

Review

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## Transthoracic Doppler echocardiography – noninvasive diagnostic window for coronary flow reserve assessment

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### Abstract

This review focuses on transthoracic Doppler echocardiography as noninvasive method used to assess coronary flow reserve (CFR) in a wide spectrum of clinical settings. Transthoracic Doppler echocardiography is rapidly gaining appreciation as popular tool to measure CFR both in stenosed and normal epicardial coronary arteries (predominantly in left anterior descending coronary artery). Post-stenotic CFR measurement is helpful in: functional assessment of moderate stenosis, detection of significant or critical stenosis, monitoring of restenosis after revascularization. In the absence of stenosis in the epicardial coronary artery, decreased CFR enable to detect impaired microvascular vasodilatation in: reperfused myocardial infarct, arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy. In these diseases, noninvasive transthoracic Doppler echocardiography allows for serial CFR evaluations to explore the effect of various pharmacological therapies.

### Introduction

Coronary flow reserve (CFR) is defined as a ratio of maximal (stimulated) to baseline (resting) coronary blood flow. CFR evaluation is important for the understanding of the pathophysiology of coronary circulation. CFR measurement is used both to assess epicardial coronary stenoses and to examine the integrity of microvascular circulation. An appreciation of coronary physiology is an integral part of clinical decision-making for cardiologists treating patients with coronary artery disease. In the absence of stenosis in epicardial coronary artery, the CFR may be decreased when coronary microvascular circulation is compromised by arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus,

hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy or other diseases [1].

### Methods to assess CFR

Several methods have been established for measuring CFR (table 1). However, these methods are either invasive (intracoronary Doppler flow wire), highly expensive and scarcely available (Positron Emission Tomography) or semi-invasive and scarcely feasible (transesophageal Doppler), thus their clinical use is limited. In addition, PET and intracoronary Doppler flow wire involve radiation exposure, with inherent risk, environmental impact and biohazard connected with use of ionizing testing [2].

**Table 1: Comparison of methods to measure CFR**

Methodology	Advantages	Limitation
PET Intra-Coronary Doppler	Non-invasive, global and regional CFR measurable CFR supplemented by measurement of fractional flow reserve provide stenosis-specific assessment	Expensive, scarce, radiation exposure Invasive, expensive, radiation exposure
TDE	Noninvasive, cheap especially without contrast agents,	Only regional flow velocity, mainly in the LAD is measured (lower feasibility of flow imaging in Cx and RCA), Difficult measurement of volumetric (absolute) coronary flow

PET – positron emission tomography, TDE-transthoracic Doppler echocardiography

Because of the clinical importance of CFR there is a need for a simple, non-invasive, repeatable and inexpensive tool capable of this functional evaluation. The value of absolute coronary blood flow may be substituted by the value of coronary blood flow velocity [3–6] measurable by Doppler technique not only invasively but also using a non-invasive approach (figure 1,2,3). The present review discusses the assessment of CFR using transthoracic Doppler echocardiography, a technique which has been validated in a series of clinical studies [1,5,7–23]. Recently the usefulness of transthoracic Doppler echocardiography to assess CFR has been reported in various clinical settings in a large general referral population. The method provides reliable measurements of CFR in the distal or middle segment of left anterior descending coronary artery (LAD), using pulsed wave Doppler echocardiography under the guidance of color Doppler flow mapping. The development of the transthoracic imaging technique (exploring various transducer beam orientations) extended the possibilities of imaging blood flow in the circumflex coronary artery [1] and right coronary artery (RCA) [24–26]. As regards the transthoracic Doppler assessment of CFR in the RCA we are able to measure the coronary flow velocity in proximal RCA and in its distal branch i.e. right posterior descending artery. Due to the fact that most relevant RCA stenoses are located proximal to the crux cordis the assessment of CFR in the right posterior descending artery usually provide post-stenotic values. The feasibility of CFR measurement with transthoracic Doppler echocardiography is improved by contrast enhancement combined with second-harmonic imaging technique. Consequently, in some reports the feasibility of transthoracic Doppler echocardiography to assess CFR achieved 100% [7,9].

## Review

### Clinical Application

There are two most relevant clinical application of transthoracic Doppler echocardiography to assess reduced CFR due to: stenosis of epicardial LAD and impairment of coronary microvascular vasodilatation.

Coronary angiography provides a limited insight into the physiological significance of coronary stenoses. Therefore,

the CFR is a useful parameter in the several important clinical setting summarized in table 2.

### Functional assessment of intermediate stenosis (40–70%)

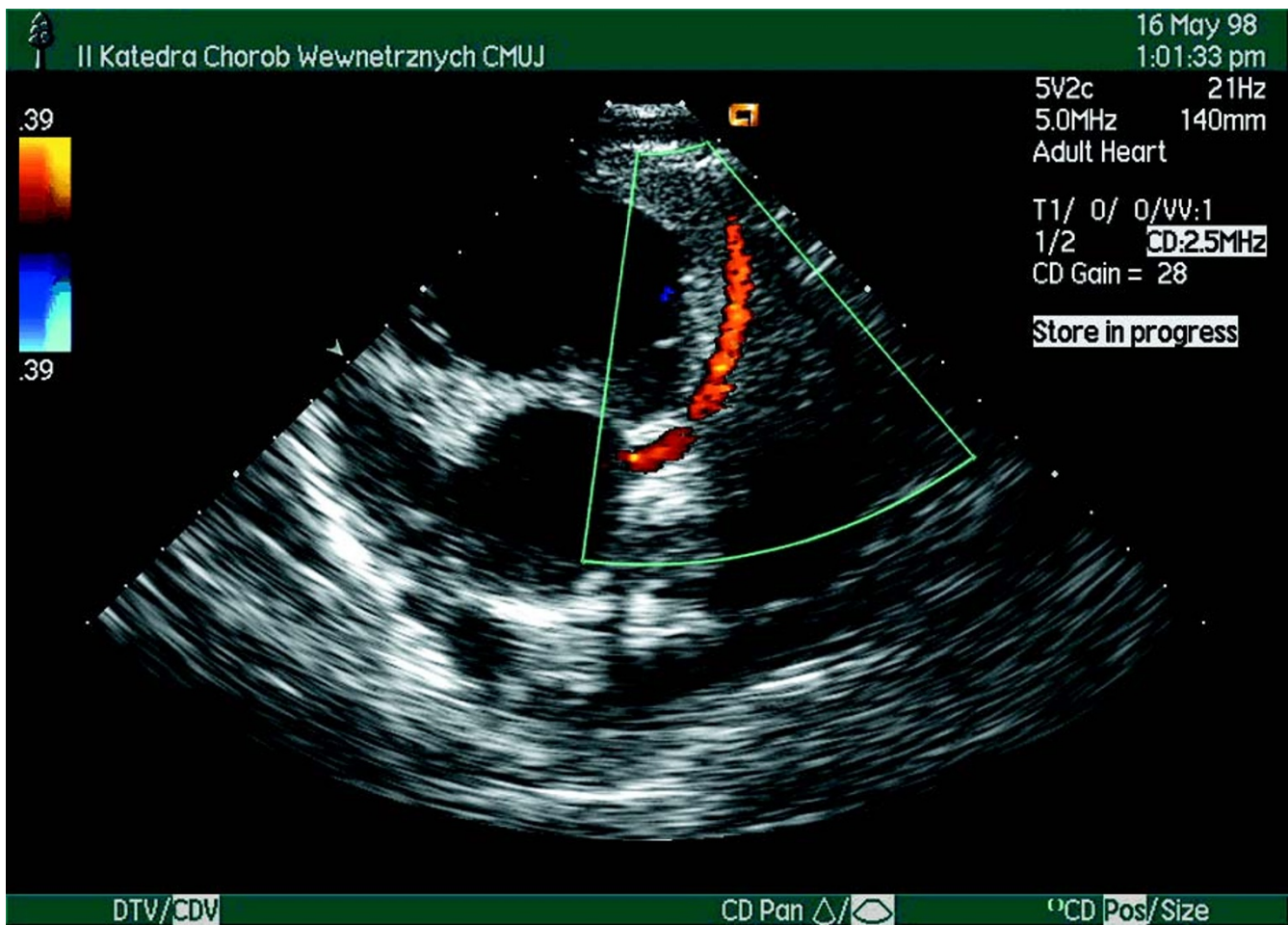
Understanding the functional impact of stenosis is important for clinical decision making (for example to refer or defer patients with intermediate stenosis to percutaneous transluminal coronary angioplasty [PTCA]). The treatment of patients with moderate stenoses is challenging, and CFR measured distally to stenosis precisely defines the hemodynamic significance of stenosis. In studies using transthoracic Doppler echocardiography, CFR <2 is associated with stress-induced ischemia [11,27] and reduced CFR is considered as manifestation of functionally important stenosis even if coronary angiography reveals intermediate severity [7–9,16]. In contrast, in patients with intermediate stenosis but an adequate CFR value, PTCA can be safely deferred. The measurement of CFR by transthoracic Doppler echocardiography provides data equivalent to those obtained by thallium-201 scintigraphy for physiologic estimation of the severity of LAD stenosis [11,27].

### Detection of critical stenosis (>90%)

Using transthoracic Doppler echocardiography it is possible to detect severe LAD stenosis >90%. The CFR <1, suggesting coronary steal may be a predictor of critical coronary stenosis [23]. Coronary steal is defined as a decrease of CFR to a certain vascular region in favor of another area during maximal coronary vasodilatation, that is, CFR <1.

### Combined assessment of coronary flow and wall motion

The CFR findings is additive and complementary to the information provided by 2DE on regional wall motion abnormalities. Combined assessment of CFR and wall motion was performed dipyridamole echocardiographic stress test. According to data from Rigo et al. report [28] coronary flow and contractile function of myocardium can be complementary in terms of predicting underlying angiographic anatomy, because abnormal wall motion can include coronary artery disease, and negative CFR can exclude it. In this study, sensitivity for detecting LAD dis-

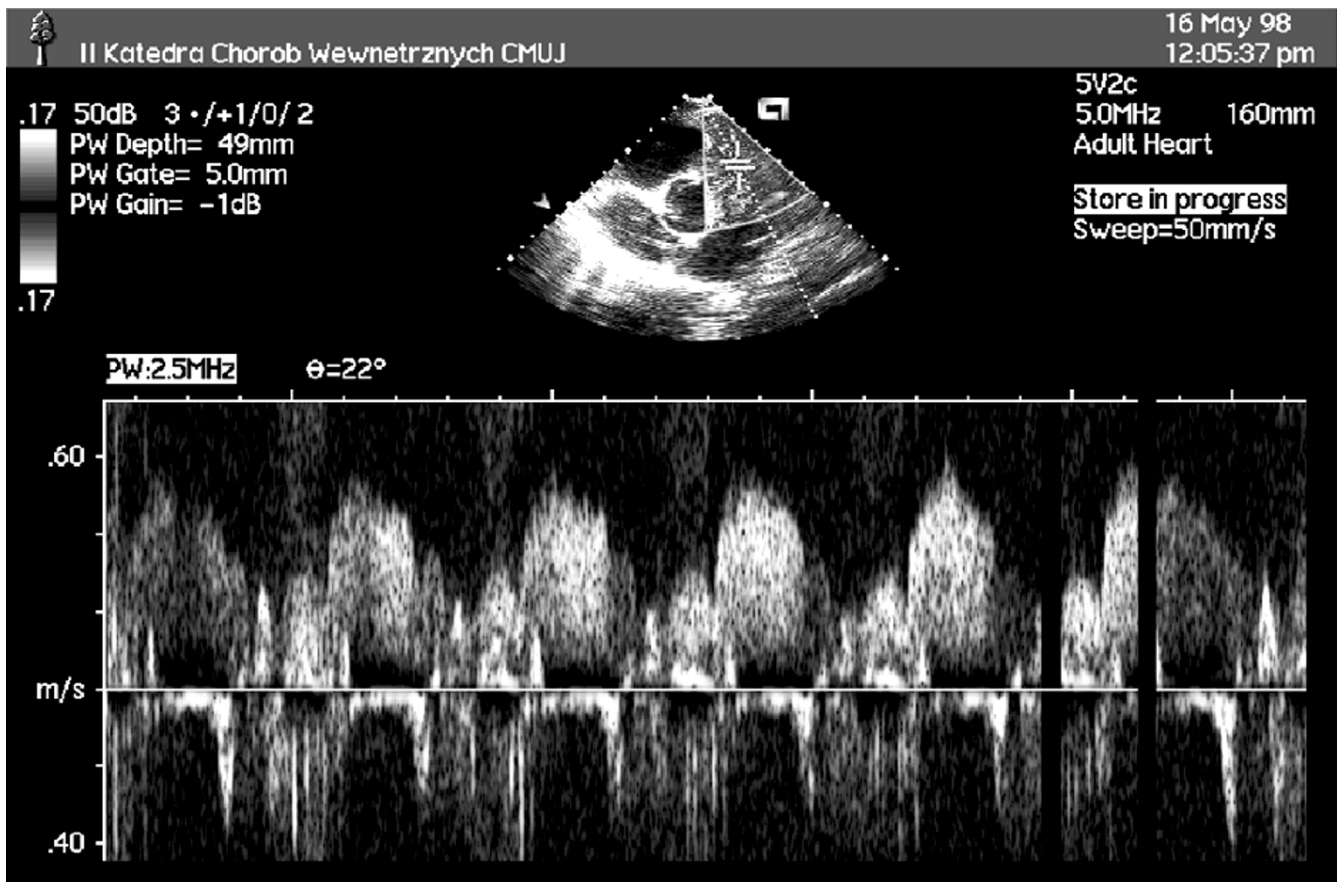


**Figure 1**  
Left main stem coronary artery and proximal segment of LAD in color-coded transthoracic Doppler echocardiography.

ease was 74% for 2-dimensional echocardiography and 81% for CFR <1.9 specificity was 91% for 2-dimensional echocardiography and 84% for CFR. Accuracy was 86% for 2-dimensional echocardiography and 83.5% for CFR. When 2-dimensional echocardiography and CFR criteria were considered, sensitivity increased to 93%, with 80.6% specificity. The recent, ground-breaking findings of Rigo et al [28] have already been confirmed by other studies from Argentina [29] and Japan [30], consistently showing that CFR, when assessed simultaneously with regional wall motion during dipyridamole stress-echocardiography, increase the sensitivity of the test, particularly in patients who are receiving beta-blockers or in patients with single vessel LAD disease, i.e., patients who are more likely to have false negative tests.

*Monitoring the changes of CFR in the early, post-PTCA period to detect artery occlusion, microvascular stunning*

Intracoronary Doppler has been introduced to optimize the results of PTCA [31–33] but it has shown a surprisingly high rate of impaired CFR after balloon angioplasty or stenting, even in the absence of any residual angiographic stenosis [34–36]. This phenomenon may be explained by the two following theories. Firstly, PTCA may induce microvascular stunning due to microembolization, thrombogenicity (by thrombin release) and vasoconstriction (by endothelin release). Alternatively, temporary reactive hyperemia, where high post-ischemic baseline flow velocity masks normal reserve. Invasive CFR is obtained after multiple balloon inflations, injection of contrast agent and administration of vasoactive drugs that may produce immediate post-procedural vasomotion instability. For these reasons, the measurement of CFR should be delayed several days after PTCA. At this time, the influence of



**Figure 2**  
Spectral Doppler coronary blood flow by sampling in proximal segment of LAD.

pharmacological, metabolic, humoral or myogenic factors affecting coronary flow autoregulation is negligible, possibly explaining the lower rate of post-procedural impaired CFR in a recent study using transthoracic Doppler echocardiography [23]. The noninvasive, repeatable, inexpensive and accessible transthoracic Doppler echocardiography is especially helpful in this clinical setting. Early reocclusion of the coronary artery is another complication after PTCA detectable by transthoracic Doppler echocardiography.

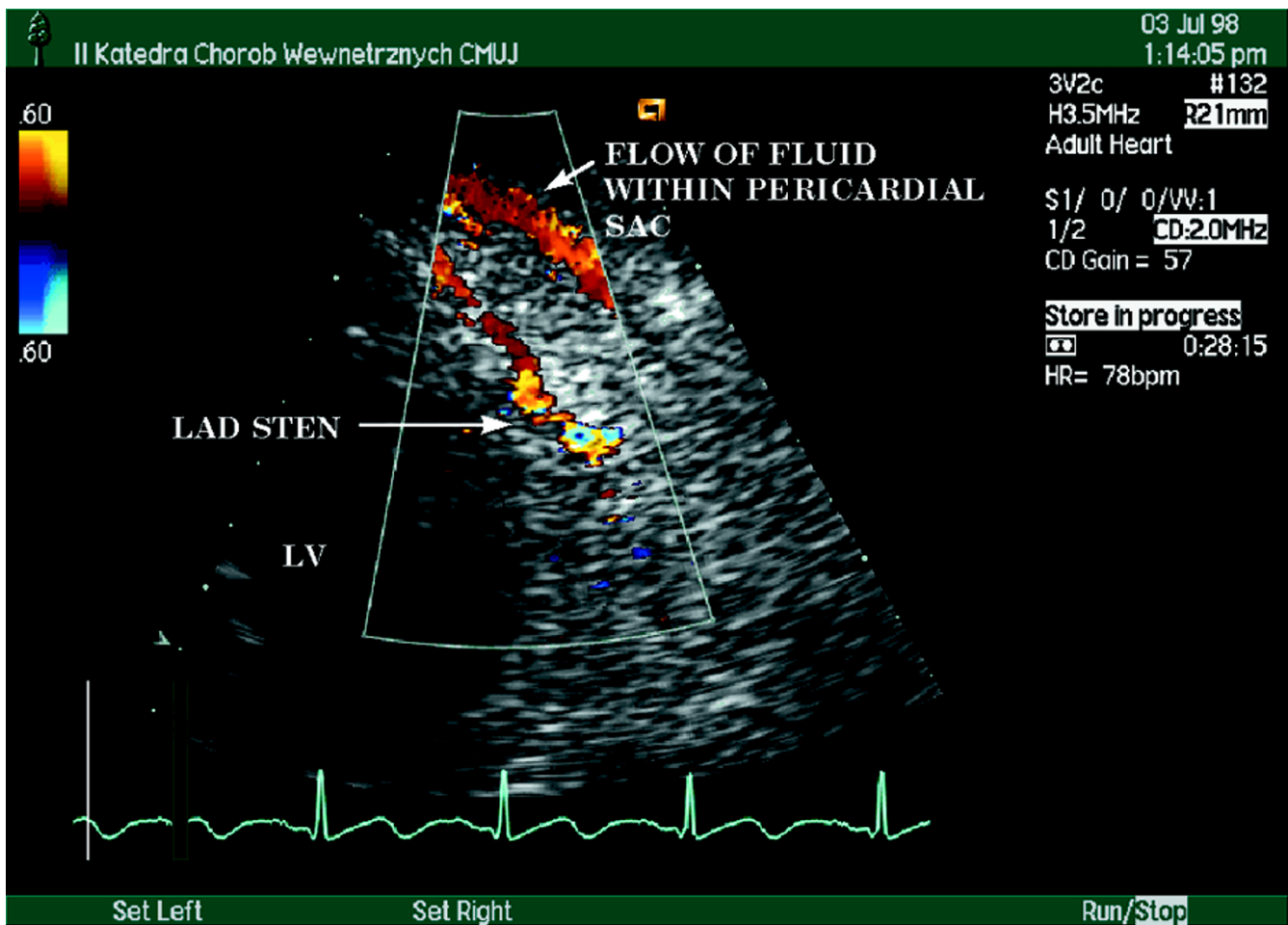
#### *Serial CFR examination after PTCA to predict restenosis*

Serial CFR examination after PTCA may be also feasible in mid- and long-term follow-up to monitor restenosis [37,38]. The decrease of CFR <2 during follow-up was proposed as a sensitive and specific predictor of restenosis [37,38]. This method may be complementary to exercise test, or may be its substitute if patients are unable to perform adequate exercise test.

Instead of CFR measurements distally to stenosis another methods has been developed to detect restenosis after PTCA. In some patients direct imaging of the stenosis/restenosis site in LAD is possible if a sufficiently long portion of LAD is visible [39,40]. The (re)-stenotic site is identified as localized color aliasing corresponding to local flow acceleration with turbulences. It is proposed to quantify the severity of restenosis by measuring the increase of coronary blood flow velocity (ratio of pre-stenotic to stenotic velocities) [39,40].

#### *Postinfarction CFR assessment*

There are several recent reports concerning the value of CFR measured transthoracically after reperfused acute anterior myocardial infarct [41,42]. In the study of Ueno et al. [41] the decreased CFR <1,5 was identified to predict an increase in left ventricular volume (remodeling) after reperfused myocardial infarct. A significant negative correlation was found between CFR and progression of left ventricular dilatation at 6-month follow-up. In the



**Figure 3**

Direct visualization of coronary artery stenosis. The portion of mid segment of LAD with color mosaic (a sign of high-velocity, turbulent flow) at stenotic site.

**Table 2: CRF for assessment of epicardial coronary artery stenosis**

- Functional assessment of intermediate stenosis (40–70%)
- Detection of critical stenosis (>90%)
- Combined assessment of coronary flow and wall motion
- Monitoring the changes of CFR in the early, post-PTCA period to detect artery occlusion, microvascular stunning
- Serial CFR examination after PTCA to predict restenosis
- Postinfarction coronary flow reserve assessment
- Assessment of coronary graft patency

study of Colonna et al [42] it was shown that preconditioning due to preinfarction angina had a protective role on microvascular function as demonstrated by CFR preservation (>2.5) after myocardial infarct.

#### *Assessment of coronary graft patency*

Another application of transthoracic Doppler echocardiography is the assessment of the patency of internal mammary artery and saphenous vein to coronary artery grafts [12,43]. In the largest study [43] the identification rate for mammary artery grafts was 100%, for saphenous

**Table 3: Proposed scheme of application of transthoracic Doppler echocardiography (with or without wall motion assessment) in diagnosis of epicardial or microvascular coronary vessel disease**

<b>Before coronary angiography (nondiagnostic or equivocal exercise stress ECG)</b>	
<ul style="list-style-type: none"> <li>• Suspected epicardial coronary stenosis (LAD, Cx, RCA)</li> </ul>	<ul style="list-style-type: none"> <li>• Suspected microvascular abnormalities (young patients with chest pain despite no risk factor for epicardial CAD)</li> </ul>
<ol style="list-style-type: none"> <li>1. WM (LV global) assessment (if negative)</li> <li>2. CFR (regional assessment of LAD)</li> </ol>	CFR in LAD
<b>After coronary angiography</b>	
Abnormal coronary angiogram	Normal coronary angiogram
<ul style="list-style-type: none"> <li>• Functional assessment of intermediate stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Confirmation or exclusion of microvascular dysfunction in patients with chest pain</li> </ul>
<ol style="list-style-type: none"> <li>1. Flow acceleration at stenotic site (if not possible)</li> <li>2. Dual assessment of WM + CFR</li> </ol>	CFR
<b>Control during follow-up after initial coronary angiogram</b>	
<ul style="list-style-type: none"> <li>• Patients deferred from PTCA due to intermediate stenosis</li> <li>• Patients with suspected restenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Verify the benefit of pharmacological interventions</li> </ul>
<ol style="list-style-type: none"> <li>1. Flow acceleration at stenotic site (if not possible)</li> <li>2. Dual assessment of WM + CFR</li> </ol>	CFR

WM – wall motion, LV – left ventricular

vein grafts to LAD coronary artery 91%, for the vein grafts to the right coronary artery 96% and for the vein grafts to circumflex artery 90% [43]. CFR <1,9 had 100% sensitivity, 98% specificity for mammary artery graft stenosis [43]. CFR <1,6 had 91% sensitivity, 87% specificity for significant vein graft stenosis [43].

*Impairment of coronary microvascular vasodilatation*

The second application of transthoracic Doppler echocardiography is the detection of reduced CFR due to impaired microvascular vasodilatation despite angiographically normal epicardial coronary arteries. It is well known that several diseases such as hypertrophy (due to aortic stenosis, hypertrophic cardiomyopathy, hypertension), diabetes mellitus, smoking, menopause cause structural and/or functional abnormalities in the microcirculation. The invasive Doppler measurement of CFR is not routinely performed in patients with chest pain and normal coronary arteries. Therefore, the extent of such microvascular disease appears to be underestimated. Accordingly, recent studies [4,44]. have demonstrated that up to 50% of the patients with chest pain and normal or near normal coronary angiograms have reduced CFR. Noninvasive assessment of CFR using transthoracic Doppler

echocardiography has been performed in patients with hypertrophic cardiomyopathy [45], aortic stenosis [46] and smokers (both active and passive) [17]. In these studies CFR was measured using adenosine (standard vasodilator to test endothelium-independent vasodilatation). In patients with hypertrophic cardiomyopathy additionally the vasomotor response to stressors testing endothelium-dependent vasomotion was studied [18–22,47]. Cold pressor test [20,21], handgrip [22,47] and pacing [19] was used as stressing stimuli. Importantly, the noninvasive approach provides an opportunity to assess asymptomatic patients [18,20] and to recruit healthy subjects to form adequate control groups [13,18,19,21,22], which is impossible in an invasive study. Additionally, the effect of physiological hypertrophy on CFR is measurable by transthoracic Doppler echocardiography [13], which could prove useful in differentiating athlete's hypertrophic heart – in which CFR is in normal to supranormal range – from hypertrophic cardiomyopathy, in which CFR is markedly attenuated.

Moreover, noninvasive transthoracic Doppler echocardiography allows for serial CFR evaluations to explore the effect of various pharmacological therapies [18] or to as-

**Table 4: Comparison between adenosine and dipyridamole**

	Adenosine	Dipyridamole
Dosage	Intravenous (i.v.) – 140 µg/kg/min	Intravenous – 0,56–0,84 mg/kg
Duration of action	30 sec	30 min
Time to max. effect	30–55 sec	6–16 min
Advantage	Short action, short-lasting adverse effects	prolonged action allow to assess CFR and wall motion abnormalities during single examination
Disadvantage	AV conduction delay (including complete heart block), Hyperventilation, hypotension, flushing, headache,	possibility of antidote-resistance prolonged ischemia, hypotension, flushing, headache, hyperventilation,

sess effect of aortic valve replacement for aortic stenosis [19–22].

The clinical applications of CFR measurement are summarized in table 3.

#### **Choosing the appropriate stimuli**

There are two pharmacological vasodilators: adenosine and dipyridamole used to recruit CFR. Both agents are compared in table 4. Both adenosine and dipyridamole have an advantage over exercise and dobutamine, which are submaximal stimuli for coronary flow reserve and are more technically demanding for imaging of CFR [1,48].

#### **Limitations of transthoracic Doppler echocardiography measurement of CFR**

##### *Absolute volumetric flow versus flow velocity*

Although the left anterior descending artery was detected with combined Doppler and two-dimensional imaging, the images were not of sufficient clarity to allow for accurate measurement of the vessel diameter in a substantial portion of the examined subjects. Without estimation of the coronary artery diameter we can measure changes only in coronary blood flow velocity, but not changes in coronary blood flow. Therefore CFR assessment by transthoracic Doppler echocardiography is limited to measurements of coronary blood flow velocity in majority of studies. However, it has been shown that CFR measured using both parameters is closely correlated (1–4). Moreover, even in large invasive studies DEBATE [49] and DESTINI [31,33] the CFR derived from changes only in the velocity of coronary blood flow was accepted instead of the absolute coronary blood flow, which is measurable during invasive studies.

Regarding the accuracy of transthoracic Doppler measurement of CBFV, its comparison with intracoronary measurement provided a highly satisfying correlation between non-invasive and invasive measurements [7,14].

##### *Contrast enhancement versus non-contrast study: learning curve and cost-effectiveness*

Another limitation is the feasibility of transthoracic coronary blood flow velocity measurement. In assessment of coronary flow in LAD, the learning curve effect was seen in most centers in which contrast agents were not used. In studies by Shapiro and coworkers, which were initiated in the beginning of the 90s, the capacity of detecting coronary flow increased from 34% to 77% [10,46,50,51]. Voci and coworkers were able to increase the capacity of coronary blood flow imaging from 76% [52] to 96% [23]. This result is fully comparable with the results of studies using contrast agents. In personal studies the capacity of detection increased with time and experience from 71% to 87% [18,20,21]. Only Hozumi et al. [15] achieved a very high feasibility of coronary flow imaging already in their first study, i.e. 94%. This limitation may be minimized by using echo-contrast agents enhancing Doppler signal intensity [7], which are however expensive. As regard cost-effectiveness balance it was calculated [23] that using 90s noncontrast/adenosine vasodilator approach the cost of the test was 14 times less expensive than 7-min contrast-enhanced approach. As regard vasodilator agents, dipyridamole is cheaper than adenosine and therefore the best cost-effectiveness profile is achieved with dipyridamole stress without contrast enhancement.

##### *Pitfalls and trouble-shooting*

CFR must be measured distally to stenosis, because erroneous CFR assessment at stenosis site is underestimated due to increased baseline flow velocity. Additionally, the flow in LAD branches could be erroneously interpreted as the flow in LAD main trunk.

#### **Conclusions**

Transthoracic Doppler echocardiography is rapidly gaining appreciation as popular tool to measure CFR both in stenosed and normal epicardial coronary arteries (predominantly in left anterior descending coronary artery). Post-stenotic CFR measurement is helpful in: functional assessment of moderate stenosis, detection of significant

or critical stenosis, monitoring of restenosis after revascularization. In the absence of stenosis in the epicardial coronary artery, decreased CFR enable to detect impaired microvascular vasodilatation in: reperfused myocardial infarct, arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy. In these diseases, noninvasive transthoracic Doppler echocardiography allows for serial CFR evaluations to explore the effect of various pharmacological therapies.

## List of Abbreviations

CFR – coronary flow reserve

LAD – left anterior descending coronary artery

RCA – right coronary artery

PTCA – percutaneous transluminal coronary angioplasty

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