Myocardial contrast echocardiography using power Doppler harmonic imaging is able to document myocardial hypoperfusion. Two case reports demonstrate the potential of intravenous bolus application of microbubbles in patients with acute chest pain due to myocardial ischaemia to detect regional low flow conditions. The case reports will focus on the necessity to present Doppler intensity kinetics by Doppler intensity vs time plots or coloured M-modes to present the data more objectively. In addition, the hypoperfusion detected with myocardial contrast echocardiography via bolus injection of microbubbles can only be proven by changes of regional perfusion between repetitive myocardial contrast echocardiography measurements or by additional perfusion analysis, e.g. by scintiscanning.

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Key Words: power Doppler harmonic imaging; myocardial contrast echocardiography; contrast agent; myocardial perfusion; bolus injection.

Introduction

In just a couple of years, development of myocardial contrast echocardiography has revealed numerous methods to determine regional myocardial perfusion\(^1\)–\(^7\). Power Doppler harmonic imaging uses a triggered image acquisition and a high mechanical index. In experimental series it could be demonstrated that qualitative, semi-quantitative, and quantitative analysis of regional myocardial perfusion is possible\(^1\)–\(^8\),\(^9\). In clinical studies, interpretation of myocardial contrast echocardiography data was generally performed by analysis due to subjective criteria\(^10\)–\(^14\). The main criticism for the usage of an intravenous bolus application is the dispersion of the microbubbles during the passage through the systemic veins, the right atrium, the right ventricle, and the pulmonary circulation. Thus, the input function is much wider than the transfer function in the myocardium. The gamma variate function, which has been shown to correlate with myocardial blood flow, is, however, only accurate when the bolus is not dispersed, such as those seen with left atrial or aortic root injections of micro-bubbles. Despite these theoretical considerations the present communication will focus on the potential of myocardial contrast echocardiography using rapid intravenous bolus application.
to detect regional myocardial hypoperfusion in clinical practice. This approach seems to be very suitable for myocardial perfusion analysis at rest in patients with acute coronary syndrome.

Methods

The described power Doppler harmonic imaging measurements were performed with a System Five Performance Ultrasound System (GE Vingmed Ultrasound AS, Horten, Norway). Imaging was acquired in continuous second harmonic (octave) mode for conventional diagnostics, in intermittent coded harmonic angio mode for perfusion imaging with a standard phased array transducer which transmits ultrasound at a mean frequency of 1.5 MHz and receives it at 3.0 MHz. Ultrasound pulses were gated to end systole once every third cardiac cycle. The transmission power was set at maximum power. Mechanical index was 1.4. The transmit focus was set between 6 and 10 cm. A maximum dynamic range of 60 dB was used. Pulse repetition frequency was 3000 Hz. Gain compensations were optimized before injection of echocardiographic contrast agent. The settings of the ultrasound system during the power Doppler harmonic imaging measurements were as follows: compression 10 (according to the scale of the ultrasound system); dynamic range 6 (according to the scale of the ultrasound system); power −2 dB; gain −29 dB; pulse repetition frequency 3.00 kHz; frequency 1.5 MHz; sample volume 1.9 mm; low velocity reject 32.5 cm/s; colour gain −18 dB. Gain settings were reported in detail in a previously published study[15]. In this study a default setting was defined which worked in the majority of patients.

The data were digitally stored as cineloops and transferred after completion of the investigation to a standard Macintosh personal computer. Quantitative analysis of the data was performed using the Echo Pac 6.2b.134 software. After storage of the cineloops, myocardial regions of interest with a size of 3 × 3 to 7 × 7 pixels were defined. To illustrate the Doppler intensity kinetics, the traces of each regions of interest are shown in a logarithmic scale with the y-axis and time in seconds on the x-axis. Coloured M-modes crossing the interventricular septum also show the alterations of the septal opacification during the intravenous bolus application. Parametric imaging using the coloured M-modes reveals additional semi-quantitative or qualitative aspects for detection of hypoperfusion. Firstly, early ‘patchy patterns’ defined as small regions of the myocardium without opacification 10–20 s after the peak maximum Doppler intensity value can be observed. Secondly, the non-uniformity of Doppler intensity-attenuation in the apical, mid and/or basal areas of the myocardium seems to be characteristic for regional hypoperfusion. Thirdly, differences of myocardial opacification between corresponding myocardial areas, e.g. using the four-chamber view Doppler intensity-kinetics of the interventricular septum vs Doppler intensity-kinetics of the lateral wall can be used for the interpretation of regional hypoperfusion[13].

Intravenous bolus application was performed by a rapid injection of 0.3–0.5 ml Optison® (Malinckrodt GmbH, Hennef, Germany) into a cubital or a forearm vein directly followed by a rapid flush of 5 ml saline. The dosage of Optison® was pre-tested because the peak maximum Doppler intensity of the ventricular cavity has to be 50 dB or higher to achieve sufficient opacification of the myocardium. The semi-quantitative analysis of regional perfusion after this standardization of the bolus application was only possible if cardiac output was in normal range according to the data of previous investigations[15]. Velocity time integral, heart rate, ejection fraction and cardiac output were measured by two-dimensional and pulsed Doppler echocardiography. Cardiac output has to be between 4.5 and 5.5 l/min and ejection fraction between 45 and 55% to be able to interpret the power Doppler harmonic imaging data. A low cardiac output results in a reduction of the Doppler intensity wash-in mainly due to the prolonged circulatory transit time and global hypoperfusion, but not due to regional myocardial hypoperfusion. On the other hand, the Doppler intensity wash-out would be prolonged due to the same reason.

Case Report 1

A 52-year-old patient was referred immediately after the onset of acute chest pain. Arterial hypertension was the only cardiovascular risk factor. Electrocardiogram (ECG) showed ST elevation in the Wilson leads V2–V4 (see Fig. 1(e)). Laboratory tests including troponin T were normal. Coronary angiography was performed immediately after admission. During the preparations for coronary angiography transthoracic echocardiography was performed documenting mid-apical septal hypokinesis without wall thinning. Fig. 1(a–d) shows the perfusion analysis using myocardial contrast echocardiography with power Doppler harmonic imaging. An impaired regional myocardial blood flow in the apical septal region was observed (pronounced difference of the Doppler intensity-kinetics during the wash-out between the apical septal and apical lateral regions). An 80% stenosis of the left anterior descending artery (see Fig. 1(f,g) was found in coronary angiography. The lesion was successfully stented. One day after the intervention the patient complained of chest pain again. ECG showed negative T waves (see Fig. 2(e)). Troponin T was 0.015 µmol/l (normal range <0.01 µmol/l). Myocardial contrast echocardiography investigation showed an impaired regional myocardial blood flow in the apical septal region similar to that seen in the previous investigation (see Fig. 2(a–d)). Repeat coronary
angiography did not show any stenosis or spasm (see Fig. 2(f,g)). Thus, at this moment a relevant impairment of regional septal microcirculation—presumably due to micro emboli after intervention—has to be considered. Eight days after intervention, the patient had no complaints and ECG was normal. Another myocardial contrast echocardiography revealed normal perfusion (Doppler intensity-kinetics—especially the wash-out of the apical septal and lateral areas show no differences) (see Fig. 3). Two-dimensional echocardiography performed 10 days after intervention showed no regional wall abnormalities.

Case Report 2

A 65-year-old female patient was admitted because of an episode of central chest pain 2 days before admission to hospital. Her risk factors include obesity, arterial hypertension and non-insulin dependent diabetes. The ECG suggested septal wall ischaemia (see Fig. 4(g,h)). Laboratory tests were normal except for elevated blood glucose and glutamic-oxalacetic transaminase. Blood gas analysis documented moderate metabolic acidosis. Immediately before angiography echocardiography was performed showing akinesis with wall thinning in the mid-apical septal area. Fig. 4(a,b and d) show the results of the power Doppler harmonic imaging assessment: severe hypoperfusion in the apical and mid septal areas as well as the apex were found (a pronounced difference of the Doppler intensity-kinetics during the wash-out between the apical septal and apical lateral regions was present). Coronary angiogram, however, demonstrated normal vessel morphology of epicardial arteries (see Fig. 4(e,f)). A thallium scan performed on the same
day showed hypoperfusion in the same areas (see Fig. 4(c)). Repeat echocardiography 1 week after angiography showed persisting akinesis of the septum. With respect to all findings, spontaneous lysis of an occluding LAD clot has to be assumed.

**Discussion**

Myocardial contrast echocardiography using power Doppler harmonic imaging can detect regional myocardial hypoperfusion in experimental and clinical settings. The most important problem of intravenous application is the spreading of the microbubble bolus due to its dispersion in the pulmonary circulation. Thus, the input function of the microbubbles into the myocardium is longer than the transfer function through the heart. In clinical practice, however, a standardized intravenous bolus application seems to be suitable to detect regional myocardial hypoperfusion with myocardial contrast echocardiography using power Doppler harmonic imaging. The reason why contrast defects appear earlier during the wash-out of contrast from the myocardium is that the concentration of microbubbles in the hypoperfused areas—which is lower than that of normal perfused areas—gets below the saturation threshold of the ultrasound system sooner than the normally perfused regions. The gamma variate function predicts also for microbubbles a delayed wash-out of contrast from hypoperfused areas like indicators used during myocardial scintiscanning. Because the

*Figure 2. Power Doppler harmonic imaging measurement of regional myocardial perfusion in the same patient featured in Fig. 1 one day after successful PTCA of the significant LAD stenosis using intravenous bolus application of Optison®. Regions of interest located into the left ventricular (yellow), the apical septum (green) and the apical lateral wall (red) in a colour-coded two-dimensional image using power Doppler harmonic imaging. The side-by-side comparison of the Doppler intensity kinetics between apical septal and apical lateral regions, as well as the Doppler intensity kinetic of the left ventricular cavum, is illustrated in (b). The colour-coded two-dimensional image with a colour-M-mode axis through the right ventricle, the septum and the left ventricle, as well as the lateral wall. (d) The corresponding colour-M-mode. Early ‘patchy patterns’ can still be observed in the septum, whereas the lateral wall is again homogeneously opacified. (e) The ECG tracings on the day after successful intervention. (f,g) The result of the second control angiography (LAO and RAO projection) excluding any restenosis or thrombosis of the epicardial vessels.*
reduction of the Doppler intensity signal is pronounced in hypoperfused areas, the effect of the early fall below the saturation threshold during the washout due to a low microbubble concentration in hypoperfused areas seems to be more important for the reduction of the Doppler intensity signals than the delayed wash-out of the micro-bubbles. It can be assumed that the difference in myocardial contrast enhancement between apical septal and apical lateral regions, as well as the Doppler intensity kinetic of the left ventricular cavity, is illustrated in (b). The colour-coded two-dimensional image with a colour-M-mode axis through the right ventricle, the septum and the left ventricle, as well as the lateral wall. (d) The corresponding colour-M-mode. The Doppler intensity wash-out of the septal areas is now similar to that of the comparable lateral wall regions and shows no differences. (e) The normalized ECG tracings 8 days after intervention.

Figure 3. Power Doppler harmonic imaging measurement of regional myocardial perfusion in the same patient featured in Figs. 1 and 2 eight days after successful PTCA of the significant LAD stenosis using intravenous bolus application of Optison®. Regions of interest located into the left ventricular (yellow), the apical septum (green) and the apical lateral wall (red) in a colour-coded two-dimensional image using power Doppler harmonic imaging. The side-by-side comparison of the Doppler intensity kinetics between apical septal and apical lateral regions, as well as the Doppler intensity kinetic of the left ventricular cavity, is illustrated in (b). The colour-coded two-dimensional image with a colour-M-mode axis through the right ventricle, the septum and the left ventricle, as well as the lateral wall. (d) The corresponding colour-M-mode. The Doppler intensity wash-out of the septal areas is now similar to that of the comparable lateral wall regions and shows no differences. (e) The normalized ECG tracings 8 days after intervention.
a prolonged uniform bolus as shown in cardiac magnetic resonance tomography\(^\text{[15]}\). A semi-quantitative analysis of the first pass of contrast agent after a standardized prolonged bolus application is established in cardiac magnetic resonance imaging for the evaluation of regional myocardial perfusion\(^\text{[16]}\). In these studies the signal intensity slope in the myocardium was correlated to the slope observed in the left ventricular cavity. It was shown that a high cardiac output and ejection fraction result in an acceleration of the slopes. Therefore, for follow-up studies it is important that cardiac output does not significantly differ because the slope of contrast kinetics depends on cardiac output.

The intravenous bolus application is able to become a clinically applicable technique because bolus injections are simpler and more convenient than setting up a contrast infusion. However, off-line analysis is time-consuming at present. Acquisition of the myocardial contrast echocardiography data requires about 90 s. It is possible to assess the recordings frame by frame in the laboratory. The data are much easier to interpret by post-processing analysis. Using coloured M-mode, diagnosis can be made within a few minutes, the Doppler intensity kinetics, however, take longer.

Both cases illustrate that the presentation of the Doppler intensity-kinetics or of a coloured M-mode is necessary to demonstrate the myocardial contrast echocardiography result more objectively. A single frame of a two-dimensional power Doppler harmonic imaging image cannot be convincing and is not sufficient for the documentation of a perfusion measurement with myocardial contrast echocardiography after an intravenous bolus injection of micro-bubbles. Myocardial contrast echocardiography with power Doppler harmonic imaging is limited by several facts, especially using intravenous bolus application. It is well known that myocardial contrast echocardiography is limited in basal segments. However, it is...
rare that only basal segments are involved. Power Doppler harmonic imaging is generally applicable in other apical views. However, in the two- and three-chamber view drop-outs due to rib shadowing are more frequent.

Conclusion
The intravenous bolus application of contrast is feasible and suitable for non-invasive monitoring of regional myocardial perfusion in patients with acute coronary syndromes. The potential of myocardial contrast echocardiography with power Doppler harmonic imaging to detect regional hypoperfusion seems to be similar to cardiac magnetic resonance imaging to detect regional hypoperfusion analyzed for the interventricular septum using power Doppler harmonic imaging with contrast echocardiography: bolus or continuous infusion? J Am Coll Cardiol 1998; 32: 252–260.

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