Myocardial positive pre-ejection velocity accurately detects presence of viable myocardium, predicts recovery of left ventricular function and bears a prognostic value after surgical revascularization

Martin Penicka¹, Petr Tousek¹, Bernard De Bruyne², William Wijns², Otto Lang³, Juraj Madaric², Marc Vanderheyden², Jaroslav Tintera⁴, Marek Maly⁵, Petr Widimsky¹, and Jozef Bartunek²*

¹From the Cardiocenter, Department of Cardiology, 3rd Medical School Charles University and University Hospital Kralovske Vinohrady Srobarova 50, 100 34 Prague, Czech Republic; ²Cardiovascular Center, OLV Hospital, Aalst, Belgium; ³Department of Nuclear Medicine (O.L.), 3rd Medical School Charles University and University Hospital Kralovske Vinohrady Prague, Czech Republic; ⁴Department of Radiology, Institute of Clinical and Experimental Medicine, Prague, Czech Republic; and ⁵Department of Biostatistics and Informatics, National Institute of Public Health, Prague, Czech Republic

Aims To assess the accuracy of tissue Doppler imaging-derived myocardial positive pre-ejection velocity (+Vic) in detecting myocardial viability defined by dobutamine stress echocardiography (DSE), fluorine-18 fluorodeoxyglucose positron emission tomography (PET), and contrast-enhanced magnetic resonance imaging (MRI), and in predicting recovery of left ventricular (LV) function after coronary artery bypass grafting (CABG) in patients with chronic ischaemic LV dysfunction.

Methods and results +Vic in dysfunctional segments was recorded in 54 patients treated medically and 65 patients undergoing CABG [age 67 ± 9 year; LV ejection fraction (EF) 30 ± 6%]. A good agreement was observed between +Vic and detection of viable myocardium at DSE, PET, and MRI (kappa = 0.76). The presence of +Vic in greater than or equal to five dysfunctional segments had the highest sensitivity (93%) and specificity (60%) to identify patients (n = 28) with ≥10% increase in LV EF between baseline and 6-month echocardiogram. During follow-up (median 333 days, interquartile range 209–490 days), 13 cardiac events (6 deaths, 7 hospitalizations) occurred in 24 patients with small extent of viable myocardium (<5+Vic), whereas only four hospitalizations in 39 patients with ≥5+Vic (54% vs. 10%; P < 0.001).

Conclusion The extent of +Vic in dysfunctional segments accurately predicts extent of viable myocardium and bears a clinical prognostic value in patients with ischaemic LV dysfunction considered for CABG.

KEYWORDS Tissue Doppler imaging; Viability; Coronary disease; Echocardiography; Bypass

Introduction Assessment of myocardial viability is based on assessment of myocardial morphology at contrast-delayed magnetic resonance imaging (MRI), assessment of perfusion or glucose metabolism at positron emission tomography (PET) or contrast response to low dobutamine infusion.¹,² Tissue Doppler imaging (TDI) allows accurate assessment of regional myocardial function during all phases of cardiac cycle.³,⁴ In experimental acute myocardial ischaemia, TDI-derived myocardial positive pre-ejection velocity occurring during isovolumic contraction could distinguish viable from non-viable myocardial segments.⁶ We have previously demonstrated high accuracy of the positive pre-ejection velocity to predict recovery of contractile function in patients with acute myocardial infarction (MI).⁷ Nevertheless, the accuracy of this index to identify viable myocardium in patients with chronic ischaemic left ventricular (LV) dysfunction when compared with current reference techniques or to recovery of contractile function after revascularization is not known. Therefore, the aim of the present study was to prospectively assess the accuracy of the TDI-derived positive pre-ejection velocity to detect myocardial viability defined by three reference techniques: low-dose dobutamine stress echocardiography (DSE), fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) and delayed Gadolinium-enhanced MRI, and to predict recovery of LV contractile function after surgical revascularization (coronary artery bypass grafting (CABG)) in patients with severe chronic ischaemic LV dysfunction.

* Corresponding author. Tel: +32 53 72 4447; fax: +32 53 72 4550. E-mail address: jozef.bartunek@olvz-aalst.be

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Methods

Patients
This is a prospective, multicentre study involving three centres. Consecutive patients (n = 152) referred for assessment of myocardial viability were included based on following criteria: (1) occluded or suboccluded left anterior descending coronary artery (LAD) at recent coronary angiography (<3 months); (2) LV ejection fraction (EF) <40% at biplane LV angiography; (3) greater than or equal to three akinetic or severely hypokinetic segments in the LAD perfusion territory at rest echocardiography. Patients with previous revascularization >6 months and persistent LV dysfunction despite revascularization were also included. Patients with recent acute coronary syndrome, atrial fibrillation, LV hypertrophy, or aneurysm, significant valvular disease, pacemakers or internal defibrillators, poor echocardiographic image quality and contraindications for MRI were excluded. Moreover, 33 out of 152 screened patients underwent partial revascularization with PCI in the non-LAD coronary artery and were also excluded. No patients refused to give their consent. The final study group consisted of 119 patients (age 67 ± 9 year; 81% males). Among them, 54 patients were treated medically and 65 patients underwent revascularization with CABG. The decision on treatment strategy was based on clinical criteria used routinely in our institutions that included: (1) clinical status and perioperative risk assessment using EuroSCORE; (2) coronary angiography findings and technical feasibility to perform revascularization; (3) discretion of referring physicians and patients preference. The physicians responsible for patient care and treatment decision did not participate in the study and were blinded to TDI-derived positive pre-ejection velocity data. The study protocol was approved by Medical Ethical Committees of all involved institutions and informed consent was obtained from all patients.

Study protocol
At baseline, all patients underwent an echocardiogram to analyse regional and global LV function and TDI-derived assessment of pre-ejection velocity. In patients assigned to medical treatment, DSE, FDG PET, and cardiac MRI were performed within 5 days after TDI. Patients scheduled for CABG did not undergo additional examinations and CABG was performed within one month after the baseline echocardiography. In patient undergoing CABG, echocardiography was repeated 6 months after operation. All patients were followed clinically.

Tissue Doppler imaging
Pulsed-wave TDI was performed using a commercially available ultrasound system as previously described. Briefly, to define the pre-ejection period, aortic flow was recorded by pulsed-wave Doppler at the level of LV outflow tract at the beginning and at the end of each examination. Pre-ejection was defined as a time interval between the onset of QRS complex and the onset of aortic flow. In apical views, longitudinal myocardial velocities were assessed in each LV segment during end-expiratory apnea. A sample volume was positioned in the centre of each myocardial segment parallel to the analysed vector of regional motion. Gains and filters were adjusted to obtain an optimal tissue signal. All studies were saved both in digital cineloop format and on S-VHS videotapes for off-line analysis. The presence or absence of positive pre-ejection velocity (+Vic) was noted in each dysfunctional segment. Echocardiography operators were blinded to viability findings by all three reference techniques. The intra and interobserver variability of the TDI-derived assessment of +Vic in humans is 7.8 ± 5.7 and 9.2 ± 7.2%, respectively.

Echocardiography and low-dose DSE
Echocardiography and low-dose DSE (5 μg kg⁻¹ min⁻¹ and 10 μg kg⁻¹ min⁻¹, each dose for 5 min) was performed as described elsewhere. Systolic wall thickening was scored as: 1, normokinesia; 2, mild hypokinesia; 3, severe hypokinesia, and 4, akinesia by consensus of two operators. Wall motion score index (WMSI) was calculated as the sum of scores in all visualized segments divided by the total number of visualized segments. LV EF was assessed from apical views using the biplane Simpson’s method. Digitalized baseline, follow-up, and DSE echocardiograms were analysed by an operator blinded to data of other imaging techniques, including TDI-derived analysis of +Vic. The inter- and intraobserver variability for assessment of LV EF in patients with LV dysfunction was 9.6 and 8.2%, respectively.

FDG uptake at PET
FDG uptake at PET was performed as described elsewhere. The mean FDG uptake for each segment was normalized to the FDG uptake in the normokinetic reference segment perfused by a coronary artery with <70% diameter stenosis.

Delayed contrast-enhanced ECG-gated MRI
Delayed contrast-enhanced ECG-gated MRI images (1.5 T scanner Siemens Symphony, Erlangen, Germany) were acquired using a phased-array receiver coil during breath-holds, as described previously. The extent of hyperenhanced tissue was assessed in each segment of the left ventricle and graded on a 5-point scale as: no hyperenhancement, hyperenhancement of 1–25%, 26–50%, 51–75%, and 76–100% of wall thickness. Both FDG PET and MRI, images were analysed off-line by independent operators blinded to the results of other techniques.

Definition of myocardial viability and data analysis
Myocardial viability and location was assessed using 16-segment model in all imaging modalities. At TDI, dysfunctional segments (severely hypokinetic and akinetic) were considered viable if +Vic was noted. In case of tiny positive but large dominantly negative pre-ejection velocity, the pre-ejection velocity was classified as negative. At low-dose DSE, segment was considered viable if showing an increase in wall thickening greater than or equal to one point of the scoring system at any dose of dobutamine. At PET, viability was defined if segment showed >50% of normalized FDG uptake and finally, at MRI, if ≤50% of transmural hypoenhancement was found. In patients undergoing CABG, viability was defined as greater than or equal to one point increase in segmental contractile function between baseline and 6-month follow-up echocardiography. Furthermore, an improvement in global LV EF ≥5% between baseline and 6-month echocardiogram was considered significant.

The accuracy of +Vic at TDI to identify viable segments was evaluated from methodological and clinical standpoints. The methodological analysis aimed at identification of individual viable or non-viable segments by comparing +Vic at TDI with viable segments detected at individual reference techniques and with segments showing match at all three reference techniques. The clinical analysis addressed the accuracy of +Vic to identify patients with regional and global LV functional recovery after CABG.

Statistical analysis
Data are presented as mean ± standard deviation or median and interquartile range (IQR). Bootstrap resampling (n = 5000) was used to obtain confidence intervals for sensitivity and specificity in case when the basic statistical unit was segment rather than...
patient. Logistic generalized linear mixed model (GLMM) treating patient as a random factor was used to account for different patient personalities and interdependencies between the data. Two-sided paired and unpaired Student’s t-test, or Pearson correlation coefficient was used as appropriate. Following statistical analyses were done to demonstrate accuracy and value of TDI-derived +Vic to detect viable myocardium. (i) The agreement between different imaging techniques was assessed using kappa statistics. Good agreement between the methods was considered if kappa was >0.6, excellent agreement was considered if kappa >0.8.\(^{13}\) (ii) The receiver-operating characteristic (ROC) curves were derived to assess the optimal cutoff values of number of dysfunctional segments with preserved +Vic to predict recovery of global LV EF >5 and 10% at 6-month follow-up echocardiogram. The optimal cutoff point was defined as the nearest point to upper left corner of the ROC curve. The authors preferred cutoff with higher sensitivity than specificity because of its practical usefulness for clinical practice. The reliability of the cutoff point was validated using bootstrap method with bias correction \((n = 5000)\). (iii) Multiple logistic regression was used to define independent predictors of global LV EF recovery. Residual vs. fitted or predictor values plots were used to look for violations of regression assumptions and no serious problem was identified. (iv) In patients with large \( (>5 \pm \text{Vic}) \) vs. small \( (<5 \pm \text{Vic}) \) extent of viable myocardium, the time to an end-point event was plotted according to the Kaplan–Meier method and differences between groups were analysed by log-rank test. Independent predictors of cardiac mortality and hospitalizations for heart failure were identified using the Cox proportional hazards model and expressed as hazard ratio (HR) and 95% confidence intervals (CI). No stepwise selection of variables was performed. We considered all explanatory variables to be on an equal footing. Generalized test of Grambsch and Therneau based on scaled Schoenfeld residuals was used to test the proportional hazard assumption. Neither the tests for individual covariates nor the global test showed any statistically significant violation of the assumption. Graphical assessment based on log–log plots gave the parallel curves. Both the logistic regression and the Cox proportional hazards model comprised the following pre-CABG parameters: age, gender, history of MI, time from previous MI, angina, and NYHA class, presence of diabetes mellitus, obesity, statin use, LV end-diastolic diameter (LVEDd), LV EF, WMSI, number of successfully implanted coronary bypass grafts, number of dysfunctional segments. Statistical significance was defined as \( P < 0.05 \).

### Results

#### Baseline characteristics

Table 1 shows baseline characteristics. The majority of patients were males with multi-vessel disease and limiting symptoms. Sixty-two (52%) patients had history of MI. Patients undergoing CABG had larger extent of coronary artery disease (CAD), more old infarctions, and lower rate of previous revascularizations than patients treated medically. In contrast, LVEDd, LV EF, and WMSI were similar in both groups.

**Table 2** shows baseline characteristics. The majority of patients were males with multi-vessel disease and limiting symptoms. Sixty-two (52%) patients had history of MI. Patients undergoing CABG had larger extent of coronary artery disease (CAD), more old infarctions, and lower rate of previous revascularizations than patients treated medically. In contrast, LVEDd, LV EF, and WMSI were similar in both groups.

#### TDI-derived +Vic vs. reference techniques to identify regional viable myocardium in patients treated medically

A total of 804 segments could be analysed by both TDI and all three reference techniques. Among them, 555 were dysfunctional and 458 showed concordant results regarding their viability status at all three reference techniques. Figures 1 and 2 show an example of presence and absence of +Vic at TDI when compared with assessment of myocardial viability at reference techniques. Figure 3 shows the relationship between percentage of dysfunctional segments with +Vic and the extent of viable myocardium as assessed by MRI or FDG PET. In both cases, logistic model (GLMM) showed strong association between the methods \((P < 0.001)\). High sensitivity and specificity of +Vic to identify viable myocardium was noted as compared to all three reference techniques (Table 2, Figure 4A–C). Finally, head-to-head comparison between TDI-derived +Vic and segments with concordant results at all three reference techniques showed the highest agreement with sensitivity of 91% and specificity of 85%. (Table 2).

#### TDI-derived +Vic to predict LV functional recovery in patients after CABG

Two patients died in an early postoperative period (sepsis, cardiogenic shock) and were excluded from the analysis. Another five patients died before the 6-month follow-up...
echocardiogram. The remaining 58 patients constituted the group to compare the value of $+\text{Vic}$ to predict LV functional recovery. Arterial graft (left internal mammary artery) on LAD was used in all patients. The majority of patients (86%) received a graft on greater than or equal to two major coronary arteries. A total of 442 dysfunctional segments (severe hypokinesis or akinesis) were analysed, out of which 291 (66%) showed functional recovery at 6-month follow-up. Sensitivity and specificity of $+\text{Vic}$ to predict recovery of regional function was 93 and 77%, respectively (Table 2, Figure 4D).

Thirty-nine patients (67%) showed moderate ($\geq 5\%$) and 28 (48%) patients had marked ($\geq 10\%$) increase in LV EF between baseline and 6-month echocardiogram. The extent of dysfunctional segments with preserved $+\text{Vic}$ significantly correlated with a decrease in LV dimensions and improvement in global LV EF and WMSI at follow-up (Figure 5). The presence of $+\text{Vic}$ in greater than or equal to five dysfunctional segments ($n=39$ patients) had the sensitivity of 92 and 93%, and specificity of 79 and 60% to predict moderate and marked increase in LV EF, respectively. Using bootstrap method, optimal cutoff value was 4.6 (95% CI 4.1–5.8) and 5.2 (95% CI 4.5–6.6), respectively, and the corresponding areas under the curve were 0.85 (95% CI 0.56–0.99) and 0.76 (95% CI 0.51–0.92).

At multiple analysis, the presence of $+\text{Vic}$ in greater than or equal to five dysfunctional segments was the only independent variable associated with moderate ($\geq 5\%$) increase in LV EF [odds ratio (OR) 2.51; 95% CI 1.39–4.53; $P=0.001$]. Likewise, the presence of $+\text{Vic}$ in greater than or equal to five dysfunctional segments and LVEDd were the only independent predictors of marked ($\geq 10\%$) increase in LV EF (OR 2.12; 95% CI 1.32–3.42; $P=0.001$; and OR 0.81; 95% CI 0.65–1.00; $P=0.05$, respectively).

**Prediction of clinical outcome**

No patient was lost to follow-up and survival status was known in all patients. In patients after CABG, 63 patients with uneventful perioperative course comprised the analysed study group. During a follow-up of 333 days (IQR 209–490 days), six patients died (five sudden cardiac deaths, one pump failure death) and 11 patients were hospitalized for heart failure. No patient had acute coronary syndrome. 13 events (six deaths, seven hospitalizations) occurred in 24 patients with small extent of viable myocardium ($<5\% +\text{Vic}$). In contrast, patients with $\geq 5\% +\text{Vic}$ ($n=39$) had only 4 hospitalizations (54 vs. 10%; $P<0.001$) (Figure 6). In a Cox proportional hazards model, presence of $\geq 5\% +\text{Vic}$ emerged as an independent predictor of cardiac mortality and hospitalizations for heart failure (HR 0.66; 95% CI 0.51–0.85; $P=0.001$).

In patients treated medically, 11 cardiac deaths (five sudden and six pump heart failure deaths) and 10 hospitalizations for heart failure were observed during a follow-up of 388 days (IQR 221–525 days). 12 events (five deaths)

<table>
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<th>Rest</th>
<th>DSE</th>
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<tr>
<td>LV EF (%)</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.56</td>
<td>1.56</td>
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</tbody>
</table>

Figure 1 Example of a patient with old anterior MI and severe wall motion abnormalities in the LAD perfusion territory. TDI tracing shows preserved positive pre-ejection velocity (yellow arrow) in the segments supplied by a suboccluded LAD indicating presence of viable myocardium. At corresponding segments, normal FDG uptake at PET (white arrows) and no hyperenhancement at MRI (orange arrows) were noted. In addition, significant functional recovery was observed after administration of low-dose dobutamine. RCA, right coronary artery.
occurred in 30 patients with large extent of viable myocardium (≥5+Vic), while nine events in 24 patients with smaller extent of viable myocardium (40 vs. 38%, \(P = \text{ns}\)).

Discussion

This study addressed the value TDI-derived myocardial positive pre-ejection velocity to assess myocardial viability in patients with chronic ischaemic LV dysfunction. Main findings are as follows: (i) Accuracy of TDI-derived +Vic to detect the presence and extent of viable myocardium was similar when compared with individual or combination of reference techniques. (ii) Presence of +Vic accurately identifies patients with regional and global LV functional recovery after CABG and may bear a prognostic value in case of revascularization. Since TDI is cheap, little operator-dependent, widely available and easy to obtain under resting conditions, TDI-derived +Vic may be proposed as a clinically reliable tool to detect viable myocardium in patients with chronic ischaemic LV dysfunction.

Techniques for assessment of myocardial viability

Several techniques are used to identify dysfunctional but viable myocardium. Cardiac MRI and PET are established as reference techniques based on either morphological description of the necrosis or assessment of glucose metabolism. The accuracy of two-dimensional low-dose DSE is image- and operator-dependent. Alternatively, TDI-derived analysis of ejection systolic velocities was shown to overcome the limitations of semiquantitative assessment with improved predictive accuracy.\(^{16,17}\) Yet, the presence of significant baso-apical velocity gradient and tethering effect hampers its clinical value.\(^{3,18}\) On the other hand, systolic strain and strain rate reflect ejectional wall motion at rest and during dobutamine infusion\(^{3,4,19}\) and show high accuracy to detect non-viable segments in combination with low-dose DSE.\(^{17}\) Nevertheless, issues such as angle dependency\(^{4,20}\) and effects of actual haemodynamics on the ejection phase\(^{3,4,6,19}\) further limit the accuracy of all these parameters.

In addition to the analysis of the ejection phase, TDI allows detailed assessment of pre-ejection phase characterized by the brief positive contraction before the opening of the aortic valve.\(^{3,6,7,21}\) Several experimental and clinical studies validated TDI-derived myocardial acceleration during isovolumic contraction (IVA) as a robust, quantitative parameter of left, and right ventricular contractile function under resting condition or during ischaemia.\(^{22-26}\) Alternatively, we assessed the pre-ejection phase qualitatively by means of detecting the solely presence or absence of positive pre-ejection velocity. In
animal model of acute myocardial ischaemia, +Vic appear to be in the direct relation with extent of viable myocardium.\(^6\) In addition, we have recently demonstrated accuracy, feasibility, and reproducibility of TDI-derived positive pre-ejection velocity to predict the recovery of contractile function in patients with acute MI.\(^7\) The present study extends these findings to patients with chronic ischaemic LV dysfunction by showing the high concordance between TDI-derived +Vic and three reference techniques to detect viable myocardium. Note, the accuracy of +Vic was highest when comparing only segments with match regarding their viability status at all three reference techniques. Second, corroborating the methodological concordance, a good agreement between +Vic and recovery of segmental contractile function at 6-month follow-up was noted in patients undergoing surgical revascularization. The presence of +Vic was proportional to the extent of LV functional recovery and reversed remodelling and at multiple analysis, +Vic emerged as independent predictor of the functional recovery in addition to baseline LVEDd. The latter observations is consistent with previous studies indicating that recovery after revascularization depends on the extent of negative LV remodelling where severe LV dilation may prevent LV functional recovery despite presence of viable myocardium.\(^27\) Finally, our data indicate that +Vic bears a prognostic value identifying patients with excellent event-free survival after CABG when compared with patients with absence of +Vic.

**Limitations**

There are several limitations. First, the binary +Vic is easy to assess and interpret, but it does not allow evaluation of regional changes in response to inotropic stimulation. In contrast, IVA, a quantitative index of pre-ejection phase, was shown recently to have high accuracy to predict coronary artery stenosis after administration of dobutamine.\(^26\) In our study, the +Vic was assessed by pulsed TDI, which is sufficient for qualitative assessment but noisy delineating curve

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**Table 2** Accuracy of the positive pre-ejection velocity to detect viable segments defined by FDG PET, MRI, DSE, and recovery of contractile function at the 6-month follow-up echocardiogram

<table>
<thead>
<tr>
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<th>+Vic sensitivity (%)</th>
<th>+Vic specificity (%)</th>
<th>Kappa</th>
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<tr>
<td>FDG PET viable segments (n = 355)</td>
<td>86 (95% CI 77–94%)</td>
<td>79 (95% CI 68–88%)</td>
<td>0.64</td>
</tr>
<tr>
<td>MRI viable segments (n = 368)</td>
<td>85 (95% CI 78–92%)</td>
<td>82 (95% CI 72–91%)</td>
<td>0.65</td>
</tr>
<tr>
<td>DSE viable segments (n = 335)</td>
<td>90 (95% CI 83–96%)</td>
<td>79 (95% CI 69–88%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Viable segments with match at all three reference techniques (n = 288)</td>
<td>91 (95% CI 84–98%)</td>
<td>85 (95% CI 74–95%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Segments with recovery at 6-month follow-up (n = 291)</td>
<td>93 (95% CI 87–98%)</td>
<td>77 (95% CI 65–89%)</td>
<td>0.72</td>
</tr>
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**Figure 3** The relationship between the proportion of dysfunctional segments with preserved positive pre-ejection velocity (+Vic) and the regional extent of viable myocardium defined by FDG PET and MRI. X-axis shows dysfunctional segments divided into five groups according to the FDG uptake at PET (on the left) or regional extent of hyperenhancement at MRI (on the right). +Vic was mostly present in segments with preserved FDG uptake or in segments with transmural hyperenhancement.
makes it inaccurate for quantification. In case of quantitative assessment, such as IVA, colour-coded TDI images obtained with frame rate of at least 130 per minute are more appropriate to use. Secondly, +Vic were compared with reference techniques only in medically treated patients. Patients scheduled for CABG did not undergo any of these examinations. Thus, the present study could not establish incremental value of +Vic over reference techniques to predict myocardial viability. Finally, though the number of cardiac deaths and hospitalization for heart failure were within the range of expected rates in similar patients with ischaemic heart failure, the sample size of our patient population is rather small. Thus, the results of Cox proportional hazards model on accuracy of +Vic to predict hard clinical events should be interpreted cautiously.

Conclusions

The present study indicates that TDI-derived +Vic showed similar accuracy to detect the presence and extent of chronically dysfunctional but viable myocardium when compared with current reference techniques. Furthermore, it demonstrates a strong relationship between the extent of TDI-derived +Vic in dysfunctional segments and recovery of LV contractile function as well as a potential prognostic value in patients undergoing surgical myocardial revascularization. Taken together, this suggests that analysis of pre-ejection phase of the cardiac contraction cycle could be used as a novel diagnostic approach for detection of the chronically dysfunctional but viable myocardium.

Acknowledgements

We would like to thank Martina Havlikova and Ilse De Wolf for excellent technical assistance throughout the study. This work was supported by the grant IGA NR: 8524-5 awarded by the Czech Ministry of Health and by the Charles University Prague Research Project MSM 0021620817 awarded by the Czech Ministry of Education.

Conflict of interest: none declared.
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