectional flow area was traced from the apical 4-chamber view. A commercially available image processing and analyzing program (Echopac, GE Vingmed Ultrasound) was used. Peak myocardial velocities during ejection period and IVR were measured in each patient as described earlier (5; 8).

**Statistics**

Data are presented as mean ± one standard deviation (SD). Dependencies between flow velocities and tissue velocities in patients at different time points and different regions were analyzed with ANOVA methods. Bonferroni post-hoc analysis for multiple comparisons was used when appropriate. Relationship between parameters was determined using Pearson’s coefficient of correlation. Differences were considered statistically significant if the p-value was <0.05.

**Results**

All recordings were of technically acceptable quality. Intraventricular flow propagation and TDI measures could be obtained from all individuals at rest and in patients during acute ischemia. The frame rate obtained during flow recordings was 32±6
frames/sec and 96±10 frames/sec during TDI recordings. In average, 3.8±1.1 frames of flow images were imaged during the IVR period.

There was a strong inverse linear correlation between intraventricular flow velocities and tissue velocities from mid septal segment during IVR (-7.0X + 7.1, r = -0.80, p<0.001) (Figure 1). This relationship was also found between apical septal velocities and flow (-10.5X + 10.3, r = -0.75, p<0.001).

**Healthy individuals**

During the IVR period, intraventricular flow propagation was directed towards apex in all individuals (Table 2). Flow was present through most of the period, but the velocities varied in different parts of the ventricle. The mean area of the apical directed flow was 9.0 ± 4.4 cm². In accordance with the flow propagation, all healthy participants demonstrated a dominant peak myocardial velocity at mid septal level directed away from apex during IVR (V_{IVR}) -2.0 ± 1.4 cm/s. The corresponding velocity in the lateral mid segment was -1.7 ± 0.8 cm/s (ns). There was no difference between tissue velocities in septum and the lateral wall when measured at the apical LV level (-1.0 ± 0.7 and -1.0 ± 1.0 cm/s, ns).

**Anterior myocardial infarct**

In contrast to the findings in normal individuals, the intraventricular flow was directed away from apex and blue encoded during IVR in patients with prior myocardial infarct. This reversed flow was mostly confined to the apical 2/3 of LV in all patients with LV dysfunction. The mean area of the flow directed to LV base was -8.3 ± 4.8 cm². This was in accordance with the TDI findings that demonstrated post-systolic shortening.
with myocardial velocities directed towards the apex (2.4 ± 1.2 cm/s, p<0.001, mid septal segment compared to healthy individuals). Apical TDI velocities from the LV septum and lateral wall showed in principle the same findings and were reversed (1.5 ± 0.7 cm/s and 0.7 ± 1.3 cm/s, respectively, p< 0.001 compared to healthy individuals). The mid segment of the lateral wall, however, showed normal tissue velocities during IVR directed away from apex -1.5 ± 0.8 cm/s (p< 0.001 compared to mid septal velocities).

**Acute LAD ischemia**

At baseline, flow propagation during IVR was directed towards apex (Figure 2 and Table 3) and similar to the flow pattern found in healthy individuals. As in normal individuals, flow was present through most of the period. TDI before balloon inflation showed a predominant $V_{IVR}$ directed away from LV apex (Figure 3) and did not differ from the healthy individuals (-2.3 ± 1.1 cm/s at mid septum level, ns ).

During the LAD occlusion all had significant (>0.1 mV) ST segment changes in the precordial electrocardiographic (ECG) recordings. Heart rate was not significantly changed during LAD occlusion.

Figure 4 shows a representative recording of the reversed intraventricular flow in a patient during balloon inflation. Flow propagation as visualized by 2-D color Doppler and color M-mode Doppler during LAD occlusion was reversed and uniformly directed towards LV base.

TDI showed reduced systolic velocities of the ischemic myocardial segments while velocities during IVR were reversed and directed towards the apex during balloon inflation (Table 3, Figure 3). In the lateral apical segment $V_{IVR}$ was also reversed during
ischemia (1.0 ± 2.1 vs -2.2 ± 1.1 cm/s, p< 0.001). The reversed septal and lateral velocities represent a post-systolic shortening that started in late systole, continued through IVR and into the filling period. There was no change in systolic shortening or $V_{IVR}$ in the non-ischemic segment at the mid lateral wall even during LAD ischemia.

**After ischemia.** Ten minutes after balloon deflation the intraventricular flow propagation during IVR was directed towards apex again, similar to the flow direction at baseline, except in one patient. Consistent with this, tissue velocities during IVR returned back to negative velocities with two exceptions. The patients had neither pain nor ECG changes at that time.

**Discussion**

This study demonstrates that modern echocardiographic technology can document the interaction between myocardial wall motion and intraventricular flow. This refinement may have impact on the ability and accuracy of diagnosing ischemic myocardial disease and furthermore to understand the underlying mechanisms of intraventricular flow. Patients with anterior acute myocardial ischemia and prior myocardial infarction were associated with an abnormal reversal of flow propagation during IVR. The reversal of IVR flow was unequivocally associated with abnormal post-systolic shortening of dyskinetic myocardium supplied by LAD as demonstrated by TDI. This post-systolic shortening or recoiling effect was acting in the long axis direction of left ventricle including the apex and thus pushing blood towards the base.

Regional wall motion abnormalities during the earliest diastolic cardiac phase has also been shown by LV angiograms and M-mode echocardiography(10; 14). This may
result in altered intraventricular pressure and flow as confirmed by Nikolic et al(20).

Sonomicrometry and LV pressure measurements in a recent experimental study demonstrated that a pressure gradient from LV outflow tract directed towards the apex is present in the non-ischemic ventricle during IVR(36). During LAD occlusion, however, this pressure gradient reversed and was directed towards the left ventricular outflow tract. These studies are in accordance with our findings and suggest that reversal of flow propagation reflects ischemia induced changes of intraventricular driving pressure.

**Intraventricular flow pattern and regional wall motion abnormalities**

The LV intraventricular flow pattern is very complex due to shifting myocardial contractile and elastic properties throughout the cardiac cycle. Current echocardiographic methods cannot depict velocities in real 3-D mode, but due to high frame rate and the ability of measuring tissue velocities, important information of this complex pattern can be obtained.

Kerber et al were the first investigators to demonstrate that segmental dysfunction occurred in normally perfused myocardium immediately adjacent to areas of ischemia(17). The LV apical lateral segment is perfused by LAD or LCX(22). Measures closer to the mid lateral segment will increase the likelihood of measuring an area perfused by LCX. The reversed myocardial velocities during IVR in the apical lateral segment found in our study are due to tethering effects from the ischemic part of apex and the ischemic area itself. The tethering effect of the adjacent segment will augment the LV area affected by LAD ischemia and thus cause further impact on intraventricular flow propagation.
Limited reports of early-diastolic flow pattern have been published and no clinical study relating myocardial properties by TDI to intraventricular flow exists. In a recent 2-D flow study, however, we were able to study flow during IVR in detail(6).

Intraventricular flow propagation during IVR is very slow and requires low velocity filter setting. Modern ultrasonic technology has increased sensitivity for detection of intraventricular flow, which can be assessed with relatively high frame rates. Othe et al found that the greater magnitude of LV elastic recoil and the faster LV relaxation in patients without LV apical asynchrony produce apically directed flow during IVR(21). Nonuniform contraction and filling is associated with ineffective shifting of blood volume within the LV. This phenomenon was most pronounced during the isovolumic periods in a study by conductance catheter in patients with coronary artery disease(27).

Regional wall motion abnormalities may also exist in non-ischemic related conditions(3). Negative inotropic interventions has been shown to cause a non-homogenous LV response with greater depression of LV apical contraction compared to LV base(4). Strum and Pinsky showed in an experimental model that effective regional stroke volume and phase angle analyses by conductance catheter were more sensitive measures of regional wall motion abnormalities than measures of maximal stroke volume(29; 30). Their analyses of effective stroke volume are comparable to our TDI measures which assess myocardial velocities throughout the cardiac cycle. They found that regional ejection may not be synchronous with global systole. Dysfunctional myocardium often continues to contract after global end-systole and this might be difficult to detect with an ordinary 2-D echocardiographic study. Our findings of delayed systolic velocities that occur after global end-ejection in ischemic patients support their
notion that the extent of regional dysfunction could be underestimated by use of wall motion analyses from 2-D echocardiography.

Furthermore, a heterogenetic wall motion pattern can also be found in normal hearts(1; 13; 23). An augmentation of the normal IVR velocities directed toward the apex have been found in patients with hyperdynamic ventricles(25). This was related to a more asynchronous relaxation of the ventricle. In our study no reversed flow pattern was observed in healthy individuals. This suggests that the usual spectrum of wall motion variation in normal persons is not enough to cause reversed flow during IVR.

Severe ischemia leads to paradoxical systolic movement of the ischemic region followed by a recoil or active contraction during end systole, continuing into the early diastolic period. These altered myocardial contraction patterns must have vital impact on the intraventricular flow pattern as clearly demonstrated in our study. One might also expect that this finding may contribute in part for the decreased mitral-to-apical flow propagation seen by color M-mode Doppler during the succeeding diastolic filling phase(2; 32). In the normal left ventricle, flow propagates rapidly to the apex during the diastolic filling period, and as earlier demonstrated by color M-mode Doppler there is almost instant onset of filling velocities along the entire LV inflow tract(24). In patients with reduced LV function, however, the mitral-to-apical flow propagation may be markedly delayed(2; 31; 32). This retarded flow propagation might depend of a decrease of LV relaxation, which causes a decrease in mitral-to-apical driving pressure(28).
**Clinical implications**

Visual interpretation of 2D wall motion in ischemia is at best semi-quantitative and may be difficult. TDI has been suggested as a helpful and accurate tool in diagnosing ischemic conditions. We have demonstrated that apical-to-mitral directed flow during IVR is closely connected to post-systolic shortening of dyskinetic myocardium and may thus represent an expression of myocardial dysfunction. Combined analyses of intraventricular flow and myocardial tissue velocities may therefore be used for echocardiographic detection of myocardial ischemia. Since the reversal of IVR flow is a distinct qualitative observation, it may be helpful in the diagnosis of ischemia when borderline velocity changes are measured by TDI.

**Strain measures versus TDI**

The current echocardiographic technology does also allow interpretation of strain Doppler echocardiography (SDE). SDE has earlier demonstrated superiority over TDI concerning location and distribution of regional ischemia(7; 37). SDE measures the intrinsic myocardial deformation while TDI measures the myocardial velocities. Strict regional diagnosis of the ischemic myocardium was, however, not considered as an essential issue in our study since the location of ischemia was predetermined. TDI measures the sum of the actual point of interest plus the tethering effects in the adjacent segments to the ischemic zone. Therefore, TDI velocities from the proximal part of the lateral apical segments include velocities from the apex curve which again most likely represent an important contribution to the flow propagation seen in this study.
Furthermore, the noise problems in measures with the SDE technique remain high and probably higher than found in measures from TDI(39). Moreover, SDE and TDI from LV apex might be difficult to interpret due to angle problems inherited in all Doppler modalities(37).

**Limitations**

Acute and chronic ischemia in the distribution areas of LCX and RCA were not studied. An earlier report from myocardial infarct in the RCA area did not show evidence of reversed flow during IVR probably due to preserved contraction of the anterior and apical parts of LV(6).

The changes in LV cavity shape during IVR are complex and the unidirectional measures used in this study are inadequate for real 3 dimensional knowledge of intracavitar flow. The imaging sequences in our study were limited to apical 4-chamber due to the short period time of balloon inflation. All our efforts were therefore made to provide reliable data from the apical 4-chamber view.

The duration of the IVR period is short. In average, 3.8 frames of 2-D flow were imaged during IVR. However, post-systolic shortening followed by apical-to-mitral directed flow propagation during IVR was demonstrated in every individual with apical and septal ischemia.

**Conclusion**

Interaction between regional myocardial wall motion and intraventricular flow could be assessed by the use of echocardiographic equipment. Reversal of
intraventricular flow during IVR in acute and chronic LAD ischemia was in each patient caused by post-systolic shortening of the apical part of LV.

**Grants**

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Figure legends

Figure 1
The relationship between intraventricular flow and myocardial tissue velocities during IVR (y = 7.09-7.04X, r = 0.80, p<0.001).

Figure 2
The 2-D image shows intraventricular flow propagation towards LV apex during IVR. Please note that the mitral valves are closed. The color M-mode image confirms a distinct red flow directed towards the LV apex (arrow) before the filling starts. The flow during early filling is partly colorized in red due to aliasing. This finding is typical in healthy individuals and angina patients at rest without LV dysfunction.

Figure 3
This figure demonstrates the striking alterations from baseline (upper panel) to acute ischemia (lower panel) in one patients undergoing PCI of his LAD. The tissue velocities during IVR are prominently negative at baseline, reversing into a marked post-systolic shortening in acute ischemia.

Figure 4
Reversed intraventricular flow propagation during IVR in a patient during PCI of LAD. The same reversed flow propagation (arrow) is demonstrated in the color M-mode image.
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Table 1. Clinical and Hemodynamic Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Normal individuals (N = 18)</th>
<th>Acute LAD ischemia (N = 16)</th>
<th>Anterior myocardial infarct (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 11</td>
<td>58 ± 11*</td>
<td>56 ± 12</td>
</tr>
<tr>
<td>Female / Male (number)</td>
<td>7 / 11</td>
<td>4 / 12</td>
<td>5 / 12</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>-</td>
<td>14 ± 6</td>
<td>19 ± 8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>68 ± 5</td>
<td>80 ± 7</td>
<td>46 ± 16†</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>63 ± 11</td>
<td>58 ± 8</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>Duration of IVR (ms)</td>
<td>77 ± 11</td>
<td>109 ± 27‡</td>
<td>109 ± 25‡</td>
</tr>
<tr>
<td>LAD lesion (area stenosis %)</td>
<td>-</td>
<td>83 ± 8</td>
<td>82 ± 33</td>
</tr>
</tbody>
</table>

Mean values ± SD. LVEDP = left ventricular end diastolic pressure; LVEF = left ventricular ejection fraction (in normals by 2-D echocardiography, in the other groups by angiography); HR = heart rate; LAD = left anterior descending coronary artery.

* p<0.05 compared to normal individuals. † p<0.001 compared to acute ischemia.‡ p<0.001 compared to normal individuals.
Table 2. Myocardial (LV septum) and intraventricular flow velocities (cm/s) from normal individuals and patients with anterior myocardial infarction.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Anterior infarct</th>
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<tbody>
<tr>
<td>VS mid segment (cm/s)</td>
<td>4.9 ± 1.1</td>
<td>1.8 ± 1.0†</td>
</tr>
<tr>
<td>VS apical segment (cm/s)</td>
<td>2.5 ± 0.9</td>
<td>1.4 ± 0.8*</td>
</tr>
<tr>
<td>V_{IVR} mid segment (cm/s)</td>
<td>-2.0 ± 1.4</td>
<td>2.4 ± 1.2†</td>
</tr>
<tr>
<td>V_{IVR} apical segment (cm/s)</td>
<td>-1.0 ± 0.7</td>
<td>1.6 ± 0.7†</td>
</tr>
<tr>
<td>Flow (cm/s)</td>
<td>25.1 ± 9.5</td>
<td>-14.3 ± 10.7†</td>
</tr>
</tbody>
</table>

Mean values ± SD. LV = left ventricular. VS = Peak myocardial systolic velocity. V_{IVR} = Peak myocardial velocity during isovolumic relaxation.

* p<0.01 compared to normal individuals. † p<0.001 compared to normal individuals
Table 3. Myocardial velocities (cm/s) from angina patients.

<table>
<thead>
<tr>
<th></th>
<th>VS (cm/s)</th>
<th>V_{IVR} (cm/s)</th>
<th>Flow (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>4.2 ± 1.5</td>
<td>-2.3 ± 1.1</td>
<td>26.0 ± 12.0</td>
</tr>
<tr>
<td><strong>Occlusion</strong></td>
<td>2.0 ± 1.0†</td>
<td>2.4 ± 1.0†</td>
<td>-14.2 ± 6.4†</td>
</tr>
<tr>
<td><strong>After</strong></td>
<td>3.8 ± 0.9</td>
<td>-0.8 ± 0.9†</td>
<td>14.8 ± 10.2*</td>
</tr>
</tbody>
</table>

Velocities were measured in the mid septal wall segment during ejection and post-systolic period at baseline, during and after LAD occlusion. Intraventricular flow velocities (cm/s) were measured during IVR from the same time points.

Mean values ± SD. VS = Peak myocardial velocity during the ejection period. V_{IVR} = Peak myocardial velocity during isovolumic relaxation.

* p<0.01 compared to baseline. † p<0.001 compared to baseline.
FIGURE 1
FIGURE 3

Tissue velocities (cm/s)

Time (ms)

Post-systolic shortening