Non-invasive assessment of myocardial ischaemia by using low amplitude oscillations of the conventional ECG signals (ECG dispersion mapping) during percutaneous coronary intervention

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Objective — The *HeartVue™ 6S System* is a recently developed novel technology that may provide non-invasive assessment of myocardial ischaemia by analysing low amplitude oscillations of the conventional ECG signals (ECG dispersion mapping). The available data to validate this new technology is limited. Therefore we performed a prospective study to assess the *HeartVueTM 6S System* for the detection of myocardial ischaemia during coronary occlusion in patients undergoing percutaneous coronary intervention (PCI).

Methods — A total of 101 patients undergoing cardiac catheterization were prospectively enrolled. *HeartVueTM 6S System* ECG dispersion mapping was obtained at baseline, and during the first balloon inflation and at the end of the procedure if PCI was performed. Parameters provided by the *HeartVueTM 6S System* were analysed.

Results — Fifty patients who underwent PCI comprised the final study population. The mean age was 63.7 ± 10 years and 58% were men. In 58% of cases the indication was acute coronary syndrome. In 98% of patients, PCI was successful. There were significant differences in the G7+G9 values between the first inflation and the end of the procedure, which reflect changes in ventricular depolarization ($P = 0.02$ by Wilcoxon signed rank test).

Conclusions — The *HeartVueTM 6S System* may have potential for a non-invasive assessment of ischaemia in patients with suspected coronary artery disease. Larger studies are warranted to confirm these preliminary findings.

Keywords: *ECG dispersion map – myocardial ischaemia – percutaneous coronary intervention.*

Introduction

A standard 12-lead electrocardiogram (ECG) is routinely used as the first tool for initial screening and diagnosis of coronary artery disease. However, sensitivity of ECG for prediction of coronary artery disease (CAD) is only 20% to 70%[1,2].

Coronary angiography remains the gold standard for morphologic diagnosis of CAD. However, there is a small, but serious, relevant procedure-related complication rate (< 2%), morbidity (0.03-0.25%), and mortality (0.01-0.05%)[3,4]. Therefore, it is desirable to develop simple reliable non-invasive ECG-based methods that could increase our ability to detect patients with myocardial ischaemia.

Several methods have been proposed and developed to enhance sensitivity and specificity of the resting ECG for diagnosis of asymptomatic CAD[5-7]. The *HeartVueTM 6S System* (Heart View, LLC, Cleveland, Ohio) is a recently developed technology that may provide non-invasive assessment of myocardial ischaemia by analysing low amplitude oscillations of conventional ECG signals (ECG dispersion mapping). This method allows us to get a stable signal of ECG micro fluctuations, reflecting not only the micro alternans of the T-wave, but also micro fluctuations of the QRS-complex and R-wave even in the resting state. The available data to validate this new technology have been limited.

We performed a prospective study to assess the *HeartVue™ 6S System* for the detection of acute

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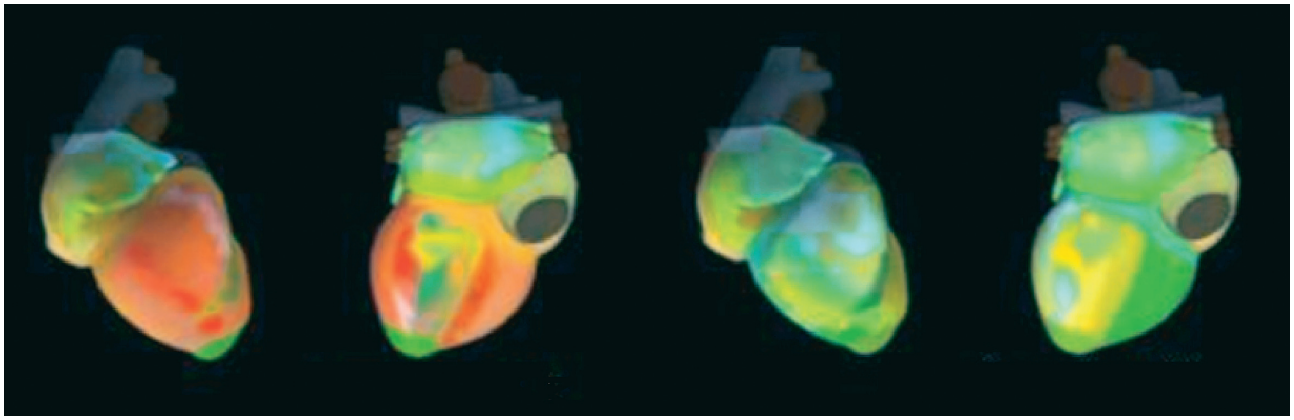

Fig. 1. – Example of the image provided by the HeartVue^{TM} 6S System (dispersive mapping). A gradated colour-coded image of the heart is presented with green indicating healthy state and red representing pathological changes.

myocardial ischaemia during coronary occlusion (balloon inflation and/or stent deployment) in patients undergoing percutaneous coronary intervention (PCI).

Methods

Inclusion and exclusion criteria

In this single-centre prospective study, we enrolled patients scheduled for coronary angiography with possible percutaneous coronary intervention. Exclusion criteria included**:** (1) age < 18 years old; (2) known significant valvular or cardiomyopathic diseases; (3) previous pacemaker implantation; and (4) inability to give informed consent.

The study protocol was approved by the institutional review board. Informed consent was obtained from all patients prior to study participation.

Patient characteristics

101 patients were included in the study, 50 of them underwent PCI and comprised the analysed study population. Baseline characteristics are shown in table 1. Indication for catheterization was 58% unstable angina/non-ST-elevation myocardial infarction.

Table 1. – *Baseline characteristics*

	Total population (n = 50)
Male sex	84%
Age, y	63.7 ± 10
DM	20%
Hypertension	74%
Hyperlipidaemia	92%
PVD	12%
Smoker (current)	20%
Previous MI	20%

Measurements

The general method of operating the *HeartVue^{TM} 6S System* was as follows: (1) four electrodes were applied in accordance with the standard arrangement of ECG limb leads: one on each forearm and one on each lower leg; (2) ECG data acquisition was performed over 30 seconds; (3) an image of the heart was formed on screen together with quantitative and qualitative analysis of cardiac electrical activity; and (4) the *HeartVue^{TM} 6S System* showed results in the form of a numeric dispersive characteristics range and a dispersive mapping. The dispersive mapping was a gradated colour-coded image of the heart in which green indicated healthy state and red represented pathological changes (figure 1).

The dynamics of the average micro fluctuations in the PQRST-complex are called dispersive characteristics. Dispersive characteristics were expressed by 9 analysed groups of deviations (G1-G9). In these groups the dispersive characteristics were analysed reflecting electrophysiological abnormalities in the depolarization and repolarization of the myocardium. Correspondence between groups G1-G9 and the QRST complex intervals are presented in figure 2. The study analysis was limited to groups G3-G9, which referred to the heart ventricles.

The manufacturer provided pre-specified parameters for the system: "*myocardium"* (measures the average micro alternans amplitude for both QRS and T wave), "*G9"* (measures the average micro alternans amplitude in the initial part of the QRS-complex), "*G7*+G9" (measures the average micro alternans amplitude in the middle part of the QRS-complex)) and *G3-G9 (*measures the average micro alternans amplitude in the final stage of depolarization and repolarization) (figure 2).

ECG signal acquisitions were performed at baseline (prior to angioplasty), during the first coronary balloon inflation or stent deployment (by protocol all

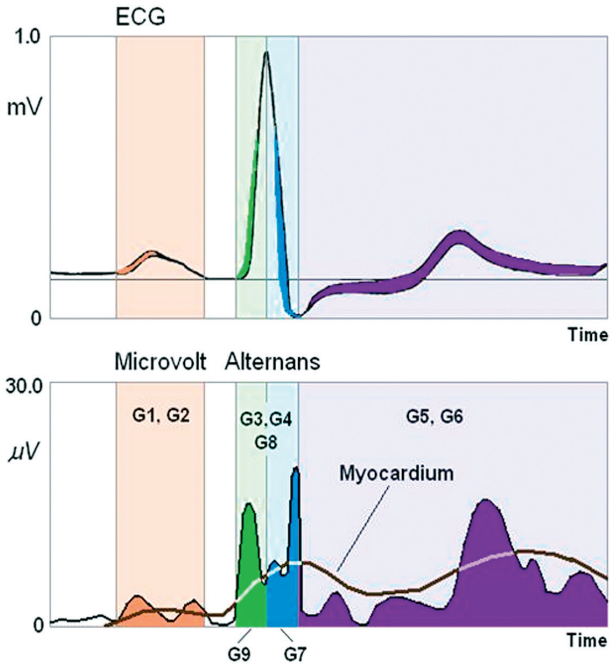

Fig. 2. – Correspondence between the groups G1-G9 (dispersive characteristics) provided by the *HeartVue^{TM} 6S System* and ECG QRST complex intervals.

inflations were at least 30 seconds) and at procedure end. If the patient did not proceed to angioplasty, then only baseline signal acquisitions were obtained. All signal acquisition was performed in the cardiac catheterization laboratory.

Endpoints

The primary endpoint was to compare the average of the parameters provided by the *HeartVue^{TM} 6S System* (*myocardium, G9, G3-G9, G7*+G9) at baseline, during artery occlusion (first balloon inflation or stent deployment) and at the end of the procedure.

Statistical analysis

No formal power calculation was performed for this study, as there were no previous data. Continuous variables are expressed as mean ± standard deviation and categorical variables as percentages. The Kolmogorov-Smirnov test showed that the distribution of the variables was not normal. Therefore, the Wilcoxon signed rank test was used to compare the differences in *myocardium, G9, G3-G9,* and *G9*+G7 between the baseline, first inflation and at procedure end. A significance level of 0.05 was used and 2-tailed test were applied. Analyses were performed using the Statistical Package for Social Scientists (SPSS Inc, 15.0 for Windows).

Result

HeartVue^{TM} 6S System parameters

In all the patients we obtained baseline data. Among the 50 patients who underwent PCI the first inflation data (balloon inflation or stent deployment) and post-procedure data were obtained in 44 (88%) and 48 (96%) patients respectively.

Dispersive mapping

At baseline in 80% of cases, the dispersive figures had a great variability and fluctuating form. These baseline findings prevented us from performing any comparison using dispersive mapping.

Dispersive characteristics

There were no statistically significant differences in the parameters *Myocardium, G3-G9* and *G9* provided by the system between baseline, first inflation and at the end of the procedure. However, there were significant differences in *G7*+G9 parameter between the first inflation and procedure end (table 2, figure 3).

Discussion

In this prospective study we showed that there are differences in the parameter G7+G9 provided by the *HeartVue^{TM} 6S System* between baseline and at the end of the procedure. The *HeartVueTM 6S System* may have potential for a non-invasive assessment of ischaemia in patients with suspected coronary artery disease undergoing PCI.

The sensitivity of the standard ECG for detection of CAD is limited[1,2], several methods have been proposed and developed to enhance sensitivity and

Table 2. – *Comparison of differences in G7+G9 parameter between baseline, first inflation and end of the procedure*

N	Average of (baseline – end of procedure)	Wilcoxon signed rank test (*P*-value)
48	0.54 ± 0.86	0.53
	Average of (baseline – first inflation)	Wilcoxon signed rank test (*P*-value)
44	-1.55 ± 1.13	0.23
	Average of (first inflation – end of procedure)	Wilcoxon signed rank test (*P*-value)
44	2.03 ± 0.92	***0.02***

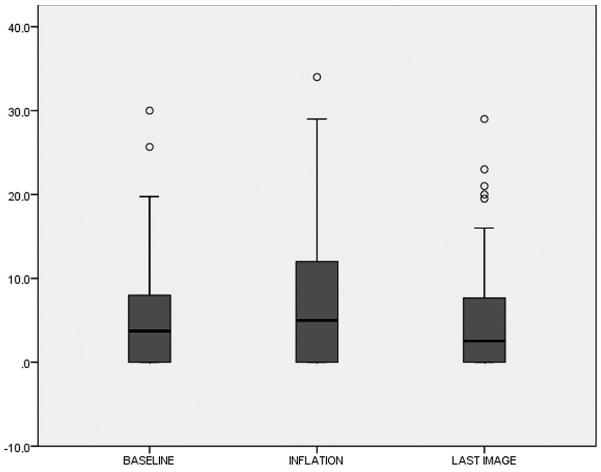

Fig. 3. – Boxplot showing G7+G9 parameter values at baseline, during first balloon inflation and at the end of the procedure. The horizontal line in the centre of the box represents the 50th percentile, the ends of the box represent the 25th and 75th percentiles, the tips of the whiskers represent the 5th and 95th percentiles and the closed circles indicate individual outliers. There were differences in the average difference for value G7+G9 per patient between first inflation and at the last image obtained at the end of the procedure ($P = 0.02$).

specificity of the resting ECG for diagnosis of symptomatic and asymptomatic CAD.

Diagnostic ECG computer programmes have been developed. However, they have not yet been shown to be superior to the specialist physician's judgment[6]. The results of a device that amplified and digitized the analogue ECG signal have been described. This device has shown a good sensitivity and specificity for the detection of patients with haemodynamically relevant stenosis[5,7]. The sensitivity and specificity of an ECG for the detection of CAD can be improved by exercise testing. The exercise ECG has a reported specificity of over 80% under ideal conditions. Clinically, however, sensitivity is typically less than 50-60%[8,9]. While these approaches provided significantly better diagnostic performance than the standard ECG, it appears that none of these methods has been implemented in broad clinical practice.

The ECG dispersion mapping method is a novel approach to ECG signal analysis. Using conventional ECG signals obtained from limb leads, low amplitude oscillations of the ECG signals are digitally amplified and assessed over several cardiac cycles. Patients with coronary heart disease display greater ECG signal fluctuation reflecting abnormal regional depolarization and repolarization processes within the myocardium. Thus dispersive changes in ECG signals may potentially reflect myocardial ischaemia.

The *HeartVue^{TM} 6S System* was developed as a non-invasive screening device for coronary heart disease. However, available data is limited and this device has not been validated prospectively in a clinical study. We performed this study using the *HeartVueTM 6S System* to determine if it detects myocardial ischaemia during coronary occlusion (balloon inflation and/or stent deployment) in patients undergoing PCI. Among several different approaches to validate the system we opted for coronary occlusion to eliminate potential confounding variables.

In this study we could not use the dispersive mapping data due to its great variability and fluctuating form. Further modifications of the system may help with this problem.

When we analysed the dispersive characteristics, we found significant differences in the G7+G9 parameter during first balloon inflation compared to procedure end. The G7+G9 parameter reflects the middle stages in ventricular depolarization, so potentially it could be the most sensitive parameter for detecting myocardial ischaemia.

This system was developed as a screening tool, it was not designed for PCI monitoring. During PCI there are factors that can influence the measurements of the *HeartVue^{TM} 6S System*: the patients receive several medications that can reduce the amplitude of microfluctuations and the presence of compensatory mechanisms could reduce the ability of the system to detect ischaemia. The ECG's micro-alternans amplitude measured by the *HeartVue™6S System* could reflect not only local myocardium hypoxia but compensatory myocardium reaction through collateral and microcirculatory mechanisms. Therefore modifications in the system may be needed to improve its ability to detect acute ischaemia during PCI. Continuous monitoring, instead of 30 sec recording, with trend analysis of the microfluctuations may be a better approach in the setting of PCI (a dynamic intervention).

Limitations

This is a single-centre study with a small number of patients. Ischaemia was induced during coronary occlusion by balloon inflation or stent deployment, ischaemia caused by platelet aggregation or spasm may induce a different type of response.

Conclusion

The *HeartVueTM 6S System* may have potential for a non-invasive assessment of ischaemia in patients with suspected coronary artery disease undergoing PCI. Larger studies and modifications of the system are warranted to confirm these preliminary findings.

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Conflict of interest

Dr Ik-Kyung Jang MD, PhD received a research grant from Heart View, LLC, Cleveland, Ohio.

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